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## NATIONAL CANCER INSTITUTE

### ANNUAL REPORT

# October 1, 1986 through September 30, 1987

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DEPARTMENT OF HEAD	TH AND HUMAN SERVICES - PUBLIC	HEALTH SERVICE					
NOTICE OF	INTRAMURAL RESEARCH PR	ROJECT	Z01	СВ	00333-24	LB	
October 1, 1986.	to September 30, 1987						
TITLE OF PROJECT (80 characters	or less. Title must fit on one line between the	borders.)					
Biochemical Basis	for Defective Different	ation in Granuloo	ytic	Let	ukemia		
PRINCIPAL INVESTIGATOR (List of	her professionel personnel below the Principal	Investigator.) (Name, title, labor	atory, an	d insti	tute affiliation)		
W.H. Evans	Research Chemist		LB	1	NCI		
S.M. Wilson	Biologist		L.B	T	NCI		
M.G. Mage	Immunochemist		LB		NCI		
0.W. McBride	Chief, Cellular Reg	ulation Section	LB	,	NCI		
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Hematology Oncol	ogy Section Walter Reed	Army Medical Cent	or				
includeo rogy, oncor	ogy section, arter aced	newy new car oen					
LAB/BRANCH	charictry DCPD						
Laboratory of Bio	chemistry, DCBD						
SECTION Cellular Regulati	on Section						
INSTITUTE AND LOCATION							
National Cancer I	nstitute, NIH, Bethesda,	MD 20892					
TOTAL MAN-YEARS:	PROFESSIONAL.	OTHER:					
		<b>1</b>					
CHECK APPROPRIATE BOX(ES)	K) (b) Human tiaquaa	(a) Maithar					
(a) Human subjects	(b) Human lissues			В			
SUMMARY OF WORK (Use standard	d unreduced type. Do not exceed the space of	rovided )		-			
	s amediced type. Do not exceed the space p						
The main thrust o	f this work is to develop	biochemical meth	nods	for	the early	7	
diagnosis of gran	ulocytic leukemia and me	chods for inducing	g leu	kem	ic cells	to .	
develop some or a	11 of their functional p	roperties as a mea	ans o	fp	artially o	or	
completely restor	ing host defense mechanis	sms in leukemia p	atien	ts.	Work is		
first aimed at es	tablishing which of the m	nany biochemical :	steps	in	volved in		
normal granulocyt	e differentiation are co	ntrolled by humora	al re	gul.	ators. Th	ne	
results will be compared with those obtained from similar studies on leukemic							
cells at corresponding stages of maturity in order to determine the nature and							
potential reversibility of the arrested differentiation steps. Biochemical							
analyses are carried out on mature and immature granulocytes isolated from							
blood and bone marrow and the effects of external cell regulators on granulocyte							
differentiation, as measured by changes in the synthesis of specific cellular							
components, are studied in a defined culture system previously developed in this							
laboratory. Poss	ible relationships betwee	en transforming g	enes	in	leukemic n	nyelo-	
blasts and factor	s involved in the regula	tion of normal gr.	anulo	cyt	e differen	ntia-	
tion are under in	vestigation.						



#### DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

#### NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 00366-17 LB

PERIOD COVERED							
October 1, 1986 to September 30, 1987							
TITLE OF PROJECT (80 charecters or less. Title must fit on one line between the borders.)							
Structure and Expression of Endogenous Retroviral Elements							
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)							
F I Kuff	Chiof	Biogypthesis Section	TR	NOT			
K K Lucdars	Chami	, biosynchesis section		NCI			
K. K. Lueders	Chemi	51	ЦВ	NCI			
7 Grossman	Visit	ing Fellow	LB	NCT			
P Arnaud	TPA	ing terrow	LB	NCI			
Li minuos			10	NOT			
COOPERATING UNITS (if any)							
E. Leiter, Jacks	on La	boratory, Bar Harbor,	ME; K. I	shizaka, Johns	Hopkins		
School of Medici	ne, B	altimore, MD	ŕ	,			
		and the second					
LAB/BRANCH							
Laboratory of Bi	ochem	istry, DCBD					
SECTION							
Biosynthesis Sec	tion						
INSTITUTE AND LOCATION							
National Cancer	Insti	tute, NIH, Bethesda, 1	1D 20892				
TOTAL MAN-YEARS:		PROFESSIONAL:	OTHER:				
5.0		3.0		2.0			
CHECK APPROPRIATE BOX(ES)							
(a) Human subjects		(b) Human tissues	(c) Neith	ner			
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SUMMARY OF WORK (Use stand	ard unred	uced type. Do not exceed the space pro	vided) We	allu distincti	a studies of		
ratrovirus-lika	alomo	nts in the mause Nu	a genetic	ally distinct	ve family of		
TAP gonomic alon	ereme	designated MIA1/ and	analysis	of the generic	arganization		
and predicted pr	otein	producte was complete	analysis ad during	the past year	Homology to		
type=D monkey vi	rue n	ermits assignment of	oding dom	ains even thou	igh the IAP		
proteins are not	ntoc	essed to the usual re-	roviral c	components. Th	e main 73 kDa		
IAP structural	rotei	n (P73) is analogous	to the und	processed gag n	recursor of		
immature retrovi	ruses	Homology with the	vpe-D ret	rovirus begins	at the p27		
coding domain.	Upstr	eam of $p_{27}$ , the seque	ice is uni	aue to the mou	se IAP genome.		
P73 N-terminates	in a	hydrophobic signal se	equence wh	ich is probabl	v the means by		
which the pascer	it par	ticles are associated	with the	endoplasmic re	ticulum		
membrane. MIA14	cont	ained two stop codons	in the po	ol reading fram	e; these have		
since been corre	cted	and now both gag and	ool are op	en. The "env"	region of the		
LAP genome conta	ins m	ultiple conserved stor	codons i	n all reading	frames, in		
agreement with t	he ob	served absence of a v	irally cod	led envelope pr	otein in IAPs.		
Sequencing was a	lso c	ompleted for two very	closely r	elated protein	-coding IAP		
cDNA clones, each isolated from thymus of a different inbred mouse strain. The							
clones are an order of magnitude more closely homologous to one another than to							
a number of other IAP clones for which comparable sequence is available. We							
plan experiments to determine whether these two clones represent allelic IAP							
elements specifically expressed in the thymus.							
We have begun investigating the binding of nuclear factors to the cloned LTR of							
MA14, previously shown to be active in promoting gene transcription. The aims							
of this work are	of this work are (1) to define the mechanism by which DNA methylation inhibits						
the promoter activity, and (2) to analyze the reported enhancement of IAP LTR							
activity by nucl	ear o	ncogene products.			and the second se		


DEPARTMENT OF HEALTH			ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEAR	CH PROJ	ECT	ZO1 CB 00945-14 LB
PERIOD COVERED October 1, 1986 to S	September 30, 198	7		
TITLE OF PROJECT (80 characters or less Factors Regulating t	s. Title must fit on one line between the Synthesis of (	veen the borde	ers.) 1 in Normal an	d Transformed Cells
PBINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the l	Principal Inves	stigator.) (Name, title, labo	pratory, and institute affiliation)
B. Peterkofsky Res	search Chemist	LB NO	CI	
I. Oyamada Vis	iting Fellow	LB NO	CI	
J. Palka Vis	iting Fellow	LB NO	CI	
E. Schalk Gue	est Researcher	LB NO	CI	
None				
LAB/BRANCH Laboratory of Bioche	emistry, DCBD			
SECTION Biological Interacti	ons Section			
INSTITUTE AND LOCATION National Cancer Inst	itute, NIH, Bethe	esda, MI	20892	
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:	
4.5	3.5		1.0	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	🗷 (b) Human tissue	es 🗆	(c) Neither	В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the	space provide	ed.)	
We have continued te in regulation of syn direct role in the b scurvy-induced fasti tion of collagen and	sting our model t thesis of the ext iosynthetic patho ng leads to chang proteoglycan syn	that pro tracellu way of c ges in H nthesis.	pposes an indi lar matrix, r collagen. The numoral factor . Specific as	rect role for ascorbate ather than through a model predicts that s involved in regula- says were performed for
carrier protein in n that ascorbic acid d I as well as inducti	ormal and scorbut eficiency in guir on of an inhibit	tic guir nea pigs or of DN	nea pig sera. s results in d NA synthesis i	The results indicated ecreased levels of IGF- n 3T3 cells and of
extracellular matrix	synthesis in cu.	llurea c	chondrocytes.	
Further studies were lagen that are synth	carried out on t esized by a chemi	two proo ically t	2(I)-like sub transformed Sy	units of type I procol- rian hamster fibroblast
but the $prog 2(I) - lik$	e chains are seco	reted as	s single chain	s. Secretion of these
chains was not affec	ted by their leve	el of pr	coline hydroxy	lation or by incorpor-
ation of the proline		-		· · ·
	analog, cis-hydr	roxyprol	line, into the	chains. Since the
chains were nonhelic cis-hydroxyproline i	analog, cis-hydr al, this result w nduced rapid, int	roxyprol was not tracellu	line, into the unexpected, b lar degradati	chains. Since the ut the finding that on of the chains did
chains were nonhelic cis-hydroxyproline i not conform with the	analog, cis-hydr al, this result w nduced rapid, int assumed mechanis	roxyprol was not tracellu sm of ac	line, into the unexpected, b lar degradati tion of the a	chains. Since the ut the finding that on of the chains did nalog. The analog is
chains were nonhelic cis-hydroxyproline i not conform with the thought to induce de	analog, cis-hydr al, this result of nduced rapid, int assumed mechanis gradation by dest	roxyprol was not tracellu sm of ac tabilizi	line, into the unexpected, b lar degradati tion of the a ing the triple	chains. Since the ut the finding that on of the chains did nalog. The analog is helical structure of
chains were nonhelic cis-hydroxyproline i not conform with the thought to induce de the normal procollag susceptible to prote	analog, cis-hydr al, this result w nduced rapid, int assumed mechanis gradation by dest en molecule and c olysis.	roxyprol was not tracellu sm of ac tabilizi conseque	line, into the unexpected, b ilar degradati tion of the a ing the triple ently renderin	chains. Since the ut the finding that on of the chains did nalog. The analog is helical structure of g the denatured chains
chains were nonhelic cis-hydroxyproline i not conform with the thought to induce de the normal procollag susceptible to prote	analog, cis-hydr al, this result w nduced rapid, int assumed mechanis gradation by dest en molecule and c olysis.	roxyprol was not tracellu sm of ac tabilizi conseque	line, into the unexpected, b ilar degradati ction of the a ing the triple ently renderin	chains. Since the ut the finding that on of the chains did nalog. The analog is helical structure of g the denatured chains



NOTICE OF INTRAMURAL RESEARCH PROJECT Z01 CB 05202-20 LB PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Isolation, Fractionation and Characterization of Native Nucleoproteins PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) O. Wesley McBride Chief, Cellular Regulation Section LB NCI A. Bale Biotechnology Fellow LB NCT S. Olson Biotechnology Fellow LB. NCI P. Burnett Biologist LB NCI COOPERATING UNITS (# any) J. Minna, F. Kaye, et al., F. Gonzalez, S. Kimura, D. Hatfield, S.A. Aaronson, S. Tronick, NCI; C. Kozak, M. Lerman, J. Chen, D. Nebert, et al., S. Detera-Wadleigh, NIH; R. Tukey, UCSD; M. Horowitz, Weizmann; R. Skoda, U. Meyer, Basal; R. Pirtle, NTS; D. Gajdusek, D. Goldgaber, CNSS; M. Smulson, Georgetown U. LAB/BRANCH Laboratory of Biochemistry, DCBD SECTION Cellular Regulation Section INSTITUTE AND LOCATION National Cancer Institute, NIH, Bethesda, MD 20892 TOTAL MAN-YEARS. PROFESSIONAL: OTHER: 4.0 3.0 1.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

В

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Analysis of interspecific somatic cell hybrids segregating human chromosomes permits the localization of human genes to specific chromosomes. We have previously constructed a large panel of human-rodent hybrids and used them to chromosomally map protooncogenes and various other human genes by Southern analysis of hybrid cell DNAs with cloned DNA probes. In collaborative studies, these hybrids have now been used to chromosomally map several additional protooncogenes and putative chromosomal neoplastic breakpoints as well as genes for the B-amyloid polypeptide of Alzheimer's disease, glucocerebrosidase (Gauche's disease), thyroid peroxidase and TSH receptor  $\beta$ -polypeptide, multiple tRNAs, calmodulin, alpha2-HS glycoprotein, poly(ADP-ribose) polymerase, epoxide hydrolase, menadione oxiodoreductase, and multiple additional P450 genes. Many pseudogenes were also chromosomally localized, RFLPs identified, and genomic restriction maps of several of the active genes constructed. Nine probes identifying restriction fragment length polymorphisms (RFLPs) have been isolated from chromosome-specific DNA libraries, subcloned, and characterized. Construction of genetic linkage maps of human chromosomes 1 and 15 is underway using cloned gene and anonymous DNA probes with DNA samples from the CEPH pedigrees. DNAs have been isolated from 50 lymphoblastoid cultures of patients with DNA repair defects and analyses are in progress to detect involvement of B-polymerase and poly(ADP-ribose) polymerase genes in any of these diseases.

(a1) Minors
 (a2) Interviews



ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	PROJECT NUMBER
RAMURAL RESEARCH PR	OJECT	ZO1 CB 05203-19 LB
September 30, 1987		
Title must fit on one line between the line in the line is and character	borders.) ization of Immuno	cytes and Components
ofessional personnel below the Principal	Investigator.) (Name, title, labora	tory, and institute affiliation)
Turnerstanist		
Immunochemist	LB N	UL .
Biologist Visiting Fellow	LB NO	
		51
mistry, DCBD		
itus NTU Datad	ND 00000	
PROFESSIONAL:	MD 20892 OTHER:	
2.0	1.0	
(b) Human tissues	🗷 (c) Neither	В
luced type. Do not exceed the space pr	ovided.)	<u> </u>
lopment of methods fo he study of the molec d 2) their application directly measure bind ve accomplished the s -soluble polymers. I e have synthesized, b njugates that can bin understanding the enh. have found that the in helper and cytotoxic e unmodified, unrejec o have features chara- ion of class II (Ia) ty.	r 1) the specific ular interactions a to problems of a ing of antigen-spa- ynthesis of conjug n order to study b y crosslinking di d two different c anced immunogenic mmune response to T cells. Further ted tumor line fro cteristic of antig antigens, and seco	isolation of antigen- that occur in their tumor immunology. In ecific receptors to gates of anti-MHC targeting of tumors fferent monoclonal lass I MHC antigens. ity of a xenogenized it is MHC restricted rmore, the xenogenized om which it was gen presenting cells, retion of material
	<pre>ND HUMAN SERVICES - PUBLIC RAMURAL RESEARCH PF eptember 30, 1987 Title must fit on one line between the ication and Character fessional personnel below the Principal Immunochemist Biologist Visiting Fellow itute, NIH, Bethesda, PROFESSIONAL: 2.0 ☐ (b) Human tissues fuced type. Do not exceed the space pr lopment of methods fo he study of the molec d 2) their applicatio directly measure bind ve accomplished the s -soluble polymers. I e have synthesized, b njugates that can bin understanding the enh have found that the i helper and cytotoxic e unmodified, unrejec o have features chara- ion of class II (Ia) ty.</pre>	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE RAMURAL RESEARCH PROJECT  eptember 30, 1987 Title must fit on one line between the borders.) ication and Characterization of Immuno. fessional personnel below the Principal Investigator.) (Name, title, labore fessional personnel below the Principal Investigator.) (Name, title, labore itus line in the labore in the borders.) ication and Characterization of Immuno. mistry, DCBD  itute, NIH, Bethesda, MD 20892 PROFESSIONAL: 2.0  (b) Human tissues (c) Neither  fuced type. Do not exceed the space provided.)  lopment of methods for 1) the specific he study of the molecular interactions d 2) their application to problems of fucetly measure binding of antigen-spic ve accomplished the synthesis of conjug- soluble polymers. In order to study di ajugates that can bind two different c understanding the enhanced immunogenic have found that the immune response to helper and cytotoxic T cells. Furtheri on diffied, unrejected tumor line fro o have features characteristic of antig ion of class II (Ia) antigens, and secuty.



NOTICE OF INTRAMURAL RESEARCH PROJECT ZO1 CB 0521	14-16 LB
PERIOD COVERED October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 cheracters or less. Title must fit on one line between the borders.) DNA Synthesis in Mammalian Cells	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliants).         S. H. Wilson       Medical Officer         LB NCI	ation)
B. ZmudzkaVisiting AssociateLB NCIP. KedarVisiting FellowLB NCIS. WidenHall-Shields FellowLB NCIJ. AbbottsIRTALB NCIC. MajumdarGuest ResearcherLB NCI	
COOPERATING UNITS (1 any) J. Mitchell, J. Oppenheim, H.R. Guy, NCI; G. Zon, F. Robey, FDA; K. Wil Yale; R. Karpel, University of Maryland; J. Collins, Virginia Commonwea University; F. Cobianchi, CNR, Pavia, Italy; S. Broder, NCI	lliams, alth
LAB/BRANCH Laboratory of Biochemistry, DCBD	
SECTION Nucleic Acid Enzymology Section	
INSTITUTE AND LOCATION National Cancer Institute, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS:         PROFESSIONAL:         OTHER:           6         5         1	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	
We continued biochemical studies of mammalian DNA replication proteins. length cDNA for human $\beta$ -polymerase was subcloned in an expression vector. protein was overproduced in <u>E. coli</u> and purified in mg quantities. Enzym characterization indicated that the recombinant enzyme is similar to the enzyme in catalytic properties. <u>In vitro</u> DNA repair activities of the re- enzyme were studied. Genomic clones spanning the gene for human $\beta$ -polyme isolated and characterized. The promoter region was sequenced and studies tion mutagenesis using a transient expression system. In other work, we the abundance of $\beta$ -polymerase mRNA in cultured human cells is both cell of lated and serum regulated. The $\beta$ -polymerase coding sequence was stably to into human fibroblast and expression of the transfected gene was studied. Steady-state kinetic analysis of the HIV DNA polymerase was conducted, overall kinetic scheme was derived. A DNA segment containing the coding for this enzyme was subcloned in an expression vector and the enzyme was produced in <u>E. coli</u> . Physical biochemical studies of a recombinant single-stranded nucleic as ing protein termed Al were conducted. The protein binds cooperatively to RNA or DNA and the full-length protein binds much tighter than a truncate protein lacking the glycine-rich COOH-terminal domain (residues 185-319). MR studies suggest the mechanism of Al binding is similar to that of sex prokaryotic ssDNA binding proteins in that binding involves close approacter aromatic amino acids with nucleotide bases. Indeed, we found that all 4 sites of covalent Al photocross-linking to [ <sup>32</sup> P]d(pT)g occur at Phe resic crosslinking sites were found within the COOH-terminal domain, yet this d clearly makes a significant contribution to the overall free energy of bi al to nucleic acids	Our full The nological natural ecombinant trase were ed by dele- found that cycle regu- transfected and an region over- ecid bind- o either ed Al Proton veral th of major lues. No lomain nding of

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PROJECT NUMBER



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 05231-13 LB

PERIOD COVERED
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Role of Subunit Interactions in Enzyme Chemistry and Cellular Regulation
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
M. L. Hubbard Visiting Fellow LB NCL (3 months)
J.L. Foster Guest Researcher LB NCI
M.H. Krinks Chemist LB NCI
J.R. Miller Technician LB NCI (3 months)
T. Jean Visiting Fellow LB NCI
J. Mackall Guest Researcher LB NCI
COOPERATING UNITS (if any) Dr. J. Schiloach, NIAMMD; Dr. P. Cohen, University of Dundee,
Scotland; Dr. L. Heppel, Cornell University, Ithaca, NY; Dr. J. Wolff, NIAMDD;
Dr. H. Plattner (University of Konstanz FRG); D.J. Tash and A.R. Means (Baylor
LAB/BRANCH
Laboratory of Biochemistry, DCBD
Protein Biochemistry
INSTITUTE AND LOCATION National Cancer Institute, NIH, Bethesda, MD 20892
TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 0.5
CHECK APPROPRIATE BOX(ES)
<ul> <li>(a) Human subjects</li> <li>(b) Human tissues</li> <li>(c) Neither</li> <li>B</li> <li>(a2) Interviews</li> </ul>
(a) Human subjects     (b) Human tissues     (c) Neither     (a1) Minors     (a2) Interviews  SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
<ul> <li>(a) Human subjects □ (b) Human tissues ★ (c) Neither</li> <li>(a1) Minors B</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Several steps in the stimulus response coupling mediated by Ca<sup>2+</sup> and calmodulin were investigated: (1) The existence of a GTP-specific diacylglycerol kinase which phosphorylates a specific pool of diacylglycerol has been demonstrated. This novel GTP-regulated protein may play a role in the release of Ca<sup>2+</sup> from internal stores upon external stimuli. (2) Ca<sup>2+</sup> binding by calmodulin is subject to a regulation by Mg<sup>2+</sup> which appears to be mediated by a Mg<sup>2+</sup>-induced conformational change in the central helix connecting the two halves of the calmodulin molecule. (3) The catalytic subunit of calcineurin, a calmodulin-regulated protein phosphatase, contains four distinct functional domains. The calmodulin-binding domain of calcineurin has been cloned and their sequence is being determined. The availability of the amino acid sequence of the two proteins will permit mapping of the functional domains of the enzyme and further our understanding of the mechanism of activation by calmodulin. (4) In collaboration with Drs. Tash and Plattner we have obtained evidence for a role of calcineurin in the regulation of cell motility and exocytosis.</li> </ul>
<ul> <li>(a) Human subjects (a) (b) Human tissues (c) Neither (a) Minors (a) Interviews</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided)</li> <li>Several steps in the stimulus response coupling mediated by Ca<sup>2+</sup> and calmodulin were investigated: (1) The existence of a GTP-specific diacylglycerol kinase which phosphorylates a specific pool of diacylglycerol has been demonstrated. This novel GTP-regulated protein may play a role in the release of Ca<sup>2+</sup> from internal stores upon external stimuli. (2) Ca<sup>2+</sup> binding by calmodulin is subject to a regulation by Mg<sup>2+</sup> which appears to be mediated by a Mg<sup>2+</sup>-induced conformational change in the central helix connecting the two halves of the calmodulin molecule. (3) The catalytic subunit of calcineurin, a calmodulin-regulated protein phosphatase, contains four distinct functional domains. The calmodulin-binding domain of calcineurin has been isolated and characterized. Genes for the two subunits of calcineurin have been cloned and their sequence is being determined. The availability of the amino acid sequence of the two proteins will permit mapping of the functional domains of the enzyme and further our understanding of the mechanism of activation by calmodulin. (4) In collaboration with Drs. Tash and Plattner we have obtained evidence for a role of calcineurin in the regulation of cell motility and exocytosis.</li> <li>Stimulus response coupling by CAMP is being studied by J. Foster who has cloned, sequenced and mapped the gene for the catalytic subunit of cAMP-dependent protein kinase of Drosophila melanogaster. The gene encoding the cGMP-dependent kinase of the same organism has also been isolated and is being sequenced.</li> </ul>



PROJECT NUMBER

## DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CB 05244-10 LB

PERIOD COVERED			
October 1, 1986 to Se	eptember 30, 1987		
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	ers.)	
Organization of Repea	ated DNA Sequences in Pri	Imates	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	tigator.) (Name, title, laboratory	y, and institute affiliation)
	The cost of the		
M. F. Singer Unier,	, Laboratory of blochemis	stry LB	NGI
R. Inayer Chemis	S C	LB	NCI
1. Fanning Expert		LB	NCI
S. Mongkolsuk Visiti	Ing Fellow	LB	NCI
G. Humphrey Guest	Researcher	LB	NCL
V. Krek Guest	Researcher	LB	NCL
G. Swergold PRAL P	ellow	LB	NCI
COOPERATING UNITS (if any)	- I Discontis P and st		
Jeilrey Sawyer, Clim	ical Diagnostic Foundatio	on, Genetics Cent	er, Corpus Christi,
lexas; U. Wesley McBr	ride, Laboratory of Bloch	nemistry, DCBD, N	ICI
LAB/BRANCH	istru DOPD		
Laboratory of blochen	nistry, DCBD		
SECTION	C. F.		
Nucleic Acid Enzymolo	bgy Section		
INSTITUTE AND LOCATION			
National Cancer Insti	tute, NIH, Bethesda, MD	20892	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
5.8	5.5	0.3	
CHECK APPROPRIATE BOX(ES)			
		(C) Neimer	
(a) Human subjects	k (b) Human tissues		-
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(a) Human subjects     (a1) Minors (lymp     (a2) Interviews     SUMMARY OF WORK (Use standard unreg     The goal of this work	k (D) Human tissues bhocytes) duced type. Do not exceed the space provide C is to understand the st	a.)	B sible function of
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<ul> <li>(a) Human Subjects</li> <li>(a1) Minors (lymp</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreg The goal of this work</li> <li>highly repeated DNA sequences are amplifi- tion to new genomic l</li> </ul>	(c) Human tissues (c) phocytes) duced type. Do not exceed the space provide (c) is to understand the st sequences and to elucidat ted either in tandem (sat loci (interspersed repeat	a) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu	B sible function of by which such through transposi- lar single copy
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<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unreprint of this work highly repeated DNA sequences are amplification to new genomic list on to new genomic list sequence that is consistent of the sequence of th</li></ul>	(c) Human tissues phocytes) duced type. Do not exceed the space provide (is to understand the st is to understand the st is decither in tandem (sat loci (interspersed repeat served in primates and ro NA in each species analyz is located close to the so, the extensive and rap i to taxonomic and evolut	a) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu- dents and is joi zed is being char Huntington's dis bid changes that tionary problems:	B sible function of s by which such through transposi- tlar single copy and to species racterized. This sease locus on human occur in satellite in particular,
<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unreprint of this work highly repeated DNA sequences are amplification to new genomic list on to new genomic list on to new genomic list on the sequence that is consequence that the sequence of the sequence</li></ul>	(c) Human fissues phocytes) duced type. Do not exceed the space provide (is to understand the st is to understand the st is dequences and to elucidat loci (interspersed repeat berved in primates and ro NA in each species analyz is located close to the so, the extensive and rap i to taxonomic and evolut iships in the carnivores	a) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu- dents and is joi zed is being char Huntington's dis bid changes that tionary problems: are being invest	B sible function of s by which such hrough transposi- lar single copy ned to species racterized. This sease locus on human occur in satellite in particular, sigated. To under-
<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unreprint of this work highly repeated DNA sequences are amplifit tion to new genomic list on to new genomic list sequence that is consequence that the sequence that the</li></ul>	(b) Human tissues phocytes) duced type. Do not exceed the space provide is to understand the st bequences and to elucidat ted either in tandem (sat loci (interspersed repeat served in primates and ro VA in each species analyz is located close to the so, the extensive and rap it to taxonomic and evolut hships in the carnivores te of the LINE-1 family of	a) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu- odents and is joi zed is being char Huntington's dis bid changes that tionary problems: are being invest of interspersed r	B sible function of s by which such hrough transposi- lar single copy ned to species cacterized. This sease locus on human occur in satellite in particular, sigated. To under- epeats, the poten-
<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unrep The goal of this work highly repeated DNA s sequences are amplific tion to new genomic 1 sequence that is cons specific satellite DN single copy sequence chromosome 4pl6. Als DNA are being applied evolutionary relation stand the significance tial for some family being in provision for stand the significance tial for some family</li> </ul>	(c) Human tissues phocytes) duced type. Do not exceed the space provide to is to understand the st bequences and to elucidat ted either in tandem (sat loci (interspersed repeat served in primates and ro NA in each species analyz is located close to the so, the extensive and rap to taxonomic and evolut this in the carnivores the of the LINE-1 family of members to be functional	a) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu odents and is joi zed is being char Huntington's dis bid changes that tionary problems: are being invest of interspersed r l genes and encod	B sible function of by which such through transposi- lar single copy ned to species racterized. This sease locus on human occur in satellite in particular, tigated. To under- repeats, the poten- le a protein is
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<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unrep. The goal of this work highly repeated DNA s sequences are amplific tion to new genomic 1 sequence that is cons specific satellite DN single copy sequence chromosome 4pl6. Als DNA are being applied evolutionary relation stand the significance tial for some family being investigated. RNA from human terate LINE-1 sequences that these cells and must sequences. Comparison two open reading fram 33 bp. Conceptual to the series of the serie</li></ul>	(c) Human tissues boocytes) duced type. Do not exceed the space provide to is to understand the st bequences and to elucidat ted either in tandem (sat loci (interspersed repeat served in primates and ro NA in each species analyze is located close to the so, the extensive and rap I to taxonomic and evolut this in the carnivores te of the LINE-1 family of members to be functional cDNA clones representing becarcinoma cells have bee tappear to be specifical thus be associated with on of the cDNAs indicates mes (ORFs) separated by the comologies to retroviral a	ed) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu odents and is joi zed is being char Huntington's dis boid changes that tionary problems: are being invest of interspersed r l genes and encod g polyadenylated, en isolated; they lly transcribed ( specific transcr s an overall stru- two in-frame stop (1284 codons) in and retrotranspos	B sible function of by which such hrough transposi- lar single copy ned to species acterized. This sease locus on human occur in satellite in particular, tigated. To under- repeats, the poten- le a protein is cytoplasmic LINE-1 define a subset of or processed) in tiptional regulatory teture that contains o codons bracketing dicates a polypep- on reverse tran-
<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(1ymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unger The goal of this work highly repeated DNA sequences are amplifit tion to new genomic 1 sequence that is consequence that the significant the significant these cells and must sequences. Comparises two open reading fram 33 bp. Conceptual that the with striking how scriptases. Sequence</li> </ul>	(b) Human fissues boocytes) duced type. Do not exceed the space provide (a) to understand the st sequences and to elucidat ted either in tandem (sat loci (interspersed repeat served in primates and ro A in each species analyz is located close to the so, the extensive and rap d to taxonomic and evolut this in the carnivores the of the LINE-1 family of members to be functional cDNA clones representing to appear to be specifical thus be associated with on of the cDNAs indicates mes (ORFs) separated by to analysis of a feline LI	ed) Tructure and poss te the mechanisms teallite DNA) or t ts). One particu- odents and is joi zed is being char Huntington's dis bid changes that tionary problems: are being invest of interspersed r l genes and encod g polyadenylated, en isolated; they lly transcribed ( specific transcri- s an overall stru- two in-frame stop (1284 codons) in and retrotranspos UNE-1 allowed us	B sible function of by which such through transposi- lar single copy ned to species acterized. This sease locus on human occur in satellite in particular, tigated. To under- repeats, the poten- le a protein is cytoplasmic LINE-1 y define a subset of or processed) in tiptional regulatory toture that contains o codons bracketing dicates a polypep- on reverse tran- to demonstrate that
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<ul> <li>(a) Human Subjects         <ul> <li>(a1) Minors</li> <li>(lymp</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK Use standard unreprint on the goal of this work highly repeated DNA is sequences are amplification to new genomic list work and the sequence that is consequence that the significance that the significance that for some family being investigated. RNA from human terated. LINE-1 sequences that these cells and must sequences. Comparised two open reading fram 33 bp. Conceptual the scriptases. Sequence the reverse transcript mammalian orders. In one of the cDNAs can</li> </ul>	(b) Human tissues phocytes) duced type. Do not exceed the space provide the stounderstand the st bequences and to elucidat the either in tandem (sat loci (interspersed repeat served in primates and ro the each species analyz is located close to the so, the extensive and rap d to taxonomic and evolut this in the carnivores to of the LINE-1 family of members to be functional cDNA clones representing ocarcinoma cells have bee cappear to be specifical thus be associated with on of the cDNAs indicates menslation of the 3' ORF analysis of a feline LI otase homology is marked i vitro translation experi-	ad) Tructure and poss te the mechanisms tellite DNA) or t ts). One particu- dents and is joi zed is being char Huntington's dis- bid changes that tionary problems: are being invest of interspersed r l genes and encod g polyadenylated, en isolated; they lly transcribed ( specific transcri- s an overall stru- two in-frame stop (1284 codons) in and retrotransposs INE-1 allowed us ly conserved in L timents demonstra mRNA for the 5'-0	B sible function of by which such through transposi- lar single copy ned to species cacterized. This sease locus on human occur in satellite in particular, tigated. To under- repeats, the poten- le a protein is cytoplasmic LINE-1 define a subset of or processed) in tiptional regulatory toture that contains codons bracketing dicates a polypep- ion reverse tran- to demonstrate that LINE-1s from 4 the that at least ORF. Overall the
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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER
	701 CP 05258 00 rp
NOTICE OF INTRAMORAL RESEARCH PROJECT	201 CB 05258-08 LB
PERIOD COVERED October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 cherecters or less. Title must fit on one line between the borders.) Molecular Studies of Eukaryotic Gene Regulation	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labor	ratory, and institute affiliation)
B.M. Paterson Research Chemist NCI & Quitosthe	Wisitia P.11 Nor
J. Eldridge Biochemist NCI L. DePonti	Visiting Fellow NCI
J. Rodriguez NRC Associate NCI ZY. Lin	Visiting Fellow NCI
B. Winter Visiting Fellow NCI	0
COOPERATING UNITS (/f any)	
None	
Laboratory of Biochemistry, DCBD	
SECTION	
Biochemistry of Gene Expression Section	
NATIONAL COATION National Cancer Institute, NIH, Bethesda MD 20892	
TOTAL MAN-YEARS: PROFESSIONAL. OTHER: 7 7 0	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects 🗵 (b) Human tissues 🗋 (c) Neither	
(a1) Minors	В
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided )	
Mussophia tisque aulture avatere revide estremelle un ful	
to study gene regulation during tissue formation. We have	isolated and charge
terized a variety of muscle specific and house-keeping gen	es that are differen-
tially expressed during myogenesis. These include the gen	es for alpha skeletal,
alpha cardiac, and beta cytoplasmic actin, and the myosin	light chain 1-3 gene.
The <u>cis</u> acting sequences responsible for the tissue specif	ic regulated expression
of these genes has been characterized and we are in the pr	ocess of identifying
proteins that interact with these regulatory regions.	
PC12 cells undergo neuronal differentiation in response to	NGF. We have iso-
lated the full-sized cDNA and corresponding gene for an mR	NA sequence that is
induced 50-80 fold in response to NGF. Antibodies to the	polypeptide, prepared
with lac fusions and various ORFs in the cDNA, demonstrate	the protein induction
In vitro and its localization in various neuronal tissues	In vivo. Preliminary
joined to a reporter gene (CAT). Regulation of this gene	and identification of
the protein are under study.	and a second at the of



	AND HUMAN SERVICES - P		SERVICE	PROJECT NUMBER	07 10
NOTICE OF INT	RAMURAL RESEARC			201 05 05262-	-07 LR
PERIOD COVERED	September 30 1987				<u> </u>
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line betwee	en the borders.)			
Eukaryotic Gene Regu	lation and Functi	on: The Me	etallothic	onein System	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the P	rincipal Investigator.	) (Name, title, lab	boratory, and institute affiliation	)
Dean H. Hamer Resea	arch Chemist LB	NCI			
M. Wong Visit	ting Fellow LB	NCI D.	Thiele (	Guest Researcher	LB NCI
I. Trnovsky Visit	ing Fellow LB	NCI P.	Hackott (	Guest Researcher	LB NCI
J. Imbert Visit	ing Fellow LB	NCI S.	Hu (	Chemist	LB NCI
M. Ernoult Visit	ing Fellow LB	NCI			
COOPERATING UNITS (if any)					
None					
none					
LAB/BRANCH Laboratory of Bioche	emistry, DCBD				
SECTION Biochemistry of Gene	e Expression Secti	on			
INSTITUTE AND LOCATION	ituto NTU Pothe	ada MD 200	202	······································	
TOTAL MAN.YEARS	PROFESSIONAL	Sda, MD 208	592 FB		
8.0	7.0		2.0		
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	🗵 (b) Human tissues	s 🗌 (c)	Neither	В	
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the s	pace provided.)			
The metallothioneins regulated and how th A mouse nuclear fact metallothionein-I ge regulation of the ma genic animal experim genes involved in me cloned. Structure f presence of preferre protein.	ance the bound exceed the s provide a useful to gene products a for that binds to the has been ident mmalian genes is bents. Using yeas stallothionein gen- function studies o d nucleation site	model to s llow cellul the metal c ified and i being studi t as a simp e expression f yeast met s for the c	tudy how ar adapta control se s being p ed by tra ble model on are bei allothion cooperativ	eukaryotic genes ation and homeost equences of the m purified. Develo ansfection and tr system, <u>trans</u> -ac ing identified an nein suggest the ve folding of thi	are asis. ouse pmental ans- ting d s



					PROJECT NUMBER		
DEPARTMENT OF HEALTH	AND HUMAN SERVICES	PUBLIC HEAL	TH SERVIC	CE			
NOTICE OF IN	TRAMURAL RESEAR	RCH PROJEC	ст		ZO1 CB 05263	8-06 L	В
				-			
October 1, 1986 to	September 30, 198	37					
TITLE OF PROJECT (80 characters or les Eukaryotic Chromatin	s. Title must fit on one line be n Structure and (	tween the borders. Gene Regula	) ation				
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the	e Principal Investig	ator.) (Name	, title, labora	tory, and institute affiliation	n)	
Carl Wu Visitin	ng Scientist LB	NCI					
B. Walker Staff I	Fellow LB	NCT B.	Davie	Labor	tory Worker	ו סד	NOT
S. Wilson Researd	ch Assistant LB	NCI L.	Brown	Visit	ing Fellow		NCI
V. Zimarino Visitin	ng Associate LB	NCI C.	Tsai	Howard	Hughes Fellow		NCI
H. Ueda Visitin	ng Fellow LB	NCI					
COOPERATING UNITS (if any)							
None							
LAB/BRANCH Laboratory of Bioch	emistry DCRD						
SECTION	childery, bobb						
Developmental Bioche	emistry and Genet	tics Section	on				
INSTITUTE AND LOCATION		1					
National Cancer Inst	TITUTE, NIH, Beth	nesda, MD	20892				
7.5	T-0		JINEN:	0.5			
CHECK APPROPRIATE BOX(ES)	1						
(a) Human subjects	🗌 (b) Human tissu	ies 🖾 i	( <mark>c) N</mark> eith	er			
(a1) Minors					В		
SUMMARY OF WORK (Use standard unre	educed type. Do not exceed th	e space provided l				<u>.</u>	
the analysis of sequences of the sequenc	ience specific DN	A binding	protei	ns in I	Drosophila has	been	
purified to homogene	ity, and mouse a	antibodies	agains	t the r	rotein have h	le Ly	
prepared. This reas	gent will be extr	emely use:	ful for	furthe	er studies on	the	
function of the pro	otein, which pre-	exists in	normal	cells.	, and is post-	trans	-
lationally modified	in response to h	neat shock	to be	a seque	ence-specific	bindi	ng
protein. NFftzl, a	nuclear protein	found in I	)rosoph	ila emb	oryos, has bee	n exte	en-
regulate the transcr	characterized bi	v of the s	segment	ation s	ein may negat vene fushi tar	azu.	
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		51					



DERADTMENT OF HEALTH			PROJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLI	C HEALTH SERVICE	701 OF 05064 06 - 7
NOTICE OF INT	RAMURAL RESEARCH P	ROJECT	201 CB 05264-06 LB
PERIOD COVERED			
October 1, 1986 to	September 30, 1987		
TITLE OF PROJECT (80 characters or less Characterization of	s. Title must fit on one line between the a Mouse Repetitive G	e borders.) Gene Family	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principa	al Investigator.) (Name, title, labora	atory, and institute affiliation)
Kira K. Lueders	Research Chemist	LB NCI	
Edward L. Kuff	Chief, Biosynthesis	Section LB NCI	
COOPERATING UNITS (if any)			
Nege			
None			
LAB/BBANCH			
Laboratory of Bioche	emistry, DCBD		
SECTION			
Biosynthesis Section	1		
National Cancer Inst	titute NIH Betheeda	MD 20802	
TOTAL MAN-YEARS	PROFESSIONAL	OTHER:	
1	1	OTHER.	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	🗵 (c) Neither	P
(a1) Minors			В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space .	provided.)	
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
Studies on the struc	tural and functional	organization of t	vpe II intracisternal
A-particle retroviru	is elements at the mo	lecular level have	continued. We have
shown that methylati	on and association w	ith two defined re	petitive sequences
appear to play a rol	e in controlling exp	ression of these g	enes in mouse cells.
on the basis of sequences	ience, a peptide repr	esenting the viral	integrase has been
us to study the inte	grase function in a	myeloma cell line	in which extensive
amplification of the	ese IAP sequences has	occurred. A cDNA	library has been made
from this cell line.	Clones for further	study have been s	elected on the basis
of IAP protein expre	ssion as well as seq	uence homology. C	loning of the inte-
grase gene will allo	w characterization o	t this protein.	



	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INTRAMURAL RESEARCH PROJECT	Z01 CB 05265-05 LB
PERIOD COVERED	<u> </u>
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
Regulation of Cytoskeletal Proteins	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboration and the principal investigator.)	atory, and institute affiliation)
P. Wagner Guest Researcher LB NCI	
ND. Vu Staff Fellow LB NCI	
A. Carroll Biologist LB NCI	
H. Foster Lab Technician LB NCI	
COOPERATING UNITS (if any)	
None	
LAB/BRANCH	
Laboratory of Biochemistry, DCBD	
SECTION	
Protein Biochemistry Section	
INSTITUTE AND LOCATION	
National Cancer Institute, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	
3.5 2.5 1	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects (b) Human tissues (c) Neither	
(a1) Minors	В
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Interactions between cytoplasmic myosin and actin are resp	onsible for a variety
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Interactions between cytoplasmic myosin and actin are resp of cellular motile activities. As in muscle contraction.	onsible for a variety hydrolysis of ATP by
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SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Interactions between cytoplasmic myosin and actin are resp of cellular motile activities. As in muscle contraction, myosin provides the required energy. While the actin-actin ties of vertabrate smooth muscle and pommuscle myosins are	onsible for a variety hydrolysis of ATP by vated ATPase activi- regulated by phos-
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SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided) Interactions between cytoplasmic myosin and actin are resp of cellular motile activities. As in muscle contraction, myosin provides the required energy. While the actin-acti ties of vertebrate smooth muscle and nonmuscle myosins are phorylation, there is disagreement as to the mechanism of head been reported that unphasebarulated eigental model.	onsible for a variety hydrolysis of ATP by vated ATPase activi- regulated by phos- this regulation. It
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SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided) Interactions between cytoplasmic myosin and actin are resp of cellular motile activities. As in muscle contraction, myosin provides the required energy. While the actin-acti ties of vertebrate smooth muscle and nonmuscle myosins are phorylation, there is disagreement as to the mechanism of has been reported that unphosphorylated gizzard myosin is phosphorylation causes a large increase in its actin-activ However, we have found that unphosphorylated calf thymus of unphosphorylation on these myosins is to increase their affi high actin concentrations, the MgATPase activities of thym are almost independent of phosphorylation. As it seemed u could stimulate unphosphorylated gizzard myosin sneeded their MgATPase activities to be activity of gizzard myosi unphosphorylated and phosphorylated gizzard myosins needed their MgATPase activities to be activited by actin. Under unphosphorylated myosin was filamentous, its MgATPase acti 10-fold by actin. Under conditions typically used by othe unphosphorylated myosin was monomeric, and its MgATPase wa actin. Active unphosphorylated smooth muscle myosin helps of smooth muscles to maintain tension in the absence of my We have also used limited proteolysis to identify reciproce	onsible for a variety hydrolysis of ATP by vated ATPase activi- regulated by phos- this regulation. It inactive and that ated ATPase activity. ytoplasmic myosin and e. The main effect of nities for actin. At us and aorta myosins nlikely that actin osphorylated gizzard n. We found that both to be filamentous for conditions where the vities were stimulated r investigators, the s not activated by explain the ability osin phosphorylation. of
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October 1, 1986 to Se	eptember 30, 1987			
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the	borders.)		
Mechanisms of Plasmi	d Maintenance			
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principa	I Investigator.) (Name, title,	laboratory, and institute affiliation)	
M. Yarmolinsky Chie	f. Developmental Bioc	hemistry & Ger	etics Section LB NCI	г
	-,			-
D. Chattoraj Resea	rch Chemist LB NCI	E. Hansen	Visiting Fellow LB M	NCI
B. Funnell Visit	ing Scientist LB NCI	S. Pal	Visiting Fellow LB M	NCI
S. Jafri Guest	Researcher LB NCI	K. Tilly	Sr. Staff Fellow LB N	NCI
K. Muraiso Guest	R Mason-Simmons Te	- chnician IB N		
COOPERATING UNITS (if any)	Re nason oranons re			
Dr. S. Wickner, LMB,	NCI; Dr. N. Sternber	g, DuPont		
LAB/BRANCH	DOPD			
Laboratory of Blocher	mistry, DCBD			
Developmental Biocher	mistry and Genetics S	Section		
INSTITUTE AND LOCATION			· · · · · · · · · · · · · · · · · · ·	
National Cancer Inst	itute, NIH, Bethesda,	MD 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
6.0	6.0	0		
CHECK APPROPRIATE BOX(ES)				
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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT PROJECT NUMBER

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PERIOD COVE	RED										···
October	1,	198	36 through	n Sept	ember 30,	1987					
TITLE OF PRO	JECT	(80 c	haracters or less	. Title mus	t fit on one line be	tween the borde	rs.)				
Tumor v	irus	s ez	xpression	in vi	tro and in	vivo		_			
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PI:	D.	R.	Lowy		Chief, La	b of Cell	lular	Oncology	NCI		
OTHER:	J.	т.	Schiller		Senior St	aff Fell	w	,	LCO	NCI	
	W.	s.	Sawchuk		Medical S	taff Fell	low		LCO	NCI	
	к.	н.	Vousden		Visiting	Fellow			LCO	NCI	
	т.	J.	Velu		Visiting	Fellow			LCO	NCI	
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	N.	L.	Hubbert		Microbiol	ogist			LCO	NCI	
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UMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This program studies oncogenes and papillomaviruses.

Oncogene studies have involved <u>ras</u> and <u>EGFR</u>. Some <u>ras</u> experiments are directed towards determining how ras proteins are stimulated to become biologically active and to identify their cellular target(s). Mutations that have been found previously not to affect cell transformation by a highly oncogenic <u>ras</u> gene have been engineered into a proto-oncogene version of <u>ras</u>. Some of these mutations have a significant effect on the ability of the proto-oncogene to induce cellular transformation. In vivo studies with Harvey murine sarcoma virus variants indicate that the target cell for tumor formation is determined, at least in part, by the transforming activity of <u>ras</u> in the virus. Experiments with a full-length EGF receptor proto-oncogene placed in a retrovirus vector have shown that established mouse cells transfected with the viral DNA or infected with a corresponding retrovirus, developed a fully transformed phenotype in vitro that required functional EGFR expression and presence of EGF in the growth medium. These results demonstrate that increased numbers of EGF receptors can contribute to the transformed phenotype.

In papillomavirus studies, the E2 open reading frame has been shown to bind to a specific motif present several times in BPV and other PVs. This motif is an enhancer whose activity depends upon E2. Enhancement requires two or more copies of the motif. Anti-E2 sera have detected two E2 protein products in BPV transformed cells. The smaller form of E2, which may competitively inhibit enhancement by the full-length E2 product, contains the DNA binding activity but lacks enhancer activity. In HPV studies, E6 protein has been identified in human cervical carcinoma cell lines known to express HPV 16 RNA and in mouse cells morphologically transformed by HPV 16 DNA. These results support the hypothosis that E6 can contribute to the transformed phenotype in human cervical cancers.



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLI	C HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH P	ROJECT	201 CB 09051-02 LCO
PERIOD COVERED			
October 1, 1986 through	1 September 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the	e borders.)	
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PI: R. A. Feldman	Senior Staff	Fellow I	CO NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Cellular	Oncology		
SECTION			
INSTITUTE AND LOCATION	the Detherde MD 20	200	
National Cancer Institu	Deserver		
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CHECK APPROPRIATE BOX(ES)	11.00	0.00	
(a) Human subjects	🗵 (b) Human tissues	(c) Neither	
(a1) Minors			В
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space	provided.)	
This project aims	at elucidating the h	iological functio	n(s) of the normal
human c-fps/fes proto-o	ncogene, and to unde	rstand the molecu	lar basis of its
oncogenic potential. W	le have generated a c	DNA copy of human	c-fps/fes from a
genomic DNA by means of	a retroviral shuttl	e vector, and hav	e begun characteriza-
tion of its biological	and biochemical prop	erties. The resc	ued cDNA encoded an
NCP92 protein that was	indistinguishable fr	om myeloid cell N	CP92, providing direct
evidence that this 92 K	da cellular tyrosine	kinase is the ge	ne product of human
c-fps/fes. We also sho	wed that human c-ips	/res is susceptib	le to oncogenic
activation by N=termina	I IIIKage with vital	gag sequences.	



			PROJECT NUMBER			
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE			Z01 CB 05550-18 LCO			
NOTICE OF INT	RAMURAL RESEARCH PROJEC	T				
October 1 1086 through	September 30 1987					
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)						
Regulation of retroviral replication and cellular oncogene expressions						
Regulation of retroviral reprication and certural oncogene expressions						
PI: K. S. S. Chang	Medical Officer	LC	O NCT			
OTHER: LC. Wang	Visiting Associat	e LC	O NCI			
C. Gao	Guest Researcher	LC	O NCI			
COOPERATING UNITS (IT any)		1				
Laboratory of Molecular	Virology and Carcinogene	sis, FCRF				
Biotech Research Labora	tories, Rockville, Maryla	п <b>а</b>				
LAB/BRANCH						
Laboratory of Cellular	Oncology					
SECTION						
INSTITUTE AND LOCATION						
National Cancer Institu	te, Bethesda, MD 20892					
TOTAL MAN-YEARS:	PROFESSIONAL: 0	THER:				
3.00	2.00	1.00	-			
CHECK APPROPRIATE BOX(ES)		N	·			
(a) Human subjects	(b) Human tissues	c) Neither	7			
(a1) Minors			В			
	iner the set owned the opport and the					
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)						

1. Certain cultured lines as well as tumor tissues of human embryonal carcinoma (EC) showed amplification and enhanced expression of c-Ki-<u>ras2</u> protooncogene. Retinoic acid treatment of EC cell lines resulted in down-regulation of c-Ki-<u>ras2</u> gene expression and morphological differentiation into neuron-like cells. This would suggest that epigenetic changes may influence the oncogenicity of EC cells.

2. Further studies on v-mos expression in S+L-mink cells superinfected with a novel retrovirus showed that the state of anchorage-independent, transformed cells growing in suspending fluid medium, is associated with a high oncogenicity and metastatic ability. This is related to greatly increased v-mos gene integration and expression accompanied by decreased production of vimentin, a component of intermediate filaments. However, ouabaine-induced adherent revertant cells exhibited a lowered oncogenicity without diminishing v-mos expression. Thus, an elevated level of v-mos expression is necessary but not sufficient for high oncogenicity.

3. Further studies on the amplification of c-<u>abl</u>-related sequence accompanied by new insertions of ecotropic provirus in the DNA of spontaneous reticulum cell neoplasms of SJL/J mice is in progress. Attempts are made to clone the 9-19 kb fragments of HindIII cleaved DNA, and to make cDNA of the mRNA.

4. A serological study using ELISA, Western blot, and immunofluorescence tests was conducted, and it was found that a high proportion of I.V. drug abusers is found to be infected with both HTLV-I and HIV (human immunodeficiency virus). Since IgM antibody against HIV was found more frequently than that against HTLV-I in these dually infected persons, the time of infection with HIV must have been more recent than that with HTLV-I.



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEALTH	SERVICE	PROJECT NUMBER		
			Z01 CB 04834-11 LCO		
NOTICE OF IN	RAMURAL RESEARCH PROJECT				
PEBIOD COVERED			· · ·		
October 1 1986 through	h September 30 1987				
TITLE OF PROJECT (80 characters or les.	s. Title must fit on one line between the borders.)				
Genetic mechanism of neoplastic transformation					
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)					
PI: S. S. Yang	Research Chemist	LC	O NCI		
OTHER: J. V. Taub	Biolab Technician	LC	O NCI		
R. Modali	Biologist	LC	O NCI		
COOPERATING UNITS (if any)					
B. J. Park, LMCB, NCI					
E. Butler, LDN, NICHD					
LAB/BRANCH					
Laboratory of Cellular	Oncology				
SECTION					
INSTITUTE AND LOCATION					
National Cancer Institu	ite, Bethesda, MD 20892				
TOTAL MAN-YEARS:	PROFESSIONAL: OT	HER:			
2.50	1.00	.50			
(a) Human subjects	(b) Human tissues	Neither			
(a) Human Subjects		) Neither	В		
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SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The thrust of this project is to elucidate the genetic mechanism of neoplastic transformation of normal cells. The experimental system centers on a 3.1 kilobasepair, poorly cell-transforming human oncogene, hHC<sup>H</sup>, isolated from an African hepatocellular carcinoma cell line, Mahlavu. In a survey of 24 additional hepatoma DNAs (17 Korean, 3 Taiwan Chinese, 2 Caucasian, and 2 African), 20 hepatomas had DNA sequences homologous to hHC<sup>H</sup>. Seven clones of these hepatocellular carcinoma oncogenes were isolated from a Chinese and a Korean hepatoma. Their cell-transformation capability was ascertained and their structural relationship analyzed. The presence of the integration site for human hepatitis B virus DNA within the hHC<sup>H</sup> was found and the relationship of HBV to hHC<sup>H</sup> was critically examined. As an on-going interest, the aflatoxin B<sub>1</sub> dG targets on hHC<sup>H</sup> were predicted by computer analysis. By a combination of recombinant DNA technology and DNA-mediated cell-transformation assay, the possible role(s) of these poorly celltransforming oncogenes, hHC, and their relationship(s) with HBV and afltoxin B<sub>1</sub>, in neoplastic transformation of cells are currently being examined.

GPO 904.91



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 05596-18 LGN

October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 cheracters or less. Tit	e must fit on one line between the border	rs.)		
Pathogenesis of plasma of	ell neoplasia: charact	erization of antig	en-binding proteins	
PRINCIPAL INVESTIGATOR (List other profess	ional personnel below the Principal Invest	tigator.) (Name, title, laboratory, an	d institute affiliation)	
P.I.: M. Potter	Chief, Laborato	ory of Genetics	LGN,NCI	
E.B. Mushinski	Bio. Lab. Techr	nician	LGN,NCI	
L. D"Hoostelaere,	Biologists		LGN,NCI	
S. Brust, R. Du	incan			
E. Shacter, K. Hu	ppi Staff Fellows		LGN,NCI	
B. Mock	Hall-Shields Fe	ellow	LGN,NCI	
K. Sanford	Chief, In Vitro	o Carcin. Sect.	LCMB,NCI	
K. Kohn	Chief		LMPH,NCI	
COOPERATING UNITS (# any) Dr. H. (	. Morse, III, NIAID; I	Dr. F. Wiener, Karo	olinska Institutet,	
Stockholm, Sweden; Dr. H	. Parshad, Howard Univ	v., Wash. DC; Dr. K	. Marcu, SUNY,	
Stony Brook, NY; Dr. L.	Blankenhorn, Hahneman	Medical School, Ph	il., PA	
LAB/BRANCH Laboratory of Genetics				
SECTION				
NCT NTH Bethesda, MD	0892			
TOTAL MAN-YEARS	OFESSIONAL	OTHER:		
9.0	5.0	4.0		
		4.0		
(a) Human subjects	(b) Human tissues	(c) Neither		
(a) Minors		(0)		
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SUMMARY OF WORK (Use standard unreduced The major project in anisms involved in the dev in BALB/c mice. BALB/cAn while most other strains a pristane have chromosomal directly or indirectly the tify the origin of mutager tissue evoked by pristane, generated by inflammatory finding that indomethacin determining the mode of a systems for finding the ge cytoma development by usin congenics. Several genes Congenic mice constructed produced even stronger res studying genes associated and C.J congenics. We have Plasmacytomas can be infection of pristane compression	d type. Do not exceed the space provide the laboratory is to of relopment of parrafin of mice are highly suscept re resistant. Over 9: translocations [rcpt() c -myc locus on chr 1: dic substances associat We hypothesize these cells. A major clue di inhibits plasmacytoma tion of indomethacin. metic basis of suscept g BALB/cAn.DBA/2 (C.D2 have been identified to by combining two weak distance. In collabora with DNA repair defici- re identified two geness induced with short lat litioned mice with retri-	B d) determine the patho oil (pristane) indu otible to developin 5% of plasmacytomas 12;15), rcpt(6:15)] 5. One aim of our ted with the chroni e are oxygen and li in this work is pro- formation. Studie We have developed tibility and resist 2) and BALB/cAn.BAI that confer partial ly active resistand ation with Dr. K. S iencies in BALB/cAr is in DBA/2. tent periods in BAI roviruses containing we action of myc ar	egenetic mech- need plasmacytomas ag these tumors induced by involving work is to iden- c inflammatory pid radicals ovided by the es are aimed at i model genetic ance to plasma- .B/cJ (C.J) t resistance. te genes have Sanford, we are n mice and C.D2 .B/cAn mice by the ng oncogenes. Our d <u>ras</u> (in col-	
SUMMARY OF WORK (Use standard unreduce The major project in anisms involved in the dev in BALB/c mice. BALB/cAn while most other strains a pristane have chromosomal directly or indirectly the tify the origin of mutager tissue evoked by pristane. generated by inflammatory finding that indomethacin determining the mode of ac systems for finding the ge cytoma development by usin congenics. Several genes Congenic mice constructed produced even stronger res studying genes associated and C.J congenics. We hav Plasmacytomas can be infection of pristane conc recent studies demonstrate laboration with K. Marcu,	d type. Do not exceed the space provide the laboratory is to of relopment of parrafin of mice are highly suscep- translocations [rcpt() c -myc locus on chr 1: dic substances associat We hypothesize these cells. A major clue di inhibits plasmacytoma tion of indomethacin. netic basis of suscept g BALB/cAn.DBA/2 (C.D) have been identified to by combining two weak sistance. In collabora with DNA repair defici- re identified two genes induced with short lat litioned mice with retri- the potent cooperation Stony Brook).	B d) determine the patho oil (pristane) indu otible to developin 5% of plasmacytomas 12;15), rcpt(6:15)] 5. One aim of our ted with the chroni e are oxygen and li in this work is pro- formation. Studie We have developed tibility and resist 2) and BALB/cAn.BAI that confer partial ly active resistance ation with Dr. K. S tencies in BALB/cAr s in DBA/2. tent periods in BAI roviruses containing we action of myc ar	egenetic mech- need plasmacytomas ing these tumors is induced by involving work is to iden- c inflammatory pid radicals ovided by the es are aimed at i model genetic cance to plasma- .B/cJ (C.J) t resistance. es genes have Sanford, we are in mice and C.D2 .B/cAn mice by the ng oncogenes. Our nd <u>ras</u> (in col-	

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 08727-10 LGN

PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 cheracters or less. Title must fit on one line between the borders.) Organization and control of genetic material in plasmacytomas PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboretory, and institute effiliation) P.I.: J.F. Mushinski Medical Director LGN,NCI G.L.C. Shen-Ong, L. Wolff Senior Staff Fellows LGN,NCI K. Huppi Staff Fellow LGN.NCI B. Mock Hall Shields Fellow LGN,NCI J. Kurie Biotech. Training Fellow LGN,NCI S.R. Bauer, L. D'Hoostelaere Biologists LGN,NCI L. Miribel Visiting Fellow LGN,NCI M. Potter Chief, Lab. of Genetics LGN,NCI COOPERATING UNITS (if any) D. Givol, Meloy Labs; K. Marcu, Dept. of Biochemistry, SUNY, Stony Brook, NY; H.C. Morse, III, LVD, NIAID; M.C. Sneller, LCI, NIAID, J. Ashwell, BRMF, NCI LAB/BRANCH Laboratory of Genetics SECTION INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892 TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 10.0 8.0 2.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews R SUMMARY OF WORK (Use standerd unreduced type. Do not exceed the space provided.) The overall goal of this research is to study the activation of particular genes in diseased and normal cells in order to understand which genes may play important roles in the development of malignancies, autoimmune diseases and normal differentiation. The immune system has been chosen as the central focus of this research, and we have concentrated on the expression of "oncogenes," especially myc, myb and ras, as well as immunoglobulin and T cell receptor genes. To this end we have been studying the lymphoid tumors (particularly the plasmacytomas) that are regularly induced in BALB/cAnN mice by intraperitoneal injections of alkane mineral oils, such as pristane. These tumors represent immortalized lines of B lymphocytes or myeloid cells at different stages of differentiation. Currently we are using this model system of tumors to learn how the genes involved in myeloid and B cell carcinogenesis are organized and regulated. Generally oil-induced plasmacytomas arise only after a long latent period, typically 12 months. In such a long time period many genetic changes could have accumulated, one or more of which could be causally involved in the carcinogenic process. The latent period can be drastically shortened by injecting certain retroviruses, e.g., Abelson virus complex or viruses incorporating avian v-myc genes. The latency period is shortened presumably by supplying one of the genetic lesions that by chance arose in the oiltreated peritoneal cells. We have also studied how endogeneous proto-oncogenes are expressed and found the frequent elevation of steady state levels of RNA from the proto-oncogenes c-myc and c-myb in certain tumors, autoimmune cells, and in dividing normal lymphocytes. Recent studies have shown changes in some of the ras family of oncogenes in a large number of these tumors. The details and consequences of these mutations are currently being analyzed. Another putative oncogene, bcl-2, has been found to be expressed at only certain periods during B cell differentiation. An extensive effort has been made to characterize the structure and control of expression of these oncogenes in normal and abnormal cells.


			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJE	ECT	ZO1 CB 05553-18 LGN
PERIOD COVERED			
October 1, 1986 to Se	ptember 30, 1987	- 1	
Timmunoglobulin structure	Title must fit on one line between the border	s.)	-11 merhadis
PRINCIPAL INVESTIGATOR (List other prot	e and diversity. Charact	igator.) (Name, title, labora	ell membrane proteins tory, and institute affiliation)
P.I.: Stuart Rudikoff	Microbiologist	I.	GN. NCT
W. Davidson	Visiting Assoc	iate L	GN, NCI
R. Nordan	Staff Fellow	L	GN, NCI
J. Hyde	Postdoctoral F	'ellow L	GN, NCI
A. Cuddihy	Graduate Stude	nt L	GN, NCI
D. Hilbert	Guest Research	ier L	GN, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Genetics			
SECTION			
INSTITUTE AND LOCATION	20002		
NIC, NIH, BETNESDA, MD	20892	OTHER	
8.0	5.0	2.0	
CHECK APPROPRIATE BOX(ES)	5.0	<u></u>	
(a) Human subjects	□ (b) Human tissues 🛛	(c) Neither	
(a1) Minors			
(a2) Interviews		В	
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the space provide	d.)	
1) In the last several y	rears a number of lymphol	cines have been	1 described which
play important roles in	the growth and/or differ	centiation of E	3- and T-lymphocytes.
Studies from this labora	itory have identified an	activity in su	for growth and
macrophage cell lines wi	nent of our ourrout int	/ plasmacycomas	a of coll growth a
major effort is being ma	de to characterize this	factor and det	ermine its role in
vivo. Illtimately, we pl	ar to extend these stud	ies to the rece	eptor for this factor
in order to assess the r	otential biological role	e of this facto	or-receptor system in
normal cell growth and/	or possibly plasmacytomag	genesis. 2) A	second major interest
in the area of growth an	nd differentiation is di	rected toward a	an attempt to isolate
and characterize genes (	and their protein produc	cts) involved i	In ontological differ-
entiation of lymphoid ce	ells. To approach this o	question, we ha	ave developed new or
selected existing cell 1	lines which can be induce	ed to different	iate. The strategy
of these experiments is	to prepare subtractive of	cDNA libraries	using the parental
line and the differentia	ited derivatives. The res	sulting clones	will then be analyzed
with the eventual aim of	transfecting isolated g	genes back into	the parental cell
type to attempt to repro	duce the differentiated	during gono of	the absence of in-
from relatively simple	such as point mutation	to considerabl	v more complex such
as recombination gone (	such as point mutation,	d contraction.	Most evolutionary
studies in higher organi	isms have involved compare	risons of simil	ar protein or gene
sequences from two or mo	ore species which are gen	nerally widely	separated in evolu-
tionary time. We have a	attempted to assess the	role of such pr	cocesses in a more
dynamic context by exami	ining gene structures amo	ong different w	vild mice species.
We have therefore initia	ated experiments to exami	ine single copy	genes, pauci-gene
families and multi-gene	families among our wild	mice colony re	presenting the
evolutionary spectrum of	this species.		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 05552-18 LGN

FRIOD COVERED
ctober 1, 1986 to September 30, 1987
TLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
ammalian cellular genetics and cell culture
RINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
.1.: H.G. Coon Research Biologist Lon, NCI
P. Curcio Visiting Scientist Low, NCI
K. Sweidlow Stall Fellow Low, Not
DOPERATING UNITS (if any)
r. M. Luisa Brandi, NIDDKD, MD; Dr. F. Saverio Ambesi-Impiombato, Istituto di
atologia Generale, Naples, Italy
B/BRANCH
aboratory of Genetics
ECTION
STITUTE AND LOCATION
CI, NIR, BELlesta, ID 20072
2.5 0.0
(a) Human subjects (b) Human tissues (c) Neither
(a1) Minors
(a2) Interviews B
JMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)
is the purpose of this project to analyze and develop new and difficult
stems for cell culture. We are now pursuing intensively a single cell system:
lture of cells from the neonatal rat olfactory epithelium (OLFE). The projects
wolving thyroid gland reconstruction and thyroid cell genetics have been post-
oned. We hope to continue these timely experiments as soon as our principal
ollaborator, Dr. F. S. Ambesi, can return to the laboratory. Meanwhile, our
ogress with the OLFE has been sufficiently exciting during the past year that
has merited our full attention. Using complex media and substrates we have
acceeded in culturing several cell types from the OLFE. The mixed, mass cul-
ares of these cells provide an appropriate conditioned medium that has permitted
he isolation of 20 clonal cell strains from 3rd to 6th passage cultures. We have
ontinued the hybridoma screen using OLFE as antigen and fluorescent anti-mouse
G staining of frozen sections of OLFE for selection. These results, too, are
ery encouraging; some of the hybridoma supernates appear to identify small patche
cells selectively in the OLFE, and others identify only the apical structures of
ther the sensory cells of the sustentacular cells. The sensory neurons of the
tractory epithelium are renewed throughout life the first remaining nourblast to
everopment of this system would make available the first mammalian helioblast to
ation dichotomy company to all black coll eventers. It is housd that basic issues
alfactory sensory physiology can be explored with this system.
· orracion, sensor, physiology can be explored with this system.

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PROJECT NUMBER DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT Z01 CB 08950-05 LGN PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Immunochemistry and genetics of protein-binding immunoglobulins PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, leboratory, and institute affiliation) P.I.: Sandra Smith-Gill Sr. Staff Fellow LGN,NCI C. Mainhart Microbiologist LGN.NCI T. B. Lavoie LGN,NCI Biologist E. Vacchio Biologist LGN,NCI R. Duncan Biologist LGN,NCI C. Mallett American Cancer Society Fel. LGN,NCI Fellow, NCI of Canada P. Hamel LGN.NCI P. Rousseau Student Volunteer LGN,NCI COOPERATING UNITS (if any) A.B. Hartman, Dept. of Biologics, Walter Reed; K. Dorrington, Dept. of Biochem., Univ. of Toronto, Toronto, Canada; D. Davies, LMB, NIADKD; B. Brooks, DCRT, NIH; A. Basten, University of Toronto, Toronto, Canada LAB/BBANCH Laboratory of Genetics SECTION INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892 TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 5.0 0.0 5.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues X (c) Neither (a1) Minors (a2) Interviews В SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Monoclonal antibodies directed against the model protein antigen, lysozyme c, are used as probes to study antibody-protein interactions and structure-function relationships, and to study developmentally regulated antigens in normal and neoplastic development. The interaction of antibodies with the epitopes are modeled and ultimately refined by protein crystallography studies. One antibodylysozyme complex has been refined to 2.5 Å by X-ray crystallography. The results confirm the serologically predicted epitope and indicate a high degree of complementarity between the opposing surfaces. Another antibody-lysozyme complex has been studied in detail utilizing a new computer method for efficiently examining the interaction between 2 proteins. The conclusions from both studies are being tested with peptide binding experiments, by site-specific mutagenesis of in vitro expressed cloned immunoglobulin genes, and utilizing transgenic mice expressing the cloned lysozyme and/or antibody genes. The development of speci-

ficity for lysozyme from an apparently multispecific available antibody repertoire is currently being examined in detail utilizing large panels of hybridoma antibodies. In addition, monoclonal antibodies are being generated against bacterially expressed mouse c-myc protein; these antibodies will be used to purify and characterize structure-function relationships in the myc protein, applying the

principles derived from the model protein studies.



## DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 08951-05 LGN

PERIOD COVERED	ambox 20 1007		
TITLE OF PROJECT (80 characters of loss	Title must fit on one line between the l	orders )	
Molecular basis for the	acute erythroleukemi	as induced by murine	retroviruses
PRINCIPAL INVESTIGATOR (List othar pro	fessional personnal below the Principal	nvestigator.) (Name, title, laboratory, a	and institute affiliation)
P.I.: S.K. Ruscetti	Senior	Investigator	LGN,NCI
L. Wolff	Senior	Staff Fellow	LGN,NCI
SW. Chung	Visiti	ng Fellow	LGN,NCI
COOPERATING UNITS (if any)			
		·	
Laboratory of Genetics			
SECTION		• • • • • • • • • • • • • • • • • • • •	
INSTITUTE AND LOCATION	00000		
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
	5.0	0.0	
(a) Human subjects	(b) Human tissues	🖙 (c) Neither	
(a1) Minors	_ (, )	(-)	
(a2) Interviews		В	
SUMMARY OF WORK (Use standard unred	lucad type. Do not axceed the space pr	ovided.)	
The Friend strain of the	spleen focus forming	virus (SFFV) causes	an acute erythro-
leukemia in mice. Studi	es have been aimed at	defining the area(s	) of the viral
genome responsible for p	SEEV alters and eryt	acil growth and dif	forantiation
the mechanisms by which	SFFV allers erythiold	ceri growin and dri	rerentration.
Using a Moloney MuLV-bas	ed retroviral vector.	we have demonstrate	d that the SFFV
env gene, when introduce	ed into mice in the ab	sence of other SFFV	genes, is patho-
genic. The disease indu	ced is indistinguisha	ble from that induce	d by the entire
SFFV genome, proving that	it the primary effect	of the virus, which	is to alter the
requirements of erythroi	d cells for erythropo	ietin (Epo), is due	solely to the
product of its env gene.	To further understa	nd how the viral env	gene product
alters erythroid cells,	we have continued our	studies of variants	of the virus,
designated SFFVp and SFF	VA, both of which ind	uce acute erythroleu	semia but differ
products We were previ	ously able to localiz	e the biological and	biochemical dif-
ferences between the two	viruses to a 678 bp	region in the 3' hal	f of the env gene.
We have now further loca	lized the critical re	gion to a 120 bp fra	gment from the
extreme 3' end of the er	w gene which encodes	the pl5E-related tra	nsmembrane domain
of the protein. Finally	, we have attempted t	o understand how the	SFFV envelope
glycoprotein alters the	requirements of eryth	roid cells for Epo b	y comparing normal
and virus-infected cells	for Epo receptors.	Our results indicate	that spleen cells
trom SFFVp-infected mice	, which proliferate a	nd differentiate in	the apparent
absence of Epo, have the	same number of Epo r	which proliferate	better in the
presence of Eno and white	h require Foo for dif	ferentiation have 4	times as many Eno
receptors. Cross-linkin	in require apo for un	LOLOLOLOLOLO MAVE 7	
	ng studies show no obv	ious quantitative di	fferences in the
receptors on normal and	ng studies show no obv SFFV-infected cells.	ious quantitative di	fferences in the



					PROJECT N	UMBER	
DEPARTMENT OF HEALTH	AND HUMAN SERV	ICES - PUBLIC HEA	LTH SERV	ICE			
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October 1, 1986 to	September 30	), 1987					
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oncogenes and cherr	cooperative	errects in a	myerora	Teukem	Las		
PRINCIPAL INVESTIGATOR (List other pro	tessionel personnel de c	Sopior Staff	Fellow	e, title, labora	tory, and insi	TCN NCT	
L. Pasamontes		uest Research	her			LGN, NCT	
K. Nason-Burche	enal (	raduate Stud	ent			LGN,NCI	
G. Shen-Ong		Senior Staff	Fellow			LGN NCT	
J.F. Mushinski	N	fedical Direc	tor			LGN NCT	
						2011,1102	
COOPERATING UNITS (if any)					·		
H.C. Morse, III, LVD,	NIAID; L. Ne	ckers, LP, N	CI				
LAB/BRANCH							
Laboratory of Genetics	;						
SECTION							
INSTITUTE AND LOCATION							
NCI, NIH, Bethesda, ML	20892						
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(a) Human subjects	(b) Human	tissues La	(c) Neit	her			
(a1) Minors							
(a2) Interviews				В			
SUMMARY OF WORK (Use standard unre-	duced type. Do not ex	ceed the space provided	d.)				
Myeloid lineage leukemi	as represent	a high propo	ortion of	of leuke	emias in	the huma	n
population. Some of th	ese leukemia	s are consist	cently a	associat	ed with	1 chromoso	mai
translocation, deletion	s and gene a	mplifications	s in whi	ich onco	genes i	nave been	
implicated. Our group	has found a	useful model	in the	murine	hemopo:	letic syst	em
for studying these type	s of leukemi	as. The over	rall goa	11 15 CC	, TOOK a	it the tra	ins-
forming effects of vari	ous oncogene	s on mouse ce	$\frac{11}{6}$ $\frac{1}{10}$	vivo ar	$\frac{1n}{1}$	tro with	а
particular emphasis on	their cooper	ative effects	s of one	cogenes	on cel.	Ls of the	
myeloid lineage.							
m1. 1.1							
The laboratory, because	of its expe	rience in cor	ISTRUCT	ing and	testing	g retrovir	uses,
uses naturally occurrin	g, as well a	s genetically	y engine	erea re	etrovir	ises, as	
venicles for introducin	g oncogenes	into cells.	we are	taking	advanta	ige of two	)
modes for leukemia indu	ction 1) one	in which one	cogenes	or pote		oncogenes	are
introduced via replicat	ion derectiv	e retrovirus	vectors	s and al	e allo	ved to tra	ins-
form cells directly, an	d 2) one in	which replica	ation co	ompetent	virus	es, such a	IS
Moloney murine leukemia	virus, are	introduced an	nd sprea	ad throu	ign mice		iey
diagonal of the by	Insertional	mutagenesis.	. inese	studie	s nave	lea to th	le
aristone pristane pristane	The one proto	cois for indu	ICLION (	n myeld	ning -		the
tumore that arise are	in one syste	hage coller	nyc gene	e contal	thor of	ecrovirus,	ng
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Some notion studies int	virus, the	truction of	hiologi	lagi ter	iyeromon	locyce cel	15.
one newer studies incl	due the cons	a the transfe	broiog:	car tes	oring of	viluses	
encoding potential onco	genes such a	S THE FLADSTE		ceptor			
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DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBL	C HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH P	BOJECT	701 CP 08000-17 IVD
			201 CB 08000-17 LMB
PERIOD COVERED			
October 1 1986 to Sent	ember 30 1987		
TITLE OF PROJECT (80 characters of less	Title must fit on one line between th	e horders )	
Regulation of Cone Act			
PRINCIPAL INVESTIGATOR // ist other or	dessional personnel below the Princip	al Investigator ) (Nemo title Jaho	retery and institute affiliations
PI: I. Pastan	Chief Laboratory	of Molecular Biol	
G. Merlino	Staff Fellow	or norecular pror	IMB NCT
			Lib, Not
COOPERATING LINITS (if any)			
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Laboratory of Molecular	втотоду		
SECTION			
Office of the Chief			
INSTITUTE AND LOCATION	00000		
NCI, NIH, Betnesda, MD	20892	1	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
6	5	1	
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(a) Human subjects	(b) Human tissues	🛍 (c) Neither	
			_
(a2) Interviews			В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space	provided.)	
Regions essential for t	he expression of the	EGF receptor gen	e have been
identified by deleting	various portions of	the promoter. Pro	oteins which
can bind to these regio	ns have been identif	ied by their abil	ity to protect
DNA from the promoter r	egion from being dig	ested by exonucle	ase III (exo-
nuclease mapping). An	oligonucleotide corr	esponding to one	of the sites
has been synthesized an	d used to purify one	of these proteins	s; this protein
is currently being char	acterized.		
A crude cell-free syste	m which carries out	transcription of t	the EGF receptor
has been developed. De	letion analysis of t	he EGF receptor to	emplate has iden-
tified a small region n	ecessary to support	transcription. A	crude transcrip-
tion extract has been s	ubjected to fraction	ation by heparin a	agarose and DEAE
cellulose chromatograph	v to identify factor	s necessary for th	ranscription.
Methylation of the DNA	template appears to	have no effect on	RNA
transcription.		are no cricer on	
cruito criptions			
Previously, EGF and pho	rhol ester (PMA) war	e shown to promote	a accumulation of
EGE recentor mRNA Cur	rently possible much	aniama responsible	
mPNA' accumulation and h	aing avaluated to di	anisms responsible	
ligando on initiation	f transportation of the	SLInguish between	errects of these
rigands on initiation o	i transcription and	WANA SCADIIIZACION	1.
1			



DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	Z01 CB 08001-16 LMB
PERIOD COVERED			
TITLE OF BRO JECT (8) chargebra of loss	The must fit on one line between the bord		
Role of Cyclic AMP and	Transforming Viruses in	the Regulation	of Cell Behavior
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	stigetor.) (Name, title, lebore	tory, and institute affiliation)
fi. i. fastall	Chier, Laboratory o	i Molecular Bio	logy NC1
COOPERATING UNITS (if any)			
LAB/BRANCH Laboratory of Molecular	Biology		
SECTION Office of the Chief			
NCT NIH Bethesda MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
0	0	0	
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews	□ (b) Human tissues □	] (c) Neither	
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	ed.)	
Work on this project ha	s been temporarily halt.	ed.	
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		•	



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZO1 CB 08010-14 LMB
PERIOD COVERED	1 20 1007		
October 1, 1986 to Sept	ember 30, 1987		
Morphologic Mechanisms	of Organelle Function an	d Transformati	on in Cultured Cells
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	tigator.) (Name, title, labori	atory, and institute affillation)
PI: M.C. Willingham	Chief, Ultrastructural	Cytochemistry	Section LMB, NCI
COOPERATING UNITS (if any)			
Laboratory of Kidney an	d Electrolyte Metabolism	, DIR, NHLBI	
Laboratory of Biochemis	try and Metabolism, DIR,	NIDDK	
LAB/BRANCH			
Laboratory of Molecular	Biology		
SECTION			
Ultrastructural Cytoche	mistry Section		
INSTITUTE AND LOCATION	20802		
TOTAL MANLYEARS	20092	OTHER	
4.0	PHOPESSIONE.	othen.	
CHECK APPROPRIATE BOX(ES)	· · ·	I	
(a) Human subjects	🛽 (b) Human tissues	(c) Neither	
(a1) Minors			
			<u>B</u>
SUMMARY OF WORK (Use standard unred Neoplastic transformati	fuced type. Do not exceed the space provide	d) in cell physi	ology, some of
which can be studied us	ing morphologic techniqu	es. We have u	sed morphologic
methods to study three	general areas: 1) We ha	ve employed li	ght microscopic
immunocytochemistry to	evaluate and select mono	clonal antibod	ies for use as
immunotoxin reagents fo	r cancer therapy. A lar	ge scale scree	ning chamber has
been devised for use wi	th immunofluorescence as	a primary sel	ection for surface-
reactive monoclonal ant.	ibodies to human ovarian	cancer cells.	Hybridoma clones
selected in this way we	re further evaluated by	screening agai	nst normal human
tissues and ovarian tum	ors using peroxidase imm	unocytochemist	ry in cryostat
sections. Using these	nethods we have found two	o nybridomas h	ighly reactive
distribution and biocher	mical properties of thes	nave character	aultured cells in
tumors and in normal ti	ssues. 2) We have studi	ed the phenome	non of multidrug-
resistance (MDR) in cult	tured cells, and have us	ed a monoclona	1 antibody (MRK-
16) to the human mdrl g	ene product (P170) as a	probe to demon	strate P170 on the
surface and in the Golg	i stacks of drug-resista	nt KB cells in	culture. We also
showed the absence of P	170 from coated pits, su	ggesting that	this protein is
immobilized in the plass	na membrane. We have al	so used this a	ntibody to examine
the distribution of P17	) in normal human tissue	s, and we have	evaluated the
amounts of P170 in prog	ressively resistant deriv	vatives of KB	cells using immuno-
fluorescence. 3) in ot	her studies, we have located	alized p55, a	major thyroid
of cultured cells in no	round in the endoplasmic	c reciculum an	a nuclear envelope
protein was found in his	whest amounts in cells t	hat have abund	ant endoplasmic
reticulum. Other cytoc	hemical studies demonstr	ated a role fo	r clathrin-coated
pits in the loss of ADH	-responsive water transp	ort in isolate	d perfused rabbit
cortical collecting duc	ts. We also demonstrate	d the localiza	tion of carbohydrate
sites reactive with whe	at germ lectin on nuclear	r pores in iso	lated nuclei.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SI	ERVICE			
NOTICE OF INTRAMURAL RESEARCH PROJECT Z01 CB 08011-13 LMB				
PERIOD COVERED October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)				
Structures and Roles of Transformation-Sensitive Cel	ll Surface Glycoproteins			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) ( PI: K. M. Yamada Chief, Membrane Biochemi	Name, title, laboratory, and institute affiliation) Estry Section LMB, NCI			
Other: M. Obara Visiting Fellow	LMB, NCI			
M. S. Kang Biotechnology Training H	Program Fellow LMB, NCI			
S. K. Akiyama Guest Researcher	LMB, NCI			
M. J. Humphries Guest Researcher	LMB, NCI			
K. Olden Guest Researcher	LMB, NCI			
COOPERATING UNITS (# any)	LMB, NCI			
Laboratory of Molecular Biology				
Membrane Biochemistry Section				
NSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892				
TOTAL MAN-YEARS: 4.4 PROFESSIONAL: 3.7	<sup>t:</sup> 0.7			
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects (b) Human tissues & (c) N	leither			
(a1) minors	В			
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	n motniu clusonnotsis			
involved in cell adhesion and migration. Synthetic	pentide inhibitors derived			
from its sequence were examined for effects on a var	iety of adhesion systems.			
The pentapeptide Gly-Arg-Gly-Asp-Ser (GRGDS) was the	most effective peptide			
against fibronectin-mediated adhesion, and a related	sequence was active for			
vitronectin. Such peptides had little activity on 1	aminin, collagen, or cell-			
cell adhesion, indicating specificity. An artificia	1 inverted peptide identi-			
fied a possible common denominator of function in fo	our of these five systems.			
GRGDS inhibited experimental metastasis of Bib melan				
measured by purmonary coronization, and the relative	oma cells in mice as			
closely matched those for inhibition of cell adhesic	oma cells in mice as activities of analogues n in vitro. Peptide treat-			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these	noma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness in vitro and in vi	oma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies .vo are under investigation.			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also	noma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition	noma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full-			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-for	noma cells in mice as a ctivities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor onal region required for full- d augmentation) is being			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-for defined by recombinant DNA expression studies. Larg	noma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor onal region required for full- d augmentation) is being the fibronectin fragments od 200% adheains estimit			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-for defined by recombinant DNA expression studies. Larg expressed in <u>E. coli</u> as \gtll fusion proteins retain eukaryotic post-translational modifications were the	noma cells in mice as activities of analogues an <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments and >80% adhesive activity; is not needed. Deletion muta-			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-fol defined by recombinant DNA expression studies. Larg expressed in <u>E. coli</u> as $\lambda$ gtll fusion proteins retain eukaryotic post-translational modifications were thus genesis experiments show that the second site is at	noma cells in mice as a activities of analogues an <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments and >80% adhesive activity; is not needed. Deletion muta- least 20kD away from the			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An additic affinity binding to the cell surface (50- to 100-foi defined by recombinant DNA expression studies. Larg expressed in <u>E. coli</u> as \gtll fusion proteins retain eukaryotic post-translational modifications were the genesis experiments show that the second site is at GRGDS site. A separate class of novel, cell-type sp	noma cells in mice as activities of analogues on <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments end >80% adhesive activity; is not needed. Deletion muta- least 20kD away from the eccific binding sites were			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-fol defined by recombinant DNA expression studies. Larg expressed in <u>E. coli</u> as \gtll fusion proteins retain eukaryotic post-translational modifications were thus genesis experiments show that the second site is at GRGDS site. A separate class of novel, cell-type sp discovered elsewhere in fibronectin at sites regulat	noma cells in mice as activities of analogues an <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments and >80% adhesive activity; is not needed. Deletion muta- least 20kD away from the eccific binding sites were ed by alternative splicing.			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An addition affinity binding to the cell surface (50- to 100-fol defined by recombinant DNA expression studies. Large expressed in <u>E. coli</u> as \gtll fusion proteins retain eukaryotic post-translational modifications were thus genesis experiments show that the second site is at GRGDS site. A separate class of novel, cell-type sp discovered elsewhere in fibronectin at sites regulat A synthetic peptide from one site was only 2.4-fold	noma cells in mice as activities of analogues an <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments and >80% adhesive activity; is not needed. Deletion muta- least 20kD away from the eccific binding sites were ed by alternative splicing. less active than intact			
closely matched those for inhibition of cell adhesic ment also substantially prolonged survival of these to increase peptide effectiveness <u>in vitro</u> and <u>in vi</u> This pentapeptide adhesive recognition sequence also <u>Drosophila</u> gastrulation and in vertebrate somite for cells showed induced cell-cell adhesion. An additic affinity binding to the cell surface (50- to 100-fol defined by recombinant DNA expression studies. Larg expressed in <u>E. coli</u> as $\lambda$ gtll fusion proteins retain eukaryotic post-translational modifications were thu genesis experiments show that the second site is at GRGDS site. A separate class of novel, cell-type sp discovered elsewhere in fibronectin at sites regulat A synthetic peptide from one site was only 2.4-fold fibronectin. The critical amino acid sequences and	noma cells in mice as a activities of analogues an <u>in vitro</u> . Peptide treat- animals. Several strategies vo are under investigation. appears to function in mation; somite precursor anal region required for full- d augmentation) is being the fibronectin fragments and >80% adhesive activity; is not needed. Deletion muta- least 20kD away from the eccific binding sites were ed by alternative splicing. less active than intact the biological functions of			

PROJECT NUMBER



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HE	TH SERVICE	PHOSEOT NOMBER
NOTICE OF IN	TRAMURAL RESEARCH BROU	ECT	
NOTICE OF IN	TRAMORAL RESEARCH PROJ		201 CB 08/00-15 LMB
October 1, 1986 to Ser	tember 30, 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line between the borde	rs.)	
Expression of Collagen	Genes in Normal and Tra	nsformed Cells	
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Principal Inves	tigetor.) (Neme, title, lebora	tory, and institute affiliation)
PI: B. de Crombrugghe	Chief, Gene Regula	tion Section	LMB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH	r Biology		
SECTION	1 biology		
Gene Regulation Section	7		
INSTITUTE AND LOCATION	11		
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
7.0	5.0	2.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the space provide	d )	
1. A tissue-specific		a.,	
tiret introp of th	transcriptional enhancer	has been ident	ified in the
	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge	has been ident	ified in the
2. A functional analy	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p	has been ident ene. promoter of the	ified in the mouse $\alpha_2(I)$
2. A functional analy collagen gene indi	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least	has been ident ene. promoter of the two different	ified in the mouse $\alpha_2(1)$ segments upstream
<ol> <li>A functional analy collagen gene indi of the start of tr</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impo	has been ident ene. promoter of the two different ortant for opti	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impo	has been ident ene. promoter of the two different prtant for opti	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chlorambenical analy</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impo- re generated in which an	has been ident ene. bromoter of the two different ortant for opti $\alpha_2(I)$ collagen	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter-
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac gormline Theore</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impo- re generated in which an etylase chimeric gene has	has been ident ene. promoter of the two different ortant for opti α <sub>2</sub> (I) collagen s been stably i	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impo- re generated in which an etylase chimeric gene has ew mouse strains show at	has been ident ene. promoter of the two different ortant for opti α <sub>2</sub> (I) collagen been stably i dissue specific	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres-
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagon genes</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impor- re generated in which an etylase chimeric gene has ew mouse strains show a t ric gene that coincides w	has been ident ene. promoter of the two different ortant for opti α <sub>2</sub> (I) collagen been stably i dissue specific with that of th	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen ge sis of deletions in the p cates there are at least anscription that are impor- re generated in which an etylase chimeric gene has ew mouse strains show a t ric gene that coincides w	has been ident ene. oromoter of the two different ortant for opti α <sub>2</sub> (I) collagen been stably i cissue specific with that of th	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified which</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show a t ric gene that coincides we esent in nuclear extracts	has been ident ene. promoter of the two different ortant for opti α <sub>2</sub> (I) collagen been stably i cissue specific with that of th cof NIH 3T3 ce	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollaren promotor
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show a t ric gene that coincides w essent in nuclear extracts bind to defined segments	has been ident ene. bromoter of the two different ortant for opti $\alpha_2(I)$ collagen been stably i tissue specific with that of th s of NIH 3T3 ce of the $\alpha_2(I)$ c	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter.
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show at ric gene that coincides w esent in nuclear extracts bind to defined segments ds to the CCAAT sequence obtained that the factor	has been ident ene. bromoter of the two different ortant for opti $\alpha_2(I)$ collagen is been stably i dissue specific with that of th of NIH 3T3 ce of the $\alpha_2(I)$ chas been exten	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified.
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show at ric gene that coincides w esent in nuclear extracts bind to defined segments ds to the CCAAT sequence obtained that the factor	has been ident ene. bromoter of the two different ortant for opti $\alpha_2(I)$ collagen is been stably i issue specific with that of th of NIH 3T3 ce of the $\alpha_2(I)$ c has been exten consists of two	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified. o components. from the α <sub>2</sub> (I)
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> <li>The hormone tumor and gi(III) collage</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show at ric gene that coincides w esent in nuclear extracts bind to defined segments ds to the CCAAT sequence obtained that the factor growth factor $\beta$ stimulate	has been ident ene. promoter of the two different ortant for opti $\alpha_2(I)$ collagen is been stably i itssue specific fith that of th of NIH 3T3 ce of the $\alpha_2(I)$ c has been exten consists of tw es transcriptio	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified. o components. n from the α <sub>2</sub> (I)
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> <li>The hormone tumor and α<sub>1</sub>(III) collage</li> </ol>	transcriptional enhancer e mouse $\alpha_2(1)$ collagen gesis of deletions in the protect of the end of	has been ident ene. promoter of the two different ortant for opti $\alpha_2(I)$ collagen is been stably i classue specific with that of th of NIH 3T3 ce of the $\alpha_2(I)$ c has been exten consists of two is transcriptio	ified in the mouse α <sub>2</sub> (I) segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified. o components. n from the α <sub>2</sub> (I) rcoma cells.
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> <li>The hormone tumor and α<sub>1</sub>(III) collage</li> </ol>	transcriptional enhancer e mouse $\alpha_2(1)$ collagen ges sis of deletions in the p cates there are at least anscription that are impor- re generated in which an etylase chimeric gene has ew mouse strains show at ric gene that coincides w esent in nuclear extracts bind to defined segments ds to the CCAAT sequence obtained that the factor growth factor $\beta$ stimulate en promoters in fibroblas	has been ident ene. bromoter of the two different ortant for opti $\alpha_2(I)$ collagen is been stably i classue specific with that of th of NIH 3T3 ce of the $\alpha_2(I)$ c has been exten consists of two is transcription its and osteosa	ified in the mouse $\alpha_2(I)$ segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified. o components. n from the $\alpha_2(I)$ rcoma cells.
<ol> <li>A functional analy collagen gene indi of the start of tr this gene.</li> <li>Transgenic mice we chloramphenicol ac germline. These n sion for the chime collagen genes.</li> <li>Several factors pr identified, which A factor which bin Evidence has been</li> <li>The hormone tumor and α<sub>1</sub>(III) collage</li> </ol>	transcriptional enhancer e mouse $\alpha_2(I)$ collagen gesis of deletions in the p cates there are at least anscription that are import re generated in which an etylase chimeric gene has ew mouse strains show at ric gene that coincides w essent in nuclear extracts bind to defined segments ds to the CCAAT sequence obtained that the factor growth factor $\beta$ stimulate en promoters in fibroblas	has been ident ene. bromoter of the two different ortant for opti a <sub>2</sub> (I) collagen been stably i dissue specific with that of th of NIH 3T3 ce of the a <sub>2</sub> (I) co has been exten consists of tw es transcriptio its and osteosa	ified in the mouse $\alpha_2(I)$ segments upstream mal expression of promoter- ntroduced in the pattern of expres- e endogenous type I lls have been ollagen promoter. sively purified. o components. n from the $\alpha_2(I)$ rcoma cells.



DEPARTMENT OF REALTH AND HU	MAN SERVICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF INTRAM	URAL RESEARCH PROJ	ECT	Z01 CB 08705-11 LMB
PERIOD COVERED			
October 1, 1986 to Septembe	r 30, 1987		
TITLE OF PROJECT (80 characters or less. Title m	ust fit on one line between the borde	rs.)	
Genetic and Biochemical Ana	Lysis of Cell Dellavi	OF	
PI: M. M. Gottesman	Chief, Molecular Ce	ell Genetics Se	ction LMB, NCI
Other: S. Goldenberg	Research Biologist		LMB, NCI
M. Chapman	Research Biologist		LMB, NCI
R. Fleischmann	Staff Fellow		LMB, NCI
S. Kumar	Visiting Fellow		LMB, NCI
COOPERATING LINITS (# anti)			
COOPERATING UNITS (If any)			
LAB/BRANCH			
Laboratory of Molecular Bio	logy		
SECTION			
Molecular Cell Genetics Sec	tion		
INSTITUTE AND LOCATION	2		
NCI, NIH, Betnesda, MD 2009	2	07050	
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□ (a) Human subjects □ (b	) Human tissues 🛛 🗵	(c) Neither	
(a1) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unreduced typ	be. Do not exceed the space provided	d.)	
we are utilizing the Chinese	e hamster ovary (CHO	) fibroblast t	o study the
Our work has emphasized more	bology and its role	le benavior of	cultured cells.
the senses is which malie		tionchin to ar	outh control and
Fne manner in which cyclic	AMP regulates cell g	tionship to gr	owth control, and
mechanism of cAMP action on	AMP regulates cell g	rowth and gene studied by iso	owth control, and expression. The lating CHO mutants
mechanism of cAMP action on resistant to growth inhibito	AMP regulates cell g CHO cells has been on by cAMP. These m	tionship to gr rowth and gene studied by iso utants have de	owth control, and expression. The lating CHO mutants fective cAMP depen-
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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	СТ	Z01 CB 08709-12 LMB
PERIOD COVERED		-	
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the borde	S.)	1 C.D
Regulation of Gene Expl	essional personnal below the Principal Inves	on by ADP-ribo:	sylation of Proteins
PI: G. S. Johnson	Research Chemist	gerer.) (Herrie, Inte, Inte, Inderina	LMB NCT
			1110, 1101
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Molecular	Biology		
SECTION			
Molecular Cell Genetics	Section		
INSTITUTE AND LOCATION	20892		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER	- <u> </u>
1.0	1.0	0.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			
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SUMMARY OF WORK (Use standard unrec Drugs which inhibit (AD ribosylation of chromos coid sensitive genes. been observed during th total amount of nuclear partial agonists are mo Interestingly, certain induce genes are also v ribosylation of some es influences expression of Nicotinamide and its sy human promyelocytic leu synergistic with retino cells. N'-methylnicoti dinucleotide. This NAD cells. Thermal stress of cultu basal and glucocorticoi about 60 min. Cyclohex loss of the RNA. A nuc	Juced type. Do not exceed the space provide PP-ribose) <sub>n</sub> synthetase ar omal proteins cause accu Considerable variations the course of this study. (ADP-ribose) <sub>n</sub> are invol- ore effective agonists in steroids which bind to the rery good agonists in the sential protein(s), poss- of steroid-sensitive generation nthetic N'-methyl derivant themia HL60 cells. The ac- dic acid, another agent with namide is converted into analog may be the active analog may be the active tred mouse mammary carcier d-induced mouse mammary the clease which is subject the sential prior to clease which is subject the tree active sential prior to the sential	d decrease enda mulation of mRI in the extent of Thus, factors ved. Glucocori cells devoid of he receptor but se cells. We of ibly the stero: s. tive induce mat ctions of these hich induces mat N'-methylnicol e intracellular oma cells result tumor virus (MI the temperatur o a rapid turn	B ogenous ADP- NA for glucocorti- of accumulation have in addition to the ticoid agonists or of (ADP-ribose) <sub>n</sub> . t do not normally conclude that ADP- id receptor, turation of cultured e compounds are aturation of these tinamide adenine r compound in the lts in a loss of (ATV) RNA within re shift prevents over may be
SUMMARY OF WORK (Use standard unrec Drugs which inhibit (AD ribosylation of chromos coid sensitive genes. been observed during th total amount of nuclear partial agonists are mo Interestingly, certain induce genes are also v ribosylation of some es influences expression of Nicotinamide and its sy human promyelocytic leu synergistic with retino cells. N'-methylnicoti dinucleotide. This NAD cells. Thermal stress of cultu basal and glucocorticoi about 60 min. Cyclohex loss of the RNA. A nuc activated by the heat s	Weed type. Do not exceed the space provide P-ribose) <sub>n</sub> synthetase ar omal proteins cause accu Considerable variations the course of this study. (ADP-ribose) <sub>n</sub> are invol- ore effective agonists in steroids which bind to the rery good agonists in the sential protein(s), poss- of steroid-sensitive generation anthetic N'-methyl derivant the course mammary carcine defined mouse mammary carcine d-induced mouse mammary carcine d-induced mouse mammary the lease which is subject the course hock.	d decrease enda mulation of mRI in the extent of Thus, factors ved. Glucocori cells devoid of he receptor but se cells. We of ibly the stero: s. tive induce mat ctions of these hich induces mat N'-methylnicol e intracellular oma cells result the temperatur o a rapid turno	B ogenous ADP- NA for glucocorti- of accumulation have in addition to the ticoid agonists or of (ADP-ribose) <sub>n</sub> . t do not normally conclude that ADP- id receptor, turation of cultured e compounds are aturation of these tinamide adenine r compound in the lts in a loss of (ATV) RNA within re shift prevents over may be
SUMMARY OF WORK (Use standard unrec Drugs which inhibit (AD ribosylation of chromos coid sensitive genes. been observed during th total amount of nuclear partial agonists are mo Interestingly, certain induce genes are also v ribosylation of some es influences expression of Nicotinamide and its sy human promyelocytic leu synergistic with retino cells. N'-methylnicoti dinucleotide. This NAD cells. Thermal stress of cultur basal and glucocorticoi about 60 min. Cyclohex loss of the RNA. A nuc activated by the heat s	Weed type. Do not exceed the space provide P-ribose) <sub>n</sub> synthetase ar omal proteins cause accu Considerable variations the course of this study. (ADP-ribose) <sub>n</sub> are invol- ore effective agonists in steroids which bind to the rery good agonists in the sential protein(s), poss- of steroid-sensitive generation anthetic N'-methyl derivant themia HL60 cells. The an- dic acid, another agent with namide is converted into analog may be the active analog may be the active tred mouse mammary carcif d-induced mouse mammary imide treatment prior to the sential subject the subject	d decrease enda mulation of mRI in the extent of Thus, factors ved. Glucocri cells devoid of he receptor but se cells. We of ibly the stero: s. tive induce man ctions of these hich induces man N'-methylnicot e intracellular oma cells result tumor virus (MI the temperatur o a rapid turno	B ogenous ADP- NA for glucocorti- of accumulation have in addition to the ticoid agonists or of (ADP-ribose) <sub>n</sub> . t do not normally conclude that ADP- id receptor, turation of cultured a compounds are aturation of these tinamide adenine r compound in the lts in a loss of ATV) RNA within re shift prevents over may be
SUMMARY OF WORK (Use standard unrec Drugs which inhibit (AD ribosylation of chromos coid sensitive genes. been observed during th total amount of nuclear partial agonists are mo Interestingly, certain induce genes are also v ribosylation of some es influences expression of Nicotinamide and its sy human promyelocytic leu synergistic with retino cells. N'-methylnicoti dinucleotide. This NAD cells. Thermal stress of cultur basal and glucocorticoi about 60 min. Cyclohex loss of the RNA. A nuc activated by the heat s	Weed type. Do not exceed the space provide PP-ribose) <sub>n</sub> synthetase ar omal proteins cause accu Considerable variations the course of this study. (ADP-ribose) <sub>n</sub> are invol- ore effective agonists in steroids which bind to the rery good agonists in the sential protein(s), poss- of steroid-sensitive generation anthetic N'-methyl derivant the course mammary carcine d-induced mouse mammary carcine d-induced mouse mammary the lease which is subject the hock.	d decrease enda mulation of mRM in the extent of Thus, factors ved. Glucocord cells devoid of he receptor but se cells. We of ibly the stero: s. tive induce man ctions of these hich induces man N'-methylnicot e intracellular oma cells resu: tumor virus (MM the temperatur o a rapid turno	B ogenous ADP- NA for glucocorti- of accumulation have in addition to the ticoid agonists or of (ADP-ribose) <sub>n</sub> . t do not normally conclude that ADP- id receptor, turation of cultured e compounds are aturation of these tinamide adenine r compound in the Ats in a loss of ATV) RNA within re shift prevents over may be



			PROJECT NUMBER	
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	701 00 00710 11	7.V.D
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZOI CB 08/10-11	LMB
October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	ars.)		
DNA Replication in vitu	<u>:0</u>			
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and institute affiliation)	
PI: S. Wickner	Research Che	emist	LMB, NCI	
COOPERATING UNITS (if any)				
LAB/BRANCH				
Laboratory of Molecular	: B1010gy			
Biochemical Genetics Se	oction			
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, MD	20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
1.0	1.0	0		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects		(C) Neither		
(a2) Interviews			В	
SUMMARY OF WORK (Use standard unred	Juced type. Do not exceed the space provide	d.)		
The molecular mechanism	is involved in DNA replic	ation are bein	g studied	
biochemically. In part	licular, in vitro replica	ation reactions	are being	
an in vitro DNA replica	tion system that replica	tes exogenous]	v added plasmid	
DNA containing the orig	in of replication of bac	teriophage Pl.	The system	
consists of a purified	Pl replication protein,	the product of	repA, and a	
partially purified mixt	ure of E. coli replicati	ion proteins pr	epared from	
uninfected cells. The	system requires the E. o	<u>coli dnaA</u> initi	ation protein	
in addition to the Pl R	epA initiation protein.	In collaborat	ion with	
b. chattoraj (LB, NCI),	tisted in the region of	the Pl origin	of replication	
and proceeds unidirecti	onally. Since Pl normal	llv exists as a	unit copy plas-	
mid, this system is bei	ng used to study the mol	lecular mechani	sms involved	
in the initiation and r	egulation of a stringent	ly controlled	replicon. I	
have also continued stu	dying the replication of	plasmid DNA c	ontaining the	
origin of replication o	t bacteriophage $\lambda$ in vit	ro. This read	tion requires	
and several other bost	proteins including the h	, many nost rep	eins dnal dnak	5
and grpE. Replication	also requires a specific	DNA site for	initiation. I	.,
have constructed deleti	ons in vitro extending i	into this regio	n and tested the	m
for activity in in vitr	O DNA replication reacti	ions dependent	on O and P pro-	
teins. The smallest pi	ece of DNA that supports	the initiatio	n of replication	L .
is 89 bp. It contains	two of the four O protei	In binding site	s and the adjoin	ing
adenine and thymine ric	In region that very likel	ly is the site	where dhas prote	in b
M. Dodson and H. Echols	MA. III a collaboracive	erection micro	scopic study wit	
	(University of CA. Berk	celey), nucleon	rotein structure	S
formed by O, P, dnaB, d	naJ, dnaK, and Ssb at or	celey), nucleop ciλ have been v	rotein structure isualized.	S



DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZO1 CB 08712-12 LMB	
October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the borde	rs.)		
Plasma Membrane Protein	s in the Regulation of C	ell Behavior a	nd Drug Resistance	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigetor.) (Name, title, lebora	tory, and institute affiliation)	
PI: I. Pastan	Chief, Laborator	y of Molecular	Biology NCI	
M.M. Gottesman	Chief, MCGS		LMB, NCI	
Other: M.C. Willingham	Chief, UCS		LMB, NCI	
N. Richert	Senior Investiga	tor	LMB, NCI	
COOPERATING UNITS (if any)				
LAB/BRANCH	Riology			
SECTION	BIOLOGY			
Office of the Chief				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, MD	20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
	4	1.5		
(a) Human subjects	1 (b) Human tissues	(c) Neither		
(a1) Minors	_ (.,	(-)		
(a2) Interviews			В	
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	d.)		
numan $NB$ cells which ar	e resistant to adriamyci	n (A), vindias	tine (V), colchicine	
responsible for the dru	g resistance A fragmen	contain an amp	has been aloned and	
used to screen a cDNA 1	ibrary and identify cDNA	s encoding a l	70 kd cell membrane	
protein also found to b	e increased in multidrug	resistant cel	ls. The 170 kd	
protein binds vinblasti	ne and related drugs, an	d this binding	is overcome by	
drugs such as verapamil, quinidine, and diltiazem which overcome multidrug				
resistance. The cDNA sequence indicates the 170 kd protein should bind ATP;				
	equence indicated the it	-		
this was directly confi	rmed by ATP binding stud	ies. Expressi	on of the mdrl gene	
this was directly confi was found to be elevate	rmed by ATP binding stud d in normal colon, kidne	ies. Expressi y, liver and a	on of the <u>mdr</u> l gene drenals and cancers	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The mdrl cDN	ies. Expressi y, liver and a as also increa A has been clo	on of the <u>mdrl</u> gene drenals and cancers sed in a few tumors	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdrl</u> cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdrl</u> gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdrl</u> cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdrl</u> cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdr</u> l cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdr</u> l cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdr</u> l cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdr</u> l cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	
this was directly confi was found to be elevate of the colon, kidney an showing acquired drug r cell expression vector drug resistant.	rmed by ATP binding stud d in normal colon, kidne d adrenal. Expression w esistance. The <u>mdr</u> l cDN and when inserted into d	ies. Expressi y, liver and a as also increa A has been clo rug sensitive	on of the <u>mdr</u> l gene drenals and cancers sed in a few tumors ned into an animal cells makes them	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SE	RVICE PROJECT NUMBER			
NOTICE OF INTRAMURAL RESEARCH PROJECT	Z01 CB 08714-10 LMB			
PERIOD COVERED				
October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the bordars.)				
Mode of Action of a Bacterial Function Involved in	Cell Growth Control			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (I	leme, title, laboratory, and institute affiliation)			
PI: S. Gottesman Chief, Biochemical Genetic	cs Section LMB, NCI			
COOPERATING UNITS (# any)	and Diagnosis			
S Pudikoff	LG NCI			
J. Pumpbrey	LG, NCI			
Laboratory of Molecular Biology				
SECTION				
Biochemical Genetics Section				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, MD 20892				
TOTAL MAN-YEARS: PROFESSIONAL: OTHER	0.0			
	0.0			
(a) Human subjects (b) Human tissues (c) N	either			
(a) Minors				
(a2) Interviews	В			
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)				
We have been studying the role that protein degrada	tion plays in regulating			
cell growth control, through the study of mutants d	efective in ATP-dependent			
protein turnover. E. coli ion mutants are derectiv	demonstrated that this			
regulation after DNA damage, and we have previously	a cell division inhibitor			
SulA lon mutants also overproduce capsular polysa	ccharide: we have identi-			
fied an unstable positive regulator of cansule synt	hesis. RcsA, which is sta-			
bilized in lon mutants. The sequence of the rcsA gene shows no striking				
similarities to other lon substrates. rcsA-lac fus	ions which we have isolated			
will allow us to examine the transcriptional and tr	anslational control of this			
gene. Using cells devoid of lon activity, we have	biochemically identified a			
novel two-component, ATP-dependent protease. Using	amino acid sequence data			
from one of the purified components, plasmids carry	ing the gene are being			
identified. Using genetic screens, we have also id	entiried and partially mapped			
a function which is capable of substituting for 100	, and presumably codes for			
another procease with potential regulatory function				
•				



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PHOJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	Z01 CB 08715-09 LMB
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	ers.)	
Synthesis and Function	of a Transformation-Depe	endent Secreted	Lysosomal Protease
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	stigator.) (Name, title, labora	tory, and institute affiliation)
II. In II. Gottesman	onier, norecular of	err denetros se	ction LAB, NCL
Other: S. Goldenberg	Research Biologist		LMB NCI
M. Chapman	Research Biologist		LMB, NCI
S. Gal	Biotechnology Fello	w	LMB, NCI
B. Troen	Medical Staff Fello	ow	LMB, NCI
S. Kane	Guest Researcher		LMB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Molecular	Biology		
SECTION	Section		
Molecular Cell Genetics	Section		
NOT NTU Debled ND	20892		
	20072		
TOTAL MANYEARS	PROFESSIONAL .	OTHER	
TOTAL MAN-YEARS: 4.0	PROFESSIONAL: 4.0	OTHER:	
TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES)	PROFESSIONAL: 4.0	OTHER: 0.0	
NCI, NIH, BEERESGA, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects	PROFESSIONAL: 4.0 (b) Human tissues	OTHER: 0.0	
NCL, NIH, Betnesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors	PROFESSIONAL: 4.0 (b) Human tissues	OTHER: 0.0	
NCI, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	PROFESSIONAL: 4.0 (b) Human tissues	отнея: 0.0	В
NCL, NIH, BEERESGA, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec	PROFESSIONAL: 4.0 (b) Human tissues uced type. Do not exceed the space provide	0.0 (c) Neither	В
NCI, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Cultured mouse fibrobla	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (b) Human tissues (c) ti	(c) Neither (c) Neither	B or treated with
NCI, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (ced type. Do not exceed the space provide sts which are malignant) uch as PDGF synthesize a	(c) Neither (c) Neither (c) Veither (c) Veither (c) Veither (c) Veither (c) Veither (c) Veither (c) Veither	B or treated with 9,000 Mr-phos-
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (ceed type. Do not exceed the space provide sts which are malignant] uch as PDGF synthesize a excreted protein, MEP) if	(c) Neither (c) Neither	B or treated with 9,000 Mr-phos- s. The purified
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (coef type. Do not exceed the space provided sts which are malignantian uch as PDGF synthesize a excreted protein, MEP) if e 6-phosphate, the lysos	(c) Neither (c) Ne	B or treated with 9,000 Mr-phos- s. The purified on marker. It is
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos processed intracellular	PROFESSIONAL: 4.0 (b) Human tissues weed type. Do not exceed the space provide sts which are malignant] uch as PDGF synthesize a excreted protein, MEP) i e 6-phosphate, the lysos ly in both transformed a	(c) Neither (c) Ne	B or treated with 9,000 Mr-phos- s. The purified on marker. It is med cells to give
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos processed intracellular two specific lower mole	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (c) (b) Human tissues (c) (c) (c) (c) (c) (c) (c) (c) (c) (c)	oTHER: 0.0 (c) Neither (c) Nei	B or treated with 9,000 Mr-phos- s. The purified on marker. It is med cells to give calization. The
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos processed intracellular two specific lower mole secreted form of MEP is	PROFESSIONAL: 4.0 (b) Human tissues (cod type. Do not exceed the space provide sts which are malignant. uch as PDGF synthesize a excreted protein, MEP) to e 6-phosphate, the lysos ly in both transformed a cular weight forms with the precursor to a lowe	oTHER: 0.0 (c) Neither (c) Nei	B or treated with 9,000 Mr-phos- s. The purified on marker. It is med cells to give calization. The ight novel thiol
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unned Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos processed intracellular two specific lower mole secreted form of MEP is protease (cathepsin) wi	PROFESSIONAL: 4.0 (b) Human tissues (b) Human tissues (ced type. Do not exceed the space provide sts which are malignant] uch as PDGF synthesize a excreted protein, MEP) i e 6-phosphate, the lysos ly in both transformed a cular weight forms with the precursor to a lowe th an acid pH optimum ca	oTHER: 0.0 (c) Neither (c) Nei	B or treated with 9,000 Mr-phos- s. The purified on marker. It is med cells to give calization. The ight novel thiol lyzing a wide
NCL, NIH, Bethesda, MD TOTAL MAN-YEARS: 4.0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Cultured mouse fibrobla TPA or growth factors s phoglycoprotein (major protein contains mannos processed intracellular two specific lower mole secreted form of MEP is protease (cathepsin) wi variety of proteins inc	PROFESSIONAL: 4.0 (b) Human tissues (ced type. Do not exceed the space provide sts which are malignant) uch as PDGF synthesize a excreted protein, MEP) is e 6-phosphate, the lysos ly in both transformed a cular weight forms with the precursor to a lowe th an acid pH optimum ca luding the extracellular	oTHER: 0.0 (c) Neither (c) Nei	B or treated with 9,000 Mr-phos- s. The purified on marker. It is med cells to give calization. The ight novel thiol lyzing a wide ns collagen, fibro-
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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	Z01 CB 08717-09 LMB
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	ars.)	
Functions, Structure, a	and Regulation of Recept	ors for Cell Ad	hesion Proteins
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigetor.) (Name, title, lebora	tory, and institute affiliation)
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Other: S Saga	Visiting Follow		IND NOT
S. K. Akiyama	Guest Researcher		LMB, NCI
S. S. Yamada	Guest Researcher		IMB NCT
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COOPERATING UNITS (if any)			
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PROJECT NUMBER



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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE			
NOTICE OF INT	RAMURAL RESEARCH PROJE	ECT	ZO1 CB	08719-07	LMB
PERIOD COVERED	ember 30 1987				
TITLE OF PROJECT (80 characters of less	Title must fit on one line between the borde	(8)			
Development and Uses of	Eukaryotic Vectors	,			
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigator.) (Name, title, lebora	tory, and insti	tute effiliation)	
PI: Bruce H. Howard	Chief, Molecular Gen	etics Section		LMB, NCI	
COOPERATING UNITS (if any)					
LNP, NINCDS					
LAB/BRANCH					
Laboratory of Molecular	Biology				
SECTION				· · · · · · · · · · · · · · · · · · ·	
Molecular Genetics Sect	ion				
INSTITUTE AND LOCATION					
National Cancer Institu	te, NIH, Bethesda, MD				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
		<u> </u>			
(a) Human subjects	(b) Human tissues	(c) Neither			
(a1) Minors					
(a2) Interviews				В	
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space provided	d.)			
growth regulation in may	mmalian cells The inve	stigation of g	routh in	s to be on	
activity detected in a	DNA-mediated gene transf	er system is e	mphasize	d within	
this framework. Molecu	lar cloning of growth in	hibitory seque	nces is	being pur	_
sued by analysis of a c	osmid library derived fr	om WI38 human	embryo f	ibroblast	
genomic DNA. From this	library a single candida	ate plasmid, w	hich con	ntains a	
7SL pseudogene, is being	g analyzed for both grow	th suppression	activit	y and	
function as an origin of	f replication. Developm	ent of two new	assays	for	
first assay employs flu	cion has been a major go	al over the pa	st year.	Ine Intifu the	
transfected cell subpon	ulation in conjunction w	ith appropriat	e staini	ing tech-	
niques to measure cell	cycle characteristics of	that subpopul.	ation.	The secon	d
assay involves the use of	of a new magnetic affinit	ty cell sorting	g (MACS)	method.	-
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Z01 CB 08750-07 LMB

PROJECT NUMBER DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Genetic Regulatory Mechanisms in Escherichia coli and its Bacteriophage PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Neme, title, laboratory, and institute affiliation) PT: S. Adhva Chief, Developmental Genetics Section LMB, NCI S. Garges Microbiologist LMB, NCI Other: J. Kim Biotechnology Fellow LMB. NCI R. Wartell IPA Investigator LMB, NCI Professor, Georgia Institute of Technology, on Sabbatical Leave COOPERATING UNITS (if any) LAB/BRANCH Laboratory of Molecular Biology SECTION Biochemical Genetics Section INSTITUTE AND LOCATION NCI, NIH, Betehsda, MD 20892 PROFESSIONAL: TOTAL MAN-YEARS: OTHER: 3.5 3.5 CHECK APPROPRIATE BOX(ES) X (c) Neither (a) Human subjects (b) Human tissues (a1) Minors (a2) Interviews В SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The cAMP receptor protein (CRP) in the presence of cAMP can modulate the transcription initiation of many operons of E. coli. The protein is inactive in the absence of cAMP; when cAMP is present, the cAMP binds to CRP, causing a conformational change to an active form. We are studying how cAMP causes the conformational change in an effort to determine how a transcriptional regulatory factor can itself be regulated and to determine how an allosteric change in a protein can be accomplished. We have isolated, using mutagen-induced as well as site-specific mutagenesis, several classes of mutations within the crp gene that encodes CRP: crp\* mutations that allow CRP to function in the absence of cAMP, crp\*-intragenic suppressor mutations that force a crp\* mutant to require cAMP, and crp\*\* mutations that have even more cAMP independence than crp\* mutants. Our current model for how cAMP induces the allosteric change in CRP is that cAMP binding alters the relative orientation of specific amino acids that are involved in subunit-subunit alignment, domain-domain alignment, and positioning of the DNAbinding F  $\alpha$ -helices. Based on the locations within the CRP molecule of the substituted amino acids that cause the change, we have identified regions of CRP that are involved in the cAMP-induced conformational change.



			PROJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF INT	FRAMURAL RESEARCH PROJ	ECT	Z01 CB 08751-07 LMB
October 1 1986 to Sent	amber 30 1987		
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Regulation of the gal (	berop of Escherichia col	rs.) 1	
PRINCIPAL INVESTIGATOR // ist other on	perional personnel below the Principal Inves	L	
PI: S. Adhya	Chief, Developmenta	1 Genetics Se	ction LMB. NCI
			,
Other: R. Haber	Microbiologist		LMB. NCI
A. Majumdar	Visiting Scientist		LMB, NCI
J. Tokeson	Guest Researcher		LMB, NCI
		_	
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Molecular	Biology		
SECTION			
Developmental Genetics	Section		
INSTITUTE AND LOCATION	00000		
NGI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
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SUMMARY OF WORK (Use standard upper	fuced time. On not exceed the same amuide	41	B
We are studying the mec	hanisms by which the two	promoters of	the gal operon of
E. coli are regulated.	We have previously sho	wn that each o	of the promoters is
negatively regulated by	binding of Gal Represso	r to two opera	ator elements, one
of which $(0_{\rm F})$ is locate	d upstream to the promot	ers and the ot	ther $(0_T)$ inside
the galE structural gen	e. $O_{\rm F}$ and $O_{\rm T}$ are separa	ted by 114 bp.	We have proposed
various models by which	Gal Repressor inhibits	transcription	by binding to two
distal sites. These mo	dels have been tested by	various genet	ic and biochemical
experiments: competiti	on binding experiments b	etween Repress	sor, RNA polymerase
and CRP; measurement of	binding energies when R	epressor binds	s to $O_E$ and $O_T$ ; the
effect of changing the	angular orientation betw	een the two Re	epressor contact
points; physical measur	ements of the effect of	Repressor bind	ling on DNA struc-
ture; changing one or b	oth of the operators int	o lac operator	r(s) by site directed
mutagenesis and then st	udying the effect of Gal	and Lac Repre	essors on operator
combinations: $0_F^G - 0_T^G$ , 0	$E = 0_1^L$ , $0_E^L = 0_1^G$ and $0_E^L = 0_1^L$ .	The results of	otained so far
suggest that Gal Repres		expression no	ot by sterically
sterically hindering th	sor binding inhibits gal		
the structure of RNA po	sor binding inhibits <u>gal</u> e binding of RNA polymer	ase and/or CRI	P, but by changing
	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive	ase and/or CRI form.	, but by changing
	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive	ase and/or CRI form.	P, but by changing
We are also studying th	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre	ase and/or CRI form. ssor and the r	P, but by changing nature of its
We are also studying th interaction with the op	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b	ase and/or CRI form. ssor and the r iochemical and	P, but by changing nature of its alysis, e.g.
We are also studying th interaction with the op mutational analysis and	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po	ase and/or CRI form. ssor and the r iochemical and ints by chemic	P, but by changing nature of its alysis, e.g. cal protection
We are also studying th interaction with the op mutational analysis and studies. The results s	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po how that each half of sy	ase and/or CRi form. ssor and the r iochemical and ints by chemic mmetrical open	P, but by changing nature of its alysis, e.g. cal protection rator is occupied
We are also studying th interaction with the op mutational analysis and studies. The results s by a subunit of dimeric	sor binding inhibits gal e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po how that each half of sy Gal Repressor. Gal Rep	ase and/or CR form. ssor and the r iochemical and ints by chemic mmetrical oper ressor contact	P, but by changing nature of its alysis, e.g. cal protection rator is occupied ts at least two
We are also studying th interaction with the op mutational analysis and studies. The results s by a subunit of dimeric major grooves lying on	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po how that each half of sy Gal Repressor. Gal Rep one face of the dyad sym	ase and/or CR form. ssor and the r iochemical and ints by chemic mmetrical oper ressor contact metry. A thin	P, but by changing nature of its alysis, e.g. cal protection rator is occupied ts at least two rd major groove
We are also studying th interaction with the op mutational analysis and studies. The results s by a subunit of dimeric major grooves lying on on the opposite face is	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po how that each half of sy Gal Repressor. Gal Rep one face of the dyad sym also affected by Repres	ase and/or CR form. ssor and the r ints by chemic mmetrical oper ressor contact metry. A this sor either th	P, but by changing nature of its alysis, e.g. cal protection rator is occupied ts at least two rd major groove rough direct
We are also studying th interaction with the op mutational analysis and studies. The results s by a subunit of dimeric major grooves lying on on the opposite face is contact by wrapping Rep	sor binding inhibits <u>gal</u> e binding of RNA polymer lymerase to an inactive e structure of Gal Repre erators by genetic and b defining the contact po how that each half of sy Gal Repressor. Gal Rep one face of the dyad sym also affected by Repres ressor around the helix,	ase and/or CR form. ssor and the r iochemical and ints by chemic mmetrical oper ressor contact metry. A this sor either this or indirectly	P, but by changing nature of its alysis, e.g. cal protection rator is occupied ts at least two rd major groove rough direct y by Repressor



0504	DTHENT OF WEAT TH			PROJECT NUMBE	ER
UEPA	NOTIOE OF HEALTH /	AND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	701 00 001	52_07 IND
	NUTICE OF IN	HAMURAL RESEARCH PRO	JECT	201 CB 08/	52-07 LMB
PERIOD COVI	ERED			L	
October	1, 1986 to Sept	ember 30, 1987			
TITLE OF PRO	DJECT (80 characters or less	s. Title must fit on one line between the bo	ders.)		
Mechanis	ms of the Trans	port of Thyroid Hormone	s into Animal C	ells	
PHINCIPAL IN	Sy. Cheng	Research Chemist	estigetor.) (Neme, title, labor	story, and institute e	ffillation) LMB, NCI
Other:	I. Pastan	Chief, Laboratory of	Molecular Biolo	gу	NCI
	C. Parkison	Chemist Visiting Follow			LMB, NCI
	T. Fukuda	Visiting Fellow			LMB, NCI
COOPERATIN	G UNITS (if any)				
LAB/BRANCH					
Laborat	ory of Molecula	r Biology			
Molecul	ar Biology Sect	ion			
INSTITUTE AN	ID LOCATION				
NCI, NI	H, Bethesda, MD	20892			
TOTAL MAN-Y	EARS:	PROFESSIONAL:	OTHER:		
OUFOK ADDD	4.1	4.1	0.0		
(a) Hu	man subjects	(b) Human tissues	(c) Neither		
🗌 🗍 (a1	) Minors				
🗌 (a2	) Interviews				В
SUMMARY OF	WORK (Use standard unred	fuced type. Do not exceed the space provi	ded.) ing protein (p5	5). A cell	ular
thyroid	hormone binding	protein was previously	purified to ho	mogeneity.	This
protein	was found conce	ntrated on the lumenal	face of the end	oplasmic re	eticulum
and nucl	ear envelope.	A cDNA encoding p55 was	cloned and its	sequence w	vas deter-
mined.	It contains a s	ingle open reading fram	e of 1524 nucle	otides which	h encodes
a polype	ptide of 491 am	ino acids and a putative	e signal sequen	ce of 1/ and	two par-
tial pro	tein sequences.	In vitro translation	of mRNA prepare	d by transc	cription
of the c	DNA clone with	T7 RNA polymerase after	cloning into p	GEM3 yielde	d proteins
which we	re immunoprecip	itated by monoclonal an	d polyclonal an	tibodies ag	gainst p55.
The isol	ation of the cD	NA clone should allow e	lucidation of t	he cellular	function
of p55.					
II. Reg	ulation of p55	by 3.3'.5-triiodo-L-thy	ronine (T <sub>3</sub> ): Th	e effect of	T <sub>3</sub> on
the stab	ility and synth	esis of p55 was evaluat	ed. Rat pituit	ary tumor G	H <sub>3</sub> cells
were gro	wn in regular,	thyroid hormone-deplete	d (Td) and Td s	upplemented	i with T <sub>3</sub>
medium.	Immunoprecipit	ation of "S-methionine	-labeled cellul	ar extracts	indicated
that poo	is two-fold mo	re abundant in cells gr	own in 1d mediu	m than in c	ference in
mRNA lev	el was detected	in cells grown in three	e different con	ditions. H	ulse-chase
experime	nt indicated th	at p55 is two-fold more	stable in cell	s grown in	Td medium.
Thus the	down regulatio	n of p55 by T3 occurs a	t a post-transl	ational lev	/el.
(n58).	Analysis of the	characterization of and	431 cells india	rmone bindi	ng protein
another	binding protein	for T <sub>3</sub> . In contrast t	o p55, this bin	ding compor	ient has an
apparent	MW of 58K. p5	8 has been purified to	homogeneity. A	ntibodies t	o p58 are
being pr	epared and its	cellular functions will	be evaluated.		



DEPARTMENT OF HEALTH	AND HUMAN SERVICES DURLIC HE	TH SERVICE	PHOJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	
NOTICE OF IN	TRAMURAL RESEARCH PROJ	ECT	Z01 CB 08753-05 LMB
October 1 1986 to Ser	tember 30 1987		
TITLE OF PROJECT (80 characters or les	s Title must fit on one line between the borde	(S.)	
Immunotoxin Therapy of	Cancer Cells		
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Principal Inves	tigator.) (Neme, title, labora	tory, and institute affiliation)
PI: I. Pastan	Chief, Laborator	y of Molecular	Biology NCI
M.C. Willingham	Chief, UCS		LMB, NCI
D. FitzGerald	Senior Staff Fel	low, UCS	LMB, NCI
Metabolism Branch. DCE	D. NCI		
Laboratory of Theoreti	cal Biology, Medicine Br	anch, DT NCI	
Cetus Corporation. Eme	rvville, CA	anon, Di, noi	
LAB/BRANCH	, , ,		
Laboratory of Molecula	r Biology		
SECTION			
Office of the Chief			
INSTITUTE AND LOCATION			-
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
5.5	4	1.5	
(a) Human subjects	X (b) Human tissues	(c) Neither	
(a) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unre-	duced type. Do not exceed the space provider	d.)	
Antibodies reacting wi	· · · · · · · · · · · · · · · · · · ·	alla have hear	
Pseudomonas toxin. Su	th human ovarian cancer	cerrs have been	i coupled to
LOCULOMONIAS CONTING OC	th human ovarian cancer ch immunotoxins kill ova	rian cancer cel	ls in tissue cul-
ture and human ovarian	th human ovarian cancer th immunotoxins kill ova cancer cells growing in	rian cancer ce the peritoneal	l coupled to lls in tissue cul- L cavity of nude
ture and human ovarian mice. Two new monoclo	th human ovarian cancer th immunotoxins kill ova cancer cells growing in nal antibodies reacting	rian cancer ce the peritonea with ovarian ca	l coupled to lls in tissue cul- l cavity of nude ancer cells have
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a	th human ovarian cancer th immunotoxins kill ova cancer cells growing in anal antibodies reacting nd OVB3. OVB3 reacts wi	the peritoneal the small num	l coupled to lls in tissue cul- l cavity of nude ancer cells have per of human tissues
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active	th human ovarian cancer ich immunotoxins kill ova i cancer cells growing in inal antibodies reacting ind OVB3. OVB3 reacts wi in an animal model. OVB	the peritonea the peritonea with ovarian ca th a small num 3-PE is being p	l coupled to lls in tissue cul- l cavity of nude ancer cells have per of human tissues prepared for a human
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with	th human ovarian cancer ich immunotoxins kill ova i cancer cells growing in inal antibodies reacting ind OVB3. OVB3 reacts wi in an animal model. OVB ovarian cancer.	rian cancer ce the peritonea with ovarian ca th a small num 3-PE is being p	locupled to lls in tissue cul- l cavity of nude ancer cells have per of human tissues prepared for a human
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with	th human ovarian cancer ich immunotoxins kill ova cancer cells growing in mal antibodies reacting ind OVB3. OVB3 reacts wi in an animal model. OVB ovarian cancer.	the peritoneal with ovarian ca ba small num 3-PE is being p	ls in tissue cul- ls in tissue cul- l cavity of nude ancer cells have ber of human tissues prepared for a human
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th	th human ovarian cancer th immunotoxins kill ova cancer cells growing in mal antibodies reacting ind OVB3. OVB3 reacts wi in an animal model. OVB ovarian cancer. ree structural domains o	f PE has been of the period of	les in tissue cul- ls in tissue cul- l cavity of nude uncer cells have per of human tissues prepared for a human defined by deletion Domain L is the
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro- cell recognition domai	th human ovarian cancer th human ovarian cancer the immunotoxins kill ova the cancer cells growing in mal antibodies reacting y and OVB3. OVB3 reacts wi in an animal model. OVB to ovarian cancer. The structural domains o moter to express the gen the omain II is the tran	the peritoneal with ovarian ca the small num 3-PE is being p f PE has been of e in <u>E. coli</u> .	les in tissue cul- les in tissue cul- les cavity of nude ancer cells have ber of human tissues prepared for a human defined by deletion Domain I is the in and domain III is
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ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGFa. The chimeri	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova the cancer cells growing in onal antibodies reacting of in an animal model. OVB to ovarian cancer. The structural domains o moter to express the gen on ain II is the tran omain. Domain I has bee c protein produced kills	the peritoneal with ovarian ca the a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and m EGF receptor b	les in tissue cul- les in tissue cul- les cavity of nude ancer cells have ber of human tissues prepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA pearing cells.
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ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGFa. The chimeri Phase I studies have b T-cell leukemia with a	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova the cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB ovarian cancer. The structural domains o moter to express the gen on, domain II is the tran omain. Domain I has bee c protein produced kills egun in collaboration wi n antibody to the IL2 re	the peritoneal with ovarian ca the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and m EGF receptor 1 th T. Waldmann ceptor (anti-Ta	les in tissue cul- les in tissue cul- les in tissue cul- les in tissue cul- ancer cells have ber of human tissues prepared for a human defined by deletion Domain I is the in and domain III is ceplaced by a cDNA bearing cells. to treat adult ac) conjugated to
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGFα. The chimeri Phase I studies have b T-cell leukemia with a Pseudomonas exotoxin.	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova a cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB a ovarian cancer. There structural domains o moter to express the gen on, domain II is the tran omain. Domain I has bee c protein produced kills egun in collaboration wi n antibody to the IL2 re	the peritoneal with ovarian ca the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and p EGF receptor 1 th T. Waldmann ceptor (anti-Ta	les in tissue cul- les in tissue cul- les in tissue cul- les in tissue cul- ancer cells have ber of human tissues orepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA bearing cells. to treat adult ac) conjugated to
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGF $\alpha$ . The chimeri Phase I studies have b T-cell leukemia with a Pseudomonas exotoxin.	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova a cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB ovarian cancer. There structural domains o moter to express the gen n, domain II is the tran lomain. Domain I has bee c protein produced kills egun in collaboration wi n antibody to the IL2 re	the peritoneal with ovarian ca the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and p EGF receptor 1 th T. Waldmann ceptor (anti-Ta	les in tissue cul- les in tissue cul- les in tissue cul- les in tissue cul- ancer cells have ber of human tissues orepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA bearing cells. to treat adult ac) conjugated to
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ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGF $\alpha$ . The chimeri Phase I studies have b T-cell leukemia with a Pseudomonas exotoxin.	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova a cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB a ovarian cancer. There structural domains o moter to express the gen n, domain II is the tran domain. Domain I has bee to protein produced kills megun in collaboration wi n antibody to the IL2 re	f PE has been of the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and p EGF receptor b th T. Waldmann ceptor (anti-Ta	les in tissue cul- les in tissue cul- les in tissue cul- les cavity of nude ancer cells have ber of human tissues orepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA bearing cells. to treat adult ac) conjugated to
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGF $\alpha$ . The chimeri Phase I studies have b T-cell leukemia with a Pseudomonas exotoxin.	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova a cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB a ovarian cancer. There structural domains o moter to express the gen- n, domain II is the tran domain. Domain I has bee to protein produced kills begun in collaboration wi an antibody to the IL2 re	f PE has been of the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and p EGF receptor b th T. Waldmann ceptor (anti-Ta	les in tissue cul- les in tissue cul- les in tissue cul- les in tissue cul- les in tissues beer of human tissues brepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA bearing cells. to treat adult ac) conjugated to
ture and human ovarian mice. Two new monoclo been isolated: OVB1 a and OVB3-PE is active trial in patients with The function of the th mapping using a T7 pro cell recognition domai the ADP ribosylating d for TGF $\alpha$ . The chimeri Phase I studies have b T-cell leukemia with a Pseudomonas exotoxin.	th human ovarian cancer th human ovarian cancer th immunotoxins kill ova a cancer cells growing in onal antibodies reacting and OVB3. OVB3 reacts wi in an animal model. OVB a ovarian cancer. There structural domains o moter to express the gen- n, domain II is the tran domain. Domain I has bee to protein produced kills begun in collaboration wi an antibody to the IL2 re	f PE has been of the peritoneal with ovarian ca th a small num 3-PE is being p f PE has been of e in <u>E. coli</u> . slocating doma: n deleted and p EGF receptor b th T. Waldmann ceptor (anti-Ta	les in tissue cul- ls in tissue cul- l cavity of nude uncer cells have ber of human tissues prepared for a human defined by deletion Domain I is the in and domain III is replaced by a cDNA bearing cells. to treat adult ac) conjugated to



	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT Z01 CB 08754-04 LMB
PEBIOD COVERED		
October 1, 1986, to Se	ptember 30, 1987	
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	ars.)
BINCIPAL INVESTIGATOR // ist other on	e Multidrug Resistance r	tigetor ) (Name title (shortley, and institute officients)
PI: M. M. Gottesman I. Pastan	Chief, Molecular C Chief, Laboratory	ell Genetics Section IMB, NCI of Molecular Biology NCI
COOPERATING UNITS (# any)		
Division of Cancer The:	rapy, NCI	
LAB/BRANCH	r Biology	
SECTION	L BIOLOgy	
Molecular Cell Genetics	s Section	
NCI, NIH, Bethesda, MD	20892	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	0.5	0.0
(a) Human subjects	🗵 (b) Human tissues	(c) Neither
(a1) Minors		
		<b>"</b>
(a2) Interviews	luced hime. On not exceed the space provide	B
(a2) Interviews SUMMARY OF WORK (Use standard unred Resistance to multiple	luced type. Do not exceed the space provide drugs is a major impedin	a) ment to the successful chemo-
(a2) Interviews SUMMARY OF WORK (Use standard unned Resistance to multiple therapy of human cancer	duced type. Do not exceed the space provide drugs is a major impedin rs. To investigate the	g) ment to the successful chemo- genetic and biochemical basis for
(a2) Interviews SUMMARY OF WORK (Use standard unred Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cells	duced type. Do not exceed the space provide drugs is a major impedi rs. To investigate the p nce (MDR) phenotype, we l	B ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for
(a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistan the cultured KB cell, a resistance to high leve	uced type. Do not exceed the space provide drugs is a major impedi- rs. To investigate the p nce (MDR) phenotype, we h human carcinoma cell 1: els of either colchicine	B a) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which
(a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to of	weed type. Do not exceed the space provide drugs is a major impedi- rs. To investigate the p nce (MDR) phenotype, we h a human carcinoma cell 1: els of either colchicine colchicine, adriamycin, y	B a) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin
(a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancen this multidrug resistan the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp DNA	uced type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p na human carcinoma cell 1: els of either colchicine colchicine, adriamycin, pression of MDR correlat	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb
(a2) Interviews SUMMARY OF WORK (Use standard unree Resistance to multiple therapy of human cancen this multidrug resistan the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp mRNA encoded by the mdn cell lines in which it	fuced type. Do not exceed the space provide drugs is a major impedia rs. To investigate the p ince (MDR) phenotype, we h a human carcinoma cell 1: els of either colchicine colchicine, adriamycin, y pression of MDR correlate el gene which was identi: is amplified. A complete	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the mdrl gene
(a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to o and actinomycin D. Exy mRNA encoded by the mdr cell lines in which it product has been obtain	fuced type. Do not exceed the space provide drugs is a major impedin rs. To investigate the p ice (MDR) phenotype, we d human carcinoma cell 1 els of either colchicine colchicine, adriamycin, pression of MDR correlate d gene which was identi- is amplified. A complete hed and the deduced amine	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the
☐ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp mRNA encoded by the mdn cell lines in which it product has been obtain membrane-spanning, nucl	Auced hype. Do not exceed the space provide drugs is a major impedia rs. To investigate the p ince (MDR) phenotype, we d a human carcinoma cell 1 els of either colchicine colchicine, adriamycin, y pression of MDR correlate l gene which was identia is amplified. A complete hed and the deduced amino- cotide-binding 170,000	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression
☐ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp mRNA encoded by the <u>mdn</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdrl</u> cDNA confers the MDR phenoty	weed type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p ince (MDR) phenotype, we la a human carcinoma cell li els of either colchicine colchicine, adriamycin, y pression of MDR correlate l gene which was identi- is amplified. A comple- ined and the deduced amind .eotide-binding 170,000 of A or the large (>100 kb) ppe. P-glycoprotein, the	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is
☐ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp mRNA encoded by the <u>mdn</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdrl</u> cDNA confers the MDR phenoty membrane located and ca	weed type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p a human carcinoma cell 1 els of either colchicine colchicine, adriamycin, y pression of MDR correlat. I gene which was identii is amplified. A complet hed and the deduced aming eotide-binding 170,000 of a or the large (>100 kb) ype. P-glycoprotein, the an be labeled with ATP an	B d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is and with a photoaffinity analog of
☐ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistan the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exp mRNA encoded by the <u>md</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdr</u> l cDNA confers the MDR phenoty membrane located and ca vinblastine. This vinb	Auced type. Do not exceed the space provide drugs is a major impedia rs. To investigate the p ince (MDR) phenotype, we d a human carcinoma cell 1 els of either colchicine colchicine, adriamycin, y pression of MDR correlate is amplified. A complet hed and the deduced amina .eotide-binding 170,000 d or the large (>100 kb) ppe. P-glycoprotein, the in be labeled with ATP at plastine binding is inhill prese MDR. These data inc	B a) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is nd with a photoaffinity analog of bited by agents such as verapamil, hicate that P-glycoprotein is an
□ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to o and actinomycin D. Exp mRNA encoded by the <u>mdn</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdrl</u> cDNA confers the MDR phenoty membrane located and ca vinblastine. This vinh which are known to reve energy-dependent drug of	Auced type. Do not exceed the space provide drugs is a major impedii rs. To investigate the y ace (MDR) phenotype, we had a human carcinoma cell 1: els of either colchicine colchicine, adriamycin, y pression of MDR correlate and the deduced amine end and the deduced amine eotide-binding 170,000 d or the large (>100 kb) ype. P-glycoprotein, the on be labeled with ATP an olastine binding is inhill erse MDR. These data ince efflux pump. Expression	a) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is nd with a photoaffinity analog of bited by agents such as verapamil, dicate that P-glycoprotein is an of <u>mdrl</u> RNA occurs in normal kid-
□ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to o and actinomycin D. Exp mRNA encoded by the <u>mdr</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdr</u> l cDN/ confers the MDR phenoty membrane located and ca vinblastine. This vint which are known to reve energy-dependent drug on ney, liver, colon, and	weed type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p ace (MDR) phenotype, we h a human carcinoma cell 1: els of either colchicine colchicine, adriamycin, v pression of MDR correlate el gene which was identi: is amplified. A complet led and the deduced amine eotide-binding 170,000 A or the large (>100 kb) ype. P-glycoprotein, the an be labeled with ATP an olastine binding is inhib erse MDR. These data ind efflux pump. Expression adrenal and in tumors de	a) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is nd with a photoaffinity analog of bited by agents such as verapamil, dicate that P-glycoprotein is an of <u>mdrl</u> RNA occurs in normal kid- erived from these tissues which are
□ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to c and actinomycin D. Exy mRNA encoded by the <u>mdr</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdrl</u> cDN/ confers the MDR phenoty membrane located and ca vinblastine. This vinh which are known to reve energy-dependent drug of ner, liver, colon, and intrinsically resistant	Weed type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p are (MDR) phenotype, we h a human carcinoma cell 1: els of either colchicine colchicine, adriamycin, y pression of MDR correlate el gene which was identi: is amplified. A complet led and the deduced amine cotide-binding 170,000 dor the large (>100 kb) ype. P-glycoprotein, the m be labeled with ATP are plastine binding is inhibit erse MDR. These data ind efflux pump. Expression adrenal and in tumors do to chemotherapy. Acqui and in pheochromocytom	d) ment to the successful chemo- genetic and biochemical basis for have developed a model system using ine selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR te cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is and with a photoaffinity analog of bited by agents such as verapamil, dicate that P-glycoprotein is an of <u>mdrl</u> RNA occurs in normal kid- erived from these tissues which are ired drug-resistance in childhood a may be associated with increased
□ (a2) Interviews SUMMARY OF WORK (Use standard unner Resistance to multiple therapy of human cancer this multidrug resistant the cultured KB cell, a resistance to high leve is cross-resistant to o and actinomycin D. Exp mRNA encoded by the <u>mdn</u> cell lines in which it product has been obtain membrane-spanning, nucl of the cloned <u>mdrl</u> cDNA confers the MDR phenoty membrane located and ca vinblastine. This vinh which are known to reve energy-dependent drug o ney, liver, colon, and intrinsically resistant leukemia, neuroblastoma mdrl RNA levels.	weed type. Do not exceed the space provide drugs is a major impedii rs. To investigate the p ince (MDR) phenotype, we h a human carcinoma cell li- els of either colchicine colchicine, adriamycin, y pression of MDR correlate and the deduced amine acotide-binding 170,000 A or the large (>100 kb) ppe. P-glycoprotein, the in be labeled with ATP an olastine binding is inhibi- rese MDR. These data ince efflux pump. Expression adrenal and in tumors do to chemotherapy. Acqui-	d, ment to the successful chemo- genetic and biochemical basis for have developed a model system using in selected independently for , adriamycin or vinblastine which vincristine, vinblastine, puromycin es with the presence of a 4.5 kb fied and cloned from highly MDR to cDNA sequence for the <u>mdrl</u> gene o acid sequence specifies the dalton P-glycoprotein. Expression <u>mdrl</u> gene in drug-sensitive cells e product of the <u>mdrl</u> gene, is no with a photoaffinity analog of bited by agents such as verapamil, ited by agents such as verapamil, ited by agents tis normal kid- erved from these tissues which are and may be associated with increased



NOTICE OF INTRAMURAL RESEARCH PROJECT	Z01 CB 08755-01 LMB
PERIOD COVERED October 1, 1986 to September 30, 1987	L
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Development of Antibodies to P-glycoprotein from Multidrug Re	sistant Human Cells
PRINCIPAL INVESTIGATOR (I ist other omfereignel personnel below the Principal Investigator ) (Alema title Johanne	
P.I. Nancy Richert Senior Investigator	tory, and institute affiliation) LMB, NCI
Other: Ira Pastan Chief, Laboratory of Molecular M.M. Gottesman Chief, MCGS M.C. Willingham Chief, UCS	Biology NCI LMB, NCI LMB, NCI
COOPERATING UNITS (# any)	
David Liu, Cetus Corporation, Palo Alto, CA 94303	
LAB/BRANCH	
Laboratory of Molecular Biology	
SECTION Ultrastructural Cytochemisty Section	
INSTITUTE AND LOCATION	
NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS: PHOFESSIONAL: OTHEH:	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	B
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews  SUMMARY CONSTRUCTION (c) WORK (in a standard unrefused tree to be set arread the same arrived to	В
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Multidrug resistance (MDR) in human tumor cells is correlated of a 170,000 dalton membrane glycoprotein called P170 or P-gl complete cDNA sequence of the <u>mdr-1</u> gene which encodes P170 i present study, monospecific antibodies to P170 were prepared bits with 11 synthetic peptides directed against 4 major doma an N-terminal intracellular domain; 2) an N-terminal extracel (3+4) two C-terminal extracellular domains. Thus far two of produced high titer antibodies. Antibody P7 is to domain 1 ( and P0 is to domain 3 (residues #741-750). Both antibodies h purified using peptide-bovine serum albumin conjugates couple Both antibodies specifically precipitate an [ <sup>35</sup> S]methionine 1 tein from vinblastine resistant KB cell extracts (KB-V1) whice in the drug-sensitive parent cell line (KB-3-1). P170 was qu seven of the resistant sublines, two revertant sublines, and lines transfected with <u>mdr</u> -DNA and found to correlate with th resistance. P170 is synthesized as a 140 kd precursor which slowly over the next four hrs. The oligosaccharide is aspara endoglycosidase H resistant, and contains no sialic acid. Th P170 in KB-V1 cells is 48-72 hrs, and increasing drug resistant to an altered turnover rate of the protein. P170 was also de membrane preparations of normal human kidneys by Western blot	B with the presence ycoprotein. The s known. In the by immunizing rab- ins of P170: 1) lular domain; and these peptides have residues # 28-35) ave been affinity d to affigel. abeled 170 kd pro- h is not present antitated in in two NIH-3T3 e level of drug- is glycosylated gine-linked, e half-life of nce is not due tected in ting with the

PROJECT NUMBER



DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	
			201 CB 08300-15 LTB
PERIOD COVERED	Actober 1, 1986 to Septer	mber 30, 1987	
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	ers.)	
SAAM, Developmen	it and Applications for A	Analogic System	ns Realizatior
PRINCIPAL INVESTIGATOR (List other pro	plessional personnel below the Principal Invest	tigator.) (Name, title, labora	atory, and institute affiliation)
	Conior Invostigat	tor	ITB NCI
Loren A. Zech, M.D.,	Detail from OD. N	NIHLB	115, 1101
	2000011 111111 111,		
Other Professional Pers	sonnel:		
	TDA Tourstinsto	_	
Vernon D. Parker, Ph.D.	. IFA, Investigator	L	LID, NOI
COOPERATING UNITS (if any)			
Dr. Ray Boston, Murdoch	n Univ.,Australia; Dr. Tu	revor Redgrave,	, Univ. Western
Australia; Dr. Charles	Schwartz, Medical Coll.	of Virginia,Ri	chmond, VA; Dr.
Waldo R. Fisher, Univ.	of Fla., Gainesville; Dr	r. Barbara Howa	ira, Phoenix
LAB/BRANCH	Laboratory of Mathemati	ical Biology	
SECTION			
	Office of the Ch	hief	
INSTITUTE AND LOCATION	NCI NIH Bothorda	VD 20892	
	PROFESSIONAL:	OTHER:	····
.5	.5	0.0	
CHECK APPROPRIATE BOX(ES)			
a) Human subjects	(b) Human tissues	(c) Neither	P
(a1) Minors			В
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the space provide	ad )	
Continuing develop	pment of a computer sys	stem (SAAM)	for the simulation,
analysis, and modelin	ng of bio-kinetic system	ms. In 1986-19	987yr we advanced the
SAAM/CONSAM extensions	to allow for increases	in the number	er of compartments,
components and adjusta	able parameters having pr	d with the	simulator. A "Unix
(Illtriv 1.5)" version	a of SAAM29/CONSAM was in	mplemented beca	ause of the number of
users which have chose	en to use this operation	ting system a	and because of the
anticipation of the co	onversion of the Laborat	ory of Mathema	tical Biology to this
standard operating syst	tem. A 30 compartment v	ersion of SAAM	and CONSAM has been
developed using these	e new tools and is pro	C and tested	using the previous
library of SAAM problem	ms. Because the UNIX-PC	functions as	both the computer and
terminal, software for	a virtual terminal	was added to	CONSAM. The 30+,
C-language, subroutine	es which makeup the vir	tual terminal	utilize the CSS-CKS C
bindings. This imple	ementation necessitated	the addition	n of a graph name
characteristic to the	e CONSAM plot command.	which informat	ion and control can
executed as separate in	to the virtual terminal	on the plot con	mmand.
The metabolism	of human IgE was stu	died in normal	s, severe atopics and
patients with the hype:	rimmunoglobulin E-recurr	ent infection	(HIE; Job's) syndrome
to understand how Ig	E metabolism is altered	in disorders w	ntal model for LaF
of serum IgE. Followin	ng the development of a	ractional cata	bolic rate for IgE is
significantly less for	atopic patients (mean	±SEM=0.20±0.01	) and for the HIE
patients $(0.15\pm0.02)$	than for the normal vo	lunteers (0.52	±0.06; P<0.01) and is
inversely related (r=-			
	0.851; P<0.001) to the s	erum IgE conce	ntration. Evaluation
of these data using	0.851; P<0.001) to the s the model further l	erum IgE conce ead to a un	ntration. Evaluation ifying hypothesis of

PROJECT NUMBER



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	PROJECT NUMBER	1
NOTICE OF INT	RAMURAL RESEARCH PF	ROJECT	701 CB 0	8303-15 ITE
	October 1, 1986 to S	September 30, 1987	201 00 0	
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the Membrane Reconstit	borders.) Lution and Fusion		
PRINCIPAL INVESTIGATOR (List other pro Robert Blumenthal, Ph	olessional personnal below the Principal	Investigator.) (Name, title, labora	tory, and institute affil	n. LTB. NCT
Other Professional Do	areannal :			,,
Other Professional Pe	rsonner.			
Anne Walter, Ph.D., S Ofer Eidelman, Ph.D.,	Senior Staff Fellow Visiting Associate			LTB, NCI LTB, NCI
Anu Bali, Ph.D., Visi	ting Fellow			LTB, NCI
COOPERATING UNITS (If any)				LIB, NC.
Dr. Kenneth Spring, N Loyter, Hebrew Univer	HBLI; Dr. Michel Olli sity, Israel.	von, CNRS, France	, Dr. Abraha	am
LAB/BRANCH	Laboratory of Math	ematical Biology		
SECTION	Membrane Structure &	Function Section		
INSTITUTE AND LOCATION	NCI, NIH, Bethes	da, MD 20892		•
TOTAL MAN-YEARS: 4.0	PROFESSIONAL: 4.0	OTHER: 0.0		
(a) Human subjects     (a) Airrors     (a2) Interviews	(b) Human tissues	<sup>™</sup> (c) Neither	В	
The research goals in towards an understand glycoproteins. We ar of Vesicular Stomat the HA protein of inf fluorescent methods intact and reconstitu development of meth iii) functional recon iv) studies of mec binding, conformation mediating membrane spike glycoproteins b activities vi) stud destabilization (perm into the cell by endo image processing usin computor to analyse the fusion protein af intermediates; xi) D viral proteins using transfected cells; of methods for using delivery of materials	the Membrane Structu ing of mechanisms of e specifically studyi itis Virus (VSV), the luenza virus. Specif to study kinetics ted virions, and l ods to analyze recon stitution of viral sp hanism based on an al changes and cooper fusion v.) studies of y pH temperature, enz ies of the relation eability changes) and cytosis using fluores g video-enhanced .flu viral entry pathways. ter the fusion event; evelopment of methods cloned viral memb xii) Structural studi reconstituted viral into cells.	membrane function membrane fusion m ng the mode of ac HN and F protein ic topics include and extent of adh iposomes and ce stitution of vira ike glycoproteins allosteric mod ativity of viral f the effects of ymes, and chemica nship between v fusion vii.) Stu cent techniques. orescent microsc ix) Examination x) Identificatio to study fusion rane protein se es of viral prote envelopes as v	Section are ediated by tion of the s of Sendai : i) deve esion and fi ls as tar l spike glyco modification ls on their irus-induced dies of v viii.) App opy control of the dis n of possil activity of quences ex ins; xiii) l ehicles for	e directed viral spike G protein Virus, and lopment of usion using rgets; ii) coproteins; d vesicles e of ligand proteins in ns of viral fusogenic d membrane iral entry lication of ble fusion mutants of pressed in Development r specific



## DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CB 08320-12 LTB

PERIOD COVERED	
October 1, 1986 to September 30, 198	7
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labor	atory, and institute affiliation)
Robert Jernigan, Ph.D. Theoretical Physical C	nemist LTB, NCI
Other Professional Personnel:	
David Covell Ph D Expert	LIB, NCI
Robert Guy. Ph.D. Sr. Staff Fellow	LTB, NCI
Kai-Li Ting, Ph.D. Computer Programmer	LTB, NCI
COOPERATING UNITS (if any)	
Dr. J. Ferretti, Laboratory of Chemistry, NIHLB; Dr. F. Wa	ng, National Bureau of
Standards, Gaithersburg, Md.	
LAB/BRANCH	
Laboratory of Mathematical Biology	
Office of the Chief	
INSTITUTE AND LOCATION	
NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects (b) Human tissues $\Box_{XX}(c)$ Neither	
(a1) Minors	В
SUMMARY OF WORK (Use standard unreduced type, Do not exceed the space provided.)	
Statistically derived Phi-psi maps for each type of residu	e indicate substantial
improvements in X-ray data over previous tabulations	Position effects in
especially proline, aromatic and polar groups.	s types of residues,
NMR investigations of Substance P, a neuropeptide,	indicates no dominant
conformations in water, but in methanol it is highly order	ed with a large number
of 2-Dimensional NMR NOE cross-peaks. With these d	ata, molecular models
additional data obtained have assisted in indicating w	nich of the alternative
conformations are most probable.	
Experimental studies of a 13 amino acid fragment of Ribonu	clease A indicated it
to be a stable helix at low temperatures. The existenc	e of such a small rela-
tively stable structure has been surprising. We have been	looking in detail at
possible molecular interactions to try to understand the	remarkable stability of
such a small peptide as a helix in water.	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT	
	Z01 CB 08335-11 LTB
PERIOD COVERED October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must hit on one line between the borders.) "Targeting" Liposomes for Selective Interaction with Specif	ic Cells and Tissues
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labora	tory, and institute affiliation)
John N. Weinstein, M.D., Ph.D. Chief, Theoretical Immuno Section,	Logy LTB, NCI
Other Professional Personnel:	
Christopher Black, Ph.D. Visiting Associate	LTB, NGI LTB NCI
Anne Lewis, B.S. Biologist	LTB, NCI
Mary Jane Talley, B.S. Biologist	LTB, NCI
COOPERATING LINITS (# any)	
LAB/BRANCH Laboratory of Mathematical Biology	
SECTION Theoretical Immunology Section	
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS: 0.8 PROFESSIONAL: 0.5 OTHER: 0	.2
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects     (b) Human tissues     (c) Neither     (a1) Minors     (a2) Interviews	В
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
We have studied three conceptually different ways of "target	ing" liposomes:
(1) Antibody-mediated targeting. We find that antibody-bear	ing liposomes bind in
large numbers to cells which bear the appropriate antigen	. However, the bound
liposomes are internalized only if endocytosis is possible.	Upon endocytosis,
liposome-entrapped methotrexate (MTX) can escape from the en	docytic apparatus and
bind to cytoplasmic dihydrofolate reductase, inhibiting grow	th of the cell. In
the course of these studies, we developed the first neteroor	d toward HIV-infected
cells.	
	anaitive" linecomer
(2) <u>Physical targeting</u> . We have designed "temperature-	drug in vivo at
temperatures achievable by local hyperthermia. These	liposomes selectively
deliver MTX to mouse tumors in vivo and inhibit their growth	
	ary of linesomes and
(3) Compartmental targeting. We have demonstrated the delivery	peritoneal, injection
and have determined cellular sites of localization. These	studies have been
extended to antibody-bearing liposomes.	

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DEPARTMENT OF HEALTH	AND HUMAN SERVICES	- PUBLIC HE	ALTH SERVICE	PROJECT	NUMBER
NOTICE OF IN	TRAMURAL RESEA	RCH PROJ	ECT		
				Z01	CB 08341-09 LTB
PERIOD COVERED	October 1, 1986	to Septe	mber 30, 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line b	etween the borde	nrs.)		(- UTV
Studies of Li	pid-Protein and	Protein-	Protein Interac	tions	in HIV
John N. Weinstein, M.D	., Ph.D.	Chief, T Section	heoretical Immu	inolog	y LTB, NCI
Other Professional Per	sonnel:				
Bobak Mozayeni, M.S.		Howard H	ughes Fellow		LTB, NCI
H. Robert Guy, Ph.D.		Senior S	taff Fellow		LTB, NCI
Robert Jernigan, Ph.D. Kai-Li Ting, Ph.D.		Computer	Programmer	iemist	LIB, NCI LTB, NCI
COOPERATING UNITS (if any) Dr. T. Innerarity and Dr. Richard Klausner, Shearer, IB, NCI. Drs.	COOPERATING UNITS (# any) Dr. T. Innerarity and Dr. R. Pitas, University of California at San Francisco; Dr. Richard Klausner, LBM, NIAMDD; Dr. R. Schwartz, LI, NIAID; Dr. G. Shearer, IB, NCI. Drs. J. Segrest & Arantharamaiah, U. Alabama, Birmingham				
LAB/BRANCH	Laboratory of	Mathemat	ical Biology		
SECTION	Theoretical	Immunolo	gy Section		
INSTITUTE AND LOCATION	NCI, NIH, B	ethesda,	MD 20892		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.3		OTHER 0.7		
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	🗌 (b) Human tiss	ues 👯	(c) Neither	В	
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed t	he space provide	d.)		
We have investiga recombinant particles HDL) all disrupt li quasistoichiometric p recombines with dimyri form discs approximate the rim. These struct scattering, electron techniques. With dipalmitoyl recombinant" particle by which proteins are process we have dev which is also being ap Lipoproteins were carbocyanine for stud The lipoproteins are fluorescence identific Statistical and devised for evaluati structure-function rel define issues of struct the envelope polyprot	ted the interac A number o posome structur rocess. In t stoyl phosphati ly 100 Å in dia ural results we microscopy, phosphatidylcho s in a process assembled into eloped a techn plied to study ilabelled with ies of interact also being ation of cells more general m ng amphipathic ationships in p ture and immuno ein of HIV. Li	tion of l f lipopro re by a he case dyl choli meter and re obtain column line, A-I which may membraness ique call incorpora the fluor ion will labelled in athero mechanical helical roteins a genicity pid membr	ipoproteins wit tein fractions n essentially of-HDL, the ma ne vesicles 40 32 Å in thickn ed by a comf chromatography also forms wha relate to phys and lipoprotei ed "phase trans tion of tubulin escent lipid cell surface li with NBD lip scleroic plaque algorithms (Ha structures nd peptides.	<pre>h lipe (VLDL irr ijor a l li less, v pinatio y, and siclon ins. ins. into 3,3 d ipopro pids es. AL, HA and This i p HLA d huma</pre>	osomes to form , IDL, LDL, and eversible and poprotein, A-I, pid-protein to with protein on on of neutron d fluorescence term "vesicular ical mechanisms To study this release" (PTR) membranes. ioctadecylindo- tein receptors. for two-color LP, HALCO) were more general s being used to antigens and to n cell isolates
characterized synthet process. The results	ic antigenic may have applic	peptides ation to	and T-cells the design of	in t vaccin	he recognition es.
		220			

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 08359-06 LTB

PERIOD COVERED	
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October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 cheracters or less. Title must fit on one line between the borders.) Monoclonal Antibodies in the Lymphatics for Diagnosis and Therapy of	Tumors	
PINCEAL INVESTIGATION // ist other professional personnel holew the Personal Investigator / Alage		
The second second second procession and provide the second s	TTR	NCT
John N. Weinstein, M.D., rh.D. Grief, insorteriear insideringy Section	LID,	NOI
Utner Professional Personnel:	T TTD	NOT
Christopher D.V. Black, Ph.D. Visiting Associate	LIB,	NCI
David G. Covell, Ph.D Expert	LTB,	NCI
Renee Eger, B.S Guest Researcher	LTB,	NCI
Anne Lewis, B.S. Biologist	LTB,	NCI
Mary J. Talley, B.S. Biologist	LTB,	NCI
COOPERATING UNITS (If any) Dr. A. Keenan, Dr. S.M. Larson, LHM, CC; Dr. R. Parker	, Dr.	s.
Sieber, DCCP; Dr. R.K. Oldham, Dr. K.M. Hwang, Dr. M.E. Key, FCRF; Dr. L	. Liot	ta,
Dr. G. Bryant, LP, DCBD; Dr. J. Schlom, Dr. D. Colcher, LTIB, DCBD; Dr. H	M. Lot	ze,
Dr. R. Rosenberg, SB. DCT; Dr. J. Mulshine, NCI-NMOB, DCT.		
LAB/BRANCH		
Laboratory of Mathematical Biology		
SECTION Theoretical Immunology Section		
INSTITUTE AND LOCATION		
NCI, NIH, Bethesda, MD 20892		
TOTAL MAN-YEARS: 3.0 PROFESSIONAL: 1.5 OTHER: 1.5		
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	11.1	6
We have defined a new approach to the use of monoclonal antibod diagnosis and therapy of tumor in lymph nodes: delivery to the lymphatic vessels after subcutaneous injection. To establish pharmacokinetic basis for this approach, we first studied antibodies of cell types in the mouse lymph node. In vitro- binding characterist combined with in vivo pharmacological parameters to develop a quar understanding of the delivery process using the SAAM computer modeling Armed with that background information, we then demonstrated and specific uptake in lymph node metastases of a guinea pig tumor. The apprextended to include endoscopic techniques for reaching lymph node g accessible by subcutaneous injection. Imaging studies were followed attempts at therapy. For diagnosis of early metastatic tumor in the m lymphatic route can be expected to provide higher sensitivity, lower back lower systemic toxicity, and faster localization than the intravenous rouse will also minimize the problem of cross-reactivity with antigen present of tissues.	dies nodes a f to nor ics w ntitat analy roach up w odes, ckgrou oute. on nor	for via irm mal pere ive ive ive was not vith the ind, It mal
The experimental design of the guinea pig studies is currently being to detection of lymph node metastases in clinical stage II malignant mel.	g appi anoma	and
The second	- Out	6

to detection of lymph node metastases in clinical stage if malignant melanoma and cutaneous T-cell lymphoma (CTCL). Similar protocols have been approved for breast carcinoma, Hodgkin's disease, small cell lung carcinoma, and non-small cell lung carcinoma. Our studies of CTCL have produced the most efficient antigen-specific imaging yet achieved in humans by any techniques.

In vitro and animal studies are being continued both to optimize the clinical procedures and to explore basic functions of the immune system (see project #Z01CB08368-2 Selective Cytotoxicity in the Lymphatics). Our longer term aim is to understand the pharmacology of monoclonal antibodies and other ligands in order to develop criteria for rational molecular design of biological antitumor agents.



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUM	BER	
NOTICE OF INT	TRAMORAL RESEARCH FROULD	Z01 CB	08363-05 LT	
PERIOD COVERED	October 1, 1986 to September 30, 1987			
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borders.) Protein Modelling	<u> </u>		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Investigator.) (Neme, title, labora	tory, and institute	affiliation)	
H. Robert Guy, Ph.D.	Senior Staff Fellow		LTB, NCI	
Other Professional Pe	ersonnal:			
Robert Jernigan, Ph.D	. Theoretical Physical Chem	ist	LTB, NCI	
David Covell, Ph.D.	Expert		LTB, NCI	
James Ferretti, Ph.D. Candice Pert, Ph.D.	Physical Chemist Pharmacologist		H IR CH M BPB	
COOPERATING UNITS (if any)			<u></u>	
LAB/BRANCH	Leboratory of Mathematical Richary			
SECTION	Laboratory of Mathematical Biology			
	Office of the Chief			
INSTITUTE AND LOCATION	NCI, NIH, Bethesda, MD 20892			
TOTAL MAN-YEARS. 1.3	PROFESSIONAL: 1.2 OTHER: 0	.1		
CHECK APPROPRIATE BOX(ES)	×**			
(a) Human subjects	(b) Human tissues (c) Neither	E	3	
(a2) Interviews				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)				
The primary goal of t	his project is to develop methods to p	redict st	ructures o	
proteins from their methods to develop st	sequences and available experimental	data and	to use thes	
developed models of t	he action potential sodium channel and	the volta	age dependen	
anion channel (VDAC) of mitochondrial membrane were improved and refined and				
methods were expanded to include peptides that act as T-cell antigens and that				
interact with Hiv receptors.				
	237			
PHS 6040 (Page 1/84)			CRO 014-01	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER			
NOTICE OF INTRAMURAL RESEARCH PROJECT				
	Z01 CB 08365-05 LTB			
PERIOD COVERED October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must lit on one line between the borders.) Prediction of T-cell Antigenic Sites from the Prim	nary Sequence			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.)	story, and institute affiliation)			
James L. Cornette, Ph.D. IPA Investigator	LTB, NCI			
Other Professional Personnel				
Hanah Margalit, Ph.D. Visiting Fellow John L. Spouge, M.D., Ph.D. Visiting Associate	LTB, NCI LTB, NCI			
COOPERATING UNITS (if any)				
Jay A. Berzofsky, Metabolism Branch, DCBD, NCI; Charles DeLisi, Director for Health & Environmental Research	1, U.S. Dept. of Energy			
LAB/BRANCH Laboratory of Mathematical Biology				
SECTION Office of the Chief				
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892				
TOTAL MAN-YEARS. 1.9 PROFESSIONAL: 1.9 OTHER:				
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)				
We have developed an algorithm to predict protein antigenic sites recognized by T lymphocytes, based on the finding that a majority of immunodominant T-cell sites tend to form amphipathic $\alpha$ -helices. We have conducted a thorough examination of hydrophobicity scales and computational procedures useful in detecting potential amphipathic helices. We also have developed a powerful statistical procedure based on Monte Carlo methods that evaluates physical-chemical properties proposed to be characteristic of T-cell antigenic sites. The computer program implementing the procedure compares any proposed property as expressed in the known T-cell sites with its expression in comparable randomly chosen sites. Other characteristics of known T-cell sites with potential predictive value are being sought. The methods developed are not unique to T-cell antigenic sites, but are useful in identifying physical-chemical characteristics of many biomolecular features (antibody binding sites, enzyme active sites, DNA promoter regions, for example). [See also report Z01 CB 04020-09 MET of Jay A. Berzofsky, who initiated many of the questions and with whom this work is closely coordinated.]				



			PROJECT N	UMBER	
DEPARTMENT OF HEALTH AND I	HUMAN SERVICES - PUBLIC HEA	LTH SERVICE			
NOTICE OF INTRA	MURAL RESEARCH PROJE	ECT			
			Z01 CB	08366-04	LTB
PERIOD COVERED Oct	ober 1, 1986 to Septe	mber 30, 1987			
TITLE OF PROJECT (80 characters or less. Title The Percol	must fit on one line between the borde ation of Monoclonal A	stibodies into	Tumors		
PRINCIPAL INVESTIGATOR (List other profession	nal personnel below the Principal Invest	igator.) (Name, title, labora	tory, and inst	tute affiliation)	
John N. Weinstein, M.D.,	Ph.D. Senior Inv	estigator		LTB,	NCI
Other Professional Person	nel:				
David G. Covell, Ph.D	Senior Sta	ff Fellow		LTB,	NCI
COOPERATING UNITS (if any)					
Dr. L. Liotta, LP, DCBD; Dr. S.M. Larson, NM, CC; Dr. B. Bunow, LAS, DCRT					
LAB/BRANCH L	aboratory of Mathemat	ical Biology			
SECTION	Theoretical Immunolo	gy Section			
INSTITUTE AND LOCATION	NCI, NIH, Bethesda,	MD 20892			
TOTAL MAN-YEARS: 0.3	DFESSIONAL: 0.3	OTHER:	0		
CHECK APPROPRIATE BOX(ES)					
(a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues	(c) Neither	В		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Before a monoclonal antibody (or other biological ligand) can label or kill a					
tumor cell, it must first reach that cell. For portions of a tumor far from the					
nearest blood vessel or other source of antibody, access may be thinted by the					
rate at which the molec	ule can percolate t	nrough the ext	Lacellu	Lai space	• •••

are investigating the spatial and temporal profiles of immunoglobulin (Ig) distribution generated by diffusion and convection through tumors, taking into account the possibilities of (a) saturable specific binding to cells, (b) nonsaturable, nonspecific binding, and (c) metabolic degradation.

We first developed theoretical models of the percolation process. Significant predictions thus far include the following: (1) The diffusion coefficient and/or hydraulic conductivity may limit flux of antitumor Ig through tumors. (2) The flux of non-binding control Ig is much less likely to be limited by diffusion or convection. Nonspecific Ig's penetrate more deeply and more quickly into the tumor. (3) Even with saturable binding (but not metabolism), the "C times T" exposure of tumor cells to antibody will be the same throughout the mass. (4) Metabolism will decrease the relative "C times T" exposure of cells farther from the source. This may be a major barrier to effective treatment of solid tumors with ligand molecules. (5) Most interesting, antibodies with low affinity may be preferable to those with high affinity for some therapeutic applications.

We plan to test predictions of the model using micrometastases of human melanoma in nude mice. The distribution of antibody will be determined by fluorescence techniques and autoradiography. Concepts arising from this study are being applied to the design of clinical studies with monoclonal antibodies.

In addition to the investigations of immunoglobulin and other ligands as administered agents, we are considering the the physiology of <u>endogenous</u> molecular species including the antibodies, lymphokines, and other growth factors.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT	NUMB	ER	
NOTICE OF INTRAMURAL RESEARCH PROJECT				
	Z01	СВ	08367-0	4 LTB
PERIOD COVERED October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 cheracters or less. Title must fit on one line between the borders.)			<u> </u>	
Selective Cytotoxicity in the Lymphati	cs		-	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labora	tory, and ins	stitute a	affiliation)	
Christopher D.V. Black, Ph.D., Visiting Fellow		LTB	, NCI	
Other Professional Personnel:				
John N. Weinstein, M.D., Ph.D., Senior Investigator		LTB	, NCI	
Anne Lewis, M.S. Biologist		LTB	, NCI	
Atcher., COP, DCT, NCI; Drs. R.A. Kroczek and E.M. Shevach.	nsow a, LI, N		R.W. D	
LAB/BRANCH Laboratory of Mathematical Biology				
SECTION Theoretical Immunology Section				
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892			-	
TOTAL MAN-YEARS: 1.2 PROFESSIONAL: 1.0 OTHER: 0.2				
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	В			
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)				
Following subcutaneous injection, radiolabeled monoclona	al an	tibo	odies	bind
efficiently to normal and tumor target cells in the lymph no	des (P	roje	ect # Z(	)1 CB
08359-03 LTB). This finding prompted us to attempt spe	cific	the	erapy (	ising
monocional antibody conjugates.				
An immunotoxin made from the A-chain of ricin coupled	i to an	ant imi	ti-mouse lar reg	MHC
have been found with ricin A-chain conjugated to monoclonal antibodies against				
subsets of mouse lymphocytes in vitro. We have also been able to augment the				
effects of these toxins by the action of certain drugs which	h are	know	wn to af	fect
cell biological pathway (the "neutral bypass") by which toxi	n mole	cule	is for es enter	the
cytoplasm from antibody conjugates to kill a cell.		uur		ciic
A further type of immunoconjugate for specific cell killing	in viv	0 CC	onsists	of a
radioactive compound chelated to an antibody. We have demonstrated selective				
ablation or lymph node B lymphocytes in mice injected subcutaneously with an anti-murine B cell antibody labeled with the alpha particle emitter <sup>212</sup> Biomyth				
The relative potency of this conjugate for B cells in vivo was 10-fold higher				
than for T cells taken from the same nodes.				0
In order to assess the effects of antibodies and antibody conjugates in vivo, we				
nave established two models of lymph node T cell activation. In one, the stimulus is the plant lectin concanavalin A administered into the footpad: the				
other stimulus is allogeneic cells. Both of these stimuli induce T cells to				
express receptors for IL-2. The concanavalin A model is susceptible to the				
inhibitory effects of cyclosporin A whereas the allogeneic m	odel i	s no	ot.	
246				



	PROJECT NUMBER			
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE				
NOTICE OF INTRAMURAL RESEARCH PROJECT				
	Z01 CB 08369-03 LTB			
PERIOD COVERED October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) System Software for Protein and Nucleic Acid Struc	ture Analysis			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labora Lewis L. Lipkin, M.D., Chief Image Processing Section	tory, and institute affiliation) n LTB, NCI			
Other Professional Personnel:				
Peter Lemkin, Ph.D., Computer Specialist	IPS, LTB, NCI			
Bruce Shapiro, Ph.D., Computer Specialist	IPS, LTB, NCI			
Morton Schultz, Senior Engineer	IPS, LTB, NCI			
COOPERATING UNITS (if any)				
LAB/BRANCH Laboratory of Mathematical Biology				
SECTION Image Processing Section				
INSTITUTE AND LOCATION				
NCI, NIH, Betnesda, MD 20892				
TOTAL MAN-YEARS: I PROFESSIONAL: OTHER:	0			
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)				
SUMMARY OF WORK (Use standard unreduced type Do not exceed the space provided.) The object of this part of the program is to make available to the general biomedical community the various microscope control and image acquisition /analysis procedures developed within the section. The plan is based on the quantitative microscopist having available to him as a minimum system a PC/AT (or a fully compatible MS-DOS machine) with a minimum of 512 Kb of memory and a standard 20 megabyte hard disk. All interfacing with the microscope will be accomplished via commercially available interface cards which have the appropriate analog and digital signal I/O. Image acquisition hardware will also be of the commercial type. We plan to place in the public domain a series of source programs, written in C (for maximum portability in the PC world) which will allow incrementally more varied and complex functions to be performed on images acquired under computer microscopic control. The procedures which the user can employ will depend upon how much additional resources he has available beyond the above noted minimum. Functionally speaking, the programs for control, will for example, apply equally well to inverted microscopy (opening up tissue cultures to controlled image acquisition). Liberal provision is being made in the software for control of additional stepping motor functions which could be user defined (e.g. condenser focus, flow of liquids into and out of a chamber, etc). It is planned to include the possibility for interactive image processing, employing a PC compatible high resolution display, with some gray level capability. This and other options are available as a function of user interest and the level of resources available on his PC.				



	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INTRAMURAL RESEARCH PROJECT	701 CR 08370-04 IT
PERIOD COVERED October 1, 1986 to September 30, 1987	201 CB 00370-04 EI
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Interactions in Globular Proteins and Protein	Folding
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the professional personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below the Principal Investigator.) (Name, title, laboration of the personnel below th	ttory, and institute affiliation)
Robert Jernigan, Ph.D. Theoretical Physical Chemist	LTB, NCI
Other Professional Personnel:	
David Covell, Ph.D. Expert	LTB, NCI
COOPERATING UNITS (If any)	
LAB/BRANCH Laboratory of Mathematical Biology	
SECTION Office of the Chief	
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS. 0.1 PROFESSIONAL: 0.1 OTHER: 0	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	В
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
Compact conformations are generated on a lattice by restric chain as it is being generated, in each direction. Thi reduces the number of conformations, especially when the populated. The intention is to generate most compact confo their quality in a general way, based upon what has been protein crystal structures. This effectively leads to a " conformations, with the major features but not all the de effective residue-residue interaction energies statisticall X-ray structures. The way these were obtained was: a latti in which each residue type has a coordination number. If an incompletely filled coordination shell, then it is assum equivalent water molecules. Derived contact energies foll favorably interacting pairs are hydrophobic residue interactions are quite non-specific. More specificity is residues. These energies will be used to assess the generated conformations. If the procedure yields appropria they can be refined subsequently with energy calculations t	ting the extent of the s procedure enormously lattice is densely rmations and to assess observed in globular fuzzy" look at protein tails. We will use y derived from protein ce-like model is used a specific residue has ed to be filled with ow intuition: the most s. However, those observed between polar qualities of lattice te conformations, then hat include all atoms


DEBARTMENT OF HEALTH AN	D HUMAN SERVICES - PUI	ALIC HEALTH SERVICE	PHOJECT NUMBER
DEPARTMENT OF HEALTH AN	D HUMAN SERVICES * FU		
NOTICE OF INTH	AMUHAL RESEARCH	PROJECT	
			<u> </u>
(	October 1, 1986 to	September 30, 198	7
TITLE OF PROJECT (80 characters or less. 7	Title must fit on one line between Conformational	the borders.) Variation in DNA	
PRINCIPAL INVESTIGATOR (List other profes	ssional personnel below the Prin	cipal Investigator.) (Neme, title, labo	pratory, and institute affiliation)
Robert Jernigan, Ph.D.	, The	pretical Physical C	hemist LTB, NCI
Other Professional Pers	sonnel:		
Akinori Sarai, Ph.D., Bruce Shapiro, Ph.D.,	Vis: Comp	iting Associate outer Specialist	LTB, NCI IPS, LTB, NCI
COOPERATING UNITS (# any) Dr. Ruth Nussinov, Inst Tel Aviv University, Te Frederick, MD	titute of Molecula el Aviv, Israel; I	ar Medicine, Sackle )r. Jacob Mazur, Pr	r Faculty of Medicine, ogram Resources, Inc.,
LAB/BRANCH	Laboratory of Ma	athematical Biology	
SECTION			
	Office of	the Chief	
INSTITUTE AND LOCATION	NCI, NIH, Beth	iesda, MD 20892	
TOTAL MAN-YEARS: 0.8	PROFESSIONAL: 0.7	OTHER:	1
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	] (b) Human tissues	⊠×(c) Neither	В
SUMMARY OF WORK (Use standard unreduc	ced type. Do not exceed the spa	ce provided.)	
_			
Conformations of DNA sp to the left handed 2 spectrum of conformatic variations in the vici or not these variations have investigated sol	pan a wide range, 2-form. Recently ons possible. Spe inity of the B-for s are large enough lvent effects on	from the usual Wat it has become clea cifically there a rm. It is interest to affect recog the DNA conformati	son-Crick B-form helix r that there is a broad re sequence dependent ing to consider whether nition processes. We ons and have found that
some specific sequences Experimentally these electrophoresis and woo good fit to a set (VT+A+X), and (VA3T3X) constructed for these 25, a slightly smaller and a nearly straigh axis of each of these of	bent DNA's exhi ld yield a higher of experiments , where V and sequence yield a radius super-hel ht rod. The momen conformations app	bends and some othe bit anomolously rapparent molecula on the sequences X are G or C. broad super-helix ix, a very tightly nt of inertia about ears to be closely	<pre>slow migration in gel slow migration in gel r weight. We obtain (VA4T4X); (V2A3T3X2); The models we have of radius 120 A for i = coilecd super-helix, the smallest principal related to the apparent</pre>



				PROJECT NUM	BER	
DEPARTMENT OF HEALTH A	IND HUMAN SEH	VICES - PUBLIC HE	ALTH SERVICE			
NOTICE OF INT	RAMURAL R	ESEARCH PROJ	ECT			
				Z01 CB	08372-04	LTB
PERIOD COVERED	October 1,	1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	s. Title must fit on on Molec	e line between the bord ular Recognit	ers.) Lion of DNA			
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel	below the Principal Inve	stigator.) (Name, title, labor	atory, and institute	affiliation)	
Akinori Sarai, Ph.D.,		Visiting	Associate		LTB,	NCI
Other Professional Pe	rsonnel:					
Robert Jernigan, Ph.D	• ,	Theoretic	al Physical Ch	emist	LTB,	NCI
COOPERATING UNITS (if any)						
Yoshinori Takeda, Ph.	D., Program	Resources Ir	c., Frederick.	Md.	LTB.	NCI
	ory rrogram		, rederica,		110,	NO1
	Laborato	ry of Mathema	tical Biology			
SECTION	0	ffice of the	Chief			
INSTITUTE AND LOCATION	NGT N					
	NCI, N	IH, Bethesda,	MD 20892			į
TOTAL MAN-YEARS: 1.0	PROFESSIONAL:	1.0	OTHER:	0.0		
CHECK APPROPRIATE BOX(ES)						
🔲 (a) Human subjects	(b) Huma	n tissues	🕈 (c) Neither	D		
(a1) Minors				D		
(a2) Interviews						
SUMMARY OF WORK (Use standard unree	duced type. Do not e	exceed the space provid	ed.)			
The binding of Cro rep	pressor to	the synthetic	operator DNA	has been	studied	Ъy
systematic base sub:	stitutions.	From this	data we deduce	specific	interacti	ions
between Cro and the op	perator DNA	and estimate	the energetic	contribut	ion of e	each
interaction to the	specific	binding. Su	ch studies c	learly sh	now that	the
recognition of speci:	fic DNA s	equences by	Cro represso	r is med	liated by	/ a
combination of bi-dem	ntate H-bon	ds between aπ	ino acid side	chains and	base pai	Irs,

recognition of specific DNA sequences by Cro repressor is mediated by a combination of bi-dentate H-bonds between amino acid side chains and base pairs, and hydrophobic interactions with thymine's methyl groups as exposed within the DNA major groove. Losses of such H-bond or hydrophobic interactions reduce the binding free energy by 0.9 to 3.1 Kcal/mol or 0.8 to 1.6 Kcal/mol, respectively. The free energy changes are principally additive for the specific binding, but not additive for nonspecific binding. These interactions described here are not only the specificity determinants in the sequence recognition, but also provide a large part of the binding free energy for the specific interaction of Cro repressor with DNA.



	PROJECT	NUMB	R		
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE					
NOTICE OF INTRAMURAL RESEARCH PROJECT					
	Z01	CB (	08374-	03	LTE
October 1, 1986 to September 30, 1987					
TITLE OF PROJECT (80 characters or less. Title must fit on one line petween the borders.) Membrane Fusion: Structure, Topology, and Dynamics of Tig	ght and	Gap	Junc	tio	ns
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laborat	tory, and ins	titute a	filiation)		
Pedro Pinto da Silva, Ph.D., Chief, Membrane Biology Sect	ion,		LTB,	NC	I
Other Professional Personnel:					
Kazushi Fujimoto, Ph.D, Visiting Fellow			LTB,	NC	I
COOPERATING UNITS (// any)					
LAB/BRANCH Laboratory of Mathematical Biology					
SECTION Membrane Biology Section					
INSTITUTE AND LOCATION NCI, FCRF, Frederick, MD 21701					
TOTAL MAN-YEARS: 1.0 PROFESSIONAL: 1.0 OTHER: 0					-
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	В				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)					
We studied the dynamics of in vitro proliferation of tight rat small intestine epithelia. The structure of the strands preparations and in published micrographs. Our aim is to general model for the structure of the tight junction morphological data and accounts for permeability charact epithelia. The work is both experimental and analytical. the massive in vitro assembly of junctional strands by in tissue (rat prostate, rat small intestine, toad bladder) in at 37°C. The tissues are then freeze-fractured, repli Detailed morphological analysis includes the examinatio comparison of the strands of tissues exposed to conditions alteration of the strand itself (lipid perturbers, solvent	juncti is re adva that e eristi To thi cubati a var cated n of s that s, che	on anal nce xpla cs s en on iety and tere ma lati	stran yzed furt ins p of d d we of e of b exa o-pai y le ng ag	ds in c her rese iven indu xcis uffe mine rs a ad ents	in our ent rse uce sed ers ed. and to s).



DEPARTMENT OF HEALTH A	ND HUMAN SERV	ICES - PUBLIC HE	ALTH SERVICE	PHOJECT NU	MBER
NOTICE OF INT	RAMURAL RE	SEARCH PROJ	ECT	501 05	00075 00 100
PERIOD COVERED			20 1007	201 CE	3 08375-03 LT
	October 1,	1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	Fra	acture-Perme	ation		
PRINCIPAL INVESTIGATOR (List other pro	lessional personnel be	low the Principal Inves	stigator.) (Name, title, labora	tory, and institu	te affiliation)
		. C. M. I.			
Pedro Pinto da Silva,	Ph.U. Ch	ier, Memoran	e Biology Sect:	lon,	LIB, NCI
Other Professional Per	sonnel:				
Maria L.F. Barbosa, Ph	n.D., Ser	nior Staff F	ellow		LTB, NCI
Catarina. Forsman, Ph.	.D., Vis	siting Fello	w		LTB, NCI
COOPERATING UNITS (if any)					
Dr. J. Chevalier, Dr.	D. Appai, &	Dr. J. Bari	ety, Department	of Rena	l and
Vascular Pathology, Br	oussais Hos	pital (INSER	M/Unit 20/, Pai	ris, Fran	
	Laboratory	y of Mathema	tical Biology		
SECTION	Memb	rane Biology	Section		
INSTITUTE AND LOCATION	NGT ECH	F. Frederick	MD 21701		
TOTAL MAN-YEARS	PROFESSIONAL	F, Frederick	, MD 21701		
.5		.5	0		
CHECK APPROPRIATE BOX(ES)	(b) Human	tissues X	K (c) Neither		
(a1) Minors	(b) (ib)			В	
(a2) Interviews	turned type. Do not over	and the sease provide			
			.,		
Fracture-permeation is	a new tech	nique develo	ped in our labo	oratory t	o probe the
compactness of the	cytomatrices	s in gluta en size are	raldehyde-fixed	i cells. Sess the	In tracture- mesh of
chemically-fixed matr	ix. Fractu	ire-permeati	on of rat ca	ardiac mu	scle revealed
details of the organiz	ation of mit	cochondria,	in particular	r variat	ions in the
compactness of the	th cationize	rial matrix ed ferritin	. In other	experime	cular spacing
in the extracellular	matrices of	rat kidney	glomeruli: the	basement	membrane and
the mesalgyal matrix.	We have als	so devised a	variant of t	the abov	e permeation
freeze-fractured. Th	is alternation	yde-rixed tive method	duplicated t	the resu	ilts of the
fracture-permeation t	echnique es	stablishing	the distribut	ion of i	ntermolecular
spaces in sarcomeres o	of striated r	nuscle and t	he structure of	of the	mitochondrial
mattix.				·	



		PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJECT	
REBIOD COVERED		Z01 CB 08376-03 LTB
PERIOD COVERED	October 1, 1986 to September 30, 198	7
TITLE OF PROJECT (80 cheracters or less	. Title must fit on one line between the borders.)	
Fracture	e-Label: Cytochemistry of Freeze-Frac	ture Cells
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Investigator.) (Name, title, lab	pratory, and institute affiliation)
Pedro Pinto da Silva,	Ph.D. Chief, Membrane Biology Sec	tion, L <mark>TB</mark> , NCI
Maria L.F. Barbosa, Ph Catarina. Forsman, Ph	n.D., Senior Staff Fellow D., Visiting Fellow	LTB, NCI LTB, NCI
COOPERATING UNITS (If any) Dept	. of Renal and Vascular Pathology, B	roussais Hosp. (INSERM/
unit 28), Paris, Franc	e (J. Chevalier, D. Appai, J. Bariet	y); Institute of Genera
Pathology, Univ. of Ro	ome School of Med., Rome, Italy (M.R.	Torrisi, A. Pavan);
LAB/BRANCH	. of Montreal School of Med., Montre	ar, canada (r.w.k. kan)
	Laboratory of Mathematical Biology	
SECTION		
	Membrane Biology Section	
INSTITUTE AND LOCATION	NCI ECRE Erederick MD 21701	·
TOTAL MAN-YEARS:	PROFESSIONAL: OTHER:	
.5	.5 0	
CHECK APPROPRIATE BOX(ES)		
(a) Human Subjects	$\Box$ (b) Human tissues $L_{xx}(c)$ Neither	
(a2) Interviews		D
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the space provided.)	
_		
We used preparative fr	eeze-fracture to crush glutaraldehyd	e fixed tissues after
impregnation in cryc	protective solution. The fragments	were thawed and labeled
fracture-permeated wit	b native ferritin and with cationize	d ferritin (see Project
Number ZO1 CB 08375)	. In autonomic ganglia, primary	sensory ganglia and
peripheral nerves, fra	icture-label provides access to all p	lasma and intracellular
membranes as well as e	extracellular matrices. Con A, WGA a	nd cationized ferritin
intensely labels the	e basal membrane. Furthermore, con	A and WGA appears to be
localized to synaptic	vesicles and the synaptic complex.	
We worked also with ra get generalized acce	nt glomeruli where freeze-fracture wa ess to the cell surfaces. This	s used as a means to new approach by-passes
successive permeabilit	y barriers (endothelial cells, basem	ent membranes) that had
to be passed in pr	evious cytochemical studies of th	e glomerulus. In human
partition of the tr	ansmembrane proteins which contain	these antigens. During
freeze- fracture, the	T4 antigen partitions completely wit	h the protoplasmic half
of the membrane, ga	ive an indication of its association	with components of the
membrane skeleton or o	of the cytoskeleton.	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - DUBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMIDAL DESEADCH DO IECT	
NOTICE OF INTRAMORAE RESEARCH PROJECT	Z01 CB 08377-03 LTE
PERIOD COVERED October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must lit on one line between the borders.) The Role of Myoglobin in Oxygen Transpo	rt
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, labora	atory, and institute affiliation)
David G. Covell, Ph.D. Senior Staff Fellow	LTB, NCI
Dr. John Jacquez, Department of Physiology & Biostatistics, Michigan, School of Medicine; Dr. Paul Ponganis, Scripps In Oceanography, Physiological Research Laboratories, La Jolla	University of stitute of , California
LAB/BRANCH Laboratory of Mathematical Biology	
SECTION Office of the Chief	
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS: 0.05 PROFESSIONAL: 0.05 OTHER: 0.	0
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews	
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
We have examined the role of myoglobin to facilitate oxygen mitochondria in skeletal muscle by constructing computer sin Steady state mitochondrial oxygen consumption under diffe supply PO <sub>2</sub> 's in a system with and without myoglobin one-dimensional slab of tissue. Oxygen consumption by saturable with the mitochondria located in bands at uniform the tissue. Under these conditions, myoglobin provides a mu oxygen transport for supply PO <sub>2</sub> 's below 10 torr and diffu for skeletal muscle fibers. We conclude that only under hypoxia lowers P below 10 torr does myoglobin begin to increase in oxygen delivery to mitochondria.	diffusion to active mulation experiments. erent conditions of were examined for a y mitochondria was intervals throughout easurable increase in sion lengths expected circumstances where provide a measurable
267	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT	NUMBER	
NOTICE OF INTRAMURAL RESEARCH PROJECT			
	Z01	CB 08378-03	LTB
PERIOD COVERED			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)			
Label-Fracture			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Neme, title, lebora	itory, and ins	stitute affiliation)	
Pedro Pinto da Silva, Ph.D., Chief, Membrane Biology Sec	ction,	LTB, NCI	
Other Professional Personnel:			
Catarina Forsman Visiting Fellow		LTB, NCI	
		,	
		11.110	
unit 28), Paris, France (J. Chevalier, D. Annai, J. Bariety	): Inst	Hosp. (INSE	RM/
Pathology, Univ. of Rome School of Med., Rome, taly (M.R.	7, inst Torrisi	. A. Pavan);	eran
Dept. of Anatomy, Univ. of Montreal School of Med., Montreal	l, Cana	da (F.W.K. K	an)
LAB/BRANCH			
Laboratory of Mathematical Biology			
Membrane Biology Section			
INSTITUTE AND LOCATION			
NCI, FCRF, Frederick, MD 21701			
O 5 O S O S			
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects (b) Human tissues $\Box_x \pm c$ Neither			
	В		
SUMMARY OF WORK (Use standard unreduced type, Do not exceed the space provided )			
The development and application of label-fracture cytochemis label-fracture cells fixed or unfixed are labeled and to Label-fracture permits the observation in a single, of distribution of surface receptors and antigens superimposed casts of freeze-fractured membranes. The resolution (Snm at the molecular level. Normal human lymphocytes were monoclonal anti-T3 and anti-T4 antibodies before and after of glutaraldehyde. In this work the experiments are desi antigens on the surface, their relation to intramembrane pe freeze-fracture and their dynamics during capping. We show glycoproteins are associated to IMP domains they do not cons- subset recognizable as a specific cluster of IMPs after capping.	stry wa chen fr coincid d on co ttainab label- chemica igned t article w that stitute ping.	s pursued. eeze-fractur ent image nventional P le) approac fractured w l fixation o map T3 and s revealed while T3 and a structu	In ed. the t/C hes ith by T4 by T4 ral
membranes. We used synaptosomal membrane preparations from binding sites of concanavalin A and WGA-ovomucoid-gold on t mainly to IMP domains.	rat br the sur	ain and sho face associa	wed ted



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT	Z01 CB 08379-03 LTB
PERIOD COVERED October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Multicompartmental Analysis of Calcium Metab	polism
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator ) (Name, title, labore	tory, and institute affiliation)
David G. Covell, Ph.D. Senior Staff Fellow	LTB, NCI
Dr. Alfred Yergev. Lab. Theoretical & Phys. Biol	ogy. NICHD
LAB/BRANCH Laboratory of Mathematical Biology	
SECTION Office of the Chief	
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892	
TOTAL MAN-YEARS. 0.1 PROFESSIONAL: 0.1 OTHER:	0.0
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors	В
(a2) Interviews     SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
Abnormal calcium metabolism in adolescent children and postr	nenopausal women can
have devastating consequences. The objective of this stud kinetics of calicum metabolism in normal children and to eva	ly is to elucidate the aluate disease related
changes in calcium metabolism in children and adults. St were administered to children and women of childbearing age	able calcium isotopes and serial samples
were obtained for two to four days. Two stable isotopic these studies: one given orally and one given intravenously	tracers were used in The use of two
tracers allows direct measurement of several important	parameters of calcium
endogenous fecal excretion. Thermal ionization isotope ra	atio mass spectrometry
was used to develop a multicompartmental model of calcium r	netabolism that better
Characterized calcium metabolic lidkes between regions of a	
·	
272	



DEPARTMENT OF HEALTH A	NO HUMAN SERVICES - PUBLIC HE		PROJECT NUME	BER	
NOTIOE OF INT	DAMURAL RESEARCH POBLIC HE	ACTH SERVICE			
NOTICE OF INT	HAMUHAL RESEARCH PROJ	ECT	701 00	00000 00	7 77 0
PERIOD COVERED	· · · · · · · · · · · · · · · · · · ·		201 CB	08380-03	LIB
	October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the bord	ers.)			
Molecular Structur	re of Animal Viruses and	Cells by Compu	itational .	Analysis	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inve	stigator.) (Name, title, labora	tory, and institute	affiliation)	
Jacob V. Maizel, Jr.,	Ph.D. Chief, Laborat	ory of Mathemat	ical Biolo	ogy,	NCI
Other Professional Per	rsonnel:				
Devjani Chatterjee, Ph	n.D. Visiting Assoc	iate		LTB,	NCI
John Owens	Computer Speci	alist		LTB,	NCI
Ruth Nussinov, Ph.D.	Consultant Chief Image D			LTB,	NCI
Lewis Lipkin, M.D.	Unier, Image P	rocessing Section	on	LIB,	NCI
COOPERATING UNITS (if any)					
Dr. George Vande Woude	e. Basic Research Progra	m, Litton Bione	etics, Inc		
Frederick, Maryland	,		· ·	, 	
LAB/BRANCH	Laboratory of Mathema	tical Biology			
SECTION	Office of the	Chief			
INSTITUTE AND LOCATION	NCI /ECRE Endoniel	MD 21701			
	NCI/FORF, Frederick	, MD 21701			
S.5	4.5		L		
CHECK APPROPRIATE BOX(ES)	A				
🔲 (a) Human subjects	(b) Human tissues	<sup>jx x</sup> (c) Neither	P		
☐ (a1) Minors ☐ (a2) Interviews			В		
SUMMARY OF WORK (Use standard unred	Juced type. Do not exceed the space provid	ad.)			
Dicorponing course	discasses tupified by	polio colo		titie	and
foot-and-mouth diseas	ses. Sequences of th	ese viruses h	ave been	examined	for
relationships among th	nem and to other known a	nd hypothetical	proteins	. Second	tary
structures of the RM	NAs have been found to v	ary in correlat	ion with y	pathologi	icaĺ
and sequence difference	es.				
	at with a seal the word	austandina aa	lu overt		
Adenoviruses are studi	the coll's motabolism	erstanding ear	Ty events	s in vi	and
late events during	which assembly and m	orphogenesis o	ccurs.	Early vi	iral
proteins, whose exist	ence was known from bio	chemical studie	es, have be	een analy	zed
by comparing their sec	quences to cellular prot	eins of known f	unction.		
Techniques of biochemi	istry, virology, electro	n microscopy ar	id compute	er analy	ysis
are used to stud	ly sequences of pi	cornaviruses,	adenovir	uses, hu	ıman
immunodeficiency virus	ses and genes. Analyses	of proteins ar	id nucleic	acids 1	nave
been developed and in	nplemented. Graphic rep	resentations re	vealing. h	omology,	and
reverse complementarit	ro splicing promotor	c and recombin	ation in a	predict	acid
molecules. Programs a	are developed locally an	d elsewhere for	applicat	ion on (	Crav
XMP, VAX and graphi	ic workstations to per	form sequence a	analysis an	nd struct	ture
predictions. Methods	to assess the significa	nce of predicti	ons use M	Monte Ca	arlo
simulations, evolution	onary comparisons and	biochemical dat	a. Prote	in second	lary
structure is being pre	edicted from amino ac	id sequences.	New see	quences	are
compared with computer	rized databases to detec	t relationships	With know	wn prote:	ins.



	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INTRAMURAL RESEARCH PROJECT	
	Z01 CB 08381-04 LTB
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must lit on one line between the borders.) Computer Aided Two-Dimensional Electrophoretic Gel An	nalysis (GELLAB)
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, lebora	tory, and institute affiliation)
Peter Lemkin, Ph.D. Computer Specialist	IPS, LTB, NCI
Other Professional Personnel:	
Lewis L. Lipkin, M.D. Chief, Image Processing Section Morton Schultz Senior Engineer	LTB, NCI IPS, LTB, NCI
COOPERATING UNITS (if any)	
Dr. Eric Lester, Univ. of Tenn. Medical School; Dr. Peter So Univ. Zurich Medical School.	ondregger,
LAB/BRANCH Laboratory of Mathematical Biology	
SECTION Image Processing Section	
INSTITUTE AND LOCATION Frederick Cancer Research Facility, Frederick,	MD 21701
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	0
CHECK APPROPRIATE BOX(ES)	
☐ (a) Human subjects ☐ (b) Human tissues ⊠ (c) Neither ☐ (a1) Minors ☐ ☐ (a2) Interviews	3
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
CELLAR is a computer based system for the analysis of a set	of 2D electrophrotic
gels. It incorporates sophisticaed subsystems for in	nage acquisition and
processing, data base manipulation and graphics as well as s	statistical analysis.
It has been applied to a variety of experimental systems	in which quantitative
and qualitative changes in one or more proteins among hundre	eds or thousands of
unaltered proteins is the basic analytic problem. Kee	eping track of changes
It has been applied to helping analyze a set of gels from	adult human leukemias
as well as axonal proteins synthesized during axonal regener	cation. The objective
of creating an exportable version of GELLAB (one that w	vill run on reasonably
powerful workstation microcomputers — affordable by a l	aboratory) is being
actively pursued.	
Much of the time this past year was spent upgrading soft	ware and hardware from
the TOPS10 environment to UNIX - moving our part of the labor	ratory from Rockville
to Frederick/FCRF and in bringing up various elements	s on the FCRF/LTB-ASCL
network.	
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			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PRO	JECT	701 CB 08382-04 ITB
PERIOD COVERED			201 CB 00302-04 LIB
0	ctober 1, 1986 to Sept	ember 30, 1987	
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the bo	ders.)	
System Softwar	e for Protein and Nucl	eic Acid Structu	re Analysis
Bruce Shapiro, Ph.D.,	Computer Speci	alist	IPS, LTB, NCI
Other Professional Pers	onnel:		
Lewis L. Lipkin, M.D.	Chief, Image P	rocessing Sectio	n LTB, NCI
Peter Lemkin, Ph.D.,	Computer Speci	alıst -	IPS, LTB, NCI
Jacob V. Maizel, Jr., P	h.D. Chief. Laborat	orv of Mathemati	cal Biology NCI
	,	,	
COOPERATING UNITS (if any)			1 5 1 1
Dr. Ruth Nussinov, Inst	itute of Molecular Med	cob Mazur Progr	aculy of Medicine
Frederick, MD.	I AVIV, ISLAEL, DL. JA		am Resources, inc.
LAB/BRANCH	Laboratory of Mathema	tical Biology	
SECTION	Image Processing	Section	
INSTITUTE AND LOCATION			
	NCI, NIH, Bethesda,	MD 20892	
TOTAL MAN-YEARS:	PROFESSIONAL: 2.5	OTHER:	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues x	🗴 (c) Neither	В .
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space prov	ded.)	
Work on nucleic acid st	ructures has continu	ed to evolve	with a variety of
collaborations and di	rections. Among the	se include DNA s	vstem that detects
structural features i	n DNA and the use of a	2-dimensional	version of the system
for comparing multiple	sequences. Futher stu	dies have ensued	related to curved
B-DNA in attempting	to relate predicted cu	rved sequences t	o their experimental
gel moblility (with Jer	nigan, Sarai and Nussi	nov). Energeti	c calculations are
progressing using the	models suggest for cu	rved DNA.	re accurate rules to
course then the current	modelo baggebt for th		
The DNA structure analy	sis program has also b	een enhanced to	include rules for
DNA melting. Using thi	s and mutation data to	r procaryotic pr	omoters research was
done on now DNA local e	nergy characterics are	related to prom	loter activity.
The one-dimensional str	uctural analysis progr	am mentioned at	ove has also been
paritally translated	to C to run on the SUN	's and/or VAXES.	Also, this program
Calladine/Dickerson rul	ty to generate 5-D coo	roinales for b-r	MA Dased upon the
Satradine, prenerson rur			
Work is also progressin	g on a new similarity	alogorithm that	will both pictorally
an quantitatively indic	ate when RNA secondary	structures are	similar with also
the possibility of deve	loping consensus struc	cures.	
Work is accelerating	on the development o	f a nucleic acid	l expert system which
would be directed to	both intelligent que	ries by resear	ch and non-ad hoc
structuring of relati	onships that exist b	etween the vario	ous software/hardware
complexes available at	the rrederick tancer k	escarch racifit;	•



DEPARTMENT OF HEALT	TH AND HUMAN SI	ERVICES - PUBLIC H	EALTH SERVICE	PROJECT NU	MBER	
NOTICE OF	INTRAMURAL	RESEARCH PRO	DJECT	Z01 CB	08384-01	ĨТВ
PERIOD COVERED	October 1	l, 1986 to Se	ptember 30, 1987		00504 01	
TITLE OF PROJECT (80 characters of	r less. Title must fit on	one line between the bo	rders.) Somal DNA			
PRINCIPAL INVESTIGATOR (List othe	er professional personn	el below the Principal In	vestigator.) (Name, title, labora	atory, and institut	e affiliation)	
James L. Cornette,	Ph.D.	IPA Investiga	ator	LTB, NCI		
COOPERATING UNITS (if any)						
Charles DeLisi, Dir	ector for He v	alth & Enviro	onmental Research	n,		
and poper of more	,					
LAB/BRANCH	Laborat	ory of Mather	natical Biology			
SECTION		Office of the	e Chief			
INSTITUTE AND LOCATION	NCI,	NIH, Bethesda	a, MD 20892		-	
TOTAL MAN-YEARS:	PROFESSIONA	L: 0.5	OTHER:			
CHECK APPROPRIATE BOX(ES)						
(a) Human subjects	🗌 (b) Hum	nan tissues	K (c) Neither B			
(a2) Interviews						
SUMMARY OF WORK (Use standard	unreduced type. Do no	ot exceed the space pro	nded.)			
In steps towards investigators are	the major developing	goal of sec ; partial ma	uencing the hi ips of chromoso	uman gen omal DNA	ome, sev . Libra	eral ries
consisting of clone	s of overlap	ping DNA frag	ments exist in a	several as they	laborator	ies.
original DNA, thus	obtaining se	quences of or	verlapping fragme	ents that	cover 1	arge
segments of the partial digestion o	DNA. The o f the DNA by	verlapping ti a single en:	agments may be or some or total dig	priginall gestion b	y obtaine y two or i	d by more
enzymes used indiv	idually. A	critical requ	irement is that	the frag	ments be	of a
identify as many	pairs of ov	erlapping fra	igments as possil	ole; theo	retically	, if
the library covers	the chromo	somal DNA a	and all interse	ecting p aching fr	airs can	be d of
the DNA to the othe	r would be o	btained. Ide	entification of o	overlappi	ng pairs	may
be made by observ fragment of the pai	ing a common r is digeste	pattern of i d with a cert	estriction fragment	ment leng ternative	ths when a lv. the	each same
subset of a pane	1 of probe	s (complement	ary DNA fragment	ts) may b	ind speci	fied
model DNA, we ar	ent of the p e evaluating	several of t	hese procedures	to deter	quence a mine whic	s a h of
them should lead to	the highest	of ordering	coverage of the	original ne fewes	chromos t number	ome, of
experimental steps.		er erdering	,,	10.00		



			PROJECT NUMBER		
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE					
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT			
			Z01 CB 08385-01 LTB		
	October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the border DNA Conformations in C	ontrol Regions			
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	stigator.) (Name, title, labore	tory, and institute affiliation)		
Robert L. Jernigan, Ph	n.D., Theoretical	Physical Chem	ist LTB, NCI		
Hanah Margalit, Ph.D.	, Visiting Fe	llow	LTB, NCI		
John Owens, Ph.D.,	Microbiolog	ist	LTB, NCI		
			,		
Dr. Ruth Nussinov, Ins	stitute of Molecular Med	icine. Sackler	Faculty of Medicine		
Tel Aviv University, 1	Cel Aviv, Israel.	reine, buckter	raculty of neutrine,		
LAB/BRANCH	Laboratory of Mathema	tical Biology			
SECTION	Office of the	Chief			
INSTITUTE AND LOCATION	NCI, NIH, Bethesda,	MD 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
0.8	0.8	0			
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews (b) Human tissues (c) Neither (c) Neither					
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	əd.)			
Extracting details of	the mechanism of promot	er function	in transcription has		
been widely studied.	We have chosen to lo	ok at one of the	he simplest aspects of		
Specifically, the st	ability of the DNA	double helix	was determined in the		
vicinity of the promot	er by computing the fre	e energy for st	rand separation as a		
function of dinucle	otide free energy va	lues taken fi	rom the calorimetric		
regions was studied w	within a window of $+/-2$	50 nucleotides	on either side of the		
mRNA start sites. We	found that for this set	of promoters	the -10 region was		
significantly the le	ast stable. We also	compared the	e free energies of 121		
promoter mutations wit	hin the $-35$ and $-10$ reg	ions with the I	free energies of their		
corresponding wild typ	be sequences and found a	correlation be	etween the free energy		
region with increased/decreased promoter activity were observed to be less/more					
stable than the wild types.					
		•			
	284				



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE			PROJECT NUMBER	
NOTICE OF INTRAMURAL RESEARCH PROJECT				
Z01 CB 08386-01 L7				
	October 1, 1986 to Se	ptember 30, 1987		
TITLE OF PROJECT (80 characters or less Analyses of	Tille must fit on one line between the the cDNA Clones for	borders.) B 1-4 Galactosylt	rasferase.	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal	Investigator.) (Neme, title, lebora	atory, and institute affiliation)	
Pradman K. Qasba, Ph.D	. Research Che	mist	LTB, NCI	
Other Professional Per	sonnel:			
Anil Puri, Ph.D.	Visiting Fel	low	LTB, NCI	
COOPERATING UNITS (if any)				
Dr. M. Braun, Fredrick	Cancer Research Cent	er, Frederick Mar	yland	
LAB/BRANCH	Laboratory of Mathe	matical Biology		
SECTION	Office of th	o Chiof		
INSTITUTE AND LOCATION	Office of th			
	NCI, NIH, Bethesd	a, MD 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
CHECK APPROPRIATE BOX(ES)	_			
(a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues	k (c) Neither B		
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space pr	ovided.)		
A specific glycosyltra	nsferase is required	for the synthesis	are referred to as	
glycoconjugates. Gal.	actsyltransferases (	gal-transf), a	subgroup of the	
transferases, constit	ute a family of e	nzymes which tr	ansfer galactose from	
UDP-gal to the non-	-reducing residues	of oligosacch ides. We have in	arides of various	
cloning approach to	understand the modu	lation of the	gal-transf activity,	
essential for genera	ting specific cell-s	urface antigenic	determinants. In our	
previous studies on the gene structural analyses of alpha-lactalbumin, a modifier				
interacts with gal-tra	nsf is coded entirely	by a separate	exon. We have now	
cloned and sequenced cDNA coding for bovine ClcNAc 1-4 gal-transf. Analysis of				
several sequence-related cDNA clones showed: 1) There are atleast two chromosomal				
share common nucleot	ide sequences encod	ing the protein	is with the same	
carboxy-terminal end	of 120 residues and	share same 3'non	coding sequence. One	
synthesized as a	proprotein and secr	eated as cleave	d product which is	
enzymaticaly active; 4	) Sereis of poly(A) s	ites present in t	he gene sequence are	
utilized to generate	) The cDNA clones whi	ch have different	nucleotide sequence	
at the 5'end compared	to the clones coding	for the 1-4 gal-	transf, do not encode	
any protein sequence i	n any of the three op	en reading frames	suggesting that they	
may represent unspliced precursor mkNAS; 6) The nucleotide sequence analysis of several related cDNA clones suggest that a complex alternative processing of the				
precursor mRNA occurs	precursor mRNA occurs to generate gal-transf mRNAs.			



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE					
NOTICE OF INTRAMURAL RESEARCH PROJECT					
Z01 CB 00853-34 LP					
October 1, 1986 to Sept	ember 30, 1987				
TITLE OF PROJECT (80 cheracters or less	. Title must fit on one line between the borde	rs.)			
Surgical Pathology	fessional personnal below the Principal Invasi	tigator.) (Neme title labore	ton, and institute affiliation)		
PI: M.J. Merino	Chief, Surgical Pathology	y Section	LP N	ICI	
OINER: (see next page)					
COOPERATING UNITS (if any)					
LAB/BRANCH					
SECTION		···· // /// ··· / · · · · · ·			
Surgical Pathology Sect	ion				
NCI. NIH. Bethesda. MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		-	
	20	0			
CHECK APPROPRIATE BOX(ES)       (a) Human subjects       (b) Human tissues       (c) Neither       (a1) Minors       A					
SUMMARY OF WORK (Use standard unred	Juced type. Do not exceed the space provide	d.)			
The Surgical Pathology Sector	Section, together with the	ne Cytopatholog	y Section, Ultra-	-	
in anatomic pathology for	or the Clinical Center pa	atients and col	laborate with the	e e	
research staff of all in	stitutes in those invest	tigations which	involve the use		
and study of human patho	constructed adjacent to	trozen section	and surgical path	101-	
been in use since April, 1983. This new facility has greatly enhanced processing					
of specimens and communication of diagnostic findings with attending physicians.					
room to facilitate communication.					
The staff is actively engaged in a variety of projects involving clinicopatho-					
Clinical Center. Up-to-date immunocytochemical techniques have been applied to					
the study of tumors and other non-neoplastic diseases. The use of immunohisto-					
and with the increasing	number of monoclonal and	tibodies availa	ble this techniqu	ises ie	
should have even greater	r value in diagnostic and	d research path	ology. A major		
space allocated for peri	logy laboratory is in the formance of special stain	e planning stag ns and immunocy	;e. This will inc tochemistry.	lude	



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER	
NOTICE OF INTRAMURAL RESEARCH PROJECT				
			Z01 CB 09145-03 LP	
PERIOD COVERED	ember 30 1987			
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	ərs.)		
Neuropathology				
PRINCIPAL INVESTIGATOR (List other pro	ofessionel personnel below the Principal Inves	stigetor.) (Neme, title, lebora	tory, end institute affilietion)	
PI: D.A. Katz	Neuropatho	logist	OCD NINCDS	
COOPERATING UNITS (if any)				
Surgical Pathology and	Postmortem Section LP	NCT		
Ultrastructural Patholo	gy Section, LP, NCI	NOT		
LAB/BRANCH				
Office of the Clinical	Director, NINCDS			
SECTION				
INSTITUTE AND LOCATION				
NINCDS, NIH, Bethesda,	MD 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
	1			
(a) Human subjects (a1) Minors (a2) Interviews	☑ (b) Human tissues	(c) Neither	•	
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the space provide	ad.)	A	
As described previously	, subspecialty expertise	in diagnostic	neuropathology is	
provided to the Laborat	ory of Pathology, NCI, a	nd to all other	: institutes, via	
integrated with the Sur	cal Director, NINCDS. T	he neuropathold	by service is	
structural Pathology Se	ction. Within the Labor	atory of Pathol	logy, both diagnostic	
(patient care) service	and teaching (of patholog	gy residents) a	ire provided. The	
service also functions	in a collaborative manne	r to provide ne	europathological	
expertise in a wide ran	ge of clinicopathologic :	investigations.	,	
	302			



DEPARTMENT OF HEAL	TH AND HUMAN S	SERVICES - PUB	LIC HEALTH SERVICE
NOTICE OF	INTRAMURAL	RESEARCH	PROJECT

PROJECT NUMBER

## Z01 CB 09154-01 LP

PERIOD COVERED					
Uctober 1, 1986 to September 30, 1987					
Prognostic Significance of Thymidine Labelling Index in Breast Cancer					
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation	)				
PI: M.J. Merino Chief, Surgical Pathology Section	LP	NCI			
OTHER: S. Kennedy Visiting Associate	LP	NCI			
S. Swaine Senior Staff Fellow	MB	NCI			
M. Lippman Head, Medical Breast Cancer Section	MB	NCI			
Medicine Branch					
LAB/BRANCH					
Laboratory of Pathology					
SECTION					
Surgical Pathology Section					
INSTITUTE AND LOCATION					
NCI, NIH, Bethesda, MD 20892					
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:					
CHECK APPHOPHIATE BOX(ES) $(a)$ Human tissues $(c)$ Neither					
(a2) Interviews		٨			
SUMMARY OF WORK (Use standard unraduced type. Do not exceed the space provided.)					
The main purpose of the study will be to determine whether the thymidine					
labelling index could provide any significant information regarding prognosi	s				
in breast carcinoma, and to what extent the TLI could identify those patient	s				
that could have an early relapse. Until now, histologic type of the tumor					
and steroid receptor status have played an important role in the planning of					
adjuvant therapy, but we believe that the proliferation characteristics of					
tumor cells may also be a critical determinant since nuclear DNA contents in					
populations of breast cancer cells have been proven to have prognostic sig-					
nificance.					
m					
The thymidine labelling technique relies on the uptake of titrated thymidine	by				
replicating cells which is then detectable by autoradiography. We will investi-					
gate the thymidine labelling index range for different histologic types of					
therapy, the changes in TI of racidual normal brasst tiesus and the effect					
of hormonal manipulation in TI					
or normonal manipulation in the					
The rapid processing of autoradiographs allows cell kinetic data for clinica	1				
evaluation in three days, which may be a useful adjunctive diagnostic tool o	n				
selected cases.					



## DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 00852-34 LP

PERIOD COVERED					
October 1, 198	6 to September	30, 1987		······	
TITLE OF PROJECT (80 characters or lass. Titla must fit on one line between the borders.)					
EXIOTIATIVE CytoTogy Applied to numan blagnostic fromensian weselich robies PRINCIPALINVESTIGATOR (is other professional personnel below the Principal Investigator ) Name site is laboratory and institute attiliation)					
PI: E.W.	Chu	Chief, Cytopathol	ogy Section	LP NCI	
OTHER: D. So	lomon	Pathologist		LP NCI	
Y. Ye		Visiting Fellow		LP NCI	
T.A.	Wood	Biologist		LP NCI	
L. Ga	lito	Biologist		LP NCI	
A.M.	Wilder	Biologist		LP NCI	
E. Sa	nders	Bio. Lab. Tech.		LP NCI	
К. Со	ndron	Microbiologist		LP NCI	
COOPERATING UNITS (if	any)				
LAB/BHANCH	Pathology.				
Laboratory of	rachorogy				
Cytopathology	Section				
INSTITUTE AND LOCATIO	N				
NCL. NIH. Beth	esda, MD 20892				
TOTAL MAN-YEARS:	PROFE	SSIONAL:	OTHER:		
8		4	4		
CHECK APPROPRIATE B	OX(ES)				
🖾 (a) Human sut	ojects 🗌 (b	) Human tissues	(c) Neither		
🛛 (a1) Minors	5				
🗌 (a2) Intervi	ews			Α	
SUMMARY OF WORK (Us	a standard unraduced typ	e. Do not exceed the space provide	d.)		
The Cytopathol	ogy Section pr	ovides complete dia	gnostic service in exfo	liative cy-	
tology, medica	1 cytogenetics	, and fine needle a	spiration cytology. Th	e section	
also routinely	applies immun	ocytochemistry tech	niques to affirm and/or	enhance	
cytological di	agnostic effic	acy. In addition,	the section collaborate	s in various	
ing	rch projects u	cilizing special te	chniques including spec	al stain-	
Ing.					


			PROJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	
NOTICE OF IN	TRAMURAL RESEARCH PRO	JECT	
REPIOD COVERED			ZUI CB 00897-04 LP
October 1 1986 to Sent	ambar 30 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line between the bo	dars.)	
Cytological Diagnosis	of Lymphomas by Immunocy	tochemistry	
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Principal Inv	estigator.) (Neme, title, labora	tory, and instituta affiliation)
PI: D. Solomon	Pathologis	t	LP NCI
OTHER: E.S. Jaffe	Chief, Hen	atopathology Se	ction LP NCI
Y. Ye	Visiting H	ellow	LP NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Pathology	7		
SECTION			
Cytopathology Section			
INSTITUTE AND LOCATION	20802		
NCI, NIH, Betnesda, MD	20892	07450	
TOTAL MAIN-TEARS.	25	25	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors		. ,	
(a2) Interviews			A
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the space provi	ded.)	
The cytological diagnos	is of malignant lymphon	a can be extrem	ely difficult because
the cytological feature	es of the malignant cell	s in small cell	and mixed small and
large cell lymphomas ma	ly be indistinguishable	from those of r	eactive lymphoid
technique and a batter	a the userulness of the	B coll markers	to the diagnosis of
lumphome in outclogical	another we conclude	o that immunoau	to the diagnosis of
useful in the cytological	al diagnosis of non-Hod	gkin's lymphoma	Further it is
possible to diagnose th	le vast majority of lym	homas using only	v the immunoglobulin
light chain markers K a	and $\lambda$ and the T-cell man	kers Leu-1, Leu	-2, and Leu-3.
We are extending the ut	ilization of lymphoid m	arkers to fine	needle aspiration
specimens of lymph node	s. Fine needle aspirat	ion may obviate	the need for repeat
biopsies in patients wi	th recurrent lymphoma.		



DEP	ARTM	ENT OF HEALTH	AND HUMAN SERVICES - PUBLI	C HEALTH SERVICE	PROJECT NUMBER	
		INTICE OF IN	TRAMURAL RECEARCH D	POJECT		
		NOTICE OF IN	TRAMURAL RESEARCH P	RUJECI	701 CP 00129-	-02 T D
					201 CB 09128-	-03 LP
October	1.	1986 to Sep	tember 30, 1987			
TITLE OF PR	OJECT	(80 characters or le	ss. Title must fit on one line between the	borders.)		
Cytolog	ic D	iagnosis of	Carcinoma Cells in Ef	fusions Using Mon	oclonal Antibo	dies
PRINCIPAL I	NVEST	GATOR (List other p	rofessional personnel below the Principe	l Investigator.) (Name, titla, labor	atory, and institute affilietion	on)
PI:	D.	Solomon	Pathologist		L	P NCI
OTHER:	J.	Simpson	Expert		LTI	B NCI
	Y.	Ye	Visiting Fello	W	I	P NCI
	J.	Schlom	Chief, Laborat	ory of Tumor Immu	nology LTI	B NCI
			and Biology			
LAB/BRANCH Laborato SECTION	ory (	of Patholog	<u>y</u>			
LYCOPALI	NDLO	SATION				
		sthood MD	20892			
TOTAL MAN	VEARS	etilesua, HD	PROFESSIONAL	OTHER:		
I OTAL MAN	( Critic	5	25	25		
		TE BOY/ES)	•25	•25		
	uman	subjects	(b) Human tissues	(c) Neither		
	1) Mi	nors				
	2) Inf	erviews				
		K (line standard une	durad time. Do not avaged the energy	annuide of A		<u> </u>
SUMMARY U	F WOR	n (Use standard uni	euuceu type. Do not exceed the spece f	rovided.)		
m1	1					
ine cyto	logi	c diagnosis	or metastatic adenoc	arcinoma in effus	lons can be ve	ry
urrricu		NOT ONLY Ca	an maiignant ceils hav	e very bland cyto	logic features	but
reactive	e mes	sochellal ce	ells can assume a very	' atypical appeara	nce. Using th	le

We are now continuing our investigations using other monoclonal pancarcinoma antibodies. We are currently evaluating the efficacy of immunocytochemistry to discriminate between primary peritoneal mesothelioma and metastatic ovarian carcinoma.

avidin-biotin immunoperoxidase technique on cytospin preparations of pleural and peritoneal effusions, we investigated the reactivity of purified monoclonal antibody B72.3 with benign and malignant effusions. Initial effusion specimens studied were carefully selected to include only cytologically malignant effusions from patients with a history of adenocarcinoma and cytologically benign effusions from patients with no history of adenocarcinoma. Of the 78 malignant effusions studied, 90% of cases demonstrated cells with specific positive staining with B72.3. There was no detectable staining of cells in reactive effusions. We conclude that immunostaining with B72.3 is useful in the cytologic diagnosis of

metastatic adenocarcinoma in effusions.



DEPA	RTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER
	NOTICE OF INT	RAMURAL RESEARCH PROJE	СТ	
				Z01 CB 09153-01 LP
PERIOD COVE	ERED			
October	1, 1986 to Sept	ember 30, 1987	- 1	
Cutophen	atypic Apalycie	of Tumor Suspensions and	TIL Cultures	in Immunotherenu
	VESTIGATOR (List other pro	of rumor suspensions and	inator ) (Name title lebora	topy and institute affiliation)
	Terrarion (Est other pro		gator.) (Marine, title, lebora	lory, and insulate annation)
PI:	D. Solomon	Pathologist	-	LP NCI
OTHER:	Y. Yee	Visiting Fe	ellow	LP NCI
	S. Topalian	Fellow		SB NCI
	S. Rosenberg	Chief		SB NCI
	K. Condron	Microbiolog	gist	LP NCI
COOPERATIN	G UNITS (if any)			
LAB/BBANCH				
Laborato	rv of Pathology			
SECTION	-,		· · · · · · · · · · · · · · · · · · ·	
Cytopath	ology Section			
INSTITUTE AN	ID LOCATION			
NCI, NIH	, Bethesda, MD	20892		
TOTAL MAN-Y	EARS:	PROFESSIONAL:	OTHER:	
	1	• 5	.5	
CHECK APPR	OPRIATE BOX(ES)			
(a) Hu	man subjects	(b) Human tissues	(c) Neither	
□ (a1	) Minors			
(az	) Interviews			D
SUMMARY OF	WORK (Use standard unrec	lucad type. Do not exceed the space provided	1.)	
Clinical	triala amplante	or the election terreform		
lumphoau	tog to potionto	ing the adoptive transfer	or expanded to	mor infiltrating
directio	n of the Surger	Branch NCI Our colle	borative offer	underway under the
involves	immunocytochem:	ical analysis of tumor of	11 suspensions	to identify
(1) the	nercentage and i	henotypic expression of	subsets of tur	or infiltrating
lymphocy	tes present in i	the tumor and $(2)$ tumor m	arkers, if any	which are
expresse	d by the tumor	cells. Once the tumor in	filtraing lymp	hocyte cultures
have been	n expanded and a	are to be harvested for r	atient therapy	, we analyze the
material	using routine of	cytologic preparations ar	d immunocytoch	emistry to ensure
the cult	ures are free of	f tumor cells.		



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT	
PERIOD COVERED	Z01 CB 00545-09 LP
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Neme, title, lebon	etory, and institute effilietion)
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
PI: T.J. Triche Chief, Ultrastructural Pathology S	Section LP NCI
S. Scarpa Visiting Fellow	LP NCI LP NCI
COOPERATING UNITS (if any)	
LAB/BRANCH	
SECTION	
Ultrastructural Pathology Section	
INSTITUTE AND LOCATION	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	
3 3 0	
CHECK APPROPRIATE BOX(ES)	
	B
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
The type and amount of matrix proteins synthesized by human t	umor cells in vitro
appears to parallel that of cultured normal cell counterparts	to some extent. We
have broadened these observations to a variety of human tumor whether these patterns might allow more precise categorization	s to determine
origins. In addition, we are characterizing a new matrix pro	tein synthesized by
some of these tumors. The identity, function, and molecular	organization within
the extracellular matrix of this component is currently unkno	wn.
This project is now complete.	
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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	701 CB 00874-05 LB
PERIOD COVERED			201 05 00074 05 6
October 1, 1986 to Sept TITLE OF PROJECT (80 characters or less	cember 30, 1987 Title must fit on one line between the borde	ars.)	
Neurone-specific Enolas	se in Childhood Tumors		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and institute affiliation)
PI: T.J. Triche	Chief, Ultrastruc	tural Pathology	Section LP NCI
R.I. Linnoila	Medical Staff Fel	c low	LP NCI LP NCI
R. Chandra	Children's Hospit	al, Washington,	D.C.
COOPERATING UNITS (if any)			
LAB/BRANCH			
SECTION	7		
Ultrastructural Patholo	bgy Section		
NCI, NIH, Bethesda, MD	20892	1	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(C) Neitner	
(a2) Interviews			A
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	Hd.)	
The diagnosis, and thus	therapy, of solid tumo	rs of childhood	l is often difficult
due to lack of distingu	ishing characteristics.	This is espec	ially true of Ewing's
ma. We have evaluated	the presence of a speci	fic neural enzy	me, neurone-specific
enolase (NSE), in paraf	fin-embedded sections of	f a diverse gro	up of solid childhood
immunocytochemistry wit	ously unrecognized variation of the second sec	ants of neural find uniform re	tumors, employing
neural tumors with this	antibody. No cross-rea	activity with n	ion-neural tumors,
save a rare example of	differentiated rhabdomy	osarcoma, was f	ound. We conclude
of neural origin. Also	, readily detected markes	r in even primi eural bistogene	tive childhood tumors
described, "round cell"	tumor of chest wall re-	sembling Ewing'	s sarcoma, the so-
called Askin tumor, whi	ch in reality is a form	of peripheral	neuroepithelioma.
neuroepithelioma, which	is NSE-positive but wh:	ich displays hy	brid neural and
Schwannian morphologic	characteristics.		
This project is now fir	ished.		



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	PROJECT NUMBER	l .	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	701 CB 001	25-04 10	
PERIOD COVERED			201 05 071	25-04 Lr	
October 1, 1986 to Sept TITLE OF PROJECT (80 characters or less	tember 30, 1987	ars.)			
Cytogenetic Abnormalit:	ies and Oncogene Express	ion of Small, Ro	ound Cell T	umors	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	tigator.) (Neme, title, laborato	ry, and institute affi	letion)	
PI: M. Israel	Senior Investigato:	r		PB NCI	
OTHER: T.J. Triche	OTHER: T.J. Triche Chief, Ultrastructural Pathology Section LP NCI				
C. Thiele	Research Associate	0		PB NCI	
E. Gelmann	Senior Investigato	r	n	LTCB NCI	
J. Miser	Expert			PB NCI	
COOPERATING UNITS (if any)					
LAB/BRANCH					
Laboratory of Pathology SECTION	<u>y</u>				
Ultrastructural Patholo	ogy Section				
NCI, NIH, Bethesda, MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
4 CHECK APPROPRIATE BOX(ES)	4	0			
<ul> <li>□ (a) Human subjects</li> <li>□ (a1) Minors</li> <li>□ (a2) Interviews</li> </ul>	(b) Human tissues	(c) Neither		_	
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space provide	id.)		<u> </u>	
B SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) We have encountered a uniform rcp (11:22) translocation in Ewing's sarcoma. This is true of all lines and tumors examined to date (~ 20). It is not true of neuroblastoma, lymphoma, or soft tissue sarcoma. Interestingly, it is also present in a unique childhood tumor, peripheral neuroepithelioma and the closely related chest wall tumor described by Askin et al., the so-called Askin tumor. The break point on chromosome 22 is close to a known oncogene, c-sis. No amplifi- cation or rearrangement of c-sis has been detected. In the case of peripheral neuroepithelioma, c-sis is not amplified, but c-myc is. Unlike classic neuro- blastoma, N-myc is not expressed. These results serve to emphasize the common abnormality found in Ewing's sarcoma, its distinction from other round cell tumors, and the unique character of peripheral neuroepithelioma. This project is complete.					



	In AND HOMAN SERVICES		
NOTICE OF	INTRAMURAL RESEA	RCH PROJECT	
PERIOD COVERED			Z01 CB 09137-03 LP
October 1, 1986 to	September 30, 1987		
TITLE OF PROJECT (80 characters	or less. Title must fit on one line b	etween the borders.)	
Ewing's Sarcoma: D PRINCIPAL INVESTIGATOR (List of	her professional personnel below t	he Principal Investigator.) (Name, title, labora	atory, and institute affiliation)
PI: T.J. Trich	e Chief, Section	Ultrastructural Patholog on	39 LP NCI
OTHER: A.O. Cavaz	zana Guest Re	esearcher	LP NCI
S.J. Mims	Biologis	st	LP NCI
J.A. Jeffe	rson Biologi:	st	LP NC1
COOPERATING UNITS (if any)			
Dr. Samuel Navarro,	U.SSpain Coopera	ative Agreement	
LAB/BRANCH	1		
SECTION	TOBÀ	, <u></u> , <u></u> , <u></u> , ,,	
Ultrastructural Pat INSTITUTE AND LOCATION	hology Section		
NCI, NIH, Bethesda,	MD 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)	1_1/3	21	· · · · · · · · · · · · · · · · · · ·
(a) Human subjects	🖾 (b) Human tiss	ues 🗌 (c) Neither	
(a1) Minors			
SUMMARY OF WORK (Use standar	d unreduced type. Do not exceed t	he space provided.)	<u> </u>
The histogenesis of date its origins.	Ewing's sarcoma row	emains enigmatic, despit at Ewing's sarcoma, in i	ce much work to eluci- its usual state of
differentiation, la	cks any specific fo	eatures of known childho	ood tumors. Certain
lines of evidence f	rom orber srudies.	such as the presence of sarcoma and peripheral r	a reciprocal (11:22)
chromosomal translo	cation in Ewing's	our eend and perepheral .	neuroepithelioma, and
chromosomal translo similar patterns of	cation in Ewing's reactivity with pa	anels of monoclonal anti	ibodies, have
chromosomal translo similar patterns of suggested a possibl	cation in Ewing's reactivity with pa e common histogene	anels of monoclonal anti sis for these otherwise	leuroepithelioma, and ibodies, have dissimilar tumors.
chromosomal translo similar patterns of suggested a possibl Since neural tumors as dibuturul cuclia	cation in Ewing's reactivity with part e common histogenes in general are known	anels of monoclonal anti sis for these otherwise own to respond to differ factor and retinoic ac	euroepithelioma, and ibodies, have dissimilar tumors. centiating agents such bid by developing
chromosomal translo similar patterns of suggested a possibl Since neural tumors as dibutyryl cyclic features of differe	cation in Ewing's reactivity with part e common histogenes in general are kno AMP, nerve growth ntiated neural tiss	anels of monoclonal anti sis for these otherwise own to respond to differ factor, and retinoic ac sues such as neurites an	euroepithelioma, and ibodies, have dissimilar tumors. centiating agents such cid by developing nd increased numbers
chromosomal translo similar patterns of suggested a possibl Since neural tumors as dibutyryl cyclic features of differe of dense core granu	cation in Ewing's reactivity with p. e common histogene in general are kno AMP, nerve growth ntiated neural tiss les, we have treat	anels of monoclonal anti sis for these otherwise own to respond to differ factor, and retinoic ac sues such as neurites an ed a series of Ewing's s	neuroepithelioma, and ibodies, have dissimilar tumors. centiating agents such bid by developing nd increased numbers sarcoma tumor cell
chromosomal translo similar patterns of suggested a possibl Since neural tumors as dibutyryl cyclic features of differe of dense core granu lines in vitro with	cation in Ewing's reactivity with p e common histogenes in general are kno AMP, nerve growth ntiated neural tiss les, we have treat these agents under	anels of monoclonal anti sis for these otherwise own to respond to differ factor, and retinoic ac sues such as neurites an ed a series of Ewing's s r a variety of condition	neuroepithelioma, and ibodies, have dissimilar tumors. centiating agents such tid by developing nd increased numbers sarcoma tumor cell ns, alone and in con-
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PROJECT NUMBER



				PROJECT NUMBER
DEPA	RTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	
	NOTICE OF INT	RAMURAL RESEARCH PROJ	CT	
				Z01 CB 09138-03 LP
PERIOD COVE	RED			
October	1, 1986 to Sept	cember 30, 1987		
TITLE OF PRO	DJECT (80 characters or less	. Titla must fit on one line between the borda	rs.)	
In situ	Hybridization S	Studies of N-myc Expressi	on by Neurobla	stoma
PRINCIPAL IN	VESTIGATOR (List other pro	fessional parsonnel below the Principal Inves	igator.) (Name, title, labora	tory, and institute affiliation)
PI:	P. Cohen	Clinical Associate		PB NCI
OTHER:	R. Seeger	Physician in Chief,	Pediatric Hem.	-Oncol.,
		Univ. of Southern	California	
	M. Israel	Sr. Attending Physic	ian	PB NCI
	T.J. Triche	Chief, Ultrastructur	al Pathology S	ection LP NCI
COOPERATIN	G UNITS (if any)			
Departme	ent of Pediatric	Hematology-Oncology, US	C, Los Angeles	, CA
LAB/BRANCH				
Laborato	ory of Pathology	/		
SECTION				
Ultrasti	cuctural Patholo	gy Section		
INSTITUTE AN	ID LOCATION			
NCI, NIH	I, Bethesda, MD	20892		
TOTAL MAN-Y	EARS:	PROFESSIONAL:	OTHER:	
	_2 1/2	2	1/2	
CHECK APPR	OPRIATE BOX(ES)			
	man subjects	(b) Human tissues	(c) Neither	
	) Minors			
	) Interviews			B
SUMMARY OF	WORK (Use standard unree	fuced type. Do not exceed the space provide	d.)	
Neurobla	astoma, alone an	ong extra-CNS childhood	tumors, has be	en shown to express
a unique	e proto-oncogene	e, N-myc. Further, eleva	ted expression	and/or amplification
of this	oncogene has be	en correlated with adver	se clinical co	urse; no stage I or
II patie	ents express the	gene abnormally, while	over 50% of st	age III and IV
patients	do. Current w	ork indicates these pati	ents fare espe	cially poorly. None-
theless,	no work to dat	e has attempted to corre	late the expre	ssion of N-myc by
individu	al tumor cells	with stage and outcome.	Bulk techniqu	es employed to date
cannot d	listinguish a sm	all population of N-myc	expressor tumo	r cells admixed with
non-expr	essors, yet suc	h patients may prove to	have a prognos	is equally adverse
as those	with high leve	els of N-myc expression.	This might be	the case with the
N-myc ne	gative stage II	I and IV patients report	ed to date.	
	0			
The pres	ent study will	examine N-myc expression	as DNA copies	. RNA transcripts
and N-my	vc protein as de	tected by in situ hybrid	ization with r	adiolabelled DNA
fromento	of the N-myc	ene transcribed in vitr	o and hybridiz	ed to frozen
sections	of approvimate	ly 80 tumore provided by	one of us (PS	) Likowise
N-myc na	otein will be	etected immunoautochamic	ally by antiba	dies enerific for
aligonar	tide regions of	the Nerve protoin and	arry by ancibo	area of positive
tumor	alla and their -	orphology will be	ed in each and	ence of positive
tion of	the study the	identity at a	eu in each cas	e, and upon comple-
cion or	the study, the	identity, stage, and sta	tus or each pa	cient Will be
corretat	ed with N-myc e	expression.		

PHS 6040 (Rev. 1/84)

1



		1	PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PRO.	ECT	
			ZO1 CB 09139-03 LP
PERIOD COVERED			
October 1, 1986 to Sept	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the bord	ers.)	
Monoclonal Antibodies t	to Ewing's Sacoma		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inve	stigator.) (Name, title, labore	tory, and institute affiliation)
PI: T.J. Triche	Chief, Ultrastruc	tural Pathology	Section LP NCI
S. Arakawa	LP NCI		
C.F. Reynolds	iissue iranspiant		NMC NCR
COOPERATING UNITS (if any)	······································		
Tissue Transplantation	Unit, NMC, NCR		
110000 11000000000			
LAB/BRANCH			
Laboratory of Pathology	7		
SECTION			
Ultrastructural Patholo	ogy Section		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
3	3	0	
3 CHECK APPROPRIATE BOX(ES)	3	0	
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects	3	0 (c) Neither	
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors	3 (b) Human tissues	0 (c) Neither	
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	3	0 (c) Neither	В
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3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred) This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monod Ewing's sarcoma lines of and compared in their of reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set positive reactivity wi g's sarcoma, or restrict ified to date. It is t clonal antibodies agains established in this labor reactivity with other more or cound to be strongly from characterized, with the imaging, and therapeut	0 (c) Neither sive studies of rived to disting th one or more ted to a few turn he aim of the p it selected, well ratory. They w noclonal antibo reactive with Ew eventual intent ic tool.	B Ewing's sarcoma and uish most from one antibodies. No anti- tors including present study to pro- 1-characterized will then be studied dies previously pring's sarcoma ion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tumo another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monod Ewing's sarcoma lines of and compared in their n reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set positive reactivity wi sarcoma, or restrict ified to date. It is to clonal antibodies agains established in this labor reactivity with other mody found to be strongly of characterized, with the imaging, and therapeut	0 (c) Neither solution to be a state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the state of the	B Ewing's sarcoma and uish most from one antibodies. No anti- tors including present study to pro- 1-characterized rill then be studied dies previously ring's sarcoma ion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monod Ewing's sarcoma lines e and compared in their n reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set positive reactivity wi sarcoma, or restrict ified to date. It is t clonal antibodies agains established in this labor reactivity with other mody found to be strongly re- characterized, with the imaging, and therapeut	0 (c) Neither solutions to ved to disting th one or more ed to a few turn he aim of the p t selected, wel tratory. They w noclonal antibo reactive with Ew eventual intent ic tool.	B Ewing's sarcoma and uish most from one antibodies. No anti- tors including present study to pro- l-characterized rill then be studied dies previously ring's sarcoma ion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monod Ewing's sarcoma lines of and compared in their n reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set f positive reactivity wi sarcoma, or restrict ified to date. It is t clonal antibodies agains established in this labor reactivity with other monty found to be strongly re- characterized, with the imaging, and therapeut	0 (c) Neither solution solution the studies of the of the second the of the second the selected, well the selected, well the selected, well the selected, well the selected with the reactive with the eventual intent ic tool.	B Ewing's sarcoma and uish most from one antibodies. No anti- ors including present study to pro- 1-characterized rill then be studied dies previously ring's sarcoma ion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monod Ewing's sarcoma lines e and compared in their m reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set f positive reactivity wi 's sarcoma, or restrict clified to date. It is t clonal antibodies agains established in this labor reactivity with other mody y found to be strongly r characterized, with the , imaging, and therapeut	0 (c) Neither solution (c) Neither (c) Nei	B Ewing's sarcoma and uish most from one antibodies. No anti- tors including present study to pro- 1-characterized will then be studied dies previously ring's sarcoma tion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monoo Ewing's sarcoma lines of and compared in their m reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues just commencing. Exter ors of childhood have set f positive reactivity wi 's sarcoma, or restrict ified to date. It is t clonal antibodies agains established in this labor reactivity with other mod y found to be strongly r characterized, with the , imaging, and therapeut	0 (c) Neither sive studies of rived to disting th one or more ed to a few turn he aim of the p t selected, well ratory. They w noclonal antibo eactive with Ew eventual intent ic tool.	B Ewing's sarcoma and uish most from one antibodies. No anti- iors including resent study to pro- l-characterized fill then be studied dies previously fing's sarcoma ion to use same as
3 CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred This is a new project, related round cell tund another on the basis of body specific for Ewing Ewing's, has been ident duce a battery of monoo Ewing's sarcoma lines of and compared in their n reported. Any antibody cells will be further of a potential diagnostic,	3 (b) Human tissues Just commencing. Exter ors of childhood have set f positive reactivity wi 's sarcoma, or restrict child to date. It is the childhood have set if ed to date. It is the childhood have set the sarcoma of the set if ed to date. It is the childhood have set the sarcoma of the set set ablished in this labbe reactivity with other mode of found to be strongly of characterized, with the h imaging, and the set the same set the sam	0 (c) Neither solution (c) Neither (c) Nei	Ewing's sarcoma and uish most from one antibodies. No anti- tors including tresent study to pro- l-characterized fill then be studied dies previously ting's sarcoma ion to use same as

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	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INTRAMURAL RESEARCH PROJECT	
	Z01 CB 09140-03 LP
PERIOD COVERED	
October 1, 1986 to September 30, 1987	
A New Wigh Molocular Moight Extracellular Matrix Protein	
PRINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Neme, title, lebora	tory, and institute affiliation)
PI: T.J. Triche Chief, Ultrastructural Patholog	y Section LP NCI
OTHER: S. Scarpa Visiting Fellow	LP NCI
P.U. Reddy Visiting Fellow	LP NCI
COOPERATING UNITS (if any)	
LAB/BRANCH	
Laboratory of Pathology	
SECTION	
Ultrastructural Pathology Section	
INSTITUTE AND LOCATION	
NCI, NIH, Bethesda, MD 20892	
OTAL MARTEANS. PROFESSIONAL. OTHER.	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects 🖾 (b) Human tissues 🗌 (c) Neither	
(a1) Minors	
(a2) Interviews	В
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	
In the course of studying extracellular matrix synthesis by	various childhood tu-
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol (500,000 D) protein secreted into the conditioned medium of a	various childhood tu- .ecular weight
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol (500,000 D) protein secreted into the conditioned medium of s lines. This protein is secreted in connection with laminin.	various childhood tu- .ecular weight several tumor cell type IV collagen.
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol (500,000 D) protein secreted into the conditioned medium of s lines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom.	various childhood tu- .ecular weight several tumor cell type IV collagen, It is also non-
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of s lines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It fails	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with erther distinguishes
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrees the secret of	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes cadation studies
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, but it is the protein is trypsin and pepsin sensitive.	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes cadation studies tt collagenase and
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, bu GAG degrading enzyme insensitive. Ultrastructural studies of purified molecular courses and a course of a course of the protein of the protein of the protecular courses and the protecular courses are courses and the protecular courses are provided when the protecular courses are courses and the protecular courses are courses and the protecular courses are coursed and the protecular courses are courses are courses and the protecular courses are courses and the protecular courses are courses are courses and the protecular courses are courses	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes radation studies to collagenase and rotary shadowed, 700 pm locath The
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, bu GAG degrading enzyme insensitive. Ultrastructural studies of purified molecules reveal a single, unbranched chain of over	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes radation studies to collagenase and rotary shadowed, 700 nm length. The pormal circumstances.
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for adiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, bu GAG degrading enzyme insensitive. Ultrastructural studies of purified molecules reveal a single, unbranched chain of over molecule co-purifies with laminin and type IV collagen under Current efforts are almed at devising preparative purification.	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes radation studies to collagenase and rotary shadowed, 700 nm length. The normal circumstances.
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In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of solines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, bu GAG degrading enzyme insensitive. Ultrastructural studies of purified molecules reveal a single, unbranched chain of over molecule co-purifies with laminin and type IV collagen under Current efforts are aimed at devising preparative purification will allow purification of quantities sufficient to initiate monoclonal antibodies and biologic function studies.	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes radation studies to collagenase and to collagenase and to collagenase and to collagenase. The normal circumstances. on techniques which the generation of
In the course of studying extracellular matrix synthesis by mors, we have encountered a previously unidentified, high mol(500,000 D) protein secreted into the conditioned medium of a lines. This protein is secreted in connection with laminin, and fibronectin, but is immunologically distinct therefrom. reactive with antibodies to basal lamina proteoglycan. It for radiolabelled sodium sulfate or glycosyl precursors, which for it from conventional proteoglycans. Selective enzymatic degrindicate that the protein is trypsin and pepsin sensitive, bu GAG degrading enzyme insensitive. Ultrastructural studies of purified molecules reveal a single, unbranched chain of over molecule co-purifies with laminin and type IV collagen under Current efforts are aimed at devising preparative purification will allow purification of quantities sufficient to initiate monoclonal antibodies and biologic function studies.	various childhood tu- ecular weight several tumor cell type IV collagen, It is also non- tils to label with orther distinguishes radation studies tt collagenase and totary shadowed, 700 nm length. The normal circumstances. on techniques which the generation of
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DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	PHOJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	
			Z01 CB 09160-01 LP
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	rs.)	
N-myc Expression in Sma PRINCIPAL INVESTIGATOR (List other pro	all Kound Cell Tumors of ofessional personnel below the Principal Inves	tigator.) (Name, title, labora	atory, and institute effiliation)
PI: T.J. Triche	Chief, Ultrastructural	Pathology Sect	tion LP NCI
COOPERATING UNITS (if any)			
C. D. Downalds D. J. Cl.		77.4	
C.P. Reynolds, D.J. Sia	amon, and K.E. Seeger, U	LA	
LAB/BRANCH			
Laboratory of Pathology SECTION	1		
Ultrastructural Patholo	ogy Section		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD TOTAL MAN-YEARS:	20892 PROFESSIONAL:	OTHER:	
1	1/2	1/2	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(C) Neither	
(a2) Interviews			в
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	d.)	
N			
biologic behavior. N-m	ton is an important facto	r in neuroblas	stoma prognosis and
tumors. Further antibo	dy detection methods have	ve recently bec	come available. We
have used a rabbit poly	clonal antibody to detec	t the N-myc pr	otein in tissue
results with convention	tumors of childhood. We	have further	correlated these
of each of these tumors	. We find no evidence of	of N-myc amplif	ication, expression,
or protein accumulation	in any of these tumors	save neuroblas	stoma.



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBL	IC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH F	PROJECT	701 CP 00162 01 TP
PERIOD COVERED			201 CB 09162-01 LP
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or les.	3. Title must fit on one line between th	e borders.)	h . h J
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Princip	al Investigator.) (Name, title, lebon	atory, and institute effilietion)
PI: M. Tsokos	Expert		LP NCI
OTHER: G. Kouraklis	Chief Ultrastru	ctural Pathology S	LP NCI
1.0. Illene	onici, oitiastia	cturar rathorogy 5	ection bi not
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Patholog	y		
SECTION			
INSTITUTE AND LOCATION	ogy Section		
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)	4	1	
(a) Human subjects	(b) Human tissues	🗋 (c) Neither	
(a1) Minors			
SUMMARY OF WORK (Use standard unre-	duced type. Do not exceed the space	provided.)	<u> </u>
There is cumulative cl	inical evidence that	alveolar (A) rhab	domyosarcoma (RMS)
carries a more aggress	ive biologic behavio	r than embryonal (	E) RMS. On the
other hand, the histor	ogic distinction of	one from another 1 is absent. The pr	s not always clear,
at: (1) establishing	a model to test biol	ogic aggressivenes	s of A vs E RMS and
(2) defining parameter	s of biologic aggres	siveness in these	tumors.
(1) Six human RMS cel	1 lines were transpl	anted into nude mi	ce. Two cell lines
were classified as E R	MS, two as A RMS and	two as solid alve	olar (SA) RMS. Tumor
growth was measured we	ekly for a total of	5 weeks. Animals	bearing tumors were
sacrificed weekly afte	r 3 weeks, and the t	umor tissue was pr	ocessed for routine
nistology and electron	microscopy.		
(2) Chromosome analys	is of the cell lines	was carried out o	n samples which had
been passaged within 2	4 hours (logarithmic	growth phase). P	atterns of proto-
by Northern blot analy	myc) expression in t	he above RMS cell	lines were examined
by dorellern broc allary	sis of cocar certula		

3

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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUME	3ER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT		
			Z01 CB 00	523-08 LP
PERIOD COVERED	1 20 1087			
October 1, 1986 to Septe	amber 30, 1987			
Complex Carbohydrate Rei	leased from Mammalian Ce	lls by Trifluor	oacetolys	is
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and institute	sffilietion)
PTA DA Zoof	Chief Discharie	-1 Dethele		
OTHER L. Cashel	Biologist	ai Pathology Se	ction	LP NCI
	510105100			LI NOI
COOPERATING UNITS (if any)				
D. Smith, Associate Prot	fessor, Virginia Polytech	hnic Institute,	Blacksbur	rg, VA;
J. Smith, Ortho Diagnost	1CS			
Laboratory of Pathology				
SECTION				
Biochemical Pathology Se	ection			
INSTITUTE AND LOCATION	20802			
TOTAL MAN-YEARS	PROFESSIONAL	OTHER:		
0.5	0.3	0.2		
CHECK APPROPRIATE BOX(ES)		········		
(a) Human subjects	🛛 (b) Human tissues	(c) Neither		
				σ
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space provide	d.)		
Carbohydrate chains rele	eased by trifluoroacetoly	ysis of whole t	issues, ti	issue
ractions, or cells grow	in in culture, are easily	y recovered in	nearly qua	antitative
saccharides containing s	six or fewer monosacchar	ide units is ne	rformed by	v combined
gas chromatography and m	lass spectrometry of per	nethylated, N-t	rifluoroad	cetylated
oligosaccharide derivati	ves. Analysis for certa	ain specific ol	igosacchar	rides is
carried out by radioimmu	inoassay using antibodies	produced agai	nst purifi	ied oligo-
saccharides coupled to p	olypeptide carriers. It	is anticipate	d that the	reper-
of cellular differentiat	ion and reveal potential	l cell surface	markers.	L SLALES



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CB 00525-08 LP

PERIOD COVERED	amber 30 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the border	rs.)	
Analysis of Oligosaccha:	rides by Combined Gas Chu	romatography-Mass Spectrometry	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	igator.) (Name, title, laboretory, and institute affilistion)	
PI: D.A. Zopf	Chief, Biochemical H	Pathology Section LP NCI	
OTHER: J. Cashel	Biologist	LP NCI	
COOPERATING UNITS (if any)			
L. Jarrett, Professor, 1	Department of Pathology,	University of Pennsylvania;	
Dr. J. Mato, Department	of Metabolism, Nutrition	n, and Hormones, Institute for	
Biomedical Investigation	n, Madrid, Spain	· · ·	
LAB/BRANCH			
Laboratory of Pathology			
SECTION			
Biochemical Pathology Se	ection		
INSTITUTE AND LOCATION	20202		
NCI, NIH, Bethesda, MD	20892	07.070	
TOTAL MAN-YEARS:	PROFESSIONAL:	0 7	
	0.1	0.1	
(a) Human subjects	X (b) Human tissues	(c) Neither	
(a1) Minors			
(a2) Interviews		В	
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provider	d.)	
Separation of reduced an	nd permethylated oligosad	ccharides by gas chromatography	
can be facilitated by the	ne use of a fused silica	capillary column coated with	
methyl silicon. The pro	esence of <u>N</u> -acetylhexosar	nines in oligosaccharides increases	
their retention time and	1 interferes with efficie	ent GC separation. Transamidation	
of hexosamines by trifle	ioroacetolysis followed h	by reduction, removal of O-tri-	
fluoroacetyl groups and	permethylation, dramatic	cally reduces the retention time of	
hexosamine-containing o.	ligosaccharides and permi	its separation of oligosaccharides	
containing up to six mol	losaccharide units, regained	cliess of now many of these are	
nexosamines. The mass s	shew upowpostedly high	bundenees of mass ions containing	
the N-trifluoroacetyl g	roup As many of these	ione are large they provide useful	
information regarding of	ligosaccharide structure	tons are large, they provide userul	
information regarding o	ingosacchariae structure		
	-		
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DEPARTMENT OF HEALTH AND	HUMAN SERVICES - PUBLIC HEAD	LTH SERVICE	
NOTICE OF INTRA	MURAL RESEARCH PROJE	ст	
			Z01 CB 00556-05 LP
PERIOD COVERED			
October 1, 1986 to Septemb	er 30, 1987		
TITLE OF PROJECT (80 characters or lass. Title	a must fit on ona line between the borders	3.)	
Expression of Glycolipids in Lymphocyte Subpopulations			
PRINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)			
PI: D.A. Zopf	Chief, Biochemical Pa	thology Sectio	n LP NCI
OTHER: K. Schroer	Senior Assistant Surg	eon	LP NCI
M. Duk	Visiting Fellow		LP NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Pathology			
SECTION			
Biochemical Pathology Sect	ion		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD 208	92		
TOTAL MAN-YEARS: PRO	OFESSIONAL:	OTHER:	
0.5	0.5		
CHECK APPROPRIATE BOX(ES)		( ) <b></b>	
(a) Human subjects	(b) Human tissues	(C) Neither	
(a) Minors			
(a2) Interviews			B
SUMMARY OF WORK (Use standard unreduced	I type. Do not axceed the space provided	.)	
Neutral glycolipids are differentially expressed in functionally distinct sub-			
populations of murine lymphocytes. Subpopulations of B cells can be studied by			
examining hybridoma lines derived from fusion of splenic B lymphocytes with the			

PROJECT NUMBER

examining hydridoma fines derived from fusion of spients is hymphocytes with the mouse myeloma SP2/0. We are analyzing total neutral glycolipids from hybridomas by thin layer chromatography and by GC/MS analysis of oligosaccharides after trifluoroacetolysis. Hybridomas from Balb/c splenocytes express glycolipids containing from two to five simple sugars. These include globoside and its precursors as well as asialo-GM2 and 2' fucosyllactosyl ceramide. The goal of this project is to correlate expression of oligosaccharide chains of glycolipids with functional parameters of B cell subsets such as responsiveness to Type I and Type II antigens.



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT			
			Z01 CB 00879-04 LP
PERIOD COVERED	antan 20 1097		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the border	rs )	
Nucleotide Sequencing o	f Hybridoma Antibodies o	f V <sub>H</sub> -GAC Family	7
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigetor.) (Name, title, labore	tory, and institute affiliation)
OTHER: L. Phung	Biologist	n	LP NCI
official of thing	bioiogise		Lr NOL
COOPERATING UNITS (if any)			
Laboratory of Pathology			
SECTION		· · · ·	
Biochemical Pathology S	ection		
INSTITUTE AND LOCATION	20802		
NCI, NIH, Bethesda, MD		OTHER	·····
1.0	1.0	0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	🗌 (b) Human tissues 🛛 🖺	(c) Neither	
(a1) Minors			
	luced type. Do not exceed the space provide		В
Antibodies of the J606	murine Vu family, GAC (g	roup A-streptod	coccal carbohydrate)
(GAC-related V <sub>H</sub> genes),	have been seen to derive	e in normal mic	e from at least 3V <sup>H</sup>
gene segments (of a loci	us whose complexity is 10	0-12). Two of	these are GAC-related
one inulin related. In	CBA/N mice, which do no	t respond to ei	ther GAC or inulin by
found to constitute abo	on methods, antibodies of	t the J606 V <sub>H</sub>	amily origin were
of expression of the me	mbers of the J606 $V_{\rm H}$ fam	ilv has been ex	camined by nucleotide
sequencing of hybridoma	derived V <sub>H</sub> J606 genes f	rom their puris	ied mRNA.



	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INTRAMURAL RESEARCH PROJECT	
	Z01 CB 09155-01 LP
PERIOD COVERED	
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
Analysis of Complex Carbohydrates by Affinity Chromatography	
PRINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Name, title, labo	retory, and institute affilietion)
PI: D.A. Zopf Chief, Biochemical Pathology	Section LP NCI
OTHER: M. Duk Visiting Fellow	LP NCI
W. Wang Visiting Fellow	LP NCI
J. Fernandez Bio Lab Tech	LP NCI
COOPERATING UNITS (if any)	

A. Lundblad, Head Physic	cian, University of Lund	, Sweden; J. Dakour	, Predoctoral	
Student, University of 1	Lund, Sweden			
LAB/BRANCH				
Laboratory of Pathology				
SECTION				
Biochemical Pathology Se	Biochemical Pathology Section			
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, MD 20892				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
2.0	0.5	1.5		
CHECK APPROPRIATE BOX(ES)				
🔲 (a) Human subjects	(b) Human tissues	(c) Neither		
(a1) Minors				
(a2) Interviews			В	

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Monoclonal antibodies coupled to solid supports provide a suitable matrix for rapid, specific chromatographic separation of oligosaccharides. Thus, antibodies that define or recognize carbohydrate determinants such as blood group-related or cancer-associated antigens can be used to identify and purify their targets. New approaches are being sought to use antibodies of relatively low affinity to analyze a spectrum of biologically interesting carbohydrates.



DEPARTMENT OF H	EALTH AND HUM	AN SERVICES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER	
NOTICE	OF INTRAMUR	AL RESEARCH PROJ	ECT		
PERIOD COVERED		<del></del>		<u>Z01 CB 00559-05</u>	LP
October 1, 1986 t	to September	30, 1987			
TITLE OF PROJECT (80 charac	cters or less. Title must	fit on one line between the borde	rs.)		
PRINCIPAL INVESTIGATOR (LI	st other professional pe	<u>1 Metastases</u> arsonnel below the Principal Inves	tigator.) (Name, title, laborat	tory, and institute affiliation)	
PI: L.A. Lic	otta	Chief, Tumor Invas	sion & Metastas	es Section L	P NCI
OTHER: U. Wewen	r D	Visiting fellow		L	P NCI
I.M.K. N	Margulies	Biologist	-	L	P NCI
COOPERATING UNITS (if any)			······································		
		· ·			
Laboratory of Dev	velopmental H	Biology and Anomal:	les, NIDR		
LAB/BRANCH					
Laboratory of Pat	thology	· · · · · · · · · · · · · · · · · · ·			
Tumor Invasion ar	d Matastasas	Section			
INSTITUTE AND LOCATION	MILLEL CALLAGES				
NCI NIH Bethese	1a, MD 20892		OTHER		
DIAL MANTEARS.	FHORESS	1 5	5		
AUTOK ADDODUATE DOWER	S)		·		
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(a) Human subject (a) Human subject (a1) Minors (a2) Interviews SUMMARY OF WORK (Use star	ndard unreduced type.	Human tissues	(c) Neither		<u>B</u>
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CHECK APPROPRIATE BOJECT  (a) Human subject  (a1) Minors  (a2) Interviews  SUMMARY OF WORK (Use star  The overall goal mechanisms involv cellular matrix. place at the inter attachment.  Accomplishments  Laminin, a gl role in metas  Laminin, a gl role in metas  C. The cell surf  Monoclonal ar human breast formation abo were also use clone from th  . The binding of functional do interface was	is (b) induced unreduced type. of the reseaved in the int A major objection of perface between lycoprotein of static tumor face laminin ntibodies and cancer lamir out the distress to screen he human gene iomain on the omains were la s developed.	Human tissues	(c) Neither (c) Neither (d) dentify and char static tumor ce to analyze the er and the basemen hes, was shown fied and partiar odies were prep se antibodies have library to iso eceptor. ligand were id and and a model	to play a major by play a major by provided new provided new provided new prote a putative entified. Addit	B mical ra- g odies cDNA ional nt
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CHECK APPROPRIATE BOJECT  (a) Human subject  (a1) Minors  (a2) Interviews  SUMMARY OF WORK (Use star  The overall goal mechanisms involv cellular matrix. place at the inter attachment.  Accomplishments  Laminin, a gl role in metass  Laminin, a gl role in metass  Che cell surf  Monoclonal at human breast formation abo were also use clone from th  Che binding c interface was  A fragment of markedly inhi in animal moc	is (b) induct unreduced type. of the reseaved in the ir A major objection of perface between lycoprotein of static tumor face laminin ntibodies and cancer lamir out the distred to screen ne human gene domain on the omains were la s developed. I the laminir litis or abolicels.	Human tissues	(c) Neither (c) Neither (c) Neither (c) Neither (c) And Char (c) An	aracterize bioche ells with the ext events which take to play a major ared against the lave provided new pptor. The antib late a putative entified. Addit of the attachme as the receptor a a a nontoxic fash	nical ra- g odies cDNA ional nt nd ion


DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 00891-04 LP

PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must hit on one line between ti	ne borders.)	
Stimulated Motility in	Tumor Cells		
PRINCIPAL INVESTIGATOR (List other pro	iessional personnel below the Princip	par investigator.) (ivame, title, laboratory, and institute	amiliation)
DI: E Schiffmann	Pocoarab Chemis	t.	
L. Liotta	Chief Tumor L	avasion & Metastases Section	
OTHER: M. Stracke	Biotechnology I	Rellow	LP NCI
R. Guirguis	Guest Researche		LP NCL
I.M.K. Marguli	es Biologist		LP NCT
			DI NOI
COOPERATING UNITS (if any)			
Robert Bassin, Chief, C	ellular and Molecula	ar Physiology Section, LTIB,	NCI:
Joel Moss, LCM, NHLBI;	B.F. Sloane, Departs	ment of Pharmacology, Wayne	State Univ.
Detroit, Michigan; Bria	n Liu, UCLA, Los Ang	geles, California; D. Salomon	DCBD, NCI
LAB/BRANCH	, ,	, ,	., 2020,
Laboratory of Pathology			
SECTION			
Tumor Invasion and Meta	stases Section		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
3.2	3.2	0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	X (b) Human tissues	🔟 (c) Neither	
(a1) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space	provided.)	-
Since locomotion is ess	ential for metastasi	is of tumor cells, we are stu	idying the
biochemical nature of t	his process. Human	melanoma and breast cancer of	cells produce
in culture proteins (~ .	55 KDa) that stimula	ate motility in the producer	cells -
autocrine motility fact	ors (AMF). These ha	we been purified in procedur	es involving
sequential gel filtration	on, hydrophobic inte	eraction and ion exchange HPI	.C. Studies
on the mechanism of act:	ion of AMF have ider	tified a pertussis-sensitive	e G protein
pathway as a requirement	t for motility and e	exclude the adenylate cyclase	e system
from having a direct rol	le in cell motility.	Requirements for extracel	lular Ca <sup>++</sup>
and for lipoxygenase me	tabolites of arachid	lonic acid were suggested in	studies
with murine tumor cell :	lines. Investigatio	ons of early morphological ev	vents in
tumor cell locomotion ha	ave indicated that p	seudopod formation may be ne	ecessary for
initiating motility. Pa	seudopod formation a	ppears to be independent of	attachment
mechanisms. Pseudopodia	a are enriched in re	ceptors for matrix component	s and
cytoskeletal proteins.	suggesting a sensory	role for them in cell locon	otion. In
exploratory studies on o	clinical application	is of cell motility, we have	found that
urine samples from patie	ents with urinary tr	act cancers contain motility	factors
whose potency is well co	orrelated with the a	ggressiveness of the tumors.	There may
well be a family of mot:	ility factors with a	common active site. This r	oint and
the role of motility fac	ctors in metastasis	would be clarified when we h	ave
achieved one of our prin	ncipal objectives:	cloning the gene for AMF.	
		J J	
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DEPARTMENT	OF HEALTH	AND HUMAN	SERVICES -	PUBLIC HEALTH SERVI	CE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 00892-04 LP

PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line between t	the borders.)	
Molecular Brology of Ch	e Helastatic Filenoty		- Millebiant
PRINCIPAL INVESTIGATOR (List other pr	biessional parsonnel below the Philop	ipar investigator.) (Name, title, laboratory, and institute	annauon)
PT: P.S. Steeg	Biotechnology	Fellow	LP NCT
OTHER: M.E. Sobel	Senior Investi	igator	LP NCT
G. Bevilacqua	Guest Research	her	LP NCI
L.A. Liotta	Chief, Tumor J	Invasion & Metastases Section	LP NCI
	,		
COOPERATING UNITS (if any)		· · · · · · · · · · · · · · · · · · ·	
LAB/BRANCH			
Laboratory of Pathology			
SECTION			
Tumor Invasion and Meta	stases Section		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
2.1	2.1	0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			
			В
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the space	ce provided.)	14 . 1
The molecular blology o	r tumor metastasis r	has been investigated. A CDN	A clone,
phm23, has been identif	1ed which recognizes	s specific KNAs present to a	greater
metastatia V1725 malana	c ki/33 murine metar	noma cell lines than in relat	ea, nighiy
three additional animal	ma cell lines. Ine	pNM23 CDNA CIONE nas been te	sted in
induced memory consine	experimental metast	tases systems: rat nitrosome	etnyiurea-
and not ambrus fibrable	ate tronefooted with	h man t adapavirus Ela In	carcinomas
NM22 PNA lovala vona in	ses transfected with	ii ras + adenovirus Eia. in e	each case,
ANALY ANA LEVELS WERE IN	t NM23 PNA lovala at	with metastatic potential. F	reliminary
human broast concor	provinctoly 750 br	of the NM22 gone have been i	sed in
and are being character	ized with the event	tual goal of transforting the	full
length NM23 gape into h	ighly matactatic cal	lia Computer analyzic of th	3! 600 bb
of the NM23 cDNA indica	to that it is a now	al game. The data identify a	
which is accoriated wit	h the metactatic pro	er gene. The data identify a	demon-
strates that tumor meta	stasis is not only a	accordated with the acquisiti	on of in-
vasive and other traits	but may also invol	lye the loss of other cellula	
functions. Experiments	underway will deter	rmine the diagnostic and ther	aneutic
potential of this findi	ng.	Turne the drughostre and ther	apeacie
Freedor of this find	···••		



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	
			Z01 CB 00893-04 LP
PERIOD COVERED			
Uctober 1, 1986 to Sep	tember 30, 1987		
DNA Mediated Transfer	of Metastatic Potential	rs.)	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	tigator.) (Name, title, laborat	tory, and institute affiliation)
PI: L.A. Liotta	Chief, Tumor Invasio	on and Metastas	es Section LP NCI
H. Krutzsch	Expert		LP NCI
K.J. Muscher	Senior investigator		LF NCI
	····		
COOPERATING UNITS (if any)			
R Pozzatti (Fellow)	IMV NCI: S Carbies Pa	lova Instituto	of Wistology Italy
R. IOZZALLI (FEIIOW),	LINV, NOI, 5. GAIDISA, FA	iova institute	of Histology, Italy
LAB/BRANCH			
Laboratory of Patholog	у		
SECTION			
Tumor Invasion and Met	astases Section		
NCT NIH Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
1	1	0	
CHECK APPROPRIATE BOX(ES)			
	🖾 (b) Human tissues	(c) Neither	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	🖾 (b) Human tissues	(c) Neither	P
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unret	(b) Human tissues	(c) Neither	В
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree Activated ras oncogene	(b) Human tissues	(c) Neither a.) ble recipient c	B ells has been shown
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree Activated ras oncogene to induce the metastat:	(b) Human tissues	<pre>(c) Neither a) ble recipient c on et al., Mol.</pre>	B ells has been shown Cell Biol. 5:
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unree Activated ras oncogene to induce the metastat 259-262, 1985). With	(b) Human tissues	<pre>(c) Neither a) ble recipient c on et al., Mol. y, we extended</pre>	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup>
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo	(b) Human tissues	(C) Neither a) ble recipient c on et al., Mol. y, we extended e also highly m	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup> netastatic when
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by	(b) Human tissues	(c) Neither d) ble recipient c on et al., Mol. y, we extended e also highly m o an enhancer.	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup> metastatic when However, when the
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E	(b) Human tissues	(c) Neither d) ble recipient c on et al., Mol. y, we extended e also highly m o an enhancer. on with ras <sup>H</sup> , m	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup> metastatic when However, when the metastasis was only perletion of becoment
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi	☑ (b) Human tissues □ duced type. Do not exceed the space provide transfection into suital ic phenotype (Thorgeirsson R. Pozzatti and G. Khoury cells. These cells were ras <sup>H</sup> or by ras <sup>H</sup> linked to la was used in conjunction used this model system to s with metastatic property	(c) Neither (c) N	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup> betastatic when However, when the metastasis was only crelation of basement interas oncogene alone
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-mvc	☑ (b) Human tissues □ duced type. Do not exceed the space provide transfection into suital ic phenotype (Thorgeirsse R. Pozzatti and G. Khoury cells. These cells were ras <sup>H</sup> or by ras <sup>H</sup> linked to la was used in conjunction used this model system to s with metastatic propense. transfected into early	(c) Neither d) ble recipient c on et al., Mol. y, we extended e also highly m o an enhancer. on with ras <sup>H</sup> , m o study the corr sity. The c-Ha passage rat em	B cells has been shown Cell Biol. 5: this work to rasH betastatic when However, when the metastasis was only crelation of basement -ras oncogene alone, bryo fibroblasts.
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B cells has been shown Cell Biol. 5: this work to rasH tetastatic when However, when the metastasis was only crelation of basement -ras oncogene alone, thryo fibroblasts, tolytic metallo-
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc	☑ (b) Human tissues auced type. Do not exceed the space provide transfection into suital ic phenotype (Thorgeirsse R. Pozzatti and G. Khoury cells. These cells were ras <sup>H</sup> or by ras <sup>H</sup> linked to la was used in conjunctio used this model system to s with metastatic propens , transfected into early secrete high levels of ty omitantly exhibit a high	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al., Mol. (c) net al., Mol. (c) study the correct (c) study the corr	B cells has been shown Cell Biol. 5: this work to rasH tetastatic when However, when the metastasis was only crelation of basement -ras oncogene alone, abryo fibroblasts, tolytic metallo- pontaneous metas-
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al., Mol. (c) net al., Mol. (c) study the correct (c) neither rasH, m (c) study the correct (c) neither rasH, m (c) study the correct (c) study the correct (c) study the correct (c) neither rasH, m (c) study the correct (c) study the c	B cells has been shown Cell Biol. 5: this work to rasH hetastatic when However, when the metastasis was only crelation of basement ras oncogene alone, abryo fibroblasts, nolytic metallo- pontaneous metas- novirus type 2 Ela
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) recipient c (c) recipient c (	B cells has been shown Cell Biol. 5: this work to ras <sup>H</sup> betastatic when However, when the metastasis was only crelation of basement ras oncogene alone, abryo fibroblasts, molytic metallo- pontaneous metas- novirus type 2 Ela tic and fail to
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration pot incre	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B sells has been shown Cell Biol. 5: this work to rasH hetastatic when However, when the metastasis was only crelation of basement ras oncogene alone, bryo fibroblasts, holytic metallo- spontaneous metas- novirus type 2 Ela tic and fail to ssion of collagenase tor and not
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration, not incre	★ (b) Human tissues Auced type. Do not exceed the space provide transfection into suital ic phenotype (Thorgeirsse R. Pozzatti and G. Khoury cells. These cells were ras <sup>H</sup> or by ras <sup>H</sup> linked to la was used in conjunctio used this model system to s with metastatic propens , transfected into early secrete high levels of ty omitantly exhibit a high otransfection of c-Ha-ras h are highly tumorigenic enase. This effect is do ased production of a col-	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B sells has been shown Cell Biol. 5: this work to rasH hetastatic when However, when the metastasis was only relation of basement ras oncogene alone, abryo fibroblasts, molytic metallo- spontaneous metas- novirus type 2 Ela ttic and fail to spon of collagenase tor, and not eristics of the
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CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration, not incre decreased production o collagenase are identi The nonmetastatic cell	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B seells has been shown Cell Biol. 5: this work to ras <sup>H</sup> netastatic when However, when the netastasis was only relation of basement ras oncogene alone, abryo fibroblasts, nolytic metallo- spontaneous metas- novirus type 2 Ela tric and fail to ssion of collagenase tor, and not eristics of the bed previously. agenase retain the
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CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration, not incre decreased production o collagenase are identi The nonmetastatic cell ability to secrete hig proto-oncogenic forms cells or chemical tran	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B seells has been shown Cell Biol. 5: this work to ras <sup>H</sup> netastatic when However, when the netastasis was only relation of basement ras oncogene alone, bryo fibroblasts, nolytic metallo- spontaneous metas- novirus type 2 Ela tic and fail to soion of collagenase tor, and not eristics of the bed previously. agenase retain the insfection with the ormation of NIH 3T3 ls which fail to
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration, not incre decreased production o collagenase are identi The nonmetastatic cell ability to secrete hig proto-oncogenic forms cells or chemical tran produce collagenase, a	★ (b) Human tissues Auced type. Do not exceed the space provide transfection into suital ic phenotype (Thorgeirsse R. Pozzatti and G. Khoury cells. These cells wery ras <sup>H</sup> or by ras <sup>H</sup> linked to la was used in conjunctio used this model system to s with metastatic propens , transfected into early secrete high levels of ty omitantly exhibit a high otransfection of c-Ha-ras h are highly tumorigenic enase. This effect is do ased production of a coll f a collagenase activato cal to tumor type IV coll s which failed to produce h levels of plasminogen of Ha-ras or mos, or spon sformation of BALB 3T3 cr re tumorigenic, but total	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B seells has been shown Cell Biol. 5: this work to ras <sup>H</sup> netastatic when However, when the netastasis was only relation of basement ras oncogene alone, abryo fibroblasts, nolytic metallo- gontaneous metas- novirus type 2 Ela tic and fail to solon of collagenase tor, and not eristics of the bed previously. agenase retain the insfection with the ormation of NIH 3T3 ls which fail to ic. These data on with the meta-
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unner Activated ras oncogene to induce the metastat 259-262, 1985). With transformed rat embryo transformed either by cooperating oncogene E rarely seen. We have membrane collagenolysi or combined with v-myc induce these cells to proteinase and to conc tases in nude mice. C gene yields cells whic produce type IV collag elaboration, not incre decreased production o collagenase are identi The nonmetastatic cell ability to secrete hig proto-oncogenic forms cells or chemical tran produce collagenase, a support a biochemical	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) net al., Mol. (c) net al.,	B seells has been shown Cell Biol. 5: this work to ras <sup>H</sup> netastatic when However, when the netastasis was only relation of basement ras oncogene alone, bryo fibroblasts, nolytic metallo- gontaneous metas- novirus type 2 Ela tic and fail to solon of collagenase tor, and not eristics of the bed previously. genase retain the insfection with the ormation of NIH 3T3 ls which fail to tic. These data on with the meta-



DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT		
			Z01 CB 08266-07	/ LP
PERIOD COVERED				
October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	of Recompart Membrane Mol	ecules		
BRINCIPAL INVESTIGATOR (List other or	OI Basement Membrane Hor	tidator ) (Name title Johorn	tone and institute effiliation)	
PRINCIPAL INVESTIGATOR (Dist other pro	nessional personnel below the Philopal inves	ugator.) (Name, title, labora	tory, and institute amiliation)	
PI: L.A. Liotta	Chief, Tumor Inva	sion & Metastas	ses Section	LP NCI
OTHER: C.N. Rao	Visiting Associat	e		LP NCI
G. Taraboletti	Visiting Fellow			LP NCI
I.M.K. Marguli	es Biologist			
COOPERATING UNITS (IT any)				
D. Roberts, Senior Staf	f Fellow, NIDDKD: K. Try	ggyasson, Oulu	Finland D. Fr	nstein
Syntex, Inc.	, , ,	88 · 400 ·, · ·	, tintunu, bi sp	potern
LAB/BRANCH				
Laboratory of Pathology				
SECTION				
Tumor Invasion and Meta	stases Section			
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, MD	20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
	1.0	0.5		
(a) Human subjects	X (b) Human tissues	(c) Neither		
(a) Minors				
(a2) Interviews	1			в
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	d.)		
The nature and assembly	of basement membrane co	nstituents name	ely IV collagen,	,
laminin and heparan sul	phate proteoglycan were	studied using a	a variety of in	vitro
binding assays. These	basement membrane macrom	olecules were :	isolated from th	ne
EHS tumor grown in C57	black mice. Protease-de	rived fragments	s of laminin and	i IV
collagen were character	ized by rotary shadowing	electron micro	oscopy. The dom	nains
required for binding of	laminin and IV collagen	were identifie	ed. Laminin is	а
cross-shaped molecule w	ith three equal short ar	ms and one long	g arm. The cell	
binding region of famin	in was also identified a	na rouna co res	side at the inte	2 <b>r</b> -
obtained and the distri	bution of sugars on the	long and short	arms of laminir	,
molecule was studied.	Type IV collagen is a ro	ne-like structu	ire (360 nm) wit	-ha
globular domain at the	carboxyterminal end and	a disulphide-ri	ich amino termir	nal
end. A major binding s	ite for laminin is ident	ified at about	100 nm away fro	om the
globular end of type IV	collagen. The binding	domain on lamin	in for its rece	ptor
has now been isolated u	sing protease treatment	of laminin. A	monoclonal anti	body
is shown to recognize t	his domain and block the	binding of lan	minin to the re-	-
ceptor. A complete mod	el has been developed fo	r the orientati	ion of the cell	
surface laminin recepto	r, laminin itself, and t	ype IV collager	in the basemen	it
membrane.				



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER		
NOTICE OF INT	NAMORAL RESEARCH PROJ	201	701 CB 09127-03 TP		
PERIOD COVERED			201 0B 07127 05 EF		
October 1, 1986 to Sept	ember 30, 1987				
TITLE OF PROJECT (80 characters or less	3. Title must fit on one line between the borde	ərs.)			
Effect of TPA on Type I	V Collagenolytic Activit	y in Normal and	Neoplastic Cells		
PHINCIPAL INVESTIGATOR (List other pro	ressional personnal below the Principal Inves	stigator.) (Name, title, labore	tory, end institute affiliation)		
PI: M. Ballin	Visiting Fellow		LP NC	т	
OTHER: U.P. Thorgeirs	son Expert		LP NC	ī	
COOPERATING UNITS (if any)					
LAB/BHANCH					
SECTION					
Tumor Invasion and Metas	stases Section				
INSTITUTE AND LOCATION					
NCI, NIH, Bethesda, MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
	L	0			
(a) Human subjects	X (b) Human tissues	(c) Neither			
(a1) Minors					
(a2) Interviews			F	3	
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space provide	d.)			
Diversified effects of 1	the tumor promoter, TPA,	on type IV col	lagenolytic activit	:у,	
Normal human diploid lur	ists at different stages	of malignant t	ransformation.		
aneuploid mouse fibrobla	asts, NIH/3T3, expressed	up to 400% inc	, but immortalized		
collagenolytic activity,	and a fibrosarcoma cel!	l line, HT1080	expressed up to		
50% increase in the pres	sence of TPA. The collag	genolytic activ	ity of the normal		
fibroblasts was not depe	endent on the stage of co	onfluency.			
These menults survey the					
initiation step in the	lat certain cellular char	nges, possibly	related to the		
type IV collagenolytic	activity by the tumor pro-	e necessary for	the induction of		
	interest of the tamor pro	Juoter IIA.			



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	DJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT	
	01 CB 09130-03 LP
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
Laminin Receptor in Breast Tissue, Benign and Malignant Tumors	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigetor.) (Name, title, laboratory,	and institute affiliation)
PI: G.J. Bryant Expert	LP NCT
OTHER: L.A. Liotta Chief, Tumor Invasion & Metastases	Section LP NCI
C.N. Rao Visiting Associate	LP NCI
COOPERATING UNITS (if any)	
A. Schwartz, George Washington University Hospital, Washington,	D.C.;
R.R. Brentani, Ludwig Institute for Cancer Research, Sao Paulo,	Brazil;
LAB/BRANCH	
Laboratory of Pathology	
SECTION	
Tumor Invasion and Metastases Section	
INSTITUTE AND LOCATION	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	
1 0.8 0.2	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects (b) Human tissues (c) Neither	
(a1) MINORS	and the second
SUMMARY OF WORK (Use standard unreduced type, Do not exceed the space provided.)	<u>B</u>
Laminin, a major glycoprotein of basement membranes, exhibits a	aturable binding
to the surface of certain neoplastic and normal cells. Examination	tion of various
cell types (i.e. human pancreatic carcinoma, melanoma and bladd	er carcinoma) via
live cell binding techniques indicate the number of receptors t	o be 50-110,000
per cell depending on cell type. In our laboratory, the lamini	n receptor has
been isolated from human breast carcinoma cells and tissue and	mouse melanoma
an important role in tumor cell attachment, one of the steps in	tumor invasion
and metastasis. The proposed study is designed to measure and	correlate laminin
receptor binding capacity of breast tissues with clinical infor	mation. Laminin
receptor binding capacity markedly differs between benign, mali	
	gnant and normal
human breast tissue. Preliminary studies indicate a 50-fold in	gnant and normal crease in specific
human breast tissue. Preliminary studies indicate a 50-fold in laminin binding activity in malignant versus benign breast tiss	gnant and normal crease in specific ues. These find-

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PROJECT NUMBER DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CB 09131-03 LP

PERIOD COVER	RED			
October 1	, 1986 to Septemb	er 30, 1987		
TITLE OF PRO.	JECT (80 characters or less. Title	must fit on one line between the border	5.)	
Molecular	Cloning of Conne	ctive Tissue Matrix Mo	olecules	
PRINCIPAL INV	ESTIGATOR (List other profession	onal personnel below the Principal Invest	igator.) (Name, title, laboretory, and insi	titute affiliation)
<b>DT</b> .	M.F. Sobol	Senior Investig	rator	LP NCT
OTUEP.	C N Pao	Visiting Associ	ate	LP NCT
OTHER.	A. Mackay	Visiting Fellow	J	LP NCI
	II. Wewer	Visiting Fellow	J	LP NCI
	M. Agelli	Breast Cancer 2	fask Force Fellow	LP NCI
	A.P. Clavsmith	Biologist		LP NCI
	F. Highsmith	Stay-in-School		LP NCI
COOPERATING	UNITS (if any)			
LAB/BRANCH				
Laborator	y of Pathology			_
SECTION				
Tumor Inv	asion and Metasta	ses Section		
INSTITUTE AND	LOCATION			
NCI, NIH,	Bethesda, MD 208	92		
TOTAL MAN-YE	ARS: PR	OFESSIONAL:	OTHER:	
	3.7	2.5	1.2	
CHECK APPRO	PRIATE BOX(ES)			
📙 (a) Hur	nan subjects	(b) Human tissues	(c) Neither	
🗌 (a1)	Minors			
🗌 (a2)	Interviews			В
SUMMARY OF	WORK (Use standard unreduced	type. Do not exceed the space provide	d.)	
The inter	action of the tum	or cell with its extra	acellular matrix may	play an
important	role in determin	ing its metastatic and	i invasive properties	. To better
understan	nd the protein com	ponents that make up t	the extracellular mat	rix, their
regulatio	on and how they in	teract with the tumor	cell, we have underta	aken to con-
struct, i	solate, and chara	cterize molecular clo	nes of laminin recept	or and of
several d	lifferent collagen	s. Laminin receptor	is a cell surface pro	tein to which
laminin (	a major component	of basement membrane	) specifically binds	with high
affinity.	We previously i	solated a human lamin:	in receptor cDNA which	h encoded the
carboxy-t	erminal half of t	he protein and showed	that laminin recepto	r mRNA in the
tumor cel	l is a rate-limit.	ing control step in the	he biosynthesis of the	e receptor, and
hence in	the regulation of	cellular attachment	to basement membranes	via laminin.
During th	ne past year, we h	ave extended our seque	ence analysis of the	laminin re-
ceptor ge	ene. In particula	r, we have obtained me	ore amino terminal se	quences. We
have disc	covered that there	is more than one lam	inin receptor gene wh	ich may encode
more than	n one protein expr	essed in the cell. W	e have also cloned a	nurine laminin
receptor	cDNA and have fou	ind that murine cells,	like their human cou	nterparts,
have mult	ciple laminin rece	ptor genes. Studies	of the regulation of	the laminin
receptor	gene indicate tha	t differentiated cells	s express less lamini:	n receptor mRNA
than do r	elated, undiffere	entiated precursor cel	ls. This is consiste	nt with the
general c	observation that a	ggressive undifferent.	lated tumors which me	castasize ex-
press mor	re laminin recepto	·r.		



DEPARTMENT OF HEALTH A	ND HUMAN SERVIC	ES - PUBLIC HEA	LTH SERVICE	PROJECT NUMBER
NOTICE OF INT	DAMUDAL DESE		CT	
NOTICE OF INT	NAMONAL RESE	Anch Fhose	.01	701 CB 09156-01 LP
PERIOD COVERED	····· ·			
October 1, 1986 to Sept	ember 30, 1983	7		
TITLE OF PROJECT (80 cheracters or less	. Title must fit on one line	e between the border	s.)	
Cloning of Human Type I	V Collagenoly	tic Gene(s)		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below	v the Principal Invest	getor.) (Name, title, labora	tory, and institute affilietion)
PI: M. Ballin		Visiting Fe	llow	LP NCI
OTHER: U.P. Thorgeirs	son	Expert		LP NCI
COOPERATING UNITS (if any)				
			··· · · · · · · · · · · · · · · · · ·	
LAB/BHANCH				
Laboratory of Pathology				
Turner Truncies and Mate	-tease Coatie			
Tumor Invasion and Meta	stases Section	n		
NGT NTU Betheade MD	20802			
NCI, NIH, Betnesda, MD			07050	
TOTAL MAN-TEAHS:	PHOPESSIONAL:		OTHER:	
	2	,	0	
	(b) Human ti		(c) Neither	
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	ward twee Do not average	d the engage provide	41	В
The approaches tone tok	are for aloring			llegenese from a
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Lumor cell CDNA library	. A numan me.	Lanoma (A2U)	00) Vgtil lidra	TV LCUSTOM MADE
	h - C - )	**		all and the la
tor Dr. Liotta by Clont	ech Co.) was i	first screen	ed with a poly	vclonal antibody
against type IV collage	ech Co.) was in ase. The co	first screen llagenase wa	ed with a poly s purified fro	vclonal antibody
against type IV collage tant of the A2058 cell	ech Co.) was in ase. The colline which was	first screen llagenase was used to ma	ed with a poly as purified from the the cDNA 1:	coloral antibody om culture superna- lbrary. The second
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for Dr. Liotta by Clont against type IV collage tant of the A2058 cell approach was to screen clone (supplied by C. B	ech Co.) was in nase. The co line which was the melanoma rinkerhoff).	first screen llagenase wa s used to ma library with After the	hed with a poly as purified fro the the cDNA list a a mammalian of first screening	colonal antibody om culture superna- tbrary. The second collagenase cDNA with the antibody,
for Dr. Liotta by Clont against type IV collage tant of the A2058 cell approach was to screen clone (supplied by C. B 18 clones were isolated	ech Co.) was a nase. The co line which was the melanoma rinkerhoff). , of which for	first screen llagenase wa s used to ma library with After the d ir were place	hed with a poly as purified from the the cDNA list a mammalian of first screening ue purified at	colonal antibody om culture superna- tbrary. The second collagenase cDNA g with the antibody, ter 4-5 rounds of
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for Dr. Liotta by Clont against type IV collage tant of the A2058 cell approach was to screen clone (supplied by C. B 18 clones were isolated screening. All four cl bearing phage, but fail the restriction pattern Likewise, negative resu screened with the mamma positive through four r blue plaques without an Since there may be prob process all over again Presently, we are begin cells in metastasis. T endothelial cDNA librar collagenase cDNA clone mammalian collagenase a	ech Co.) was in nase. The col- line which was the melanoma in rinkerhoff). , of which for ones produced ed to demonstri- was identical lits were obtained insert as just lian collagena- ounds of scree- insert as just lems with the using another ning to focus herefore, we as y, purchased in under low stri- and other relation	first screen llagenase was s used to mu library with After the f ir were place clear plaque rate an inse l to that of ined when the ase clone. ening turnes melanoma 1: tumor cell our attent: are in the p from the Cle ingent cond:	the with a poly as purified from take the cDNA 1: a mammalian of first screening ue purified and tes, which indi- tert by restrict a wild type be same melanor Six clones whill out to product triction analysy brary, we will cDNA library.	colonal antibody om culture superna- tbrary. The second collagenase cDNA g with the antibody, fter 4-5 rounds of tcates an insert- cion analysis; (gtll phage DNA. the cDNA library was tch were strongly te non-recombinant sis of phage DNA. I start the cloning e of endothelial cening a human ing the mammalian tet to pull out hoothelial cells.



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES	- PUBLIC HE	ALTH SERVICE	PROJECT NUMBER	4
NOTICE OF INTRAMURAL RESEARCH PROJECT					
REPIOD COVERED				ZOT CB 0915	57-01 LP
October 1, 1986 to Sept	ember 30, 1987				
TITLE OF PROJECT (80 characters or less	. Title must fit on one line be	tween the bord	lers.)		
	othelial Cells	and Tumo	r Cells During	ascular inv	vasion
PRINCIPAL INVESTIGATOR (LIST BUILDI PID	lessional personnel below in	e rincipal inve	sugator.) (Name, une, labora	nory, and institute am	wauon)
PI: U.P. Thorgeirs:	son Exp	pert			LP NCI
M. Ballin	Vi	siting Fe	ellow		LP NCI
J. Haltziel	r II.	SILAI D	Tence Technicia	311	LP NCI
COOPERATING UNITS (if any)					
LAB/BRANCH			·····		
Laboratory of Pathology					
SECTION					
Tumor Invasion and Metas	stases Section				
NCI, NIH, Bethesda, MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:		
	1	•••••	1		
(a) Human subjects	🖾 (b) Human tissi	ues 🗆	(c) Neither		
(a1) Minors			. ,		
(a2) Interviews					В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed th	le space provid	ed.)		
Over the next year a new	v project study:	ing the e	effect of tumor	endothelial	cell
interaction on vascular	invasion, will	be initi	lated. Quantita	ation of tur	or cell
collagenase gene express	sion will be use	ed at fin	st as a marker	for invasiv	7e
potential. Secreted fac	ctors that eithe	er inhibi	it or stimulate	the tumor o	:e11
collagenase will be loop	ked for in cond:	tioned m	nedia from capil	Llary, venou	is and
tumor cells on collagen:	ase expression i	ill be a	studied in co-ci	iltures of t	he two
cell types. Tumor cell	collagenase exi	ression	in the co-cultu	ires will be	ane Ewo
quantitated by using in	situ hybridizat	ion tech	nique, followed	by positiv	/e
identification of the en	ndothelial cells	through	n immunostaining	g for factor	. VIII
antigen. If collagenase	e stimulating fa	actors en	pressed by endo	thelial cel	ls,
either as secreted or co	ell surface prot	eins wil	l be identified	l, we will p	roceed
to isolate and purify su	ich factors.				



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES -	PUBLIC HEA	LTH SERVICE	PHOJECT N	UMBER
NOTICE OF INT	RAMURAL RESEAR	CH PROJE	СТ		
				ZO1 CB	09158-01 LP
PERIOD COVERED					
October 1, 1986 to Sept	ember 30, 1987				
TITLE OF PROJECT (80 characters or less	. Title must fit on one line betw	veen the border	rs.) etastatic Poter	+1-1	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the	Principal Invest	tigator.) (Neme, title, labore	tory and insti	tute affiliation)
PI: U.P. Thorgeirs	son	Expert			LP NCI
OTHER: M. Ballin		Visiting	g Fellow		LP NCI
J. Hartzler		Physical	l Science Techr	lician	LP NCI
COOPERATING UNITS (if any)					
LAB/BRANCH					
Laboratory of Pathology					
SECTION					
Tumor Invasion and Meta	stases Section				
INSTITUTE AND LOCATION	20002				
NGI, NIH, Betnesda, MD	PROFESSIONAL		OTHER		
1 1/2	1		1/2		
CHECK APPROPRIATE BOX(ES)					
(a) Human subjects	(b) Human tissue	es 🖾	(c) Neither		
(a1) Minors					
L (az) Interviews	duced time. Do not exceed the	space provide	d)		В
Activated ras oncogenes	have been shown	to conf	er the metastat	ic phen	otype upon
different non-neoplasti	c and benign neor	plastic	cell types. We	have e	valuated the
effect of amplified exp	ression of v-H-ra	as in an	NIH/3T3 line,	433, wh	ich contains
the ras under a transcr	iptional control	of the g	glucocorticoid-	sensiti	ve mammary
tumor virus long termin	al repeat. Thus	, treatme	ent with a gluo	cocortic	oid, such as
dexamethasone for 6 day	s, results in a .	20-IOId :	increase in P2	colle	Sis, and The untreated
433 cells produced expe	rimental metasta:	ses but i	not spontaneous	metast	ases in nude
mice. However, after d	examethasone trea	atment,	the lung coloni	zing ca	pacity was
decreased two- to three	-fold.		Ū	Ū	
These data show that am	plification of en	xpression	n of the <u>ras</u> ge	ene unde	r the control
transfected cells	moter does not at	igment ti	ne metastatic (	apacity	or the ras
cransiecceu corrs.					

PROJECT NUMBER



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC REALTH SERVI	
NOTICE OF INT	RAMURAL RESEARCH PROJECT	701 CR 00150 01 ID
October 1, 1986 to Septe	ember 30, 1987	
TITLE OF PROJECT (80 characters or less.	Title must fit on one line between the borders.)	
Thrombospondin and its R	eceptors: Role in Cell Adhesio	n and Motility
PRINCIPAL INVESTIGATOR (List other prod	fessional personnel below the Principal Investigator.) (Name	, title, laboratory, and institute affiliation)
DT. O Manshalatti	Western Reller	
OTHER, LA Lights	Chief Tumor Invasion & M	LP NCI
OTHER: L.A. LIOLLA	chief, idmoi invasion a M	elastases section LF NGI
COOPERATING UNITS (if any)		
D. Roberts, Laboratory o	f Structural Biology, NIDDKD, N	IH
LAB/BRANCH		
SECTION		
Tumor Invasion and Metas	tases Section	
INSTITUTE AND LOCATION		
NCI, NIH, Bethesda, MD 2	0892	
TOTAL MAN-YEARS:	PROFESSIONAL: OTHER:	
1	1 0	
CHECK APPROPRIATE BOX(ES)		
(a) Human subjects	🖾 (b) Human tissues 🗀 (c) Neith	ier
(a1) Minors		
	used type. Do not exceed the paper provided )	В
Thrombospondin induces t	he migration of human melanoma	and carcinoma cells. Using
a modified Boyden chambe	r assav, tumor cells migrated t	o a gradient of either
soluble thrombospondin (	chemotaxis) or substratum bound	thrombospondin (hapto-
taxis). A series of hum	an melanoma and carcinoma cells	exhibited different levels
of response when compare	d for their relative motility s	timulation by thrombospondin
haptotaxis versus chemot	axis. Human A2058 melanoma cel	ls which exhibit a strong
haptotaxic and chemotaxi	c response to thrombospondin we	re used to study the
structural domains of th	rombospondin required for the r	esponse. Monoclonal anti-
body Co./ which binds to	the COOH terminal region of th	rombospondin inhibited
thrombospondin chemotavi	andent optimal manner. Co./ nac	d no significant effect on
fucoidan which hind to t	he NHo terminal benarin binding	domain of thrombospondin
inhibited thrombognondin	ne mig cerminar neparin binding	domain of chrombospondin,
THUTDILEG LULOMDOSDOUGIU	chemotaxis but not haptotaxis.	Monoclonal antibody
A6.1 directed against th	chemotaxis but not haptotaxis. e internal core region of throm	Monoclonal antibody bospondin had no signifi-
A6.1 directed against th cant effect on hepatotax	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin
A6.1 directed against th cant effect on hepatotax lacking the heparin bind	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH r	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag-
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6.	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH re 7 binding site, was cleaved off	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6. fragment (which retains	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH r. 7 binding site, was cleaved off the RGDA sequence) failed to inc	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa duce haptotaxis. Separate
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6. fragment (which retains structural domains of th haptotaxis versus chemet	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH re 7 binding site, was cleaved off the RGDA sequence) failed to im- rombospondin are therefore requi- axis. This may have implication	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa duce haptotaxis. Separate ired for tumor cell ns during hematoranous
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6. fragment (which retains structural domains of th haptotaxis versus chemot cancer metastases format	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH ro 7 binding site, was cleaved off the RGDA sequence) failed to inc rombospondin are therefore requi- axis. This may have implication ion.	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa duce haptotaxis. Separate ired for tumor cell ns during hematogenous
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6. fragment (which retains structural domains of th haptotaxis versus chemot cancer metastases format	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH ro 7 binding site, was cleaved off the RGDA sequence) failed to inc rombospondin are therefore requi- axis. This may have implication ion.	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa duce haptotaxis. Separate ired for tumor cell ns during hematogenous
A6.1 directed against th cant effect on hepatotax lacking the heparin bind mediate haptotaxis but n ment, containing the C6. fragment (which retains structural domains of th haptotaxis versus chemot cancer metastases format	chemotaxis but not haptotaxis. e internal core region of throm is or chemotaxis. The 140 kDa ing amino terminal region, reta ot chemotaxis. When the COOH ro 7 binding site, was cleaved off the RGDA sequence) failed to inc rombospondin are therefore requi axis. This may have implication ion.	Monoclonal antibody bospondin had no signifi- fragment of thrombospondin ined the property to fully egion of the 140 kDa frag- , the resulting 120 kDa duce haptotaxis. Separate ired for tumor cell ns during hematogenous



	PROJECT NUMBER	
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		
NOTICE OF INTRAMURAL RESEARCH PROJECT		
	Z01 CB 09161-01 LP	
PERIOD COVERED		
October 1, 1986 to September 30, 1987		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)		
Laminin Receptor and its Role in the Function of Natural Kill	er Cells	
	tory, and institute effilietion)	
PL C I Brucht Export	LD NCT	
OTHER: LA Lights Chief Tumor Invesion & Metastases	Section IP NCI	
offick. E.K. Elocta Ghief, fumor invasion a netastases	Section LF NCI	
COOPERATING UNITS (if any)		
J. Hiserodt, Pittsburgh Cancer Institute, Pittsburgh, PA		
Section		
Tumor Investor and Motastason Section		
INSTITUTE AND LOCATION		
NCT NIH Bethesda MD 20892		
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:		
1 0.8 0.2		
CHECK APPROPRIATE BOX(ES)		
(a) Human subjects (b) Human tissues (c) Neither		
(a1) Minors		
(a2) Interviews	В	
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)		
Natural killer (NK) cells, a subpopulation of large granular	lymphocytes (LGL)	
are involved in the spontaneous lysing of tumor or virally in	fected target	
cells. The killing action requires binding of the killer cel	ls to the target	
cells. The role of the laminin receptor in this process of s	pecific binding	
is being examined in our laboratories. Using murine NK cells	, the presence of	
laminin-like molecule and a receptor for laminin binding has been established		
(Kd 10 ++ M, approximately 990,000 receptors/cell).		
Further studies will attempt to define and summer the	on on NV ocilia	
versus the already established leminin recenter leasted on me	or on NK cells	
the interactions between these two recentors during cell lysi	s will be explored	
the interactions between these two receptors during terr rysr	s will be explored.	
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DEPARTMENT OF HEALTH A	PROJECT NUMBER		
NOTICE OF INTRAMURAL RESEARCH PROJECT			
			Z01 CB 00550-07 LP
PERIOD COVERED	ember 30 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the borders	.)	
Immunologic Characteriz	ation of Malignant Lympho	mas	
PRINCIPAL INVESTIGATOR (List other pro	fessionel personnel below the Principel Investig	pator.) (Name, title, laborat	ory, and institute affiliation)
PI: E.S. Jaffe	Chief, Hematopath	ology Section	LP NCI
OTHER: J. Cossman	IR: J. Cossman Senior Investigator LP NC		
D.L. Longo	Senior Investigator MB		
L.M. Neckers M.A. Bookman	Kesearch Chemist Senior Investigat	or	LP NCL MB NCL
Dookman	Schior investigat	01	HD NOI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Laboratory of Pathology			
Hematonathology Section			
INSTITUTE AND LOCATION			······································
NCI, NIH, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)	3.0	2.0	
(a) Human subjects	🛛 (b) Human tissues	(c) Neither	
(a1) Minors	·		A
SUMMARY OF WORK (Use standard unred	исеа туре. Do not ехсееа те space providea.	)	
In order to assess the	clinical and pathologic s	ignificance of	the immunologic
characterization of hum	an malignant lymphomas, f	resh biopsy ti	ssues are
obtained from patients	referred to the Clinical	Center for tre	atment. Biopsies
are obtained with patient permission prior to therapy and processed in the			
Hematopathology Section. The neoplastic cells are characterized as to their			
as belonging to specific developmental and functional subpopulations. This data			
as belonging to specifi	cells, or histiocytes, an c developmental and funct	d in addition ional subpopul	can be identified ations. This data
as belonging to specifi is then correlated with	cells, or histiocytes, an c developmental and funct clinical and pathologic	d in addition ional subpopul data. Morphol	can be identified ations. This data ogic features are
as belonging to specifi is then correlated with analyzed to achieve imp	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of l	d in addition ional subpopul data. Morphol ymphoprolifera	can be identified ations. This data ogic features are tive lesions.
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of l	d in addition ional subpopul data. Morphol ymphoprolifera	can be identified ations. This data ogic features are tive lesions.
as belonging to specifi is then correlated with analyzed to achieve imp This information is util distinguish new clinico	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for
as belonging to specifi is then correlated with analyzed to achieve imp This information is util distinguish new clinico potential immunotherapy	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of l lized to develop improved pathologic entities. It or adjunctive immunother	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of l lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of l lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous
as belonging to specifi is then correlated with analyzed to achieve imp This information is uti. distinguish new clinico potential immunotherapy bone marrow transplanta	cells, or histiocytes, an c developmental and funct clinical and pathologic roved classification of 1 lized to develop improved pathologic entities. It or adjunctive immunother tion.	d in addition ional subpopul data. Morphol ymphoprolifera classificatio also will be u apy in a progr	can be identified ations. This data ogic features are tive lesions. ns of disease and to sed as a basis for am of autologous



			PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE			
NOTICE OF INTRAMURAL RESEARCH PROJECT			
			Z01 CB 00552-07 LP
PERIOD COVERED			
October 1, 1986 to Septe	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	rs.)	
Molecular Basis of the I	Diagnosis of Human Lympho	oproliferative	Disease
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	igator.) (Name, title, labora	tory, and institute affiliation)
PI: J. Cossman	Senior Investigat	or	LP NCI
OTHER: M. Raffeld	Senior Staff Fell	Low	LP NCI
J. Sundeen	Biotechnology Fe.	llow	LP NCI
P. Conen	Biotechnology Fe.	llow	LP NCI
M. Uppenkamp Guest Researcher			LP NCI
R. Coupland P. Andrado	Visiting Fallow		
COOPERATING UNITS (if any)	VISICING FEIIOW		LP NCI_
Surgery Branch, NCI: Med	licine Branch, NCI: Metal	olism Branch	NCI
,,,,,,,	, nor, nera	June Station,	
LAB/BRANCH			
Laboratory of Pathology			· · · · · · · · · · · · · · · · · · ·
SECTION			
Hematopathology Section			·
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD 2	20892		
TOTAL MAN-YEARS:	PHOFESSIONAL:	UTHEN:	
	5	.50	
CHECK APPROPRIATE BUA(ES)			
(a) Human subjects	(h) Human tissues	(c) Neither	
(a) Human subjects	(b) Human tissues	(c) Neither	
(a) Human subjects (a1) Minors (a2) Interviews	🖄 (b) Human tissues 🗌	(c) Neither	R
(a) Human subjects     (a1) Minors     (a2) Interviews     SUMMARY OF WORK (Use standard unred	(b) Human tissues	(c) Neither	B
(a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred We have undertaken invest	(b) Human tissues	(c) Neither	BB
<ul> <li>(a) Human subjects</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unred</li> <li>We have undertaken invest the pathogenesis of lymp</li> </ul>	(b) Human tissues	(c) Neither a.) the molecula ts and Hodgkin'	B r genetic basis of s disease.
(a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred We have undertaken inves the pathogenesis of lymp	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz ohoproliferative disorder	(c) Neither a.) the molecula ts and Hodgkin'	B r genetic basis of s disease.
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred the have undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization analysis</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz phoproliferative disorder alysis, our investigation	(c) Neither a.) the molecula the molecula the molecula the molecula the molecula the molecula the molecula	r genetic basis of s disease. rated the existence
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred) where undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization ana of "benign clonal lympha"</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz phoproliferative disorder alysis, our investigation adenopathy" and the evolu	(c) Neither d.) the molecula the molecula	r genetic basis of s disease. rated the existence ant transformation
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred the pathogenesis of lymp</li> <li>By DNA hybridization ana of "benign clonal lymphato high grade lymphoma.</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolution The significance of the	(c) Neither d.) the molecula the molecula	r genetic basis of s disease. rated the existence ant transformation rom a diagnostic
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred) the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma.</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteria oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of the polonality is not necessa	(c) Neither d) the molecula the molecula	r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreaded to the pathogenesis of lymphone in the pathogenesis of lymphone is t</li></ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteria oboproliferative disorder alysis, our investigation adenopathy" and the evolut The significance of the poclonality is not necessation is blot hybridizations	(c) Neither d) the the molecula the molec	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed the pathogenesis of lymphotes of lymphotes of the pathogenesis of lymphotes of "benign clonal lymphato high grade lymphoma. standpoint, is that mono have further applied gervariable genes of the T</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of the boclonality is not necessation cell receptor gamma locu	(c) Neither d) the molecula the molecula	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred We have undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lympha to high grade lymphoma.</li> <li>standpoint, is that monon have further applied ger variable genes of the T are not selected during</li> </ul>	(b) Human tissues duced type. Do not exceed the spece provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolution The significance of this boclonality is not necessar homic blot hybridizations cell receptor gamma locution a wide variety of human	(c) Neither (c) N	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno-
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed the pathogenesis of lymphome standard unreed to high grade lymphoma. Standpoint, is that mono have further applied gervariable genes of the T are not selected during deficiency disorders.</li> </ul>	(b) Human tissues duced type. Do not exceed the spece provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of this polonality is not necessan nomic blot hybridizations cell receptor gamma locu a wide variety of human	(c) Neither (c) N	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno-
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed we have undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma. standpoint, is that mono have further applied gervariable genes of the T are not selected during deficiency disorders.</li> </ul>	(b) Human tissues duced type. Do not exceed the spece provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of this bolonality is not necessation cell receptor gamma locu a wide variety of human	(c) Neither (c) N	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno-
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed we have undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization ana of "benign clonal lymphato high grade lymphoma. standpoint, is that monor have further applied ger variable genes of the T are not selected during deficiency disorders.</li> <li>The defective mutants we a single critical standard.</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of the bolonality is not necessa homic blot hybridizations cell receptor gamma locu a wide variety of human	(c) Neither (c) N	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno- ne, CEM, demonstrate egulation of T cell
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed we have undertaken invest the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma. standpoint, is that monor have further applied ger variable genes of the T are not selected during deficiency disorders.</li> <li>The defective mutants we a single critical step of receptor alpha gene transmission.</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz ohoproliferative disorder alysis, our investigation adenopathy" and the evolu- the significance of this oclonality is not necessar nomic blot hybridizations cell receptor gamma locu- a wide variety of human the have developed of the evo- on T cell development sur- pertintion.	(c) Neither d) the the molecular the molecular	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno- ne, CEM, demonstrate egulation of T cell
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unreed the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma. standpoint, is that monor have further applied gervariable genes of the T are not selected during deficiency disorders.</li> <li>The defective mutants we a single critical step or receptor alpha gene transplant</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of this oclonality is not necessa nomic blot hybridizations cell receptor gamma locu a wide variety of human the have developed of the evolution of the tell development sur-	(c) Neither (c) N	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno- ne, CEM, demonstrate egulation of T cell
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred) the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma. standpoint, is that mondon have further applied ger variable genes of the T are not selected during deficiency disorders.</li> <li>The defective mutants we a single critical step of receptor alpha gene transition the origins</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolu The significance of this oclonality is not necessa nomic blot hybridizations cell receptor gamma locu a wide variety of human the have developed of the evolution scription.	(c) Neither (c) N	T genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno- ne, CEM, demonstrate egulation of T cell arly cloned the re-
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>SUMMARY OF WORK (Use standard unred) the pathogenesis of lymp</li> <li>By DNA hybridization and of "benign clonal lymphato high grade lymphoma. standpoint, is that monor have further applied ger variable genes of the T are not selected during deficiency disorders.</li> <li>The defective mutants we a single critical step or receptor alpha gene transformed the origins arranged immunoglobulin</li> </ul>	(b) Human tissues duced type. Do not exceed the space provide stigations to characteriz oboproliferative disorder alysis, our investigation adenopathy" and the evolut The significance of the oclonality is not necessar nomic blot hybridizations cell receptor gamma lock a wide variety of human the have developed of the evolution on T cell development sur- nscription.	(c) Neither d) the the molecular the molecular	B r genetic basis of s disease. rated the existence ant transformation rom a diagnostic t to malignancy. We e use of specific amma variable genes es and immuno- ne, CEM, demonstrate egulation of T cell arly cloned the re- rom a Hodgkin's cell
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DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJE	СТ	
			Z01 CB 00850-05 LP
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the border	s.)	
Clonal Evolution of Lym	phoid Neoplasms		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Invest	gator.) (Name, title, laboret	ory, and institute affiliation)
PI: J. Cossman	Senior Investiga	tor	LP NCI
OTHER: M. Raffeld	Senior Staff Fel	low	LP NCT
M. Uppenkamp	Guest Researcher		LP NCT
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COOPERATING UNITS (if any)			
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CHECK APPHONIATE BOK(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree By means of Southern bloch lymphoma, in particular is resistant to therapy years apart demonstrate common stem cell in all evolution was frequent ( events affecting rearran bcl-2 locus in follicular remained stable.  To further analyze minin tecting rare follicular Southern blot analysis. following clinical remis We have developed cell 1 telangiectasia. A chroof field electrophoresis to Our leukemia cell lines evolution of T cell neop sites.	(b) Human tissues	(c) Neither (c) Neither (c) Neither (c) overed that re- derived from or patients obtain d recurrences of eoplasms were a aracterized by . Despite this e of t(14;18) for have developed de detection by seful for predi- oma. kemia of a patha 4;18) is being the T-alpha go ia provide a mu f breakage of o	B currence in B cell coult disease which ned as much as ten were derived from a seen. Clonal secondary genetic s, the rearranged translocation, a method for de- y conventional iction of recurrence int with atexia analyzed by pulse- ene at band 14q11. odel of clonal chromosomal fragment
CHECK APPHONENTE BOK(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree By means of Southern blo lymphoma, in particular is resistant to therapy years apart demonstrate common stem cell in all evolution was frequent ( events affecting rearran bcl-2 locus in follicular remained stable.  To further analyze minim tecting rare follicular Southern blot analysis. following clinical remis We have developed cell telangiectasia. A chroof field electrophoresis to our leukemia cell lines evolution of T cell neop sites.	☑ (b) Human tissues □ duced type. Do not exceed the space provides ot analysis, we have disc follicular lymphoma, is . Multiple samples from that primary neoplasm an patients. No biclonal m (42% of cases) and was ch nged immunoglobulin geness ar lymphoma, a consequence nal residual disease, we lymphoma cells which elu This method may prove u sion in follicular lympho lines from the T cell leu mosomal translocation t(1 to identify involvement of from ataxia telangiectas plasms as a consequence of	<pre>(c) Neither (c) Neither (c) overed that red derived from opatients obtain d recurrences of eoplasms were a aracterized by . Despite this e of t(14;18) f have developed de detection by seful for pred oma. kemia of a pat: 4;18) is being the T-alpha ge ia provide a me f breakage of open </pre>	B currence in B cell cult disease which ned as much as ten were derived from a secondary genetic s, the rearranged translocation, a method for de- genetication of recurrence int with atexia analyzed by pulse- ene at band 14q11. odel of clonal chromosomal fragment
CHECK APPHONENTE BOK(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree By means of Southern blo lymphoma, in particular is resistant to therapy, years apart demonstrate common stem cell in all evolution was frequent ( events affecting rearran bcl-2 locus in follicular remained stable.  To further analyze minim tecting rare follicular Southern blot analysis. following clinical remis We have developed cell ( telangiectasia. A chroo field electrophoresis to Our leukemia cell lines evolution of T cell neop sites.	☑ (b) Human tissues □ duced type. Do not exceed the space provides ot analysis, we have disc follicular lymphoma, is . Multiple samples from that primary neoplasm an patients. No biclonal m (42% of cases) and was ch nged immunoglobulin geness ar lymphoma, a consequence nal residual disease, we lymphoma cells which elu This method may prove u sion in follicular lymph lines from the T cell leu mosomal translocation t(1 to identify involvement of from ataxia telangiectas plasms as a consequence of	<ul> <li>(c) Neither</li> <li>(c) Neither</li> <li>(c) overed that rederived from options obtained for the second /li></ul>	B         currence in B cell         cult disease which         keed as much as ten         seen. Clonal         seen. Clonal         stenslocation,         a method for de-         sconventional         iction of recurrence         int with atexia         analyzed by pulse-         int band l4qll,         ictions omal fragment
CHECK APPHONENTE BOK(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree By means of Southern blo lymphoma, in particular is resistant to therapy years apart demonstrate common stem cell in all evolution was frequent ( events affecting rearran bcl-2 locus in follicular remained stable.  To further analyze minim tecting rare follicular Southern blot analysis. following clinical remis We have developed cell ( telangiectasia. A chroo field electrophoresis to Our leukemia cell lines evolution of T cell neop sites.	☑ (b) Human tissues □ duced type. Do not exceed the space provides ot analysis, we have disc follicular lymphoma, is . Multiple samples from that primary neoplasm an patients. No biclonal m (42% of cases) and was ch nged immunoglobulin geness ar lymphoma, a consequence nal residual disease, we lymphoma cells which elu This method may prove u ssion in follicular lymph lines from the T cell leu mosomal translocation t(1 to identify involvement of from ataxia telangiectas plasms as a consequence of	<pre>(c) Neither (c) Neither (c) vered that red derived from or patients obtain d recurrences re eoplasms were re aracterized by . Despite this e of t(14;18) fr have developed de detection by seful for pred oma. kemia of a pat: 4;18) is being the T-alpha g ia provide a mu f breakage of o </pre>	B         currence in B cell         secondary genetic         secondary genetic         steam location.         a method for de-         sconventional         currence         analyzed by pulse-         analyzed by pulse- <t< td=""></t<>
CHECK APPHONENTE BOK(ES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unree By means of Southern blu lymphoma, in particular is resistant to therapy years apart demonstrate common stem cell in all evolution was frequent ( events affecting rearran bcl-2 locus in follicular remained stable.  To further analyze minin tecting rare follicular Southern blot analysis. following clinical remis We have developed cell 1 telangiectasia. A chron field electrophoresis to Our leukemia cell lines evolution of T cell neop sites.	☑ (b) Human tissues □ duced type. Do not exceed the space provides ot analysis, we have disc follicular lymphoma, is . Multiple samples from that primary neoplasm and patients. No biclonal m (42% of cases) and was ch nged immunoglobulin geness ar lymphoma, a consequence mal residual disease, we lymphoma cells which elu This method may prove u ssion in follicular lymph lines from the T cell leu mosomal translocation t(1 to identify involvement of from ataxia telangiectas plasms as a consequence of	(c) Neither (c) Neither (c) Neither (c) overed that re- derived from or- patients obtain (c) recurrences of eoplasms were an aracterized by . Despite this e of t(14;18) for have developed de detection by seful for predi- oma. kemia of a path 4;18) is being the T-alpha go ia provide a mu f breakage of o	B         currence in B cell         secondary genetic         secondary genetic         stanslocation,         a method for de-         sconventional         ction of recurrence         analyzed by pulse-         analyzed by pulse-         analyzed by currence



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE			
NOTICE OF INTRAMURAL RESEARCH PROJECT			
	Z01 CB 00855-05 LP		
PERIOD COVERED			
October 1, 1986 to September 30, 1987			
TITLE OF PROJECT (80 characters or less. Intermust int on one line between the borders.)			
PRINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Name, title, lebora	tory, and institute affiliation)		
PI: E.S. Jaffe Chief, Hematopathology Section	LP NCI		
OTHER: W.A. Blattner Senior Investigator	EEB NCI		
R.C. Gallo Senior Investigator	LTCB NCI		
P. Levine Senior Investigator	EEB NCI		
LAB/BRANCH			
Laboratory of Pathology			
SECTION			
Hematopathology Section			
INSTITUTE AND LOCATION			
NCI, NIH, BETNESDA, MD 20092	······		
101AL MAN-TEARS: PROFESSIONAL. 0100.02			
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects (b) Human tissues (c) Neither			
(a1) Minors			
(a2) Interviews	Α		
SUMMARY OF WORK (Use standerd unreduced type. Do not exceed the space provided.)			
Pathologic material from patients identified to be seropositiv	ve for HTLV-I is		
reviewed and correlated with clinical and epidemiologic featur	es of disease.		
Material is derived from patients in the United States as well	as other parts of		
the world. Where possible, immunologic phenotyping of the lym	phomas is performed		
and tumor DNA is directly analyzed for viral genome.			
In calcoted populations where HTLU-I is endemic, such as lamai	ca prospective		
studies of all newly diagnosed lymphoma patients are conducted	Such studies are		
useful in identifying the clinicopathologic spectrum of HTLV-I	associated		
diseases. Prospective studies of all lymphomas in similar geo	graphic regions		
with differing incidences of adult T cell leukemia/lymphomas are studies to			
discern factors which make an impact on the incidence of HTLV-	I and HTLV-I		
associated diseases.			
· ·			



DEPARTMENT OF HEA	LTH AND HUMAN SERVI	ICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF	INTRAMURAL RES	SEARCH PROJE	ECT	
				ZOI CB 00881-06 LP
PERIOD COVERED		07		
UCEODER 1, 1980 EO	or less Title must fit on one	0 /	re )	
Regulation of Lympho	or was not in one of the or one of the original of the origina	and Prolife	ration	
PRINCIPAL INVESTIGATOR (List of	her professional personnal be	low the Principal Invest	igator.) (Name, title, labora	tory, and institute affiliation)
PI: L.M. Neckers	3	Research Che	emist	LP NCI
OTHER: J.B. Trepel		Biologist		NMOB NCI
R. Nordan		Staff Fellow	V   1	LG NCI
0. Colamonia	21	Visiting Fe.	reber	
5. LOKE		Guest Resea	Cher	LE NOI
COOPERATING UNITS (if any)		·····		
Laboratory of Geneti	Lcs, NCI			
Naval Medical Oncold	ogy Branch, NCI			
LAB/BHANCH	0.000			
SECTION	Logy			
Hematopathology Sect	ion			
INSTITUTE AND LOCATION			··	
NCI, NIH, Bethesda,	MD 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:	
4.0	4.	0	0	
(a) Human subjects	(b) Human		(c) Neither	
(a) (a1) Minors				
(a2) Interviews				В
SUMMARY OF WORK (Use standar	d unreduced type. Do not exc	eed the space provided	<u>d.)</u>	
All cells studied to	date require t	ransferrin fo	or growth. We	and others have
shown that antibodie	es to the transf	errin recepto	or block the g	rowth of lympho-
blastoid cell lines.	In mitogen-st	imulated lymp	phocytes, these	antibodies block
proliferation. We a	are studying the	processes wh	nich regulate t	the appearance of
these receptors in J	lymphocytes and	lymphoblasto:	ud cell lines,	and the function of
these receptors in cell growth and metabolism. We have demonstrated that $G_1$				
blocked, even if cells are expressing high levels of growth factor receptors are				
messenger RNA and c-myc and c-myb messenger RNA. Furthermore, either blockade of				
calcium channels or addition of cAMP to cells results in G1 arrest and loss of				
transferrin receptor mRNA. The effect of cAMP can be detected at the level of				
transcription.				
Ve have been to at	du the sele of		dua in the tax	mainian of T collo
from G to S phase	In an initial	study a com	eins in the tra	ligomer completely
blocked the appearan	ice of c-myc pro	tein in mitor	ven treated T	cells, vet these
cells went on to exp	press IL-2 recep	tors, transfe	errin receptors	and DNA polymerase a
protein. Yet they f	ailed to synthe	size DNA. We	e plan to conti	Inue to use anti-
sense constructs to	various nuclear	proteins to	study their ro	ole(s) in cell growth
and activation. Initially, we are examining the requirements for several nuclear				
proteins in DNA poly	merase α activi	ty. To date	, we have deter	mined that two such
proteins, c-myc and	Ki-6/, are requ	ired for poly	ymerase $\alpha$ activ	ity in vitro.



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PROJE	ECT		
			201 CB 09146-02 LP	
PERIOD COVERED				
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the border	rs.)		
Molecular Biology of Tra	ansferrin Receptor Expres	ssion		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigator.) (Name, title, labora	tory, and institute effiliation)	
PI: L.M. Neckers	Research Chemist	t	LP NCI	
UIHER: J. Irepel	Senior Investig	ator	NMOB NCI	
L. WOIII	Senior investige	acor	LG NCI	
COOPERATING UNITS (if any)				
Laboratory of Constice	NCI			
Navy Medical Oncology B	ranch. NCI			
LAB/BRANCH	culony not		· · · · · · · · · · · · · · · · · · ·	
Laboratory of Pathology				
SECTION				
Hematopathology Section				
INSTITUTE AND LOCATION	20802			
NCI, NIH, Betnesda, MD	PROFESSIONAL	OTHER		
2-0	2-0	0		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects	🖾 (b) Human tissues	(c) Neither		
(a1) Minors				
(a2) Interviews			B	
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	d.)		
Although it is clear that	at transferrin receptors	are regulated	in part by intra-	
Since probes to the trai	so clear that other regul	ave recently be	acome available we	
are utilizing molecular	biology techniques to st	tudy the regula	ation of transferrin	
receptor expression at 1	the molecular level. One	e part of this	project involves	
the study of mouse plasm	the study of mouse plasmacytoma mRNA. We have found that there are two trans-			
ferrin receptor mRNAs in	n these cells. One messa	age lacks the u	intranslated part of	
the full-length mRNA, while retaining the coding sequences for the protein.				
Using this model system, we plan to study the ability of iron to regulate TfR				
mkNA levels at the level of the message. We will determine if the untranslated				
part of the message is necessary for from regulation.				
Another part of the proj	ject involves the regulat	tion of TfR ger	ne transcription in	
HL-60 cells by cAMP. We	e have shown that cAMP sh	huts off transc	cription of both	
c-myc and TfR within 30' - 2 hrs after addition. We will investigate the mechanism				
of this shut-off and det	termine if the c-myc gene	e has any effec	t on transcription	
of the Tik gene.				
We have produced a TfR	construct which contains	only the codir	g region of the cDNA	
under LTR control. We h	have successfully transfe	ected 3T3 cells	with this construct	
and have demonstrated th	ne existence of human TfH	R on their surf	ace by immunopre-	
cipitation and FACS anal	lysis. We will use these	e cells to stud	ly the regulation of	
the virally controlled 1	ffR sequence.			


					PROJECT NUMBER	
DEPA	RTMENT OF HEALTH					
	NOTICE OF INT					
					Z01 CB 09147-02 LP	
PERIOD COVE	ERED					
October	1, 1986 to Sept	ember 30, 198	7			
TITLE OF PRO	DJECT (80 characters or less	. Title must fit on one lir	ne between the borde	ors.)		
Defectiv	e TfR in HTLV-I	Infected Hum	an T cells			
PRINCIPAL IN	IVESTIGATOR (List other pro	ofessional personnel belo	w tha Principal Inves	tigator.) (Name, title, labora	tory, and institute affiliation)	
DT.	I M Neckers		Research Cl	homist	LP NOT	
OTHER.	C A Vidal-Sot	<b>^</b>	Guest Rese	archer	LP NCT	
OTHER.	O.R. Colamoni	ci	Visiting F	ellow	LP NCT	
	S. Matsushiva		Fogarty Fe	11ow	COP NCT	
	H. Mitsuva		Fogarty Fe	11ow	COP NCI	
	S. Broder		Senior Inv	estigator	COP NCI	
				U		
COOPERATIN	G UNITS (if any)					
Clinical	Oncology Progr	am, NCI				
LAB/BRANCH						
Laborato	ry of Pathology					
SECTION	theless Costies					
INSTITUTE AN	ID LOCATION					
NCT NTH	Bethesda MD	20892				
TOTAL MAN-Y	FARS:	PROFESSIONAL		OTHER		
	0.5	0.5		0		
CHECK APPR	OPRIATE BOX(ES)				· · · · · · · · · · · · · · · · · · ·	
🗌 (a) Hu	man subjects	🖾 (b) Human t	issues 🗌	(c) Neither		
🗌 🗍 (a1	) Minors					
🗌 (a2	2) Interviews					в
SUMMARY OF	WORK (Use standard unred	duced type. Do not exce	ed the space provide	d.)		
We have :	found that HTLV	-I infected T	cells expr	ess 10-20 fold	more TfR on their	
surface,	but that this :	is due to a r	edistributi	on of the recep	tor from cytoplasm	
to surfa	ce and not to a	n increased r	eceptor syn	thesis. Furthe	r, the TfR in thes	e
cells is	poorly internal	lized and poo	rly phospho:	rylated by phor	bol ester. The	
receptor	cannot deliver	iron to thes	e cells, what	ich nevertheles	s require iron for	
prolifer	ation. Antibod:	ies which pre	vent iron b:	inding to the I	fR still inhibit	
the grow	th of these cel.	ls.				



			PROJECT NUMBER
DEPARTMENT OF HEALTH A			
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	
			Z01 CB 09149-02 LP
October 1 1986 to Sept	ambor 30 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the borde	rs.)	
Differentiation of Immat	cure T Cell Neoplasms by	Interleukin-2	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigator.) (Name, title, lebo	ratory, and institute affiliation)
PI: L.M. Neckers	Research	Chemist	LP NCI
OTHER: O.R. Colamonici	Visiting Pielegist	Fellow	LP NCI
D.G. Poplack	Senior I	Westigator	DB NCT
T. Kirsh	Senior II	vestigator	NMOB NCI
1. 11101	Jenior I	incoting actor	MIOD NOT
COOPERATING UNITS (if any)			
NMUB, NCI; PB, NCI			
LAB/BRANCH			
Laboratory of Pathology			
SECTION			
Hematopathology Section			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, MD 2		OTHER:	······································
TOTAL MAN-TEARS.	A A	OTHER.	
CHECK APPROPRIATE BOX(ES)	4	0	
X (a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	d.)	
We have studied 45 cases	of T cell and myeloid 1	leukemia tryin	g to further charac-
terize them. In 15 case	es, these cells respond t	treatment w	ith IL-2, in that
they develop the ability	to kill tumor cells.	Their phenotyp	e changes to resemble
that of a more mature T	cell. Using these cases	s, we have stu	died the role of the
T cell receptor in gener	ation of cytotoxic activ	vity. In one	case, IL-2 induced a
proliferation of cells u	itilizing TCR yo. We den	nonstrated that	t this TCR was
functional in that anti-	CD3 stimulated an elevat	ion of intrac	eliular [Ca <sup>2</sup> ] and
augmented MHC-unrestrict	ed cytolysis. Trigerrin	ng of the TCR	yo in this case
leads directly to releas	se of cycofycic granule e	enzymes.	
In studying the role of	IL-2 in this process, we	observed tha	t the changes we
recorded following IL-2	were transduced solely	via the P75 IL	-2 binding protein
and not the P55 (TAC) pr	cotein. Based on these f	indings, we h	ave begun a clinical
protocol, in collaborati	lon with DRS. Poplack an	nd Kirsh, to s	tudy the effectiveness
of rIL-2 in vivo as a tr	reatment for immature T o	cell malignanc	ies.



			LTH SERVICE	PROJECT	IUMBER
NOTICE OF INT	RAMURAL RESEAR			ZO1 CB	09150-02 LP
PERIOD COVERED					
October 1, 1986 to Sept	ember 30, 1987 s. Title must fit on one line betw	ween the borde	(S.)	·	
Induction of Monocytic	Differentiation 1	by Sphing	gomyelinase		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the	Principal Invest	tigator.) (Name, title, lebor	atory, and inst	itute affilietion)
PI: O.P. Colamonia	i V	iciting I	Fallow		LD NCT
OTHER: L.M. Neckers	Re	esearch (	Chemist		LP NCI LP NCI
COOPERATING UNITS (# eny)					
Laboratory of Pathology					
SECTION				1.17	
Hematopathology Section					
NCI, NIH, Bethesda, MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:		
	0.5		0		
(a) Human subjects	🖾 (b) Human tissue	es 🗌	(c) Neither		
(a2) Interviews					в
SUMMARY OF WORK (Use standard unrac	duced type. Do not exceed the	space provide	d.)		
17. have descented at					11.55
tiation of the promyelo	cvtic cell line H	HL-60.	This new pathw	av for m	onocytic
differentiation may exp.	lain the ability	of TPA t	o differentia	te HL-60	cells.
Differentiation is media	ated by the break	cdown pro	oduct of sphin	gomyelin	:phosphory1-
tiates HL-60 cells via	vidence suggests stimulation of su	that the	e phorbol este	r, TPA, t via C-	differen-
	or and the state of the state o	Jurugouje			KINGSC.
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		202			
		392			



			PROJECT NUMBER					
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEA	TH SERVICE						
NOTICE OF INT	RAMURAL RESEARCH PROJE	-CT	701 CR 00151 02 TR					
			201 CB 09131-02 LP					
October 1, 1986 to Sept	ember 30, 1987		and the second					
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the border	rs.)						
Immunopathology of LAK-	IL2 Treated Tumors							
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	igator.) (Name, title, labora	tory, and institute affiliation)					
PI: E.S. Jaffe Chief Hematonathology Section ID NCT								
OTHER: P. Cohen	Biotech. Fellow.	Hematopath. Se	ection LP NCI					
M. Lotze	Senior Investigat	tor, Surgery Br	anch C DCT COP					
S. Rosenberg	Chief, Surgery B	ranch	C DCT COP					
R. Steis	Acting Chief, Cl:	inical Res. Bra	inch BRMP FCRF					
J. Clark	Senior investigat	tor	BRMP FCRF					
COOPERATING UNITS (if any)								
Surgery Branch, DCT, NC	ſ							
BRMP, FCRF								
Laboratory of Pathology								
SECTION								
Hematopathology Section								
INSTITUTE AND LOCATION								
NCI, NIH, Bethesda, MD	20892	OTUER						
TOTAL MAN-YEARS:	PROFESSIONAL:							
CHECK APPROPRIATE BOX(ES)	1.0	0.5						
(a) Human subjects	🛛 (b) Human tissues	(c) Neither						
(a1) Minors								
(a2) Interviews			A					
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the space provided	a.) 	ains word for the					
experimental treatment	of human malignancies	The mechanism of	f action of this					
therapy is not clearly of	established, and it is no	ot known whethe	r those lymphokine-					
activated killer cells (	(LAK) infused actually mi	Igrate and infi	ltrate tumors, or					
whether other effector of	cells mediate the observe	ed tumor regres	sion. In order to					
better understand the pa	thophysiology of LAK-IL2	2 treatment, tu	mor biopsy specimens					
are obtained before, du	ing, and after conclusion	on of LAK-1L2 t	reatment. Specimens					
as well as markers capal	ale of identifying T cell	le for a baller ls. B cells, hi	stincytes NK cells					
and other effector cells	. These data are then o	correlated with	conventional.					
clinical and pathologic	data to determine whethe	er the immunopa	thology observed					
can predict clinical res	sponse.							



DEPARTMENT OF HEALTH A	Incoren	NOMBER						
NOTICE OF INT								
			Z01 CB	09144-03	LP			
PERIOD COVERED	anhan 20 1087							
UCLOBER 1, 1986 to Sept	Ember 30, 1987							
Identification of Prote	ins Binding to c-myc Regu	ilatory Sequenc	es					
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigator.) (Name, title, labora	tory, and in:	stitute affiliation)				
PI: D.L. Levens	Senior Staff	f Fellow		LP I	NCI			
OTHER: J. Quinn	Visiting Fel	llow		LP I	NCI			
M. Takimoto	Visiting Fe. Medical Stat	Ff Fellow			NCL			
n. Avigan	neurcar star	II FEIIOW		51 1	NOL			
COOPERATING UNITS (if any)								
LAB/BBANCH								
Laboratory of Pathology								
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INSTITUTE AND LOCATION	20000							
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LUTAL MAN-TEARS:	PROFESSIONAL:	1 1						
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(a) Human subjects	□ (b) Human tissues ☑	(c) Neither						
(a1) Minors								
(a2) Interviews					В			
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space provide	d.)						
Mol. Cell. Biol. 5: 230	7-2316 1985) for the rat	id identificat	ion of	wiey, P.,				
specific DNA binding pro	oteins to examine transci	ciptional regul	atory	factors				
binding to the c-myc one	cogene. By combining thi	is technique wi	thas	ensitive en	xo-			
nuclease footprinting as	ssay (Wu, C., Nature 317:	84-87, 1985),	DNA-p	rotein com-	-			
plexes can be formed, ra	apidly separated from the	e vast majority	of pr	otein and				
competitor nucleic acids	s, centrifugally concentr	ated and "foot	printe	d".				
This approach has lad to	the identification of a	ultiple footor	a hiad					
2.3 kb region unstream	From the comparation of p	Pl and P2 Th		ing to a	_			
teins binding, reflects	the physiological state	and particular	cell	source of	the			
proteins. One of the fa	actors examined has also	been shown in	our la	boratory to	0			
bind to the enhancer of	the gibbon ape leukemia	virus and corr	elates	well with	the			
activity of that enhance	er. This protein has been	en enriched and	ident	ified from				
nuclear extracts with a	single step of two cycle	es. The protei	n is a	38-40 kd				
peptide. We are current	ly devising a purificati	lon scheme for	this a	nd other				
c-myc regulatory protein	ns. The role of these fa	actors in c-myc	regul	ation will				
properties of the physic	logical regulation of a	myc to reconsti	Luce s	ome of the				
properties of the physic	regulation of C-	my C.						

PROJECT NUMBER



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NOMBER
NOTICE OF INTRAMIIPAL DESEARCH PROJECT	
NOTICE OF INTRAMORAE RESEARCH FRODEOT	701 CB 02657 12 D
PERIOD COVERED	1 201 CB 03637-13 0
October 1, 1986 to September 30, 1987	
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)	
Immunopathologic Mechanisms Involved in Inflammatory Skin Di	seases
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, lab	retory, and institute amiliation)
P.I.: S.I. Katz, Branch Chief, Dermatology Branch, DCBD N	CT
OTHER: S. Shimada, Guest Researcher, Dermatology Branch, DC	BD. NCI
W. Caughman, Senior Staff Fellow, Dermatology Branch	, DCBD, NCI
A. Gaspari, Medical Staff Fellow, Dermatology Branch	, DCBD, NCI
C. Hauser, Guest Researcher, Dermatology Branch, DCB	D, NCI
1. Furue, Visiting Fellow, Dermatology Branch, DCBD,	NCL
COOPERATING UNITS (if any)	
Dermatology Branch, USUHS, Bethesda	
Immunology Branch, DCBD, NCI	
1	
Dermatology Branch	
SECTION	
INSTITUTE AND LOCATION	
NCI, NIH, Bethesda, Maryland 20892	
TOTAL MAN-YEARS: PHOFESSIONAL: OTHER:	
CHECK APPROPRIATE BOX(ES)	
(a) Human subjects (b) Human tissues (c) Neither	
(a1) Minors	P
(a2) Interviews	D
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) The majo	r area of study
We have found that epidermal Langerhans calls are derived fr	Logical organ.
in the bone marrow and play an essential role in many of the	immunological
reactions affecting the skin. We have also identified an ep	Idermal
Interleukin 1-like cytokine which may serve as a second sign	al in the
generation of T cell responses as well as a proinflammatory	agent affecting
other cells - especially neutrophils. We have demonstrated	that when
notent antigen presenting cells compared to freshly prepared	Langerhans
cells. We have therefore utilized cultured Langerhans cells	for the generation
of primary immune responses in resting unsensitized T cells.	We have
demonstrated that when cultured cells are modified with hapt	en, they can
generate primary immune responses. The sensitized T cells t	nus generated
our efforts on the characterization of murino dondritic the	also concentrated
epidermal cells. We have utilized highly enriched population	as of freshly
prepared cells and identified their T cell nature by demons	rating that
they express -like T cell receptor along with the associat	ed T3 components.
As these cells are also present in nude mice they may represent	ent an extra
focus of this laboratory has been the study of the function	e other major
bearing keratinocytes which appear in humans and mice during	cell-mediated
reactions in the skin. We have demonstrated that these cell	s can 1) present
peptide fragments to T cell hybridomas, 2) serve as targets	or class II
specific cytotoxic T lymphocytes, and 3) induce secondary al.	oreactive T
ceri responses.	



			PROJECT NUMBER				
DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE					
NOTICE OF INT	RAMURAL RESEARCH PROJE	CT					
			ZO1 CB 03667-03 D				
PERIOD COVERED							
October 1, 1986 to Sept	ember 30, 1987						
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the border	rs.)					
Molecules Defined by Au	toantibody - Mediated Sk:	In Diseases					
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Invest	igator.) (Name, title, laborat	ory, and institute affiliation)				
P.L.: John R. Stanley	M.D., Dermatology Brand	ch. DCBD. NCT					
	,,	,,,					
OTHER: Russell Evre. M	.D., Medical Staff Fellow	. Dermatology	Branch, DCBD, NCI				
Stephan Muller,	M.D., Visiting Fellow, I	Dermatology Bra	nch, DCBD, NCI				
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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:					
4	3	1					
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(a) Human subjects	(b) Human tissues	(c) Neither					
a1) Minors							
(a2) Interviews	· · · · · · · · · · · · · · · · · · ·		В				
SUMMARY OF WORK (Use standard unred	duced type. Do not axceed the space provide	a) The genera	1 and long-				
term goal of my laborat	ory is to study autoantil	ody-mediated s	kin diseases				
in order to further our	understanding not only o	of the pathophy	siology of				
these diseases but also	of the structure and fur	nction of norma	l epidermis				
and epidermal basement	membrane zone. Specifica	ally, antibodie	s in these				
diseases define molecul	es in the normal epidermi	ls. We have ch	aracterized				
the antigens defined by	three of these diseases:	: bullous pemp	higoid (BP),				
pemphigus vulgaris (PV)	, and pemphigus foliaceus	s (PF). We hav	e defined the				
cells which synthesize	these antigens, as well a	as the antigen	defined by				
the autoantibodies found	d in patients with epider	molysis bullos	a acquisita (EBA).				
We have used the binding	g of antibodies to specif	fic molecules t	o make				
diagnoses of BP, EBA, P	V or PF in various compli	lcated cases of	these				
diseases. We have also	used antibodies to BP an	tigen, as well	as to other				
basement membrane compos	nents, to rapidly diagnos	se various type	s of				
epidermolysis bullosa,	often within the first fe	w days after b	irth. We				
have demonstrated that	autoantibodies from patie	ents with fogo	selvagem, a				
form of pemphigus endem	form of nemphique endemic to Brazil have similar encodifications to						
autoantibodies from pat.	automithodies from patients with sporadic North Aperican DW Mo have						
autoantibodies from patients with sporadic North American PF. We have							
demonstrated that PF antibodies bind a protein found in desmosomes, and							
demonstrated that PF an define a calcium-sensit	ients with sporadic North tibodies bind a protein f	Ar specificitie A American PF. Sound in desmos	s to We have omes, and plex. Thus.				
demonstrated that PF an define a calcium-sensit: PF is an autoimmune disc	ic to brazil, nave simila ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antiboo	Ar specificitie American PF. Found in desmos nal protein com	s to We have omes, and plex. Thus, e desmosome.				
demonstrated that PF an define a calcium-sensit: PF is an autoimmune dis We have demonstrated th	ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibodies from all P	Ar specificitie American PF. Sound in desmos hal protein com by target is th E patients bind	s to We have omes, and plex. Thus, e desmosome. a unique				
demonstrated that PF an define a calcium-sensit: PF is an autoimmune dis We have demonstrated the complex of proteins the	ic to brazil, have simila ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibod at antibodies from all PH is distinct from the co	Ar specificitie A American PF. Found in desmos nal protein com ly target is th F patients bind bumbley bound by	s to We have omes, and plex. Thus, e desmosome. a unique PV antibodies				
demonstrated that PF an define a calcium-sensit PF is an autoimmune dis We have demonstrated the complex of proteins that	ic to brazil, have simila ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibod at antibodies from all PH t is distinct from the co	Ar specificitie A American PF. Found in desmos nal protein com dy target is th F patients bind omplex bound by dealeted a - PN	s to We have omes, and plex. Thus, e desmosome. a unique PV antibodies.				
demonstrated that PF an define a calcium-sensit PF is an autoimmune dis We have demonstrated the complex of proteins that Using a lambda gtll exp	ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibod at antibodies from all PH t is distinct from the co ression library, we have	Ar specificitie A American PF. Sound in desmos nal protein com ly target is th F patients bind omplex bound by isolated a cDN	s to We have omes, and plex. Thus, e desmosome. a unique PV antibodies. A clone that				
demonstrated that PF an define a calcium-sensit PF is an autoimmune dis We have demonstrated the complex of proteins that Using a lambda gtll exp synthesizes part of the this clone.	ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibod at antibodies from all PH t is distinct from the co ression library, we have BP antigen. We are just	Ar specificitie on American PF. Found in desmos and protein com by target is th F patients bind omplex bound by isolated a cDN to beginning to	s to We have omes, and plex. Thus, e desmosome. a unique PV antibodies. A clone that characterize				
demonstrated that PF an define a calcium-sensit PF is an autoimmune dis We have demonstrated the complex of proteins that Using a lambda gtll exp synthesizes part of the this clone.	ients with sporadic North tibodies bind a protein f ive epitope on a desmoson ease in which the antibod at antibodies from all PH t is distinct from the co ression library, we have BP antigen. We are just	Ar specificitie on American PF. Found in desmos and protein com by target is th F patients bind omplex bound by isolated a cDN to beginning to	s to We have omes, and plex. Thus, e desmosome. a unique PV antibodies. A clone that characterize				



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PERIOD COVERED			ZUL CB 0.3666-09 D
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	vs.)	
Chemical Mediators of I	nflammation		
PRINCIPAL INVESTIGATOR (List other pro	lessional personnel below the Principal Invest	tigator.) (Name, title, labora	tory, and institute affiliation)
PI: Thomas J. Lawle	y, M.D., Dermatology Bran	nch, DCBD, NCI	
OTHER: Robert Swerlick Yasuo Kubota, M Carol McNeely, J	, M.D., Medical Staff Fe D., Visiting Fellow, Der M.D., Medical Staff Fello	llow, Dermatolo rmatology Branc ow, Dermatology	ogy Branch, DCBD, NCI ch, DCBD, NCI 7 Branch, DCBD, NCI
Joseph Cason T	achnician Dermatology Bu	Dermatology Br	anch, DCBD, NCI
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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
6.0	5.0	1.0	·
CHECK APPROPRIATE BOX(ES)		(a) Maithar	
(a) Human subjects		(c) Normal	3
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	d) Colubio mo	distance of
inflammation such as the	complement derived anar	hvlatoxins pla	v important
roles in a variety of in	munologically mediated h	uman systemic	and cutaneous
diseases. We have purif	ied human C5a and C5a de	s Arg and stud	ied their in
vivo and in vitro reacti	vity. Their in vivo rol	e was assessed	by the first
in-depth analyses of the	cutaneous reactivity of	these complem	ent fragments
in man. We have also do	cumented the ability of	C5a and C3a to	modulate
leukocytes. We have ass	or immunoglobulin and co	mplement on th	e surface of
(PMN's) and mast cells it	o C5a induced cutaneous	inflammation b	clear neutrophils
the cutaneous reactivity	of patients with bone m	arrow failure	who lack
PMN's and by selectively	depleting the mast cell	s in the skin	of volunteers
prior to skin testing wi	th C5a. Increasing evid	ence indicates	that human
endothelial cells, under	certain circumstances,	can be induced	to become
dermal microwscouler	t. We have isolated hum	an umbilical v	ein and
them for the presence of	immunologically releven	m in cell cult	ure, examined
receptors before and aft	er stimulation with solu	ble mediatore	antigens and
In addition we have indu	ced human endothelial ce	lls to differen	ntiate in
vitro. Under specific c	ulture conditions the en	dothelial cells	s undergo
angiogenesis forming sma	11 tubular structures th	at possess lum	ens and
resemble blood vessels.	We have also developed	an assay to de	tect antiendothelial
with certain forms of ya	sera and have detected t	hese antibodies	s in patients
line of the forms of va	Coultin.		



DEPARTMENT OF HEALTH			
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NOTICE OF IN	TRAMURAL RESEARCH P	PROJECT	
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October 1, 1986 to S	eptember 30, 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line between th	e borders.)	
Therapy of Skin Canc	er, Disorders of Kera	tinization, and Cys	stic Acne
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Princip	el Investigator.) (Name, title, labora	tory, and institute affiliation)
P.I.: G.L. Peck, S	enior Investigator, L	ermatology Branch,	DCBD, NCI
OTHER: J.J.DiGiovan	na. Senior Staff Fell	ow. Dermatology Bra	anch DCBD NCI
I. Tokar, Re	gistered Nurse, Derma	tology Branch, DCBI	D. NCI
K. Kraemer,	Senior Investigator,	Cell Genetics Br.,	NCI
Cancer Prevention St	udies Branch DCPC N	CT NIH Bothoada	Manuland 20802
Sumeer revention be	dates branch, boro, h	or, Min, Bechesua,	Maryrand 20092
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Dermatology Branch			
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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
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(a) Human subjects	(b) Human tissues	(c) Neither	
		-	
(a2) Interviews		D	
(a2) Interviews	duced type. Do not axceed the space	provided.) Oral iso	otretinoin was
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev	duced type. Do not exceed the space vention of skin cance	provided.) Oral iso r and in the treatm	otretinoin was ment of a variety
<ul> <li>(a) Interviews</li> <li>SUMMARY OF WORK (Use standard unre effective in the pre- of disorders of keral</li> </ul>	duced type. Do not exceed the space Vention of skin cance cinization (lamellar	provided) Oral iso r and in the treatm ichthyosis, Darier	otretinoin was ment of a variety 's disease, pityriasis
(a) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of	duced type. Do not exceed the space vention of skin cance inization (lamellar systic acne. Oral et	provided) Oral iso r and in the treatm ichthyosis, Darier retinate was more e	otretinoin was ment of a variety s disease, pityriasis effective and less
(a) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotretime	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment r revealed deserves	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of	otretinoin was ment of a variety s disease, pityriasis effective and less f keratinization.
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotreting	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress p. One obronic tox	otretinoin was ment of a variety 's disease, pityriasis effective and less E keratinization. Sion in cystic acne ricity "retinoid
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charac	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi terized by anterior	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne wicity, "retinoid cification and
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charac osteophyte formation	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80%	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. sion in cystic acne kicity, "retinoid lcification and of patients treated
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high-	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be -dose isotretinoin.	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid cification and of patients treated one patients with
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of isot	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin.	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. sion in cystic acne dicity, "retinoid leification and of patients treated one patients with vertebral osteophytes.
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extraspect	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal sixty percent of ac hs also developed we ment calcification	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. sion in cystic acne dicity, "retinoid cification and of patients treated one patients with vertebral osteophytes. occurred commonly
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detetinoin for 9 mont binal tendon and liga y for psoriasis and d	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin-
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic ret;	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles,
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic reti- pelvis and knees.	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga y for psoriasis and d inoid. The usual sit	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated ene patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles,
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic reti- pelvis and knees.	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detetinoin for 9 mont binal tendon and liga y for psoriasis and d inoid. The usual sit	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- were the ankles, a cancer chemopreven-
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isot	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detetinoin for 9 mont binal tendon and liga y for psoriasis and d inoid. The usual sit	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate	otretinoin was ment of a variety 's disease, pityriasis effective and less is deratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- were the ankles, a cancer chemopreven- e significant partial
(a2) Interviews SUMMARY OF WORK (Use standard unre effective in the prev of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isod inhibition of new ture	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga y for psoriasis and d inoid. The usual sit ereoderma pigmentosum cretinoin: Prelimina nor formation during	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more of of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles, a cancer chemopreven- e significant partial d increase in new
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrass after chronic therapy ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isod inhibition of new tur tumor formation after	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit ereoderma pigmentosum cretinoin: Prelimina nor formation during the rapy. The need	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasp after chronic therapp ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isod inhibition of new tur tumor formation after chemoprevention of si	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit ereroderma pigmentosum cretinoin: Prelimina nor formation during therapy. The need tin cancer with isotr environmental of the	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke for continuous main etinoin may vary wi natient's twoare	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid loification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for th the underlying
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrass after chronic therapy ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isod inhibition of new tur tumor formation after chemoprevention of sl etiology (genetic or	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit eccoderma pigmentosum cretinoin: Prelimina nor formation during t therapy. The need tin cancer with isotr environmental of the	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke for continuous main etinoin may vary wi patient's tumors.	otretinoin was ment of a variety 's disease, pityriasis effective and less f keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for th the underlying
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrasy after chronic therapy ate, an aromatic reti- pelvis and knees. Seven patients with of tion study using isod inhibition of new tur tumor formation after chemoprevention of sl etiology (genetic or	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga y for psoriasis and d inoid. The usual sit eccoderma pigmentosum cretinoin: Prelimina nor formation during therapy. The need tin cancer with isotr environmental of the	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke for continuous main etinoin may vary wi patient's tumors.	otretinoin was ment of a variety 's disease, pityriasis effective and less is keratinization. Sion in cystic acne dicity, "retinoid locification and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- vere the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for th the underlying
(a2) Interviews SUMMARY OF WORK (Use standard unreflective in the prevof disorders of kerating rubra pilaris), and of toxic than isotreting patients after treating patients after treating patients after treating with long-term, high-moderate doses of isotredominantly extrass after chronic therapy ate, an aromatic retipelvis and knees. Seven patients with of tion study using isot inhibition of new tur tumor formation after chemoprevention of sletiology (genetic or study (genetic or study)	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit eccoderma pigmentosum cretinoin: Prelimina nor formation during therapy. The need tin cancer with isotr environmental of the	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke for continuous main etinoin may vary wi patient's tumors.	otretinoin was ment of a variety 's disease, pityriasis effective and less is keratinization. Sion in cystic acne dicity, "retinoid leffication and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- were the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for th the underlying
(a2) Interviews SUMMARY OF WORK (Use standard unre- effective in the prev- of disorders of kerat rubra pilaris), and of toxic than isotreting Psychological testing patients after treat hyperostosis," charad osteophyte formation with long-term, high- moderate doses of iso Predominantly extrass after chronic therapy ate, an aromatic ret: pelvis and knees. Seven patients with of tion study using isod inhibition of new tur tumor formation after chemoprevention of sl etiology (genetic or	duced type. Do not exceed the space vention of skin cance inization (lamellar cystic acne. Oral et in in the treatment g revealed decreased ment with isotretinoi cterized by anterior of vertebrae, has be dose isotretinoin. Detretinoin for 9 mont binal tendon and liga v for psoriasis and d inoid. The usual sit eccoderma pigmentosum cretinoin: Prelimina nor formation during therapy. The need tin cancer with isotr environmental of the	provided) Oral iso r and in the treatm ichthyosis, Darier' retinate was more e of the disorders of anxiety and depress n. One chronic tox spinal ligament cal en observed in 80% Sixty percent of ac hs also developed w ment calcification isorders of keratir es of involvement w were entered into ry results indicate therapy and a marke for continuous main etinoin may vary wi patient's tumors.	otretinoin was ment of a variety 's disease, pityriasis effective and less is keratinization. Sion in cystic acne dicity, "retinoid leffication and of patients treated one patients with vertebral osteophytes. occurred commonly mization with etretin- were the ankles, a cancer chemopreven- e significant partial ed increase in new itenance therapy for th the underlying



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER					
NOTICE OF INTRAMURAL RESEARCH PROJECT						
	Z01 CB 03630-17 D					
October 1, 1986 to September 30, 1987						
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)						
Effects of Vitamin A and Analogs on Chick, Mouse and Human S	kin atory, and institute affiliation)					
P.I.: G.L.Peck, Senior Investigator, Dermatology Branch, D	CBD, NCI					
OTHER: J.J. DiGiovanna, Senior Staff Fellow, Dermatology Br T. Mehrel, Visiting Fellow, Laboratory for Cellular Tumor Promotion, DCE, NCI	anch, DCBD, NCI Carinogenesis and					
COOPERATING UNITS (if any)						
Laboratory for Cellular Carcinogenesis and Tumor Promotion,	dce, nci					
LAB/BRANCH Dermatology Branch						
SECTION						
NSTITUTE AND LOCATION NCI, NIH, Bethesda, Maryland 20892						
TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 0.1 O.1						
CHECK APPROPRIATE BOX(ES)						
(a) Human subjects     (b) Human tissues     (c) Neither     (a1) Minors     (a2) Interviews	B					
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)						
This project proposed to morphologically and biochemically define the mechanism of action of vitamin A and its derivatives (retinoids) in altering epidermal differentiation in normal skin and in benign and malignant lesions of skin. Topical all- trans retinoic acid, but not systemic 13-cis-retinoic acid, increased gap junction density and decreased desmosome density in treated basal cell carcinomas. This indicates that topical and systemic retinoids may exert their antineoplastic activity by different cellular mechanisms.						
in normal human skin, newborn mouse skin and human skin from patients with Darier's disease, psoriasis and basal cell carcinomas. A specific cytosol retinoic acid binding protein (CRABP) has also been identified in newborn mouse and normal human adult skin and newborn foreskin. The qualitative						
and quantitative distribution between the epidermis and dermi and CRABP has been determined in adult human lower limbskin.	is of both CRBP					
keratin genes, keratin gene expression in skin cancer and cu	taneous disorders					
of keratinization indicate the following. In contrast to not where the expression of proliferation-associated keratin gene after cells migrate from the basement membrane, hyperprolifer of the epidermis exhibit inappropriate expression of prolifer keratin genes in the more superficial layers of the epidermi skin cancers fail to express differentiation-associated keration of their undifferentiated state.	rmal epidermis es is suppressed rative disorders ration-associated s. In addition, tins, indicative					



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	LTH SERVICE	PROJECT NUMBER
	PANUPAL RESEARCH PROJ	FCT	
NOTICE OF INT	NAMONAL RESEARCH PROD		701 CD 03(30 10 -
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	rs.)	
Studies of DNA Repair i	n Human Degenerative Dis	eases	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	tigator.) (Name, title, labora	tory, and institute affiliation)
	M.D. During I and During I	DODD WOT	
PI: J. H. RODDINS,	M.D., Dermatology Branch	, DCBD, NCI	
COUPERATING UNITS (# 8/19)			
Biostatistics Branch, D	CCP. NCT		
LAB/BRANCH			
Dermatology Branch			
SECTION			
INSTITUTE AND LOCATION	1 1 00000		
TOTAL MANYYEARS	PROFESSIONAL:	OTHER	
5.2	3.2		2 0
CHECK APPROPRIATE BOX(ES)		L	<b>2</b> • 0
(a) Human subjects	🗌 (b) Human tissues 🗌	(c) Neither	
(a1) Minors		D	
(a2) Interviews		D	
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provided	d.) Studies in	n this laboratory
are designed to elucidat	te the role of DNA repair	r processes in	carcinogenesis
and in normal and abnorn	nal aging. Most studies	have been cond	lucted with
cells from patients with	n xeroderma pigmentosum	who have detect	tive DNA
skin and of the nervous	system Colls from pat	premature agin	ng of sun-exposed
muscular, and retinal de	egenerations are also be	ing studiod	Those diseases
include ataxia telangie	ctasia. Alzheimer diseas	Parkinson di	sease Huntington
disease, Duchenne muscu	lar dystrophy, retinitis	pigmentosa, Fi	iedreich ataxia.
and Cockayne syndrome.	These studies are design	ned to elucidat	te the pathogenesis
of these disorders. We	assess the biological en	ffectiveness of	DNA repair
by 1) in vitro assays of	f cell survival after tre	eatment of the	cells with
DNA-damaging agents; 2)	analysis of chromosome a	and chromatid a	aberrations in
cells treated with DNA-o	lamaging agents; and 3)	transfection st	udies using
irradiated shuttle vecto	or plasmids. We search i	for DNA damage	by 1) extracting
the DNA and having it su	ubjected to analysis by a	capillary-gas-c	hromatography
cells by chemical correit	udying unscheduled DNA s	synthesis induc	ced in cultured
profile of DNA from ould	tured cells after their	treatmost with	
agents.	Larca certs arter their t	rearment with	DIA-uamag Ing



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - P	UBLIC HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARC	H PROJECT	
			Z01 CB 03656-14 D
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line betwe	en the borders.)	and the second
Chemistry, Structure a	nd Biosynthesis o	f Mammalian Epidermal	Keratin Filaments
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the P	nincipal Investigator.) (Name, title, labor	story, and institute affiliation)
P.I.: P.M. Steinert, V	isiting Scientist	, Dermatology Branch,	NCI
	•		
COOPERATING UNITS (if any)		<u> </u>	
Experimental Pathology	Branch, DCCP, NCT	: Laboratory of Molec	ular Biology
DCBD, NCI; Laboratory o	f Physical Biolog	v. NIDDK	biology,
, ,, ,		,	
LAB/BRANCH	· · · · · · · · · · · · · · · · · · ·		
Dermatology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
7.5	5.5	2.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues		
		В	
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the s	pace provided.) The biosy	nthesis,
structure and function	of the principal	differentiation produ	cts of human
and mouse epidermis are	being studied.	Keratin subunits poly	merize in
vitro into native-type	incermediate rila	nents. Details of th	eir structure
filmonta: transmission	by use of: solid	state NMK on isotopi	cally-labeled
filments, transmission	and scanning tra	ismission electron mi	croscopy of intact
procedures; and limited	tous forms; optic	al diffraction and im	age analysis
procedures, and itmited	Model atmustures	riments to ascertain	alignment or
being computationally t	nodel structures	generated by these me	thods are
data and amino acid sog	uence information	on individual subuni	
clones to kerating 1 an	d 10 are being up	on individual subuni	LS. CDNA
organization and comple	with of their gen	ed to characterize th	e number,
The expression of the h	uman genes is boi	es isolated from cosm	duction of
transgenic mice produce	d from various con	etructe of these gos	
clones are being used to	o isolate and char	racterize the genes f	or mouse and
human filaggrin which	appear to be init	ally expressed as a	very large
polyprotein precursor	cDNA clones enco	ting a major coll on	elon protein
have been isolated and	are being sequence	and Constructs of ko	rating filogarin
and the cell envelop pr	otein clones are	aing accombled with	DCFM vectors
for use in insitu hybri	dization experimen	in order to study	the expression
of these proteins in ep	idermal keratiniz	ing disorders.	ene expression
-			



			PROJECT NUMBER			
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE				
NOTICE OF INT	RAMURAL RESEARCH PR	ROJECT	Z01 CB 04002-18 MET			
October 1, 1986 throug	h September 30, 1987					
TITLE OF PROJECT (80 characters or less Defects in Immunoregul	atory Cell Interaction	<sup>borders.)</sup> ns in Patients wi	th Immune Dysfunctions			
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal	Investigator.) (Name, title, labor	atory, and institute affiliation)			
Michael Davey	Medical	Staff Fellow	MET, NCI			
Robert Kozak	Guest R	esearcher	MET, NCI			
Mitsura Tsudo	visitin b Visitin	g Fellow g Fellow	MET, NCI			
WIIIIam Raulleisc	n visitin	greilow	MEL, NOL			
COOPERATING UNITS (if any)						
Metabolism Branch						
SECTION						
DCBD, NCI, NIH, Bethes	da, Maryland					
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:				
	5	2				
(a) Human subjects	🖾 (b) Human tissues	(c) Neither				
(a1) Minors		. ,				
(a2) Interviews		- fot-sta				
Resting T cells do not	express high-affinit	y IL-2 receptors,	but receptors are			
rapidly expressed on T	cells after activati	on with antigen o	or mitogen. There are			
two classes of IL-2 receptors that differ in their affinity for IL-2, including						
one with a very high affinity and the other with a much lower affinity. In a						
was identified. Cell lines bearing either the 55-kDa Tac or the p75 peptide alone						
manifested low-affinity IL-2 binding, whereas cell lines bearing both peptides						
manifested both high- and low-affinity receptors. Fusion of cell membranes from						
a cell line bearing th	e p75 peptide alone g	enerated hybrid m	embranes bearing high-			
affinity receptors. T	hese observations sug	gested a multicha	in model for the high-			
atfinity IL-2 receptor	in which both the p5	5 Tac and the p75	IL-2 binding peptides			
that the T cell be act	ivated and express bo	th the 55-kDa Tac	peptide as well as			
the novel 75-kDa IL-2	binding peptide. The	pattern with lym	phokine-activated			
killer (LAK) cells and	natural killer (NK)	cells is quite di	fferent. Over the			
past year, it was shown that such LAK and NK precursor cells, as well as different types of leukemias of large granular lymphocytes with NK activity, express the p75						
but not the 55-kDa IL-	2 binding peptide.					



				PROJECT N	UMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICE	S - PUBLIC HE	ALTH SERVICE		
NOTICE OF INT	RAMURAL RESE	ARCH PROJ	ECT	701 0	B 0/00/-25 Mpm
PERIOD COVERED				201 01	B 04004-25 MEI
October 1, 1986 throug	gh September 30	), 1987			
TITLE OF PROJECT (80 characters or less Amino Acids and Growth	s. Title must fit on one line n Factors in Ce	ell Activat	ors.) Lion		
PRINCIPAL INVESTIGATOR (List other pro PI: James M. Phang	ofessional personnel below	the Principal Invest Section He	tigator.) (Name, title, labora ad	tory, and instit	tute affiliation) MET, NCI
A. James Mixson		Medical St	aff Fellow		MET, NCI
Patricia Cortaza	<b>c</b>	Guest Rese	earcher		MET, NCI
COOPERATING UNITS (if any)	r NCT				
David Valle, M.D., Joh	ns Hopkins Hos	pital Scho	ol of Medicine	. Baltin	more, MD
	•			,	
LAB/BRANCH					
Metabolism Branch					
Endocrinology Section					
INSTITUTE AND LOCATION			· · · · · · · · · · · · · · · · · · ·		
DCBD, NCI, NIH, Bethes	sda, Maryland				
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:		
CHECK APPROPRIATE BOX(ES)	1		1		
🖾 (a) Human subjects	🖾 (b) Human tis	sues 🗌	(c) Neither		
(a1) Minors					
	duced time. Do not exceed	the second provide			
The findings during th	nis past year s	trongly su	ipport our hypo	thesis t	that pyrroline
5-carboxylate (P5C) is	a novel media	tor of int	ercellular com	municati	ion and trans-
membrane signaling. H	first, we showe	d that P50	stimulates the	e turnov	ver of membran
phosphoinositides. Wi	th the P5C sti	mulation of	of PRPP product	ion in i	intact cells
as an endpoint, we fou	ind a pattern o	f synergis	interpretation	c growth	n factors and
sensitivity to inhibitors consistent with the interpretation that PSC produced its					
diacylglycerol. Relat	ed and perhaps	linked to	this mechanis	m for ti	ransmembrane
signaling, a novel uptake mechanism for P5C was identified and characterized.					
This mechanism is specific, carrier mediated, energy dependent, but sodium inde-					
pendent. Importantly,	, P5C is conver	ted to pro	line concomita	nt to ce	ellular entry.
This group translocation directly couples the uptake of P5C to the transfer of					
redox within or at the plasma membrane. Finally, the functional association of					
For translocation to For reductase, the enzyme that mediates redox transfers, has					
plasma membranes. Using sucrose density gradients, we showed that PSC reductase.					
previously considered	to be cytosoli	c, is, in	fact, associat	ed with	cellular
organelles. One compo	onent is associ	ated with	plasma membran	es and a	a second with
mitochondria. The men	abrane componen	t has 7-fo	ld higher affi	nity for	r NADPH than
the mitochondrial comp	ponent.				



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 04015-16 MET

PERIOD COVERED					
October 1, 1986 through Se	ptember 30, 1987				
TITLE OF PROJECT (80 characters or less. Title	must fit on one line between the border	s.)			
Development and Function of	f Humoral and Cellular	: Immune Mechanism			
PRINCIPAL INVESTIGATOR (List other profession	nal personnel below the Principal Investi	igator.) (Name, title, laboretory, and -	f institute affilietion)		
Pl: R. Michael Blaese	Section Chief		MET, NCI		
Andrew V. Muchmore	Modical Staff	Elgator E Follow	MET, NCL		
Thomas Floisher	Senior Invest	tigator	CPD CC		
Robert Moen	Senior Staff	Fellow	IMH NHTRT		
French Anderson	Chief	ICIIOW	IMH, NHLBI		
Alan Palestine	Senior Invest	igator	NET		
Michael Wood	Howard Hughes	s Scholar	MET, NCI		
COOPERATING UNITS (if any)					
LAB/BRANCH					
Metabolism Branch					
SECTION					
Cellular Immunology Section	n	· · · · · · · · · · · · · · · · · · ·			
INSTITUTE AND LOCATION					
DCBD, NCI, NIH, Bethesda, I		OTHER			
8	6	2 DINER.			
kx (a) Human subjects	(b) Human tissues	(c) Neither			
xx (a1) Minors	(-)	(0)			
(a2) Interviews					
SUMMARY OF WORK (Use standard unreduced	type. Do not exceed the space provided	(.)			
A principal project is dire	ected toward gene the	rapy of the immune	deficiency dis-		
ease caused by the absence	of adenosine deaminas	se (ADA). We have	established T-		
cell lines from ADA-defici	ent patients and shown	that these cell 1	ines are sensi-		
tive to deoxyadenosine and	are ADA deficient, ju	ist as the cells fr	om these		
patients are in vivo. A mu	urine retrovirus vecto	or gene transfer sy	stem has been		
modified to contain the gen	ne for human ADA. Our	data show that su	ch a gene vector		
system can successfully tra	ansfer a functioning h	uman ADA gene into	these defective		
cells with a high efficience	cy and that such "gene	e-treated" cells ar	e reconstituted		
to normal function. We have	ve continued to study	Wiskott-Aldrich sy	ndrome (WAS)		
patients and have developed	d a new test to detect	carriers of this	X-linked dis-		
ease. The test is based on	n the observation that	, although all fem	ale somatic		
cells contain two X chromosomes, only one X chromosome is active in each cell.					
Using restriction fragment length polymorphisms to distinguish the two X chromo-					
somes and methylation-sensitive restriction endonucleases to determine which of					
the X chromosomes was inactivated, we have shown that carrier females of the WAS					
gene have a predictable unbalanced pattern of X inactivation involving their T					
lymphocytes, B lymphocytes, and granulocytes. This unbalanced pattern of X in-					
activation is not seen in normal females and presumably reflects selection against					
the expression in the carrier females of the X chromosome bearing the mutant WAS					
gene. Our studies developing and defining the new immunosuppressive drug suc-					
cinylacetone (SA) nave cont	imuno we have found	a chat this agent 1	s pernaps the		
allocation and B-cell :	immunosuppressive comp	(CVUD) in El coi	male and pro-		
allograft rejection and gra	all-versus-nost diseas	trancolastation	hile allowing		
normal engraftment and reco	and the second second	SA is also a very	potent inhihi-		
tor of both primery and constitution to occur. SA is also a very potent innibi-					
tor or outcomprimely and secondary antibody responses. Experimental triars of SA					
a type of update that usually results in blindness in synarimatia and ale					



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		IMBER
		04016-14 MET
October 1, 1986 through September 30, 1987		
TITLE OF PROJECT (80 cheracters or less. Title must fit on one line between the borders.) Mechanism of Action of Insulin-like Growth Factors ('B')	_	
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Mame, title, labore PI: S. Peter Nissley Senior Investigator Marie Gelato Medical Staff Fellow Wieland Kiess Guest Researcher Matthew M. Rechler Senior Investigator Wayne Anderson Senior Investigator	tory, end institu	ne affilietion) MET, NCI MET, NCI MET, NCI NIADDK LTIB, NCI
COOPERATING UNITS (IF any)		
LAB/BRANCH Metabolism Branch		
SECTION Endocrinology Section		
INSTITUTE AND LOCATION DCBD, NCI, NIH, Bethesda, Maryland		····
TOTAL MAN-YEARS: 4.5 PROFESSIONAL: 0THER: 1.5		
CHECK APPROPRIATE BOX(ES)           Image: Check appropriate Box(es)		
We previously identified in fetal rat serum a binding species cally binding $^{125}I$ -IGF-II that is considerably larger than the carrier proteins. We now have immunologic and affinity cross that this binding species is the type II IGF receptor. Rat so on a Sephadex G-200 column (0.05 M NH4HCO3, pH 8), and $^{125}I$ -I was measured in individual column fractions. $^{125}I$ -IGF-II bin found in the void volume (Vo) in addition to the carrier prot petitive binding studies using $^{125}I$ -IGF-II and binding activi Vo showed the characteristics of the type II receptor: IGF-I than IGF-I, and insulin did not compete. Importantly, a spec receptor IgG that recognizes neither the 40- and 150-kDa seru teins nor the type I IGF receptor completely blocked $^{125}I$ -IGF $^{125}I$ -IGF-I did not bind to the Vo fractions, demonstrating at I IGF receptor. Independent support for identification as the tor came from affinity crosslinking experiments using disuccin Crosslinking of $^{125}I$ -IGF-II to the G-200 Vo material demonstr band at 210 kDa without reduction and 240 kDa with reduction The size was confirmed by Western blotting of G-200 Vo materi II receptor IgG which revealed a band slightly smaller (10 kD receptor from rat placental membranes. Immunoquantitation by using pure type II receptor from rat placental membranes as a developmental pattern. In fetal rat serum (19 days gestation 3- and 10-day-old rats, 1-5 g/ml receptor protein was measure type II receptor declined dramatically between age 20 days an receptor is found in rat serum and is developmentally regulat receptor is found in rat serum and is developmentally regulat receptor is found in rat serum and is developmentally regulat receptor is found in rat serum and is developmentally regulat	a capable the 150- a slinking serum was GF-II bit GF-II bit if was mo- serif can the type i nimidyls ated as of disul- tal with ba than western tal with ba than that the sed. The slible the	e of specifi- and 40-kDa data to show s gel filtered inding civity was lons. Com- the G-200 bre potent ci-type II arrier pro- ling. The type II II IGF recep- suberate. Specific the type II a blotting showed a a sera from a levels of rs, but e type II IGF a circulating at the



				PROJECT	NUMBER	
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - P	UBLIC HEALT	H SERVICE			
NOTICE OF INT	RAMURAL RESEARC	H PROJEC	r	Z01 CI	B 04017-09 M	1ET
PERIOD COVERED October 1, 1986 throug	h September 30, 19	987				
TITLE OF PROJECT (80 characters or less Biology of the Immune	s. Title must fit on one line betwee Response	en the borders.)				
PRINCIPAL INVESTIGATOR (List other pre	ofessional personnel below the Pi	rincipal Investigat	or.) (Nama, title, lebora	tory, and inst	tituta affiliation)	
PI: David L. Nelson	Sent	lor Invest	igator		MET, NCI	
Javid K. Wagner	Medi Visi	iting Fell	t fellow		MET, NCI	
Luigi Notarangelo	Gues	st Researd	cher		MET, NCI	
0						
COOPERATING UNITS (if any)				··· · · · · · · · · · · · · · · · · ·		
						_
LAB/BRANCH Metabolism Branch						
SECTION						
Immunophysiology						
INSTITUTE AND LOCATION						
DCBD, NCI, NIH, Bethes	da, Maryland					
TOTAL MAN-YEARS:	PROFESSIONAL:	01	THER:			
CHECK APPROPRIATE BOX(ES)	<u></u>					
(a) Human subjects	(b) Human tissues	i 🗌 (d	) Neither			
(a1) Minors						
(a2) Interviews						
Studies were performed	Jucad type. Do not axceed the sp	pace provided.)	and regulati	ion of t	he human	
immune response in nor	mal individuals ar	nd in pat:	lents with co	ongenita	al and acoui	red
immune deficiency stat	es associated with	n a high i	requency of	cancer	The inter	-
action of T lymphocyte	-derived lymphokir	ne, interl	leukin-2 (IL-	-2), wit	h its cell	
membrane receptor (IL-2R) plays a major role in the establishment and maintenance						
of the immune response. Soluble Tac protein from the human IL-2R is secreted by						
activated normal lymphocytes/monocytes and by leukemic cells in vitro. Soluble						
cally binds IL-2 with	low affinity (20 r	M). Solu	ible Tac prot	ein was	measurable	
in the serum of all no	rmal individuals.	Elevated	l serum Tac	protein	levels were	
found at the time of d	iagnosis in severa	al human n	etroviral-re	elated d	lisorders,	
including the HTLV-I-associated adult T-cell leukemia (ATL), hairy cell leukemia						
(HCL), and the HIV-related acquired immunodeficiency syndrome (AIDS). In patients						
in serum levels of Tac protein. In patients with non-Hodgkin's lymphoma, serum						
Tac proteins levels at the time of diagnosis were the best predictor of survival.						
The administration of recombinant IL-2 to cancer patients in vivo caused a 1000-						
fold elevation in serum levels of Tac protein. Measurement of Tac protein in						
serum is useful in the diagnosis and management of certain cancer patients, as						
"orr op in monitoring	ene searce of filling	at				
			•			



			PROJECT NU	MBER							
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE									
NOTICE OF INT	RAMURAL RESEARCH PR	OJECT	701 CB	04019-11	MEE						
			201 05	04018-11	MET						
October 1, 1986 throug	sh September 30, 1987										
TITLE OF PROJECT (80 characters or less Immunoregulatory Glyco	. Title must fit on one line between the oproteins Purification	borders.) a and Characteriz	ation								
PRINCIPAL INVESTIGATOR (List other pro PI: And rew V. Muchmor	fessional personnel below the Principal	Investigator.) (Name, title, labo	ratory, and institu	te affilietion)							
Anne Sherblom	IPA	Investigator		Univ. Mai	ne						
COOPERATING UNITS (if any)											
LAB/BRANCH Metabolism Branch, DCB	3D, NCI										
SECTION			- A 1								
DCBD, NCI, NIH, Bethes	da, Maryland										
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:									
2	2	0									
CHECK APPROPRIATE BOX(ES)	XX (b) Human ticsuos										
(a) Human subjects	a (b) numan ussues										
(a2) Interviews											
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space p	ovided.)									
Our laboratory has con	centrated on the puri	fication and cha	racterizat	tion of a							
unique 85-kilodalton i	mmunosuppressive gly	oprotein termed	uromoduli	n, which w	as						
specific proliferative	om numan pregnancy un	ndent upon T cel	lar prolife:	s antigen-							
concentrations of 10 <sup>-1</sup>	<sup>0</sup> M. Uromodulin is a	lso a specific in	nhibitor (	of inter-							
leukin-1 (IL-1) and bl	ocks both thymocyte a	nd IL-1-dependen	t T cell	lines at							
concentrations of 10 <sup>-1</sup>	<sup>0</sup> M. Interestingly,	uromodulin is a	specific a	and high-							
affinity ligand for both recombinant IL-1 alpha and IL-1 beta, and it appears											
that this is the mecha	nism by which uromodu	lin is able to r	egulate th	he activit	У						
over 200 amino acide o	nded these studies and	I recently have	ence data	to sequen	ted						
a full-length message for uromodulin. This message has been inserted into several											
different vectors and is in the process of being expressed in several transient											
expression systems. We have also been characterizing the mechanism of binding of											
IL-1 to uromodulin and find that IL-1 actually recognizes carbohydrate sequences											
expressed by uromodulin. A number of studies have been utilized, including diges-											
tion with endoglucoaminidase F, pronase, and isolation of released fragments by											
carbohydrate sequence responsible for hinding to IL-1. Clinical studies have also											
been instituted. We h	ave developed a number	r of ELISA assays	s based or	n several							
monoclonal antibodies	generated in our labo	ratory, and evid	ence sugge	ests that							
uromodulin is elevated	in a number of clini	cal conditions th	hat are as	ssociated	monoclonal antibodies generated in our laboratory, and evidence suggests that						
that interloukin-2 and	nese observations have	e peen generaliz	eq, and we		uromodulin is elevated in a number of clinical conditions that are associated with						
chat interieukin-2 and	that interleukin-2 and tumor pecrosis factor also exhibit combabylants by iter										
specificity.	tumor necrosis facto	r also exhibit ca	rbohydrat	e binding							


DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 04020-10 MET

October 1, 1986 throug			
	h September 30, 19	87	
TITLE OF PROJECT (80 characters or less.	Title must fit on one line between	the borders.)	
Antigen-Specific T-Cel	1 Activation and G	enetic Control of Immune R	esponses
PRINCIPAL INVESTIGATOR (List other prof	MD PhD	Senior Investigator, (Name, Utile, laboratory, and in	MET. NCT
Kemp B Cease M	D	Medical Staff Fellow	MET, NCI
Shoichi Ozaki M	D., Ph.D.	Fogarty Visiting Fellow	MET, NCI
Masaharu Kojima.	Ph.D.	Fogarty Visiting Fellow	MET, NCI
Sara Brett, Ph.D.		Guest Researcher	MET, NCI
Akihiko Kurata. M	D. Ph.D.	Guest Researcher	MET, NCI
Hidemi Takabashi.	M.D., Ph.D.	Fogarty Visiting Fellow	MET. NCI
continued next pa	ge		
COOPERATING UNITS (if any)	<u>0</u>		
See next page			
1.9.			
LAB/BRANCH			
Metabolism Branch			
SECTION			
INSTITUTE AND LOCATION			
NIH, NCI, DCBD, Bethes	da, Maryland 2089	2	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
10.5	8.5	2	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	KX (c) Neither	
(a1) Minors			
(a2) Interviews			-
SUMMARY OF WORK (Use standard unreg	luced type. Do not exceed the spin	complex process involving process	sing of the antigen
into fragments by another cel	l and presentation of th	ese to T cells in association with	a major histocom-
mo nagments by another cer	and presentation of th	ese to i cens in association with	a major mstocom
natibility (MHC) molecule or	n the surface of that oth	er cell Therefore only a few set	oments of a protein
patibility (MHC) molecule of	n the surface of that oth	dies For vaccine development	gments of a protein
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm	n the surface of that off ls, in contrast to antibo unodominant antigenic	dies. For vaccine development,	gments of a protein it will therefore be one advantage over
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro	n the surface of that oth ls, in contrast to antibo unodominant antigenic ssreact with short synth	ter cell. Therefore, only a few set dies. For vaccine development, i e sites. Fortunately, T cells have o leftic pentides of the protein much	gments of a protein it will therefore be one advantage over more effectively
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro than do most antibodies. We	n the surface of that oth ls, in contrast to antibo unodominant antigenic ssreact with short synth have used synthetic per	ter cell. Therefore, only a few set dies. For vaccine development, i e sites. Fortunately, T cells have of letic peptides of the protein much nucles to characterize in detail the	gments of a protein it will therefore be one advantage over more effectively antigenic sites of a
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro than do most antibodies. We model protein antigen myog	n the surface of that oth ls, in contrast to antiboo uunodominant antigenic ssreact with short synth have used synthetic pe lobin recognized by m	ter cell. Therefore, only a few set dies. For vaccine development, i e sites. Fortunately, T cells have of hetic peptides of the protein much optides to characterize in detail the urine T cells and T-cell clones es	gments of a protein it will therefore be one advantage over more effectively e antigenic sites of a tablished in this
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patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro than do most antibodies. We model protein antigen, myog lab. These studies indicated hydrophilic and hydrophobic algorithm which locates pote of the amino acid sequence. 12 proteins (p< 0.001). We sporozoite protein (CSP) of n major T-cell antigenic sites, cell immunity in mice. In the izing antibodies to construct mice that could not respond to design and construction of sy ing of presentation of biotiny on the cell surface where it w antibodies to the antigen. Fin cess, and present antigens to sterically hinders processing	n the surface of that off ls, in contrast to antibo unodominant antigenic ssreact with short synth have used synthetic pe lobin, recognized by m that such sites tended residues separated on nitial amphipathic helic This algorithm identif applied this to two prot malaria, and the HIV ( synthesized the corresp e malaria case, we coup a totally synthetic imm to the antibody site alon nthetic and recombina lated peptide to specifi- vas suspected but had m nally, we demonstrated T cells via their surfac- of part of the antigen a	ter cell. Therefore, only a few set dies. For vaccine development, i e sites. Fortunately, T cells have of tetic peptides of the protein much potides to characterize in detail the urine T cells and T-cell clones es to be amphipathic helices, i.e., he opposite sides. We have develop al segments of proteins and requiri eins of importance for vaccine de AIDS virus) envelope. In both of bonding peptides, and showed that bled the T-cell site to a known targ unogen capable of eliciting antibo he. These approaches should be u nt fragment vaccines. Also, we c T-cell clones to demonstrate the ot previously been demonstrable that B lymphocytes very efficier e immunoglobulin, but that this is nd so leads to selective processin	gments of a protein it will therefore be one advantage over more effectively e antigenic sites of a tablished in this lices that have bed a computer res knowledge only nant T cell sites on esign, the circum- f these we predicted tt these elicited T- get site of neutral- odies in strains of iseful in the rational useful in the rational usef avidin block- presence of peptide in most cases with ntly take up, pro- nmunoglobulin g and presentation
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro than do most antibodies. We model protein antigen, myog lab. These studies indicated hydrophilic and hydrophobic algorithm which locates pote of the amino acid sequence. 12 proteins (p< 0.001). We sporozoite protein (CSP) of r major T-cell antigenic sites, cell immunity in mice. In the izing antibodies to construct a mice that could not respond to design and construction of sy ing of presentation of biotiny on the cell surface where it v antibodies to the antigen. Fo sterically hinders processing to only a subset of antigen-st	n the surface of that off ls, in contrast to antibo unodominant antigenic ssreact with short synth have used synthetic pe lobin, recognized by m that such sites tended residues separated on nitial amphipathic helic This algorithm identif applied this to two prot nalaria, and the HIV ( synthesized the corresp e malaria case, we coup a totally synthetic imm to the antibody site alor ynthetic and recombina lated peptide to specific rasily, we demonstrated T cells via their surface of part of the antigen a pecific T cells. This ma	ther cell. Therefore, only a few set dies. For vaccine development, is esites. Fortunately, T cells have of the peptides of the protein much potides to characterize in detail the urine T cells and T-cell clones ess to be amphipathic helices, i.e., he opposite sides. We have develop al segments of proteins and requiri- eins of importance for vaccine de AIDS virus) envelope. In both of oonding peptides, and showed that bled the T-cell site to a known targ unogen capable of eliciting antibo- ne. These approaches should be un that fragment vaccines. Also, we c T-cell clones to demonstrate the ot previously been demonstrable that B lymphocytes very efficier e immunoglobulin, but that this is nd so leads to selective processin ay provide a mechanism to explai	gments of a protein it will therefore be one advantage over more effectively e antigenic sites of a tablished in this lices that have bed a computer res knowledge only nant T cell sites on esign, the circum- f these we predicted t these elicited T- get site of neutral- odies in strains of iseful in the rational used avidin block- presence of peptide in most cases with ntly take up, pro- mmunoglobulin g and presentation n how immune
patibility (MHC) molecule or antigen will be seen by T cell important to locate such imm antibodies in that T cells cro than do most antibodies. We model protein antigen, myog lab. These studies indicated hydrophilic and hydrophobic algorithm which locates pote of the amino acid sequence. 12 proteins (p< 0.001). We a sporozoite protein (CSP) of major T-cell antigenic sites, cell immunity in mice. In the izing antibodies to construct a mice that could not respond design and construction of sy ing of presentation of biotiny on the cell surface where it w antibodies to the antigen. Fit cess, and present antigens to sterically hinders processing to only a subset of antigen-sp response genes, which control	n the surface of that oth ls, in contrast to antibo unodominant antigenic ssreact with short synth- have used synthetic pe lobin, recognized by m that such sites tended residues separated on nitial amphipathic helic This algorithm identif applied this to two proto nalaria, and the HIV ( synthesized the corresp e malaria case, we coup a totally synthetic imm to the antibody site alor ynthetic and recombina lated peptide to specifi vas suspected but had m nally, we demonstrated T cells via their surface of part of the antigen a pecific T cells. This ma ol T-cell specificity, car	ther cell. Therefore, only a few set dies. For vaccine development, is esites. Fortunately, T cells have of the peptides of the protein much prides to characterize in detail the urine T cells and T-cell clones ess to be amphipathic helices, i.e., he opposite sides. We have develop al segments of proteins and requiri- eins of importance for vaccine de AIDS virus) envelope. In both of bonding peptides, and showed that bled the T-cell site to a known targ- unogen capable of eliciting antibo- ne. These approaches should be un the fragment vaccines. Also, we c T-cell clones to demonstrate the ot previously been demonstrate the ot previously been demonstrate the ot previously been demonstrate the ot previously been demonstrate the ot previously be	gments of a protein it will therefore be one advantage over more effectively e antigenic sites of a tablished in this lices that have bed a computer res knowledge only nant T cell sites on esign, the circum- f these we predicted T- get site of neutral- odies in strains of useful in the rational used avidin block- presence of peptide in most cases with ntly take up, pro- nmunoglobulin g and presentation n how immune ficity of antibodies



			PROJECT NU	IMBER	
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE					
NOTICE OF INT	RAMURAL RESEARCH PROJE	CT	Z01 CB	04023-01	MET
PERIOD COVERED					
October 1, 1986 throug	h September 30, 1987				
TITLE OF PROJECT (80 characters or less Molecular Mechanisms of	Title must fit on one line between the border of Lymphoid Development as	s.) nd Transformat:	ion		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Invest Senior Inve	gator.) (Name, title, labora	tory, and institu	MET NCT	
John J. Wright	Medical Sta	ff Fellow		MET. NCT	
Suzanne Zorn	Guest Resea	rcher		MET, NCI	
Christine Hua	Fogarty Vis	iting Fellow		MET, NCI	
Hon-Sum Ko	Fogarty Vis:	iting Fellow		MET, NCI	
Robert Coupland	Guest Resea:	rcher		LP, NCI	
Jeifrey Cossman	Senior inve	stigator		LP, NCI	
COOPERATING UNITS (if any)					
LAB/BRANCH Metabolism Branch					
SECTION					
INSTITUTE AND LOCATION					
DCBD, NCI, NIH, Bethes	da, Maryland				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
7	/	0			
(a) Human subjects (a) Auman subjects (a1) Minors	🛛 (b) Human tissues	(c) Neither			
SUMMARY OF WORK (Use standard upred	duced type. Do not exceed the space provider	0			
To understand normal a	nd abnormal B lymphocyte	development,	we have w	undertake	n
studies to identify an	d characterize genes imp	ortant in these	e process	ses. We	
characterized the t(14	;18)(q32;q21) chromosoma	l translocation	n present	t in huma	n
follicular lymphoma an	d identified a candidate	transforming ;	gene at 1	18q21. T	his
gene, termed BCL2, 1s	presumably also important	t in normal pro	e-B-cell	developm	ent.
translocation to defin	e the mechanism of this	exchange. To	elucidate	e the str	uc-
tural consequences of	this recombination, we say	equenced normal	1 and tra	anslocate	d
BCL2 cDNAs. The norma	1 BCL2 gene uses six pot	ential polyade	nylation	signals	in
exon 3 and two differe	ent 5' exons (exons 1 and	2) with their	respect	ive promo	ters.
The t(14;18) transloca	tion results in the dere	gulated express	sion of a	chimeric	
BCL2/IgH mRNA transcri	.pts with somatic mutation	ns in the BCL2	protein	coding	14
help define the function	op of the normal and tra	nslocated BCL2	protein	. We hav	P
extended the approach	of identifying new putat	ive proto-onco	genes by	cloning	
chromosomal breakpoint	s to the analysis of Hod	gkin's disease	and have	e cloned	
potential breakpoints	within the immunoglobuli	n heavy chain	(14q32) a	and T-cel	1
receptor beta chain (7	q35) loci. Finally, we	screened an ex;	pression	lambda g	tll
library with an antibo	dy that recognizes a 120	-kDa Lymphocyto	e activa	cion anci orming an	gen d
and identified one pos	d provide important insi	phts into B-ce	11 trans:	formation	1
differentiation.	a provide important indi				

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			PROJECT	NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUL	BLIC HEALTH SERV	ICE	
NOTICE OF IN	TRAMURAL RESEARCH	PROJECT	Z01	CB 05003-22 I
REPIOD COVERED				
October 1 1986 to Sor	tombor 30 1987			
TITLE OF PROJECT (80 cheracters or less	s. Title must fit on one line between	the borders.)		
Cell-Mediated Cytotoxi	city			
PRINCIPAL INVESTIGATOR (List other principal in the second	ofessional personnel below the Print	cipel Investigator.) (Nam	e, title, laboratory, and ins	titute effiliation)
PI: J. R. Wunderl	.ich	Senior Inves	tigator	IB, NCI
Otherse C. C. Ting		Madiaal Offi		
D. Segal		Senior Tryes	tigator	IB, NCI
R. Yetter		Guest Resear	cher	NTATD
H. Morse		Laboratory C	hief	NIAID
COOPERATING UNITS (if emu)				
LAB/BRANCH				
Immunology Branch				
SECTION				
INSTITUTE AND LOCATION				
NCI NIH Bethesda Ma	rvland 20892			·
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
1.9	0.9	1.0		
CHECK APPROPRIATE BOX(ES)	(b) Human ticques		h	
(a) Human subjects			ner	
(a2) Interviews				В
SUMMARY OF WORK (Use standard unre-	duced type. Do not exceed the spa	ce provided.)		
The cellular basis for	in vitro generatio	n of mouse M	HC-nonrestrict	ed, activated
killer cells against t	umor cells has been	further est	ablished by ce	ll reconsti-
tution tests. Results	confirm and extend	previous ob	servations tha	t the genera-
tion of activated kill	er cells in respons	e to the non	specific induc	ing agent
polyinosinic acid requ	ires accessory cell	s, T-helper	cells (L3T4 o	r Lyt2'),
thumic veto cells which	or cells. Inis know	tolorance	en used 1) to	generate
establishing tolerance	to self. and 2) to	identify an	d circumvent d	epressed in
vitro generation of ac	tivated killer cell	s by splenoc	ytes from mice	with acquired
immunodeficiency disea	se induced by murin	e leukemia v	iruses.	
				And the second second
Normal human PBL have	been activated in w	itro with re-	combinant 1L-2	and retar-
bodies which crosslipk	immune cells via s	elected activ	vation sites w	ith the tumor
cells. Retargeted eff	ector cells are cyt	otoxic in vi	tro for ovaria	n carcinoma
cells and block intrap	eritoneal growth of	the tumor c	ells in nude m	ice when the
mice are treated 4-6 d	ays after tumor gro	wth.		
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				PROJECT NUMBER
DEPARTMENT OF HEALTH A		ADCH DDO	ILTH SERVICE	
NOTICE OF INT	RAMURAL RESE	ANCH PHUJE		201 CB 05018-17 I
PERIOD COVERED				L
October 1, 1986 to Sept	ember 30, 198	7		
Target Coll Demogo by	mmuno. Mochanie	a between the border	s.)	
PRINCIPAL INVESTIGATOR (List other pro	dessional personnel below	the Principal Invest	igator.) (Nama, title, labora	atory, and institute affiliation)
PI: P. A. Henkart		Senior Inv	estigator	IB, NCI
Others: C. Yue		Medical St	aff Fellow	IB, NCI
W. Munger		Investigat	or	IB, NCI
T. Soares		Microbiolo	gist	IB, NCI
C. W. Reynolds	3	Investigat	or	BTB, FCRF, NCI
H. Young		Expert	agu Fallan	BTB, FCRF, NCL
A. Kuta		BIOLECIIIOI	ogy reliow	IB, NCI
COOPERATING UNITS (if any)				
Transal age Branch				
SECTION		·····		
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Mar	yland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:	
	3.0		0.5	
(a) Human subjects	(b) Human tis		(c) Neither	
(a) Minors				n
(a2) Interviews				В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed	d the space provided	1.)	
The functional and bioc	hemical proper	rties of cy	toplasmic gran	ules of rat large
granular lymphocyte tum	ors have been	further de	lineated. Ant	ibodies against the
two BLT esterases purif	ied to homoger	neity were	used to show t	hat these proteins
are serologically not o	ross-reactive	, confirming	g previous enz	ymatic inhibition
data. The possible int	eractions of t	these enzym	es in cytolysi	n function was examied
by mixing the pure LGL	granule cytoly	ysin and th	e pure major B	LT esterase and
distic offect was obser	rund which con	r Largel Ce.	the externet	ed cells), a syner-
ten-fold. Target prein	cubation with	the enzyme	did not cause	this effect nor was
it seen with the minor	BLT esterase.	While the	se results sug	gest that the major
enzyme can potentially	increase the 1	lytic effic	iency of cytot	oxic lymphocytes. the
mechanism of this effect	t is still und	clear. The	ability of gr	anules of cytotoxic
lymphocytes to release	DNA from targe	et nuclei w	as studied in	order to explain the

while the purified cytolysin causes lysis with no DNA breakdown. Two additional granule components cause DNA release from detergent permeabilized cells, but these appear to be minor granule proteins. Our results suggest that target cell DNA breakdown can be accounted for by the granule exocytosis mechanism. In order to begin a molecular biology approach to LGL granule proteins, a cDNA library in lambda gt10 was constructed from rat LGL tumor cell mRNA. The purified cytolysin protein was subjected to cyanogen bromide digestion and the resulting peptides separated by HPLC. Sequences of 25 amino acid residues of two of these were obtained by Edman degradation. Based on these sequences, synthetic oligonucleotide probes were synthesized in order to probe the cDNA library for the cytolysin clone.

rapid DNA degradation seen when cytotoxic lymphocytes attack target cells. Purified LGL tumor granules cause nuclear DNA release along with lysis of tumor cells,



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 05021-16 I

PERIOD COVERED						
October 1, 1986 to Septe	ember 30, 1987					
TITLE OF PROJECT (80 characters or less. Title must it on one line between the borders.)						
Antigens Determined by the Murine Major Histocompatibility Locus						
PRINCIPAL INVESTIGATOR (List other profess	sional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)					
PI: D. H. Sachs	Chief, Transplantation Biology Section IB, NCI					
Others: J. A. Bluestone	e Senior Investigator IB. NCI					
C. H. Chester	Guest Researcher IB, NCI					
Y. Sharabi	Visiting Fellow IB, NCI					
N. Shinohara	Visiting Scientist IB, NCI					
M. Sykes	Visiting Associate IB, NCI					
COOPERATING UNITS (if any)						
S. L. Epstein, Senior St	aff Fellow, National Center for Drugs and Biologics, FDA					
LAB/BRANCH						
Immunology Branch						
SECTION						
Transplantation Biology	Section					
INSTITUTE AND LOCATION						
NCI, NIH, Bethesda, Mary	/land 20892					
TOTAL MAN-YEARS: PR	ROFESSIONAL: OTHER:					
4.5	3.0 1.5					
(a) Human subjects (a1) Minors (a2) Interviews	) (b) Human tissues $\Box_{\mathbf{x}}$ (c) Neither					
SUMMARY OF WORK (Use standard unreduce	ed type. Do not exceed the space provided.)					
Studies are being direct complex, the structure a tions of immune response terization of major hist mice are developed, main of the MHC products of t Ia antigens: Hybridoma cells with mouse myeloma produced by these hybrid	ed toward understanding the major histocompatibility ind function of the products of this complex, and manipula- is to these products. Current studies include: 1) Charac- cocompatibility antigens: Congenic resistant strains of itained, and used in serologic and immunochemical analyses the mouse; 2) Studies of monoclonal antibodies to H-2 and cell lines are produced by fusion of immune mouse spleen in cells. The monoclonal anti-H-2 and anti-Ia antibodies lomas are analyzed by serologic and immunochemical means characterize the fine structure of the MHC; 3) Characteri- for histocompatibility antigens: Anti-idiotypic antisera					
and are used to further zation of receptor sites are produced against ant of these antisera on in assessed; 4) Mechanism o cellular responses of ra ism for maintenance of t geneic and xenogeneic ch mixtures of T-cell deple of tolerance and of immu in vitro.	i-H-2 and anti-Ia hybridoma antibodies, and the effects vitro and in vivo parameters of histocompatibility are of tolerance to H-2 and Ia antigens: The humoral and diation bone marrow chimeras are examined, and the mechan- olerance in these animals is studied; and 5) Mixed allo- imeras, in which irradiated animals are reconstituted with ted donor and host marrow, are produced and the mechanism ne responsiveness in these animals is studied in vivo and					



PROJECT NUMBER DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT ZO1 CB 05023-16 T PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Transplantation Antigens of Swine PRINCIPAL INVESTIGATOR (List other professionel personnel below the Principal Investigator.) (Name, title, leboretory, and institute affiliation) PI: D. H. Sachs Chief, Transplantation Biology Section IB, NCI Others: S. A. Rosenberg Chief, Surgery Branch SB, NCI E. O. Kortz Medical Staff Fellow IB, NCI Medical Officer R. E. Gress IB, NCI K. Pratt Senior Staff Fellow IB, NCI D. S. Singer Senior Investigator IB, NCI T. Suzuki Visiting Fellow IB, NCI F. Hirsch Guest Researcher IB, NCI COOPERATING UNITS (if env) NIH Animal Center, Poolesville, Maryland J. K. Lunney, Research Chemist, USDA Animal Parasitology Institute, Beltsville, MD

LAB/BRANCH					
Immunology Branch					
SECTION					
Transplantation Biolog	y Section				
INSTITUTE AND LOCATION					
NCI, NIH, Bethesda, Ma	ryland 20205				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
4.0	3.0	1	•0		
CHECK APPROPRIATE BOX(ES)	and a second				
a) Human subjects	(b) Human tissues	$\Box_{\mathbf{X}}(\mathbf{c})$ N	either		
a1) Minors				В	
(a2) Interviews					

SUMMARY OF WORK (Use stenderd unreduced type. Do not exceed the space provided.)

Three herds of miniature swine, each homozygous for a different set of histocompatibility antigens at the MHC have been developed. Current projects include: 1) Assessment of survival of organs and tissue transplants among and between members of these herds as a model for human transplantation; 2) Assessment of the immunologic parameters involved in tolerance to allografts in this species; 3) Detection and characterization of intra-MHC recombinants: three intra-MHC recombinants have been obtained and bred to homozygosity. Kidney transplants utilizing these new recombinants have shown that selective matching for Class II antigens frequently permits long-term kidney graft survival across a Class I difference; 4) Bone marrow transplants in miniature swine: the effect of mixing autologous plus allogeneic marrow in the reconstituting inoculum are being examined. This modality is being assessed as a specific preparative regimen for allogeneic organ transplantation; 5) Production and characterization of monoclonal antibodies reactive with subsets of pig lymphocytes: antibodies corresponding to many of the OKT series in man have been identified (including T4, T8, and T11). The effects of these antibodies on in vitro and in vivo transplantation immunity are being assessed, and they are also being used to assess mechanism of tolerance; and 6) Analysis of MHC genes: Southern blot analyses using cDNA probes from human class II genes have been performed, and indicate that genes corresponding to each of the major human class II loci are present in the pig genome. In addition, a genomic library in the EMBL-3 phage vector has been constructed and screened with these probes. Class II genes from the pig herds have been isolated and are being characterized and used in in vitro and in vivo transfection studies.



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	701 OD 05000 16 T
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZUI CB 05033-16 1
PERIOD COVERED			
October 1, 1986 to Sep	ptember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	rs.)	
Immunotherapy of Human	1 Cancer		
PRINCIPAL INVESTIGATOR (List other pro	ifessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and institute affiliation)
PI: R. J. Hodes	chief, mmunoci	lerapy Section	IB, NCI
Others: S. A. Rosenbe	erg Chief		SB, NCI
	8		,
COOPERATING UNITS (if any)			
LAB/BRANCH			
SECTION			
Immunotherapy Section			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Ma	iryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
0.2	0.1	0.1	
CHECK APPROPRIATE BOX(ES)	(b) Human tissues	(c) Neither	
(a1) Minors			D
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	d.)	
A controlled, randomiz	ed trial comparing immur	otherapy to ch	emotherapy in
stage 1 and stage 11 m	the trial which is also	en initiated.	A total of 181
Preliminary evaluation	of data has demonstrate	d no significa	accrual of patients.
adjuvant therapies on	clinical course.	a no significa	ne cricce or



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PR	OJECT	Z01 CB 05035-15 I
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the l	borders.)	
Function of B Lymphocy	te Fcy Receptors		
PRINCIPAL INVESTIGATOR (List other pro PI: H. B. Dickler	fessionel personnel below the Principal Senior L	Investigator.) (Name, titla, labora nvestigator	itory, and institute affiliation)
Others: G. Lazlo	Visting	Fellow	IB, NCI
COOPERATING UNITS (if any)			
LAB/BBANCH			
Immunology Branch			
SECTION			
NCI, NIH, Bethesda, Ma	ryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
1.9	1.0	0.9	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	L (c) Neither	В
(a2) Interviews			_
SUMMARY OF WORK (Use standard unred	fuced type. Do not exceed the space pr	rovided.)	
The goal of this proje	ct is to characterize	the function of	B lymphocyte Fcγ
receptors. Previous f	indings indicate that	the Fcy receptor	s of B lymphocytes
d) surface IgM and a)	surface IgD Fach o	on, b) la antigen f these interacti	s, c) Lym antigens,
specific, and non-rand	om. Studies utilizin	g antigen-antibod	v complexes indicate
that B lymphocyte Fcy	receptors cross-linke	d by their physio	logic ligand down-
regulate B lymphocyte	differentiation witho	ut affecting prol	iferation. Resting
but not activated B ly	mphocytes are suscept	ible to this nega	tive regulation.
Occupancy of B lymphoc	yte surface IgM by a	separate ligand i	s necessary for
these two membrane rec	entors may be involve	d in generating t	he negative signal.
Studies using monoclon	al anti-FcyR antibody	(2.4G2) in a var	iety of forms
including native, chem	ically cross-linked i	nto homodimers or	heterodimers with
anti- $\delta$ or F(ab') <sub>2</sub> anti	- $\mu$ antibodies, and on	a Sepharose matr	ix indicate that
the monoclonal antibod	y only generates the	negative regulato	ry signal if
effective cross-linkin	g of the receptor 1s	obtained. Variou	s B lymphocyte popu-
regulation. LyB5 nega	tive B cells are-susc	entible but antig	en-primed B cells
are not. B cells from	autoimmune MRL/1 mic	e are susceptible	but not those from
autoimmune NZB mice.	Lack of responsivenes	s to Fcy receptor	downregulation
may play a pathogenic	role in NZB autoimmun	e mice.	



DEPARTMENT	OF HEALTH	AND HUMAN SERVICES	PUBLIC HEALTH SERVICE
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## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 05036-15 I

PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	Brs.)	
Genetic Control of the	Immune Response to Staph	nylococcal Nuclease	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	stigator.) (Name, title, laboratory, and institute a	ffiliation)
PI: D. H. Sachs	Chief, Transplantatio	on Biology Section	IB, NCI
Others: R. J. Hodes	Chief, Immunotherapy	Section	IB, NCI
A. Finnegan	Guest Worker, Immunot	therapy Section	IB, NCI
COOPERATING UNITS (if any)		······································	
LAB/BRANCH			
Immunology Branch			
SECTION			
Transplantation Biology	Section		
NCT NTY Bothoode Man	w1 and 20205		
TOTAL MANYEARS		OTHER	
1.5	1.0	0.5	
CHECK APPROPRIATE BOX(ES)	1	1 000	
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			в
			2
(a2) Interviews	· · · · · · · · · · · · · · · · · · ·		2
(a2) Interviews	luced type. Do not exceed the space provide	ad.)	
(a2) Interviews SUMMARY OF WORK (Use standard unred Several hybridomas reac	duced type. Do not exceed the space provide tive with nuclease and/c	od) or anti-idiotype have beer	n produced
(a2) Interviews SUMMARY OF WORK (Use standard unred Several hybridomas reac and characterized. Sym	uced type. Do not exceed the space provide tive with nuclease and/c geneic anti-idiotypes ha	ad) or anti-idiotype have beer ave also been produced and	n produced l are
(a2) Interviews SUMMARY OF WORK (Use standard unred Several hybridomas reac and characterized. Syn presently being charact	uced type. Do not exceed the space provide tive with nuclease and/c geneic anti-idiotypes ha erized in both antibody	ad) or anti-idiotype have beer ave also been produced and and T cell systems. Comp	n produced l are petitive
(a2) Interviews SUMMARY OF WORK (Use standard unred Several hybridomas react and characterized. Syn presently being charact binding studies are use monoclonal antibodies.	duced type. Do not exceed the space provide tive with nuclease and/c geneic anti-idiotypes ha erized in both antibody d to determine epitopes Examination of the king	ad) or anti-idiotype have beer ave also been produced and and T cell systems. Comp of nuclease as defined by	n produced l are petitive v available
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DEPARIMENT	OF HEALTH	AND HUMAN	SCHVICES -	FUDLIC HEALT	JENVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 05050-13 I

PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the bo	rders.)	
The Manipulation of Imm	une Processes With Het	erocrosslinked Antil	odies
PRINCIPAL INVESTIGATOR (List other pro	tessional personnel below the Principal In	vestigator.) (Name, title, laboratory, a	nd institute affiliation)
PI: D. M. Segal	Senior Invest:	igator	IB, NCI
Otheras D. P. Spider	Visiting Foll		
Others: D. F. Shider	Visiting relia	Uw ham	IB, NCI
Q. Jia-nua	Guest Research	igator	IB, NCI
M Carrido	Visiting Folly		IB, NGL
T. Hecht	Associate Pro	fessor	ID, NOI Univ MD
i i neene	ASSociate II.	103301	
COOPERATING UNITS (if any)		······	
LAB/BRANCH			
Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
6.0	4.5	1.5	
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			D
(a2) Interviews			d
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space prov	ided.)	
1. Human T cells and K	cells targeted with a	ti-T3 and anti-FcR	heterocrosslinked
to anti-tumor antibodie	s eradicate established	t human ovarian cano	er cells in nude
mice.			er corro in nucc
2. Heterocrosslinked a	ntibodies containing an	n antibody against a	soluble antigen
linked to an antibody a	gainst a cell surface of	leterminant on an ar	tigen presenting
cell (APC), greatly enh	ance the efficiency of	antigen presentatio	on. Enhanced
presentation has been so	een when antigen was ta	argeted to Fc recept	ors. surface
immunoglobulin, MHC clas	ss I and MHC class II r	nolecules on the APC	. Targeted
antigen presentation is	antigen specific and	I-A restricted.	0



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 CB 05062-12 I

October 1 1986 to September 30 1987	
TITLE OF PROJECT (80 characters or lass. Title must fit on one line between the borders )	
Application of Papid Flow Microflycrometry to Coll Biology	
Apprication of Kapia Flow microritation account holes the Biographic States (Mars and States)	
Principal Investigator. (Name, title, laboratory, and institute affiliation)	NOT
III. J. K. Wunderlich Senior investigator IB,	NCI
S. U. Snarrow Chemist IB,	NCI
Uthers: Members of the Immunology Branch (see text) IB,	NCI
COOPERATING UNITS (if any) R. Schwartz, Immunol Lab, NIAID; R. Klausner, NICHHD; S	. I.
Katz, Chief, Dermatology Branch, NCI; A. Schultz, CSL, DCRT; L. Barden, CSL,	
DCRT; J. D. Shanley, VA Med Ctr, U. of CT; D. DeLuca, U. of SC; L. E. Hood, C	al
Tech; T. Springer, Dana Farber Cancer Inst.; H. Young, BRMP, NCI/Frederick.	
LAB/BRANCH	
Immunology Branch	
SECTION	
INSTITUTE AND LOCATION	
NCI, NIH, Bethesda, Maryland 20892	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	
2.1 1.1 1.0	
CHECK APPROPRIATE BOX(ES)	
a) Human subjects 😨 (b) Human tissues 🗌 (c) Neither	
□ (a) Human subjects  □ (b) Human tissues  □ (c) Neither □ (a1) Minors	в
<ul> <li>□ (a) Human subjects</li> <li>□ (a1) Minors</li> <li>□ (a2) Interviews</li> <li>□ (a2) Interviews</li> </ul>	В
(a) Human subjects	В
<ul> <li>(a) Human subjects (b) Human tissues (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FME) for analysis and sorting of cells</li> </ul>	В
<ul> <li>(a) Human subjects</li></ul>	B
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of talarance (2) atud</li> </ul>	B
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) stud of the natherparenes of graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of the cellular basis for graft reversions (3) analysis of graft reversis (3) analysis (3) analysis (3) analysis (3) analysis (3) a</li></ul>	B of ies
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) stud of the pathogenesis of graft-vs-host disease, (3) analysis of the relationship</li> </ul>	B of ies P
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) stud of the pathogenesis of graft-vs-host disease, (3) analysis of the relationshibetween memory T cells and their expression of adhesion molecules, (4) invest</li> </ul>	B of ies p i-
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) stud of the pathogenesis of graft-vs-host disease, (3) analysis of the relationshibetween memory T cells and their expression of adhesion molecules, (4) invest gation of the immune system localized in the skin, (5) investigation of murin</li> </ul>	B of ies p i- e
<ul> <li>(a) Human subjects  (b) Human tissues  (c) Neither</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)</li> <li>Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) studies the pathogenesis of graft-vs-host disease, (3) analysis of the relationshi between memory T cells and their expression of adhesion molecules, (4) invest gation of the immune system localized in the skin, (5) investigation of murin MHC class I molecules controlled by genes in the Qa-2 region of chromosome 17</li> </ul>	B of ies p i- e ,
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(a) Human subjects ☑ (b) Human tissues ☑ (c) Neither	B of ies p i- e ,
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☐ (a) Human subjects	B of ies p i- e ,
☐ (a) Human subjects	B of ies p i- e ,
□ (a) Human subjects □ (b) Human tissues □ (c) Neither □ (a1) Minors □ (a2) Interviews SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Using rapid flow microfluorometry (FMF) for analysis and sorting of cells, aspects of the following projects have been supported this year: (1) studies the cellular basis for graft rejection and development of tolerance, (2) stud of the pathogenesis of graft-vs-host disease, (3) analysis of the relationshib between memory T cells and their expression of adhesion molecules, (4) invest gation of the immune system localized in the skin, (5) investigation of murin MHC class I molecules controlled by genes in the Qa-2 region of chromosome 17 and (6) development of an automated computer aid for multiparameter data processing.	B of ies p i- e ,



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUB	LIC HEALTH SERVICE	PHOJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH	PROJECT	Z01 CB 05064-11 I
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between	the borders.)	
	Instante Response In	VILIO	
PI: A. Singer	Senior Inve	stigator	IB, NCI
Others: R. Gress	Senior Inve	stigator	IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH Immunology Branch			
SECTION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
1.5	0.5	1.0	
(a) Human subjects (a) Auman subjects (a1) Minors	□ (b) Human tissues	$\Box_{\mathbf{x}}(\mathbf{c})$ Neither	В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space	ce provided.)	
The influence of class	I MHC gene products	on selection of th	e L3T4 <sup>+</sup> T helper
cell repertoire was inv	estigated. It was	found that the gene	ration of immune
specific for a composit	e MHC determinant c	omposed of $I-A^b + K$	bm6 determinants.
Most interestingly, it	was found that the	selection of L3T4 <sup>+</sup>	T helper cells
of $I-A^b + K^b$ composite	MHC determinants.	In other words the	selection of Ia-
restricted Th cells spe	cific for mutant cl	ass I determinants	required expression
by intrathymic cellular nants. This is the fir	elements of self-c	lass II and self cl	ass I MHC determi-
involved in the selecti	on of the T cell re	pertoire.	e comprementation



			PROJECT N	IUMBER
DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	701	CP 05067-12 T
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	201	CB 03007-12 1
PEBIOD COVERED			L	
October 1, 1986 to Ser	ptember 30, 1987			
TITLE OF PROJECT (80 characters or less Mechanisms of In Vitro	s. Title must fit on one line between the borde o Cellular Immune Respons	rs.) Ses		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Invest	igator.) (Name, title, labora	tory, and insti	itute affiliation)
Others: W. Makgoba	Fogarty Fellow	I		IB, NCI
M. Sanders	Medical Staff	Fellow		IB, NCI
G. Ginther-Lu	uce Chemist			IB, NCI
COOPERATING UNITS (if any)				
Timothy A. Springer,	Ph.D., Department of Memb	orane Immunoche	mistry,	Dana Farber
Cancer Institute, Bos	ton, MA 02115			
Immunology Branch				
SECTION				
NCT. NTH. Bethesda. M	arvland 20892			
TOTAL MAN-YEARS	PROFESSIONAL	OTHER		
3.0	3.0	UTIER.		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects	X(b) Human tissues	(c) Neither		
(a1) Minors				В
SUMMARY OF WORK (Use stenderd unred	duced type. Do not exceed the space provider	<del>/</del> )		
Our work in the last	two years has led to the	realization th	at anti	gen-independent
adhesion is a critical	l early event in T lympho	ocyte interacti	ons wit	h other cells,
and we hypothesized the	CD2 (T1) Farosette reco	ar palnways by	ing wit	h its ligand
LFA-3 and T cell LFA-	l interacting with an un	nown ligand.	This ve	ar's work has
confirmed and extended	d those concepts. Bioche	emical studies	of puri	fied CD2 and
LFA-3 have confirmed	the binding of each to th	ne other cor	roborat	ing our
inference based on fur	nctional studies that LFA	A-3 is the liga	ind for	CD2. A
particularly interesting example of adhesion mediated by these two pathways is				
T cells. Furthermore IFA-3 has been shown to be the erythrocyte ligand which				
mediates autologous rosetting. The concept of two pathways of adhesion has been				
extended to indicate its relevance to T-cell mediated cytotoxicity (CML) as well				
as conjugate formation. Studies of CML as well as adhesion demonstrate function-				
ally that ICAM-1 is the principal ligand for LFA-1 in T cell interaction with				
interactions with other targets. Because of the functional importance of these				
adhesion molecules, we have carefully investigated their expression on peripheral				
blood T cells. Our studies demonstrate that expression of LFA-3, CD2, and LFA-1				
is increased on a majo	or subset of peripheral h	blood T cells w	ith the	functional
properties of memory of these function	cells and raise the possi	Dility that su	ch enha	ncea expres-
sion of these functionally important molecules may contribute to the enhanced				
	,			



			PROJECT NUMBER	
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	Z01 CB 05069-	11 I
PERIOD COVERED	tombox 20 1097			
TITLE OF BEO JECT (80 characters of loss	Title must fit on one line between the bord	ars )		
Expression of Ta Antig	rens on Functional Cell S	Subpopulations		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inves	stigetor,) (Neme, title, labore	tory, and institute affilietion)	
PI: R. J. Hodes	Chief, Immunother	apy Section	IB. I	NCI
	,		,	
Others: A. Finnegan	Senior Staff Fell	Low	IB, J	NCI
COOPERATING UNITS (if any)				
Immunology Branch				
SECTION				
Immunotherany Section				
INSTITUTE AND LOCATION				
NCL. NIH. Bethesda, Ma	rvland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
0.1	0.1			
CHECK APPROPRIATE BOX(ES)				
🔲 (a) Human subjects	(b) Human tissues	(c) Neither		
(a1) Minors				В
(a2) Interviews				
SUMMARY OF WORK (Use stenderd unrac	fuced type. Do not exceed the space provide	ad.)		
A series of T cell clo	nes which recognized the	same antigenio	c molecule in ass	soci-
ation with a given $E_{\alpha}E$	B class II molecule were	e studied for th	neir susceptibili	ity
to inhibition by a pan	el of 15 different anti	I-E monoclonal	antibodies speci	ific
for determinants on th	e same I-E molecule. Th	e results demon	nstrated that dif	ffer-
ent T cell clones appe	ar to recognize antigen	in association	with distinct de	eter-
minants or conformatio	ns on the same I-E molec	ule. The respo	onses of T cell o	clones
to the mitogen Mycopla	sma arthritidis supernat	ant (MAS) were	also analyzed.	It
was determined that ap	proximately 15% of the c	lones tested re	esponded to MAS v	when
presented in the conte	xt of 1-E bearing antige	in presenting co	ells, and that the	nis
reactivity was indepen	dent of the primary spec	ificity or MHC	restriction of t	those
clones to conventional	antigens.			
Then the shility of di	fferent To overseeing as			-
when the ability of di	ll of the cloped tested	pulations to p	resent to cloned	1
cell=containing irradi	ated stimulating colls c	were able to re	troated purific	4
resting B cell populat	ione In contrast only	a subpopulatio	on of cloned T	1
cells was responsive t	o IPS activated B cell b	laste in enite	of the enhance	t Ta
expression by these B	cell blasts indicating	that the signal	s required for	r 10
cell activation may va	ry among T cell clones.	and that distin	oct Ta bearing	-
antigen presenting cel	1s may be competent for	presentation to	different T cel	
another presenting cerrs may be competent for presentation to different f terrs.				11s -
				lls.
				lls.
				11s.
				lls.
				lls.
				11s.



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	PHOLEOF NOMBER	
NOTICE OF IN	FRAMURAL RESEARCH PROJ	ECT	ZO1 CB 05086-09 I	
PERIOD COVERED October 1, 1986 to Sep	tember 30, 1987			
TITLE OF PROJECT (80 cheracters or les	s. Title must fit on one line between the borde	ars.)		
Immune Response Gene R	egulation of the Immune	Response In Vit	ro	
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Principal Inves	tigetor.) (Name, title, laboret	ory, and institute affilietion)	
PI: R. J. Hodes	Chief, Immunothe	erapy Section	IB, NCI	
Others: D. H. Sachs	Chief, Transp. 1	Biol. Sec.	IB, NCI	
A. Finnegan	Senior Staff Fe	11ow	IB, NCI	
J. Berzofsky	Senior Investiga	ator	MB, NCI	
Dr John A Smith Den	t of Pathology Harvard	Medical School	Boston MA 02114	
Dr. John A. Smith, Dep	c. of fathology, harvard	Medical School	, Boston, MA 02114	
LAB/BRANCH Immunology Branch				
SECTION				
Immunotherapy Section				
INSTITUTE AND LOCATION	1 1 20202			
NCI, NIH, Betnesda, Ma	ryland 20892	LOTHER:		
0.6	0-3	0.3		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects (a1) Minors	(b) Human tissues	x(c) Neither	В	
	durad huna. On ant available analysis			
SUMMARY OF WORK (Use standard unreduced type Do not exceed the space provided.) The function of accessory cells in primary and secondary in vitro antibody responses to TNP-(T,G)-AL and TNP-(H,G)-AL is under the control of immune response (Ir) genes which map to I-A. The expression of Ir gene function by B cells is related to the B cell activation pathway; Ir gene function is expressed by B cells activated under conditions involving MHC-restricted T-B interaction. In vitro augmented primary and secondary responses to TNP-nuclease (TNP-NASE) have also been established and documented to be under the control of H-2 linked Ir gene(s) mapping to the I-B subregion. For these responses, accessory cell function was shown to be under Ir gene control. Recent data employing monoclonal anti-Ia reagents have suggested that genes in the I-A subregion may also be involved in regulating responses to TNP-NASE. In order to further analyze the genetic regulation of T cell responses to NASE, a series of cloned lines were generated in BALB/c (H-2 <sup>d</sup> ) as well as (H-2 <sup>b</sup> x H-2 <sup>a</sup> )F <sub>1</sub> T cells. Individual clones were restricted to recognizing NASE in the context of either A <sub>a</sub> A <sub>b</sub> or E <sub>a</sub> E <sub>b</sub> products. The antigen fine specificity of cloned NASE-specific T cells was also probed through the use of mutant NASE molecules and synthetic peptides corresponding to segments of NASE. A consistent correlation was found between the fine specificity of a given clone and its MHC restriction specificity. A <sup>b</sup> <sub>a</sub> A <sup>b</sup> <sub>b</sub> restricted clones were selectively responsive to peptide 91-110; E <sup>k</sup> E <sup>k</sup> <sub>b</sub> restricted clones were responsive to peptide 81-100.				

PROJECT NUMBER



DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PU	BLIC HEALTH SERVICE	THOSE OF NOMBER
NOTICE OF INT	RAMURAL RESEARCH	PROJECT	ZO1 CB 05088-09 I
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between	n the borders.)	
PRINCIPAL INVESTIGATOR (List other or	st Reactions on Ce.	cipal Investigator) (Name title Jabo	ratory and institute affiliation)
PI: G. M. Shearer	Senio	or Investigator	IB. NCI
		0	,
Others: F. Hakim	Guest	t Worker	IB, NCI
C. S. Via	Medio	cal Staff Fellow	IB, NCI
M. Fukuzawa	Visi	ing Fellow	IB, NCI
5. Sharrow	Chem		IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)	5.0	1.5	······································
(a) Human subjects	(b) Human tissues	$\Box_{\mathbf{k}}$ (c) Neither	
(a1) Minors			В
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the spe	ace provided.)	
The intravenous injection	on of F <sub>1</sub> hybrid mic	e with parental T c	ells result in a loss
to graft-versus-host im	une deficiency (G	(HID). Recognition	of host class II MHC
antigens by donor cells	is required to inf	tiate GVHID. Recog	nition of host class I
MHC antigens may or may	not induce GVHID,	depending on the cl	ass I determinants
required. Recognition of	of class II only at	progates L3T4 <sup>+</sup> T hel	per cell responses but
not Lyt2 <sup>+</sup> T helper cell	responses; recogni	tion of class I and	II results in loss of
both L3T4' and Lyt2' T I	helper cell respons	ses. Induction of G	WHID by class I and II
only recognition require	es only L3T4 <sup>+</sup> parer	tal T cells.	GVHID by class II
Inoculation of parental	T cells into F1 mi	ce can also result	in different immune
abnormalities, depending	g on the donor and	host strains used.	Injection of C57BL/6
cells into B6D2F1 mice 1	esulted in extensi	ve immune suppressi	on, hypogamma-
globulinema, and suscept	ibility to infecti	on. Injection of D	BA/2 cells into
bypergammaglobulinema	selective suppress	oduction with SIE-1	ike symptoms The
differences in these two	forms of SLE were	attributed to a de	fect in DBA/2 anti-
F1 CTL precursor frequen	icy.		
The parent-into-F1 GVH n	eaction also resul	ts in severe defect	s in bone marrow stem
cell function, as well a	is in a defect in t	the self MHC restric	tion ability of the
1 cuymus.			

PROJECT NUMBER



DEPARTMENT OF HEALTH A NOTICE OF INT	ND HUMAN SERVICES - PUBLIC HEA RAMURAL RESEARCH PROJE	LTH SERVICE	ZO1 CB 05099-07 I
PERIOD COVERED October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less. Synergistic Effects of	Title must fit on one line between the border Murine Cytomegalovirus an	s.) nd Graft-versus	s-host Reaction
PRINCIPAL INVESTIGATOR (List other proj PI: G. M. Shearer	essional personnel below the Principal Investi Senior Invest	gator.) (Name, title, laborat Stigator	lory, and institute affiliation) IB, NCI
Others: D. M. Segal	Senior Inve Chemist	stigator	IB, NCI IB NCI
C. Via	Medical Sta	ff Fellow	IB, NCI
S. Sharrow	Chemist		IB, NCI
COOPERATING UNITS (if any)	nital Newington CT		
5. D. Shanrey, V.K. 105	pital, newington, of		
LAB/BRANCH Immunology Branch			
SECTION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 0.5	OTHER: 0.5	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	□ (b) Human tissues □	<sup>x</sup> (c) Neither	В
(a) Interviews           Guinterviews           SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)           Injection of F1 hybrid mice with either murine cytomegalovirus (MCMV) or parental spleen cells (graft-versus-host reaction - GVHR) results in rapid and severe immuno suppression. Inoculation of either the virus or parental cells were selected so that they would be below the threshold for severe immunosuppression. However, when these two inocula were combined, severe immunosuppression was observed. Furthermore, injection of F1 mice with parental lymphocytes that recognize only class I MHC determinants does not result in immune suppression. However, a combination of class I recognition and MCMV infection results in profound immune suppression. Infection of host mice with MCMV prior to induction of GVH resulted in augmented immune suppression, whereas infection of donor mice with MCMV before induction of GVH resulted in reduced immune suppression. The combination of MCM and GVHR also resulted in interstitial pneumonitis, whereas either insult alone had no detectable pathogenic effect on the lungs. These studies permit the investigation of the immunosuppression of MCMV infection and the possibility consequences of CMV infection coupled with a GVHR.           Mice were treated in vivo in such a way as to render them deficient in L3T4 <sup>+</sup> or both L3T4 <sup>+</sup> and Lyt2 <sup>+</sup> cells died. This observation may be relevant for determining the T cell subsets important for protection against CMV infection.			



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - P	UBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF IN	TRAMURAL RESEARC	H PROJECT	Z01 CB 05100-07 I
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or le	ss. Title must fit on one line betwe	en the borders.)	
The Role of HLA Genes	in Human Disease		
PRINCIPAL INVESTIGATOR (List other p	vofessional personnel below the P	rincipal Investigator.) (Name, title, lab	oratory, and institute affilietion)
PI: S. Shaw	Senior In	nvestigator	IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	cyland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
	0	0	
<ul> <li>(a) Human subjects</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul>	👿 (b) Human tissues	s 🗋 (c) Neither	A
SUMMARY OF WORK (Use standard unr	educed type. Do not exceed the s	pace provided.)	
but no work has been no	erformed in this 1:	horatory	ed in such studies
but no work nub been p	server in child it	bordeory.	
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		524	
PHS 6040 (Rev. 1/84)			GPO 914-918


PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Definition of Human Histocompatibility Antigens PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: S. Shaw Senior Investigator IB, NCI Others: E. Gugel Biological Lab Tech IB, NCI
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)         Definition of Human Histocompatibility Antigens         PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)         PI:       S. Shaw       Senior Investigator       IB, NCI         Others:       E. Gugel       Biological Lab Tech       IB, NCI
PRINCIPAL INVESTIGATOR (List other protessional personnel below the Principal Investigator.) (Name, title, laboratory, and institute atfiliation)         PI:       S. Shaw       Senior Investigator       IB, NCI         Others:       E. Gugel       Biological Lab Tech       IB, NCI
PI:S. ShawSenior InvestigatorIB, NCIOthers:E. GugelBiological Lab TechIB, NCI
E. Long Investigator NIAID
COOPERATING UNITS (# any) R. DeMars, U. of Wisconsin, Madison, WI; M. Sanchez-Perez, Universidad Complutens de Madrid, Madrid, Spain
LAB/BRANCH Immunology Branch
SECTION
INSTITUTE AND LOCATION NCI, NIH, Bethesda, Maryland 20892
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:
CHECK APPROPRIATE BOX(ES)
□ (a) Human subjects       □ (b) Human tissues       □ (c) Neither         □ (a1) Minors       □ (a2) Interviews
Using T cell recognition (primarily cell-mediated lysis) we have continued to prot the complexities of T cell recognition of HLA alloantigens. We have pursued the novel approach of using cytotoxic T lymphocyte (CTL) clones as the selective agen to enrich for ICR-191 mutagenized lymphoblastoid cell lines (LCL) which have lost their capacity to be lysed by that clone. Using that approach, 24 mutant LCL hav been derived which are not lysed by the "selecting" DPw2-allospecific CTL clone. Serological analysis confirms the loss of DPw2 and Nothern blot analysis demon- strates loss of DPa or DPß mRNA in many of the mutants. These mutants have subsequently been used as informative probes to demonstrate the requirement for DPa and DPß recognition by other putatively "DPw2-specific" CTL clones with more complex specificity. The specificity of these clones suggests that they may recognize peptide fragments of another HLA gene(s) in a DP-restricted fashion.



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBL	IC HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH	PROJECT	Z01 CB 05103-06 I
PERIOD COVERED			L
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between th	he borders.)	
Structure and Function	of Cytotoxic Helper	T Lymphocyte Granu	Les
PRINCIPAL INVESTIGATOR (List other pro	ressional personnel below the Princip	or Towostigator.) (Name, title, labora	tory, and institute affiliation)
Others: T. Soares	Micr	obiologist	IB, NCI
W. Munger	Staf	f Fellow	IB, NOI IB NCI
J. Bluestone	Labo	ratory leader	IB, NOI
C. Yue	Medi	cal Staff Fellow	IB, NCI
R. Hodes	Seni	or Investigator	IB, NCI
M. Taplits	Medi	cal Staff Fellow	IB, NCI
R. Quinones	Seni	or Staff Fellow	IB, NCI
COOPERATING UNITS (if any)			
R. Gress	Seni	or Investigator	IB, NCI
R. R. Dourmars	nkin		
LAB/BRANCH			
Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCL. NIH. Bethesda, Mary	vland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
2.5	2.5	0.5	
CHECK APPROPRIATE BOX(ES)	1 <u></u>		
(a) Human subjects	(b) Human tissues	$\Box_{\mathbf{x}}$ (c) Neither	
(a1) Minors			В
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space	provided.)	
The role of granule series	lne proteases in CTL	lytic function was	probed by treatment
or intact CIL with PMSF	in combination with	agents which raise	the pH of acidic
activity with the reaid	its, and then compare	ed the residual gra	Inule BLT esterase
in lutic activity and 90	al lytte activity.	while DMCF and amo	losses of about 50%
losses of about 70% in 1	vtic activity and 9	of in BIT esterase	These results sug-
gest that serine esteras	ses in low pH compar	tmente are unlikely	to be directly in-
volved in the lytic fund	tion. One of the m	aior CTL granule n	oteases a BLT ester-
ase, has been useful as	a granule marker for	r measuring exocyto	sis. With mouse
CTL, the envyme is secre	ted after stimulation	on by target cell a	intigen or immobilized
antibodies against the T	cell receptor coml	ex, and with human	CTL, immobilized
anti-T3 stimulate. In h	ooth these systems,	anti LFA-l antibodi	es block secretion,
showing this can act din	ectly on effector co	ells rather than ne	cessarily blocking a
target cell binding. Us	sing in vivo generate	ed CTL, BLT esterse	was found in granule
by the same approaches u	used for cloned CTL.	Secretion of this	enzyme was triggered
specifically by tumor ta	arget cells and prec	eded cytotoxicity.	Cytolysin activity
was found in dense granu	les of these CTL, b	ut was about 100 x	lower than found in
cloned CTL. Cloned help	per T cells also con	tain granules with	high levels of BLT
esterase which reacts wi	th antibodies to the	e dimeric "major" I	GL serine protease.
Using BLT esterase relea	ise as a marker, gra	nule exocytosis fro	om these cells has
been triggered by antige	n atter processing	by class 2 matched	presenting cells, by
Con A, by PMA and calciu	im ionophore, and by	immobilized anti-I	cell receptor anti-
podles. In the latter s	ituation, secretion	can be measured wi	thin one hour, and
secretion of the lysoson	ial enzyme β-N-acety	1 hexosaminidase is	also detected.
En studies of these help	er cells have reveal	led cytoplasmic gra	nules containing
striking and unusual lan	lellar tigures underg	going exocytosis.	Using B-N-acetyl
No. Contraction of the second se			



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			PROJECT NUMBER
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HEA	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	Z01 CB 05106-06 I
PERIOD COVERED	tombor 20 1097		
	Title must fit on one line between the borrie		
Analysis of the T Cell	Alloreactive Repertoire	ars.)	
PRINCIPAL INVESTIGATOR (List other pro	dessional personnel below the Principal Inves	tigator) (Name title Jahors	atony and institute affiliation)
PI: R. J. Hodes	Chief, Immunothe	rapy Section	IB. NCI
			,
Others: R. Abe	Visiting Fellow		IB, NCI
J. Bluestone	Senior Investiga	tor	IB, NCI
D. Singer	Senior Investiga	tor	IB, NCI
COOPERATING UNITS (# any)	y University of Utah	alt Jaka City	THE
bepartment of Patholog	y, oniversity of otan, 5	all Lake City,	01
LAB/BRANCH			
Immunology Branch			
SECTION			
Immunotherapy Section			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Ma	ryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
	1.0		
CHECK APPROPRIATE BOX(ES)			
	(b) Human tissues	(C) Neither	
(a1) Minors			В
	durand type. Do not exceed the appear provide		
The autotoxic T coll r	apartoire spacific for a	lace I allogon	aid and vanaganaid
determinante was studi	ed. Through the use of	radiation hone	marrow chimeras it
was demonstrated that	responsiveness to K <sup>b</sup> mut	ant determinan	ts was the outcome of
unique interactions be	tween both T cell genoty	pe and maturat	ion environment.
	encen been i ceri genee)	po and material	
Through the use of a t	ransgenic mouse model, i	n which porcin	e class I genes had
been introduced into t	he germ line of murine c	ells, it was d	emonstrated that norma
murine T cells express	ed a cytotoxic T cell re	pertoire speci	fic for xenogeneic
class I determinants e	xpressed on mouse cells.	This reperto	ire was cross reactive
with the alloreactive	cytotoxic T cell reperto	ire.	
The nature of polymorp	hism and allelism were r	e-evaluated in	the minor lymphocyte
stimulating (MIs) syst	em. Mis determinants ar	e defined by t	he ability to stimulate
primary proliferative	T cell responses between	major histoco	mpatibility complex
(MHC) identical cells.	Originally, Mis was de	scribed as a s	ingle locus system
involving at least fou	r polymorphic alleles.	Proliferating	i cell clones were
generated which were s	pecific for miss, miss,	ben employed t	e, in combination with
ship between Maa Ma	c and Mad determinants	Tt was found	d that Migd calls
appear to avarage the	sum of Miea and Mic dat	erminante To	addition formal
appear to express the	carried out to identify	the relationsh	in between the genes
encoding Ms <sup>a</sup> , Ms <sup>c</sup> , a	nd Misd. It was found t	hat Mis <sup>a</sup> and M	ls <sup>c</sup> are encoded by
non-allelic and in fac	t unlinked genes. Moreo	ver, an Misd s	train expresses inde-
pendently the products	of unlinked Mis <sup>a</sup> -like a	nd Mis <sup>c</sup> -like g	enes. Thus, in con-
trast to previous unde	rstanding, the Ms syste	m is composed	of the products of at
least two unlinked loc	i, with no evidence for	structural pol	umorphicm of oith-
locus at the present t	ime.	occuccular por	ymorphism at either
present t			



		PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE	701 CD 05109 05 T
NOTICE OF INT	RAMURAL RESEARCH PROJECT	201 CB 05108-05 1
PERIOD COVERED		
October 1, 1986 to Sep	tember 30, 1987	
TITLE OF PROJECT (80 cheracters or less. T Cell Regulation of B	. Title must fit on one line between the borders.)	
PRINCIPAL INVESTIGATOR (List other prot	fessional personnel below the Principel Investigetor.) (Name, title	, leboratory, and institute affiliation)
PI: R. J. Hodes	Chief, Immunotherapy Secti	on IB, NCI
Others: M. Taplits	Medical Staff Fellow	TB NCT
A. Finnegan	Senior Staff Fellow	IB, NCI
K. Hathcock	Chemist	IB, NCI
D. Segal	Senior Investigator	IB, NCI
R. Guy	Visiting Fellow	IB, NCI
COOPERATING UNITS (if any)		
Department of Immunolo	gy, University of Tokyo, Tokyo, Ja	pan
•		
LAB/BRANCH Immunology Branch		
SECTION		
Immunotherapy Section		
INSTITUTE AND LOCATION		
NCI, NIH, Bethesda, Ma	ryland 20892	
1.5	1.5	
CHECK APPROPRIATE BOX(ES)		
🗌 (a) Human subjects	(b) Human tissues (c) Neither	
(a1) Minors		В
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It had previously been	demonstrated that B cell antibody	responses can be acti-
vated by helper T cell	s through two distinct pathways.	Individual cloned T cell
populations are in fac	t capable of mediating both MHC-re	stricted and non-MHC-
restricted pathways of	B cell activation. Recent studie	s have demonstrated the
activation of B calls	through an II-2 dependent pathway	B coll responses modiate
by antigen specific T	helper cells are regulated by T su	ppressor cells through two
distinct MHC restricted	d pathways. It was subsequently d	emonstrated that cloned
lines of Lyt 1+ 2- L3T	4 <sup>+</sup> antigen specific and MHC restri	cted suppressor cells
could also mediate sup	pressor effector function in these	T dependent antibody
Autoreactive T cell ch	ones, specific for syngeneic I-A o	r I-E products were shown
to function as T helpe	r cells through two distinct pathw	ays: One pathway was poly-
clonal and MHC unrestr	icted at the level of T helper-B c	ell interaction and the
other was MHC restrict	ed and dependent upon antigen spec	ific triggering of
responding B cells. M	HC restricted, antigen-nonspecific	suppressor populations
function to regulate th	he responses mediated by autoreact	ive T helper cells
Activation of B cells	by antigen specific and autoreacti	ve T helper cells therefor
appears to share susce	ptibility to similar regulatory in	fluences.
The role of T cells in	regulating the fine specificity o	f B cell antibody response
was studied by examining	ng the T15 idiotype dominant respo	nse to phosphocholine (PC)
and the UKIA dominant	response to Ars. It was found that	t cloned populations of
or CRIA idiotype domin	ant responses in R cells of approp	riate haplotype These
findings demonstrated	that no absolute requirement exist	s for the participation
of idiotype specific T	H2 cells in the generation of optim	mally idiotype dominant
responses in this exper-	rimental system.	



DEPA	RTMENT	OF HEALTH A	ND HUMAN SERVI	CES - PUBLIC H	EALTH SERVICE	I HOLEOT HOMBEN	
	NOT		RAMURAL RES	SEARCH PRO	JECT		
						Z01 CB 05110	-05 I
PERIOD COVE	RED						
October	1, 198	6 to Sept	ember 30, 198	37			
TITLE OF PRO	DJECT (80	characters or less	a. Title must fit on one li	ine between the bo	rders.)		
Immune S	tudies	in Homos	exual Men at	Risk for	cquired Immune	Deficiency Syndr	ome
DT.		Chaseman	ilosaidinai personnei ben		osugator.) (Name, une, lebor	alory, and institute animation)	
P1:	G• М• н в	Dickler		Senior Ir	ivestigator	LB,	NCI
	II. D.	DICKICI		Senior I	Westigator	ID,	NCI
Others:	C. S.	Via		Medical S	Staff Fellow	IB.	NCI
	R. C.	Gallo		Chief		LTCB,	NCI
	R. Ya	rchoan		Senior In	vestigator	COP,	NCI
	S. Br	oder		Director		COP,	NCI
COORERATIN	J. Be	rzofsky		Senior In	vestigator	MB,	NCT
COOPERATIN		any)					
LAB/BRANCH		· · · · · ·					
Immunolo	øv Bra	nch					
SECTION	0,						
INSTITUTE AN	ID LOCATI	UN					
NCI NIH	Beth	esda, Mary	PROFESSIONAL:		OTHER:		
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T (a) Hu							
🖵 (a) 🗖 u	man su	bjects	📋 (b) Human I	tissues	(c) Neither		
(a) Hu	) Minor	bj <del>ects</del> s	📋 (b) Human t	tissues	☐ (c) Neither		
(a) Hu (a1 (a2	man su ) Minor !) Interv	bjects s iews	📋 (b) Human (	tissues	☐ (c) Neither		A
(a) Hu (a1 (a2 SUMMARY OF	Minor ) Minor ) Interv	bjects S iews se standard unrec	(b) Human t	tissues	(c) Neither		A
(a) Hu (a1 (a2 SUMMARY OF Peripher:	man su ) Minor ) Interv work (U аl blo	bjects s iews se standard unred od leukocy	(b) Human f duced type. Do not exce ytes (PBL) fr	tissues	☐ (c) Neither	and (-) donors w	A
(a) Hu (a1 (a2 SUMMARY OF Periphera tested for	man su ) Minor ) Interv work (υ al blo or pro	bjects s iews se standard unred od leukocy liferative	<b>(b)</b> Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce	tissues	☐ (C) Neither (ded.) I antibody (+) d lympholysis (	and (-) donors w CML) to influenz	A ere a
(a) Hu (a1 (a2 SUMMARY OF Periphera tested for virus (S-	man su ) Minor ) Interv woпк (u al blo or pro +X) an	bjects s iews se standard unred od leukocy liferative d to HLA a	<b>(b)</b> Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce	tissues the space provision to m HTLV-II ell-mediate ells (ALLO)	<pre>ded.) if antibody (+) d lympholysis (     Among antibo</pre>	and (-) donors w CML) to influenz dy (+) donors,	A ere a
(a) Hu (a1 (a2 SUMMARY OF Periphera tested for virus (S- approxima	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately	bjects s iews od leukocy liferative d to HLA a 50% failed	<b>(b)</b> Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh	<pre>ded.) .1 antibody (+) .4 lympholysis ( .4 Among antibo .5 Among antibo .5 antibo</pre>	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, exc	A ere a cept
Cal fu (a1) SUMMARY OF Periphera tested fo virus (S- approxima patients	man su ) Minor ) Interv WORK (U al blo or pro +X) an ately in th	bjects s iews od leukocy liferative d to HLA a 50% failed e critica	<b>b</b> (b) Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A	tissues the space provi- com HTLV-II hll-mediate hlls (ALLO) to S+X, wh hlDS, who r	<pre>ded.) if antibody (+) id lympholysis (    Among antibo ereas all responsesponded to nei</pre>	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm	A ere a cept unogen
L (a) Hu (a1 (a2 SUMMARY OF Peripher: tested for virus (S- approxima patients	man su ) Minor ) Interv WORK (U al blo or pro +X) an ately in th	bjects s iews se standard unrec od leukocy liferativo d to HLA a 50% failec e critica	(b) Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh AIDS, who r	<pre>ded.) if antibody (+) id lympholysis (    Among antibo ereas all responsesponded to nei </pre>	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm	A ere a cept unogen
(a) (a) (a) (a2 SUMMARY OF Peripher: tested f virus (S- approxima patients Using PB that Sty	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from	bjects s iews se standard unrec od leukocy liferativo d to HLA a 50% failed e critical antibody	(b) Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors w or are obliged	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh hIDS, who r we demonstr	☐ (c) Neither (ded.) I antibody (+) (-) d lympholysis ( • Among antibourses ereas all respondent to nei ated by cell fr. m(+) T cells (+)	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech	A ere a cept unogen niques
L (a) (a) (a) (a2 SUMMARY OF Peripher: tested f virus (S- approxima patients Using PB that S+X can be go	man su ) Minor ) Interv work (U: al blo or pro +X) an ately in th L from T cel	bjects s iews se standard unrec od leukocy liferative d to HLA a 50% failed e critical antibody l response d by eith	(b) Human f duced type. Do not exce ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we es are oblige or CD <sup>4</sup> or O	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh hIDS, who r re demonstr ed to use C DV-T r coll	☐ (c) Neither (ded.) I antibody (+) (-) (d lympholysis ( . Among antibourses) (ereas all respondences) (ereas all r	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech ereas ALLO respon	A ere a cept unogen niques nses
L (a) (a) (a2 SUMMARY OF Peripher: tested f virus (S- approxima- patients Using PB that S+X can be ga	man su ) Minor ) Interv wORK (U al blo or pro +X) an ately in th L from T cel enerates prob	bjects s sestandard unnec od leukocy liferative d to HLA is 50% failec e critical antibody l response ed by eith	<b>b</b> (b) Human f <i>duced type. Do not exce</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we es are oblige her CD4 <sup>+</sup> or C	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh hIDS, who r we demonstr ed to use C CD4 <sup></sup> T cell of CD4 <sup>+-</sup> a	☐ (c) Neither (ded.) I antibody (+) d lympholysis ( Among antibourses ereas all respondent to neither ated by cell fr.  D4 <sup>+</sup> T cells, while s. Thus, the set alls during All	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech ereas ALLO respon elective loss of S dovelopment	A ere a cept unogen niques nses S+X
L (a) (a) (a) (a2 SUMMARY OF Peripher: tested f virus (S- approxima- patients Using PB that S+X can be generations	man su ) Minor ) Interv wORK (U al blo or pro +X) an ately in th L from T cel enerat s prob	bjects s siews od leukocy liferative d to HLA a 50% faileg e critica antibody l response ed by eith ably refle	(b) Human f <i>duced type. Do not excer-</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we es are oblige her CD4 <sup>+</sup> or C ects the loss	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh hIDS, who r we demonstr ed to use C CD4 <sup></sup> T cell a of CD4 <sup>+-</sup> c	☐ (c) Neither (ced.) I antibody (+) (-) (d lympholysis ( • Among antibou- ereas all respon- responded to nei- ated by cell fr. (D4 <sup>+</sup> T cells, wh- s. Thus, the second	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech ereas ALLO respon elective loss of S development.	A ere a cept unogen niques nses S+X
L (a) (a) (a) (a2 SUMMARY OF Peripher: tested for virus (S- approxima- patients Using PB that S+X can be go responses Using the	man su ) Minor ) Interv WORK (U: al blo or pro tately in th L from T cel enerat s prob.	bjects s iews od leukocy liferative d to HLA a c critica antibody l response ed by eith ably refle e approach	(b) Human is duced type. Do not excert ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we es are oblige her CD4 <sup>+</sup> or C ects the loss n, we have te	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh ALDS, who r re demonstr ed to use C CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cel	☐ (c) Neither (ded.) I antibody (+) ( d lympholysis ( . Among antibourses) ereas all respondent to neither ated by cell fr. 2D4 <sup>+</sup> T cells, while s. Thus, the sells ells during AID 1 functions in (	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech ereas ALLO respon elective loss of S development. ALDS patients un	A ere a cept unogen niques nses S+X der-
L (a) (a) (a) SUMMARY OF Periphera tested for virus (S- approxime patients Using PB that S+X can be go responses Using the going the	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat: s prob	bjects s iews se standard unnec od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t	(b) Human for the second type. Do not except type. Do not except to second the second of the seco	tissues the space provi- com HTLV-II ell-mediate ells (ALLO) to S+X, wh ALDS, who r we demonstr ed to use C CD4 <sup>-</sup> T cell of CD4 <sup>+</sup> c ested T cell log AZT.	☐ (c) Neither (c) Neither (c) (c) (c) (c) (c) (c) (c) (c) (c) (c)	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex ther type of imm actionation tech ereas ALLO respon elective loss of S development. ALDS patients una ndergoing AZT ex	A ere a cept unogen niques nses S+X der- hibi-
L (a) (a) (a) (a2 SUMMARY OF Periphera tested for virus (S- approxima patients Using PB that S+X can be go responses Using that going that ted a responses	man su ) Minor ) Interv ) Interv wORK (U: al blo or pro +X) an ately in th L from T cel enerat. s prob e abov erapy storat:	bjects s iews sestandard unnec od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t ion of T o	(b) Human f duced type. Do not excer- ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we es are oblige her CD4 <sup>+</sup> or C ects the loss n, we have te chymidine ana cell immune f	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh AIDS, who r we demonstr ed to use C CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cell log AZT. unction, b	☐ (c) Neither (c) Neither (c) (c) (c) (c) (c) (c) (c) (c) (c) (c)	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex. ther type of imm actionation tech ereas ALLO respon elective loss of S development. ALDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
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Using PB that S+X can be gy responses Using that going the going the ted a res gradually	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat. s prob e abov erapy storat. y decre	bjects s iews sestandard unned od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t ion of T d eased with	(b) Human f <i>duced type. Do not exce</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors w es are oblige her CD4 <sup>+</sup> or C ects the loss n, we have te chymidine ana cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh hIDS, who r we demonstr ed to use CC CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cell llog AZT. unction, b	☐ (c) Neither (ced.) I antibody (+) d lympholysis ( Among antibo- ereas all respon- responded to nei- ated by cell fr. 204 <sup>+</sup> T cells, wh- s. Thus, the se- ells during AID l functions in Some patients un ut this restoration	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex. ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
Using PB that S+X can be go responses Using that go using that s+X can be go responses Using that go going that ted a res gradually	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat. s prob e abov erapy storat. y decre	bjects s iews sestandard unred od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t ion of T d eased with	(b) Human f <i>duced type. Do not exce</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors w es are oblige her CD4 <sup>+</sup> or C ects the loss h, we have te chymidine ana cell immune fo n time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r we demonstr ed to use C CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cell log AZT. unction, b	☐ (c) Neither (ced.) I antibody (+) . d lympholysis ( . Among antibo- responded to nei ated by cell fr. cD4 <sup>+</sup> T cells, wh s. Thus, the se ells during AID l functions in . Some patients un ut this restora	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex. ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
Using PB that S+X can be going that going that going that gradually	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat. s prob e above erapy storat. y decre	bjects s iews sestandard unrec od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t ion of T c eased with	(b) Human is <i>buced type. Do not excer-</i> ytes (PBL) free ( <sup>3</sup> H) and cer- allogeneic cer- d to respond l stages of A (-) donors we have cobligeneir CD4 <sup>+</sup> or Co- ects the loss h, we have ter- thymidine ana- cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r re demonstr ed to use C CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cell log AZT. unction, b	☐ (c) Neither (ced.) I antibody (+) . d lympholysis ( . Among antibo- responded to nei ated by cell fr. 204 <sup>+</sup> T cells, wh s. Thus, the se ells during AID l functions in . Some patients un ut this restora	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex. ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
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Using the going the graduall	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat s prob e above erapy storat y decre	bjects s iews sestandard unrec od leukocy liferative d to HLA a 50% failed e critica. antibody 1 response ed by eith ably refle e approach with the t ion of T o eased with	(b) Human is <i>fuced type. Do not exce</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce i to respond l stages of A (-) donors we have the loss n, we have the thymidine ana cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r we demonstr d to use C CD4 <sup>-</sup> T cell of CD4 <sup>+</sup> c ested T cel Hog AZT. function, b	☐ (c) Neither (ced.) I antibody (+) . d lympholysis ( . Among antibo- ereas all respon- responded to nei ated by cell fr. 204 <sup>+</sup> T cells, wh s. Thus, the se ells during AID l functions in . Some patients un ut this restora	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, exc ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
Using the going the graduall	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat s prob e above erapy storat y decre	bjects s iews sestandard unrec od leukocy liferative d to HLA a 50% failed e critica: antibody 1 response ed by eith ably refle e approach with the t ion of T o eased with	(b) Human is fuced type. Do not excer- ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we have the loss n, we have the thymidine ana cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r we demonstr d to use C CD4 <sup>-</sup> T cell of CD4 <sup>+</sup> c ested T cel Hog AZT. function, b	☐ (c) Neither (ced.) I antibody (+) (-) I antibody (+) (-) I antibody (+) (-) (-) (-) (-) (-) (-) (-) (-)	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, exc ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
Using the going that set a response.	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat: s prob e above erapy storat: y decre	bjects s iews sestandard unrec od leukocy liferative d to HLA a 50% failed e critica. antibody 1 response ed by eith ably refle e approach with the t ion of T o eased with	(b) Human is fuced type. Do not excer- ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce i to respond l stages of A (-) donors we have the loss n, we have the thymidine ana cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r we demonstr d to use C CD4 <sup>-</sup> T cell of CD4 <sup>+</sup> c ested T cel Hog AZT. function, b	☐ (c) Neither (ced.) I antibody (+) . d lympholysis ( . Among antibo- ereas all respon- responded to nei ated by cell fr. 204 <sup>+</sup> T cells, wh s. Thus, the se ells during AID l functions in . Some patients un ut this restora	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, exc ther type of imm actionation tech ereas ALLO respon- elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has
Using the going the graduall	man su ) Minor ) Interv WORK (U: al blo or pro +X) an ately in th L from T cel enerat. s prob e abov erapy storat. y decre	bjects s iews sestandard unred od leukocy liferative d to HLA a 50% failed e critical antibody l response ed by eith ably refle e approach with the t ion of T o eased with	(b) Human f <i>buced type. Do not excert</i> ytes (PBL) fr e ( <sup>3</sup> H) and ce allogeneic ce d to respond l stages of A (-) donors we have coblige her CD4 <sup>+</sup> or Co ects the loss h, we have te chymidine ana cell immune for time.	tissues and the space prov. com HTLV-II ell-mediate ells (ALLO) to S+X, wh HIDS, who r re demonstr ed to use C CD4 <sup>-</sup> T cell a of CD4 <sup>+</sup> c ested T cell log AZT. unction, b	☐ (c) Neither (ced.) II antibody (+) d lympholysis ( Among antibo- ereas all respon- responded to nei- ated by cell fr. 204 <sup>+</sup> T cells, wh s. Thus, the se ells during AID l functions in Some patients un ut this restora	and (-) donors w CML) to influenz dy (+) donors, nded to ALLO, ex, ther type of imm actionation tech ereas ALLO respon elective loss of S development. AIDS patients und ndergoing AZT ext tion of function	A ere a cept unogen niques nses S+X der- hibi- has

3



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	IECT	Z01 CB 05111-05 I
PERIOD COVERED			
October 1, 1986 to Sept	cember 30, 1987		
TITLE OF PROJECT (80 characters or less	). Little must fit on one line between the bord i fit a CTT	ers.)	
Generation of Allospech	find GIL	atigator \ (Name title John	
PI: S. McCarthy	Senior Staff	Fellow	TB NCT
ti. 5. nedateny	benior bearr	ICIIOW	15, 101
Others: A. Singer	Senior Inves	tigator	TB. NCT
			,
COOPERATING UNITS (if any)			
		<u> </u>	
LAB/BHANCH			
SECTION		· · · · · · · · · · · · · · · · · · ·	
SECTION			
INSTITUTE AND LOCATION			
NCL. NIH. Bethesda, Mar	rvland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
0.2	0.2		
CHECK APPROPRIATE BOX(ES)	1		
(a) Human subjects	(b) Human tissues	x (c) Neither	
(a1) Minors			В
(a2) Interviews			
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	ed.)	
We have begun analyzing	g the factors influencin	g the regulation	on of the MHC class
II-specific CTL reperto	vire in vivo. We have u	sed a neonatal	injection protocol
to study the requirement	its for induction of ant	igen-specific (	colerance to non-
self class II determina	ants. Our initial exper-	iments have der	nonstrated that
class II allospecific (	CTL can be effectively to	olerized by our	r protocol and
represents (to our know	vledge) the first succes	sful tolerizati	ion of this T cell
population. We can not	v compare and contrast t	he recognition	and signalling
requirements of L3T4 a	and Lyt2' class II-speci	fic immature C	IL populations
during neonatal toleran	ice induction, and relate	e those finding	is to what we have
already established reg	arding the recognition	and signalling	requirements for
activation of mature ci	lass II-specific Cit pop	ulations.	



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZO1 CB 05112-05 I
PERIOD COVERED October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less Analysis of Recognition	Title must fit on one line between the bord Structures on T Cells	ers.)	
PRINCIPAL INVESTIGATOR (List other pro PI: J. A. Blueston	fessional personnel below the Principal Inve e Senior Investigato	stigator.) (Name, title, labora ) r	ntory, and institute effiliation) IB, NCI
Others: D. H. Sachs R. Cron	Chief, Transplanta Howard Hughes Medi Research Fellow	ation Biology So Ical Institute	ection IB, NCI IB, NCI
COOPERATING UNITS (if any) Larry Samelson and Rich Institute of Child Heal	ard Klausner, Cell Biolo th and Human Development	ogy and Metabol	ism Branch, National
LAB/BRANCH Immunology Branch			
SECTION Transplantation Biology	Section		
INSTITUTE AND LOCATION NCI, NIH, Bethesda, Mary	yland 20892		
TOTAL MAN-YEARS: 5.0	PROFESSIONAL: 4.0	OTHER:	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues	(c) Neither	В
SUMMARY OF WORK (Use standard urreat The recognition structure bodies and anti-T cells toxic T cell clones. Main immunized against the C receptor and other cell cally activates CTL clor receptor. This mAb, 83- similar to that observed by the mAb resulted in 1 nal alloantigen recognin antibodies which recognin T cell clones has been a class I specific CTL in activate CTL clones and designed to analyze the better define the struct are involved in T cell are involved in T cell this monoclonal antibod mild denaturing condition on the surface of fetal This T cell receptor.	tweed type. Do not exceed the space provideres of T cells have been surface antigen specific onoclonal antibodies properties of the space provider of the surface antigens. One ness by binding in a clore-7-2, precipitates a 90 d for other anti-receptor tanzed by the clone. In activation, the subset of Lyt2 <sup>+</sup> T cells a subset of Lyt2 <sup>+</sup>	ad) a examined using c antibodies pro- bduced from mico- tified which ro- mAb has been gu- notypic fashion kd heterodimer: or antibodies. gets that did <u>p</u> dition, a seri- ile on the surfa- conal antibodies. Is. Further si- which have been essed on cytoto: ly, a mAb react- $-\epsilon$ protein has whole T cell reac- to identify a ma- c dentified T cells.	g anti-receptor anti- epared against cyto- e and hamsters eact with the T cell enerated that specifi- to the T cell ic glycoprotein The activation of CTL not express the nomi- es of other monoclonal ace of the cytotoxic s appear to subdivide ch mAb, 143-4-2 can tudies will be developed and to xic T cells which ting with the murine been developed. ceptor complex under ovel T cell receptor dult thymocytes. ll receptor gene, the ne the role of T



		PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJECT	Z01 CB 05114-04 I
252102 001/5252		
PERIOD COVERED	1 1007	
TITLE OF PROJECT (80 cheracters or less	. Title must fit on one line between the borders.)	
Sequence Organization o PRINCIPAL INVESTIGATOR (List other pro	f Class I Major Histocompatibility Gene fessionel personnel below the Principal Investigator.) (Name, title, labora	es tory, and institute affiliation)
PI: D. S. Singer	Senior Investigator	IB, NCI
Others: S. Rudikoff	Senior Investigator	LG NCT
R. Ehrlich	Visiting Fellow	IB, NCI
H. Golding	Visiting Associate	IB, NCI
M. Hinners	Chemist	IB, NCI
_		
COOPERATING UNITS (if any)		
LAB/BRANCH	······································	
Immunology Branch		
SECTION		
		······
INSTITUTE AND LOCATION		
NCL, NIH, Bethesda, Mar TOTAL MAN-YEARS:	PROFESSIONAL: OTHER:	
2.0	2.0	
CHECK APPROPRIATE BOX(ES)		
(a) Human subjects	$\Box$ (b) Human tissues $\Box$ (c) Neither	
		В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provided.)	
The aim of this work is	to determine the DNA sequence organization	ation of class I genes
The aim of this work is contained in the swine w	to determine the DNA sequence organization of the termine the DNA sequence organization of the termination of terminatio of termination of termination of termination of termin	ation of class I genes • We have established
The aim of this work is contained in the swine that this gene family i	to determine the DNA sequence organiza major histocompatibility complex (SLA) n the miniature swine contains only sev	ation of class I genes • We have established ven members, making
The aim of this work is contained in the swine that this gene family is it amenable for a compre-	to determine the DNA sequence organiza major histocompatibility complex (SLA) n the miniature swine contains only sev ehensive analysis. To date, we have is	ation of class I genes We have established ven members, making solated six of these
The aim of this work is contained in the swine of that this gene family i it amenable for a compro- genes. DNA sequence an oldte for the more of	to determine the DNA sequence organization major histocompatibility complex (SLA) in the miniature swine contains only set ehensive analysis. To date, we have is alysis is complete for three of the get	ation of class I genes We have established ven members, making solated six of these nes and nearly com-
The aim of this work is contained in the swine of that this gene family i it amenable for a compr genes. DNA sequence an plete for two more. It class I SLA genes is si	to determine the DNA sequence organization major histocompatibility complex (SLA) in the miniature swine contains only set ehensive analysis. To date, we have is alysis is complete for three of the gen has been established that the sequence milar to that of other class I genes.	ation of class I genes We have established ven members, making solated six of these nes and nearly com- e organization of the Within the family.
The aim of this work is contained in the swine of that this gene family if it amenable for a compre genes. DNA sequence an plete for two more. It class I SLA genes is sin it is possible to define	to determine the DNA sequence organization major histocompatibility complex (SLA) in the miniature swine contains only sevine ehensive analysis. To date, we have is alysis is complete for three of the gen has been established that the sequence milar to that of other class I genes. e at least two sub-families, based on the	ation of class I genes We have established ven members, making solated six of these nes and nearly com- e organization of the Within the family, their sequences.
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The aim of this work is contained in the swine of that this gene family if it amenable for a compre- genes. DNA sequence an plete for two more. It class I SLA genes is sin it is possible to define Homologies between the sub-family, to 60% between	to determine the DNA sequence organization major histocompatibility complex (SLA) in the miniature swine contains only seven ehensive analysis. To date, we have is alysis is complete for three of the gen has been established that the sequence milar to that of other class I genes. e at least two sub-families, based on the SLA genes range from 85% between the two even sub-families. Complex alterations	ation of class I genes We have established ven members, making solated six of these hes and nearly com- e organization of the Within the family, their sequences. No genes within a are observed, con-
The aim of this work is contained in the swine of that this gene family if it amenable for a compre- genes. DNA sequence an plete for two more. It class I SLA genes is sin it is possible to define Homologies between the sub-family, to 60% between sistent with the interp	to determine the DNA sequence organization major histocompatibility complex (SLA) in the miniature swine contains only set ehensive analysis. To date, we have is alysis is complete for three of the get has been established that the sequence milar to that of other class I genes. e at least two sub-families, based on the SLA genes range from 85% between the two set sub-families. Complex alterations retation that some mechanism of gene co	ation of class I genes We have established ven members, making solated six of these hes and nearly com- e organization of the Within the family, their sequences. Wo genes within a are observed, con- powersion may operate
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DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	FROJECT NOMBER
NOTICE OF INT	RAMURAL RESEARCH PRO	JECT	ZO1 CB 05115-04 I
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the bor	ders.)	
Regulation of Expressio	n of Class I MHC Genes		
PRINCIPAL INVESTIGATOR (List other pro	ofessionel personnel below the Principal Inve	estigator.) (Name, title, labora	tory, and institute affiliation)
PI: D. S. Singer	Senior	Investigator	IB, NCI
Others: R. Ehrlich	Visiti	ng Fellow	IB NCT
I. Maguire	Biotec	hnology Fellow	TB, NOT
ov inguitte	brotee	moiogy reriow	ID, NCI
COOPERATING UNITS (Ir any)			
LAB/BRANCH			
Immunology Branch			
SECTION			
INSTITUTE AND LOCATION	1 1 20202		
NCI, NIH, Betnesda, Mar	yland 20892	OTUER	
TOTAL MAN-TEARS:	PROFESSIONAL:	OTHER:	
(a) Human subjects (a1) Minors	(b) Human tissues	🗴 (c) Neither	в
(a2) Interviews			-
SUMMARY OF WORK (Use standard unred	Juced type. Do not exceed the space provid	ded.)	
The aim of this work is	to investigate the mec	hanisms control	ling the expression
of a multi-gene family,	namely the class I MHC	genes. The min	niature swine has
been chosen as an exper	imental model because t	here are only 7	members of the
family, of which 6 have	been isolated. Five h	ave been extensi	lvely structurally
characterized. To addr	ess the question of the	molecular regul	lation of the
expression of the class	1 MHC genes, two appro-	aches have been	taken: 1) analysis
bath in the ministure of	expression of each of t	ne genes in a va	arlety of tissues
swine gape and 2) shar	actorization of regulat	ary alorente ag	only a single
genes. Three categorie	s of MHC games have been	n identified thi	is way: 1) A set of
closely related genes e	ach of which are expres	sed in L cells	and in nearly all
swine somatic tissues.	although at different 1	evels. At least	one of these
genes is also expressed	in a transgenic mouse	with the same th	issue distribution
as in the swine. These	genes encode products	which are expres	ssed on the cell
surface and are able to	bind a monoclonal anti	body which recog	gnizes a common
determinant, also found	on classical transplan	tation antigens.	. 2) A distantly
related gene which is e	xpressed both in L cell	s and in vivo bu	it whose pattern of
expression is distinct	from that of transplant.	ation antigens.	3) A set of genes
which is expressed neit	her in L cells nor in v	ivo.	
Pogulatory cogueres of	this and of the trans-1	entetion entire	a anna have beer
identified by generation	a series of 5' and do	letion mutants	The transcrip-
tional promoter has been	g a series of J end de	ed as well as an	interferon-
responsive element. In	addition, novel nositi	ve and negative	regulatory sequence
elements have been iden	tified. It has been fu	rther shown that	these elements
function through the bi	nding of transacting fa	ctors.	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	
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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 05116-04 I

PERIOD COVERED			
October 1, 1986 to Sept	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the borde	urs.)	
	ase Prophylaxis in Alloge	tigetor (Name title laboratory and institute offil	ation
PI: R. E. Gress	Senior Inve	estigator	IB, NCI
Others: R. R. Ouinones	s Senior Staf	f Fellow	TB. NCT
R. Moses	Biotechnolo	ogy Fellow	IB, NCI
H. Nakamura	Visiting Fe	ellow	IB, NCI
			ŕ
COOPERATING UNITS (if any)			
LAB/BRANCH			
Immunology Branch			1
SECTION			
INSTITUTE AND LOCATION	1 1 00000		
NCI, NIH, Bethesda, Man	ryland 20892	OTHER	
3.0	2.0	1.0	
CHECK APPROPRIATE BOX(ES)	2.00	1.0	
□ <sub>x</sub> (a) Human subjects	🕞 (b) Human tissues	(c) Neither	
🔲 (a1) Minors			В
(a2) Interviews	·		
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	id.)	
Efforts are directed to	owards the prevention or	control of graft-versus-ho	st disease
is mediated by alloread	ctive T cells in the inor	ulated marrow reagents ar	d tech-
niques have been develo	oped to remove these T ce	alls from the marrow inocul	um.
Murine monoclonal antik	bodies specific for antig	gens expressed on human T o	ells have
been developed and util	lized for complement-medi	lated lysis of T cells in m	arrow.
By a new limiting dilut	tion assay, residual T ce	ells in marrow following de	pletion
are at a level less that	an 0.01% of the total cel	ll population. A bank of s	uch T
cell depleted, characte	erized marrows has been g	generated for use in the tr	erapy of
hematologically and im	munologically reconstitut	e a host has been examined	in murine
models. The role of T	cells in the infused mar	row and the susceptibility	of host
rejecting cells to radi	iation and monoclonal ant	ibodies administered in vi	vo are
also under study. With	hin the T cell population	, the fine specificity of	human CTL
has been demonstrated t	to be sufficient to disti	inguish among alpha 1 and a	lpha 2
domain changes of class	s I major histocompatibil	lity complex molecules. Su	ich human
cytotoxic I cells have	been further studied wit	in respect to cell surface	molecules
interventions with the	intent of preventing tis	sue damage mediated by suc	h allo-
reactive cytotoxic T ce	ells. It has been shown	that inhibition by a monoc	lonal
antibody with specifici	ity for CD18 occurs in th	ne absence of target cells	, tonat I
raising the possibility	a shap ship inhibition in		thereby
Further studies have ic	y that this indibition is	s independent of cell-cell	thereby adhesion.
face molecule interacti	dentified the site of thi	s independent of cell-cell is inhibition as involving	thereby adhesion. cell sur-
withe generated inf	dentified the site of thi ion or the T cell recepto	s independent of cell-cell Is inhibition as involving or associated G protein.	thereby adhesion. cell sur- This in
vitro generated informa in monkey and swine.	dentified the site of thi ion or the T cell recepto ation has been applied to Utilizing T cell deplated	s independent of cell-cell Is inhibition as involving or associated G protein. To bone marrow transplantati i marrow extended solid or	thereby adhesion. cell sur- This in on models
vitro generated informa in monkey and swine. I graft survival (without	dentified the site of thi ion or the T cell recepto ation has been applied to Utilizing T cell depleted t exogoneous immunosuppre	s independent of cell-cell ls inhibition as involving or associated G protein. To boone marrow transplantati 1 marrow, extended solid or assion), but not long term	thereby adhesion. cell sur- this in on models gan allo- tolerance
vitro generated informa in monkey and swine. I graft survival (without induction, can be achie	dentified the site of thi ion or the T cell recepto ation has been applied to Utilizing T cell depleted t exogoneous immunosuppre eved in primates.	s independent of cell-cell ls inhibition as involving or associated G protein. To b bone marrow transplantati l marrow, extended solid or ession), but not long term	thereby adhesion. cell sur- chis in on models gan allo- tolerance



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER			
NOTICE OF INTRAMURAL RESEARCH PROJECT ZO1 CB 05117-04 I				
PERIOD COVERED October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Allodeterminants of Class I Major Histocompatibility Antis	gens			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, PI: J. A. Bluestone Senior Investigator	laboratory, and institute affiliation) IB, NCI			
Others: J. A. Lewis Howard Hughes Medical Fellow	IB, NCI			
	7			
COOPERATING UNITS (# any) S. G. Nathenson and S. Geier, Dept. Microbiology & Immuno Col. of Med., Bronx, NY; David Margulies, Laboratory of In Rajan and Terry Potter, Dept/Genetics, Albert Einstein Co	logy, Albert Einstein mmunology, NAIAD; T. V. l. of Med., Bronx, NY			
LAB/BRANCH Immunology Branch				
SECTION Transplantation Biology Section				
NCI, NIH, Bethesda, Maryland 20892				
TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 3.0 2.0 1.0				
CHECK APPROPRIATE BOX(ES)  (a) Human subjects (b) Human tissues (c) Neither (a1) Minors (a2) Interviews (a2) Interviews (b) Human tissues (c) Neither				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided) Current efforts have been devoted to examining the nature recognized by cloned T cell populations. To examine this mutants have been isolated from a somatic cell line by mut selection using monoclonal anti-H-2 antibodies. Examinat: specific CTL clones on these mutants suggest that the major nize determinants different from those which elicit antibo of the in vitro-derived mutants has shown that new determin mAb immunoselection procedure which can be recognized by onew allodeterminants expressed on the in vitro-derived CTT plantation antigens in vivo and appear linked to a single In addition, the regions of the MHC molecule involved in C studied using L cells transfected with H-2 genes construct between the H-2L <sup>d</sup> and H-2D <sup>d</sup> genes. The findings suggested can recognize determinants influenced by the interaction domains. In one instance, CTL can recognize a hybrid D <sup>d</sup> /1 However, the CTL employ a restricted T cell receptor (TCR) Other altered MHC class I genes have also been examined in have been transfected with truncated L <sup>d</sup> and D <sup>d</sup> genes and control of the molecule. The finding demonstrated that CC against truncated MHC gene products. Finally, the role of has been examined. In some instances, CTL clones which re fected L cells do not recognize MHC hybrid molecules using In addition, a single point mutation at amino acid 227 in leads to the total loss of CTL recognition of that MHC and ficity of CTL although predominently determined by the al- critically influenced by $\alpha_3$ .	of the allo-determinants question, H-2 structural tagenesis and immuno- ion of alloantigen- ority of CTL clones recog- ody production. Analysis inants are created by the cytotoxic T cells. The L can function as trans- amino acid substitution. CTL recognition were ted by shuffling exons d that unlike mAbs which majority of the CTL on of the two external L <sup>d</sup> molecule (T9-10-3). ) V <sub>g</sub> chain family. ncluding L cells which express only the $\alpha$ 3/TM TL can be generated f the MHC $\alpha$ 3 domain ecognize native K <sup>b</sup> -trans- g a human MHC $\alpha$ 3 domain. the H-2D <sup>d</sup> molecule tigen. Thus, the speci- + $\alpha$ 2 domains is			



NOTICE OF INTRAMURAL RESEARCH PROJECT 701 CB 05118-04 T				
PERIOD COVERED	ombor 30 1987			
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	rs.)	····	
Regulation of Immune Re	sponse to Tumor Cells an	d Alloantigen	4	
PT: C. C. Ting	Senior Inve	stigator) (Name, uue, labora	tory, and institute attiliation) TRN	ICT
	benior inve	Stigator	15, 4	01
Others: M. E. Hargrove	Microbiolog	ist	IB, N	CI
J. Bluestone	Senior Inve Senior Inve	stigator	IB, N TB N	CI
		ougueor	10, 11	01
COOPERATING UNITS (if any)				
LAB/BRANCH				
Immunology Branch	· · · · · · · · · · · · · · · · · · ·			
SECTION				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Mar	vland 20892	OTHER		
2.0	2.0	OTHER.		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects	(b) Human tissues	(c) Neither		
(a2) Interviews			В	
SUMMARY OF WORK (Use standerd unred	luced type. Do not exceed the space provide	d.)		
1. Expression and Func	tion of Asialo GMI (AsGM	(I) in Alloreact	tive Cytotoxic T	
differently in CTL and	LAK cells. AsGM was ex	pressed on the	LAK precursors but	
its expression disappea	red when LAK precursors	were fully diff	erentiated into	
effectors. The reverse	was true for CTL, AsGM	was not expres	ssed on CTL precurs	ors
tested. AsGM was found	to be expressed on a ma	iority (7 out of	of 8) of L3T4 CTL	
clones. The cytotoxici	ty mediated by AsGM+ cl	oned CTL was bi	locked by aAsGM	
or AsGM alone, indicating that AsGM is involved in the CTL- target interaction				
to mediate lytic reaction.				
2. Tumor Immunology. Activated killer (AK) cells were generated in spleen cell				
culture derived from tumor bearing hosts (TS). In many aspects, these AK cells				
hosts were AsGM <sup>+</sup> cells and the LAK precursors from TS were AsGM <sup>-</sup> , suggesting				
that the latter was in an "activated" state. These findings indicate that in the				
tumor bearing hosts, tumor cells trigger the activation of LAK precursors, but the				
of LAK precursors into	LAK effectors.	prevents the	tull differenciatio	

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			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PRO	JECT	Z01 CB 05119-04 I
25510D 00/585D			
Ostobor 1 1986 to Son	tombor 30 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between the bo	rders.)	
Role of Helper T Cells	in Allogeneic Response	S	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principel In	vestigetor.) (Neme, title, lebora	tory, and institute affilietion)
PI: T. Mizuochi	Visiting As	sociate	IB, NCI
Others: A. Singer	Senior Inve	stigator	TR NCT
	501101 5111		12, 101
COOPERATING UNITS (if any)			
LAB/BRANCH			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Man	ryland 20892	071150	
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)	1.1		
(a) Human subjects	(b) Human tissues	$\Box_{\rm x}$ (c) Neither	
(a1) Minors			В
(a2) Interviews			
LID domonstrated provide	Juced type. Do not exceed the space prov		6 T 2 T / + T 1 - 1
cells and Lyt2 <sup>+</sup> T help	er cells were very dist	inct. In contra	1 L314 I helper
helper cells, Lyt2 <sup>+</sup> T 1	helper cells responded	only to class I	alloantigens. This
year, the recognition	repertoires of Lyt2+, I	'h and CTL were i	nvestigated.
		, h.	
Both CTL and Th activit	ties of Lyt2' T cells f	rom B6 (H-2 <sup>b</sup> ) mi	ce against a series
stimulated B6 Lyt2 <sup>+</sup> CT	its were compared. All	us Kbm determine	nts differed
dramatically in their a	ability to stimulate B6	Lvt2 <sup>+</sup> T cells t	o function as IL-2
secreting helper cells. Particularly, K <sup>bm6</sup> determinants only stimulated B6			
Lyt2 <sup>+</sup> T cells to become cytolytic but failed to stimulate them to secrete IL-2.			
These results demonstrated that the recognition requirements for stimulating			
primary Lyt2' T cells to secrete IL-2 and to function as Th cells are distinguish- able from these for stimulating primary Lyt2 <sup>+</sup> T cells to become sytelutic and to			
function as CTL effector cells.			
	and the second sec		
Finally, the role of the	ne thymus in inducing t	he self-tolerand	e of Lyt2 <sup>+</sup> IL-2
secreting Th cells and	IL-2 dependent CTL eff	ector cells was	assessed by using
allogeneic thymus engratted Bio athymic hude mice. It was demonstrated that			
thymic class I MHC determinants, namely Lyt2 <sup>+</sup> Th but not CTL are tolerant to			
class I MHC antigens expressed in the thymus.			



			PROJECT NUMBER
DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBL	IC HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH P	ROJECT	Z01 CB 05120-04 I
October 1 1986 to Sent	ember 30 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between th	e borders.)	
The Regulation of Lymph	ocyte Proliferation		
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principa	al Investigator.) (Name, title, lebora	tory, and institute affiliation)
PI: K. Kelly	Senior	Investigator	IB, NCI
Others: S. Irving	Guest	Researcher	IB, NCI
Illrich Siebenlist Jaho	ratory of Immune Reg	ulation NTATE NT	1
office Stebeniise, moo	racory or immune keg	didtion, MIAID, MI	•
LAB/BRANCH			
Immunology Branch			
SECTION			
The second second second			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
2.75	1.75	1.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	_
		;	В
	duced type. Do not exceed the second	Drawided )	
The goal of this project	t is to broaden our	understanding of th	a physiology and rag-
ulation of early events	in T cell activation	n. Ivmphocyte met	abolism and effector
function expression are	regulated by antiger	n/mitogen and lymph	okine binding to cell
surface receptors. We	are investigating co	nsequences of mitor	en mediated signals
by isolating and charac	terizing genes which	are transcriptiona	ally regulated by
these events. We expec	t that genes induced	within a few hours	s after antigen or
mitogen activation of 1	ymphocytes will enco	de functions that a	are fundamentally
important for the initia	ation of proliferation	on and effector fur	nction expression in
these cells. Known ind	uced early genes inc.	lude oncogenes (c-m	nyc and c-fos), lympho-
kines (IL-2, y-IFN, GM-	CSF), and lymphokine	receptors (IL-2 re	eceptor), all of
which are thought to have significant effects on T cell proliferation and effector			
function. We have constructed a subtracted cDNA library enriched for genes that			
are transcriptionally induced within four hours after stimulating peripheral blood			
T cells with PHA and PMA. After amplification, 20,000 phage were screened with a			
subtracted CDNA probe en	included for mitogen-	induced mRNA's, and	a 528 positively
then forty unique genera	have been icelated	Although known in	duced genes (e-mus
and II-2 recentor) are included within these clones as expected, the large majority			
of clones represent novel, as yet undescribed genes. We have begun characterizing			
inducible gene sequences with regard to 1) structure, i.e. sequencing analyses, 2)			
expression pattern anal	vses that allow broad	d categorization of	potential function.
and 3) expression patte	rn analyses that def	ine distinct patter	rns of gene regulation.
Initial results indicat	e that a variety of	classes of genes ha	ave been isolated
including T cell-specif:	ic, lymphocyte-speci:	fic, and proliferat	ion-specific genes.
In addition, distinct regulatory networks acting upon these induced genes have			
been defined by differential kinetics of expression and discriminating effects of			
the drug cyclosporin A	and the HTLV-I encode	ed trans-activating	g factor (TATI) upon
transcription patterns.	571		
PHS 6040 (Rev. 1/84)			GPO 914-918



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZO1 CB 05122-03 I
PERIOD COVERED October 1, 1986 to Se	eptember 30, 1987		
TITLE OF PROJECT (80 characters or less Mechanisms of Allogra	s. Title must fit on one line between the bord aft Rejection	ers.)	
PRINCIPAL INVESTIGATOR (List other pro PI: A. Rosenberg	olessional personnel below the Principal Inves g Medical Staf	stigator.) (Name, title, labora E Fellow	tory, and institute affiliation) IB, NCI
Others: A. Singer	Senior Inves	tigator	IB, NCI
COOPERATING UNITS (it any)			
LAB/BRANCH Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NIC, NIH, Bethesda, 1	Maryland 20892		
TOTAL MAN-YEARS: 1 • 1	PROFESSIONAL: 1.1	OTHER:	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues	] (c) Neither	В
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provide	ad.)	
This project continue	es our studies of the ce	llular interact	ions involved in skin
allograft rejection.	The focus of our studie	es is the abili	ty of phenotypically
disparate skin grafts	. We have previously en	stablished the	importance of Lyt2 <sup>+</sup>
Th in the rejection of	of class I disparate gra	fts. Further,	we have shown that
L3T4' class I specifi	c Th fail to participate	e in the reject	ion of these grafts
determinants necessar	cy for their activation.	We are curren	tly exploring the
conditions under which	these class I specific	L3T4 <sup>+</sup> Th can	be activated in vivo.
We have taken two app	proaches: the first invo	lves attempts t	o increase the
and second, to trigge	erminants known to trigger these cells by a rout	er this cell of e other than sk	in grafting. A
second phase of the p	project explored the abil	lities of pheno	typically distinct
Th populaitons to int	eract with separate effe	ector cell popu	lations in rejecting
collaborate with effe	ector cells of a different	nt specificity.	We have previously
demonstrated the abil	lity of L3T4 <sup>+</sup> Th specific	c for class II	determinants to
function in this way. suggesting that they	However, Lyt2' class may induce graft reject	l specífic help lon via a "dual	ers fail to do so, function" mechanism.



				PROJECT NUMBER
DEPARTMENT OF HEALTH A	AND HUMAN SERVIC	CES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RES	EARCH PROJ	ECT	ZO1 CB 05124-03 I
October 1, 1986 to Sept	tember 30, 19	87		
TITLE OF PROJECT (80 characters or less	. Title must fit on one lin	ne between the borde	ars.)	
Expression and Function	n of a Porcin	e Class I M	HC Gene in Tran	sgenic Mice
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel belo	w the Principel Inves	tigator.) (Name, title, labore	tory, and institute affiliation)
PI: D. Singer		Senior invo	estigator	IB, NCI
Others: J. Bluestone		Laboratory	Leader	TR NOT
R. Hodes		Chief. Imm	unotherapy Sect	ion IB NCI
W. Frels		Agricultura	al Research Ser	vice IISDA
		0		
COOPERATING UNITS (if any)				
Immunology Branch				
SECTION				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Man	yland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:	
1.0	1.0			
		iseuee 🔽	(a) Maithas	
(a) Human Subjects		issues	k (c) Neither	<b>"</b>
(a1) Interviews				В
SUMMARY OF WORK (Use standard unred	luced type. Do not exce	ed the space provide	nd.)	
A porcine class I major	histocompat:	ibility com	olex (SLA) gene	has been introduced
into the genome of a C	57 BL/10 mouse	. This tran	isgenic mouse e	xpressed SLA antigen
on its cell surfaces an	nd transmitte	d the gene f	to off-spring,	in which the gene is
also expressed. Skin g	rafts of such	h transgenio	mice were rej	ected by normal
C57BL/10 mice, suggesti	ing that the :	foreign SLA	antigen expres	sed in the trans-
genic mice is recognize	d as a funct:	ional transp	lantation anti	gen. The cellular
basis for this recognit	ion is under	investigat	ion.	
1 ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) (				



DEPARTMENT OF HEALTH A NOTICE OF INT	ND HUMAN SERVICES - PUB		ZO1 CB 09200-02 I
PERIOD COVERED	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between i	the borders.)	
Production of Mab Spec	ific for B Lymphocy	te Receptors for Ly	mphokines
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Princi	pal Investigator.) (Name, title, labo	retory, and institute affiliation)
PI: G. Laszlo	Visiti	ng Fellow	IB, NCI
Other: H. B. Dickler	Senior	Investigator	IB, NCI
COOPERATING UNITS (if any)		-	
LAB/BRANCH Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Ma	ryland 20892		****
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
	1.0	0.1	
(a) Human subjects (a1) Minors (a2) Interviews	🗋 (b) Human tissues	$\Box_{\mathbf{x}}$ (c) Neither	В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space	e provided.)	· · · · · · · · · · · · · · · · · · ·
The goal of this project for lymphokines via the development of monoclous subpopulations of B lympreferentially expresses after activation using B lymphocytes and a sul and is absent from thym Mapping studies using B expression of the Fl-10 and acry-1. These resus suggest that Fl-10 is a expressed on activated new hybridoma screening fluorescence which is a are expressed at very	et is to identify are e production of mono- nal antibodies which mphocytes. Monoclor ed on activated B ly LPS. The Fl-10 der opopulation of bone- mocytes, splenic T l BXD recombinant inbo- 0 determinant is loc- alts together with a letecting a previous B lymphocytes which g method has been de- capable of detecting low levels (500-1000	nd characterize B 1 boclonal antibodies. In distinguish funct nal antibody F1-10 ymphocytes. Express terminant is also e marrow cells but a lymphocytes, and ac ced mice indicate a cated on chromosome a unique strain dis sly undescribed det n may be a receptor eveloped using part g antibodies bindin D molecules per cel	ymphocyte receptors A secondary goal is cionally distinct detects a determinant sion peaks 60 hours expressed on splenic th much lower levels citvated T lymphocytes. agene controlling 17 between hbap-4 trribution pattern erminant selectively for lymphokines. A ficle concentration ag to molecules which 1).


			PROJECT NUMBER
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PRO	JECT	Z01 CB 09201-02 I
PERIOD COVERED			L
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or lass.	Title must fit on one line between the bord	ders.)	
Interaction of B Lymph	ocyte Subpopulations		
PRINCIPAL INVESTIGATOR (List other prof	assional personnel below the Principal Inve	astigator.) (Nama, titla, labore	story, and institute affiliation)
PI: H. B. DICKIEF	Senior Inv	estigator	IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Ma	ryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
	0	0	
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors	- ()	A ( 7	В
(a2) Interviews	1		
SUMMARY OF WORK (Use standard unredu	uced type. Do not exceed the space provid	led.)	
The goal of this proje	ct is to characterize i	nteractions bet	ween B lymphocyte sub-
populations which regu	Late responses of these	(2, 4C2) previo	us work from this lab-
weight substance(s) whi	ich triggered B lymphor	(2.4G2) produce	oliferate and secrete
antibody. This result	suggested that certain	B lymphocytes	might regulate the
response of other B ce.	11s. Our current studi	es have shown t	hat large "activated"
B lymphocytes obtained	directly from mice or	B lymphoblasts	induced in vitro with
F(ab') <sub>2</sub> anti-mu signif:	icantly augment the res	ponses of small	"resting" B lympho-
cytes to F(ab') <sub>2</sub> and 1	ymphokines. Proliferat	ion was augment	ed 2-4 fold while
antibody production was	s augmented 4-5 fold.	This effect was	specific for "acti-
experiments revealed th	h that other cell types	ald not have t	a after stimulation
via antigen receptors	but prior to the effect	s of lymphokine	s. The augmenting
effect does not appear	to be genetically rest	ricted. Invest	igation of the nature
of the signal revealed	that neither supernata	nts nor plasma	membranes from
activated B cells alone	e augmented responses b	ut both togethe	r did. These studies
suggest that interaction	ons between B lymphocyt	es are importan	t in regulating
numoral immune response	es.		



DEPARTMENT OF HEALT	AND HUMAN SER	VICES - PUBI		LTH SERVICE	PHOJECT NU	IMBEH
NOTICE OF INTRAMURAL RESEARCH PROJECT			Z01 C	B 09202-02 I		
PERIOD COVERED	eptember 30.	1987				
TITLE OF PROJECT (80 charactars or	less. Titla must fit on on	a lina between ti	ha bordar	s.)		
Characterization of	T Cell Recept	or Genes	in Al	loreactive	Clones	
PRINCIPAL INVESTIGATOR (List other	profassional personnel	below the Princip	oai Invasti	gator.) (Name, titla, li	aboratory, and institu	ute affiliation)
PI: Hana Goldin	5	rogarty	VISI	lling Scient	lst	IB, NCI
Others: Dinah Singe	r	Senior	Inves	stigator		TB. NCI
William Bid	lison	Senior	Inves	stigator		NI, N
						·
COOPERATING UNITS (if any)						
LAB/BRANCH						
SECTION						
INSTITUTE AND LOCATION						-
NCI, NIH, Bethesda,	Maryland 2089	2				
TOTAL MAN-YEARS:	PROFESSIONAL:			OTHER:		
CHECK APPROPRIATE BOX(ES)	•/					
(a) Human subjects	🗌 (b) Huma	n tissues	Q	(c) Neither		
(a1) Minors						
(a2) Interviews						В
SUMMARY OF WORK (Use standard u.	nreducad type. Do not a	exceed the space	provideo	1.)		
A panel of alloreact	ive T cell cl	ones deri	ved t	rom a singl	e donor has	s been
been possible to ass	ign each of t	he clones	to c	one of four	fine specif	ficity
groups. In order to	attempt to c	orrelate	fine	specificity	with recen	otor gene
utilization, the TcR	alpha and be	ta variab	le ge	ene segments	used by th	nese clones
are being analyzed.	An alpha var	iable ger	le der	ived from a	member of	the most
common group is being	g isolated fr	om a rest	ricte	ed cDNA libr	ary. Its	representation
in the other members	of the panel	will be	asses	sed.		
						•
		-				
				•		



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALT	'H SERVICE	OSECT NOMBER
NOTICE OF INT	т	ZO1 CB 09203-02 I	
PERIOD COVERED			
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borders.)		
Isolation and Character	ization of a Novel H-2 Cla	iss I Gene	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Investiga	tor.) (Neme, title, laboratory,	and institute affiliation)
PI: D. Singer	Senior Invest:	lgator	IB, NCI
Others: S. Rudikoff	Senior Investi	lgator	LG, NCI
J. Hare	Summer Guest V	Vorker	IB, NCI
H. Golding	Visiting Assoc	liate	IB, NCI
COOPERATING UNITS (if any)			
LAB/BBANCH			
Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCL. NIH. Bethesda, Mar	vland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL: 0	THER:	
1.75	1.75		
CHECK APPROPRIATE BOX(ES)	_		
(a) Human subjects (a1) Minors (a2) Interviews	└ (b) Human tissues kg (d	;) Neither	В
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the space provided.)		
A new sub-family of H-2 C57BL/10 mouse. The fa previously identified. ized. Using a series of restriction enzyme poly the right of the Qa loc exon organization of th more, it is capable of to other class I molecu to other class I molecu to other H-2 genes is n more, the over-all orga mouse. Whereas all pre 1.2-2 kb, Mbl has an in class I genes. Taken t direct descendant of a support of this conclus representing millions of genomes. Although othe direct evidence for Mbl is a structurally funct	We dype. Do not exceed the space provided.) 2 class I genes has been in mily consists of at least One of these, Mbl, has no of recombinant strains of m morphisms, it has been pos- cus. DNA sequence analysis dis gene resembles that of encoding a transmembrane p thes. However, the level of the greater than to either h mization of Mbl is more si- viously reported H-2 class attron of 600 bp, similar to ogether, these data sugges primordial class I gene, w ion is the observation that of years of evolutionary di- er members of the Mbl famil- expression has been obtainional gene.	lentified in the two genes which we been extensiv- ince, and taking sible to map the of Mbl demonstration other class I go other class I go ot	e genome of the h have not been vely character- g advantage of he Mbl gene to trates that the genes. Further- structure similar homology of Mbl rabbit. Further- nd pig than to third introns of n and porcine represent a speciation. In wild mouse, ain Mbl in their expressed, no he fact that it

PROJECT NUMBER



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PR	ROJECT	201 CB 09204-02 I
PERIOD COVERED			
October 1, 1986 to Sept TITLE OF PROJECT (80 characters or less	ember 30, 1987 Title must fit on one line between the	borders.)	
Function of Accessory N	blecules in T Cell In	Iteractions	tone and institute officiation)
PT. S McCarthy	Sopior Str	ff Follow	tory, and institute amination)
ri. 5. recartiny	Senior Sta	III FEIIOW	IB, NCI
Other: E. Kaldjian	Howard Hug	hes Fellow	IB, NCI
A. Singer	Senior Inv	restigator	IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
Immunology Branch	· · · · · · · · · · · · · · · · · · ·		
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	vland 20892	07450	
1 3	1 1		
CHECK APPROPRIATE BOX(ES)	I & I		
(a) Human subjects	(b) Human tissues	$\frac{1}{x}$ (c) Neither	
(a1) Minors			В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space p	rovided.)	
Precursor and effector	CTL specific for dete	rminants present of	on allogeneic MHC
class I molecules have	previously been shown	to bear the Lyt2	cell surface
cells because antibodie	s directed against Ly	t2 block the cytol	lytic activity of
most in vitro-generated	MHC class I allospec	ific mature CTL.	Based on those
studies, Lyt2 has been	proposed to be either	an accessory mole	cule contributing to
on the role of Lyt? dur	ing the initial activ	ature. CIL. Our s	specific CTL in
vitro. CTL induced in	vitro in the presence	of anti-Lyt2 mono	oclonal antibody are
resistant to subsequent	blocking of lytic ef	fector function by	y anti-Ly2 antibody,
in sharp contrast to CT	L generated in conven	tional (antibody-	ree) cultures. We
body actively induces t	he generation of Lvt2	-resistant CTL ef	fector cells, and
does not merely permit	the selective outgrow	th of a minority p	oopulation of Lyt2-
resistant precursor CTL	. Furthermore, in co	ntrast to convent:	lonal class I-
undergo down-modulation	of their cell surfac	e Lvt2, and exhibit	it an Lvt2-"dull"
phenotype. We are curr	ently investigating t	he functional rela	ationship between
antibody-induced down-m	odulation of Lyt2 and	Lyt2-resistant C	TL activity. Since
Lyt2 antibody, Lyt2 eng	agement by antibody d	uring activation of	ne presence of anti-
alternative differentia	tion program in at le	ast some precurson	CTL. Thus, Lyt2
may function to generat	e an "on" signal duri	ng CTL activation.	

PROJECT NUMBER



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PR	OJECT	201 CB 09203-02 1
PERIOD COVERED October 1, 1986 to Septe	mber 30, 1987		<u> </u>
TITLE OF PROJECT (80 characters or less Receptor Mediated T Cell	Title must fit on one line between the b Activation	orders.)	
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal I	nvestigator.) (Name, title, lebor	etory, and institute affiliation)
thers: K. S. Hathcock	Chier, immuno Chemist	cherapy Section	IB, NCI IB, NCI
D. M. Segal	Senior Invest	igator	IB, NCI
M. Taplits	Medical Staff	Fellow	IB, NCI
E. Anglade	Howard Hughes	Fellow	IB, NCI
P. Henkart	Senior Invest	igator	IB, NCI
J. Bluestone	Senior Invest	igator	IB, NCI IB, NCI
COOPERATING UNITS (if any)			
LAB/BRANCH			
mmunology Branch			
SECTION			
ICI, NIH, Bethesda, Mary	land 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			R
	luced hipe. Do not exceed the proce or	wided )	B
the mechanism of T cell	activation has been s	tudied employing	both cloned T cell
opulations and naive he	terogeneous T cell po	pulations. Compa	arison has been
ade of T cell stimulati	on by antibodies dire	cted to allotypic	determinants on
he T cell receptor, T c	ell activation by spe	cific antigen, an	id T cell activation
nd naive T cells can be	triggered by the mon	oclonal antibody	F23.1. directed
oward determinants on t	he T cell receptor.	Naive Lyt2 <sup>+</sup> T cel	lls were activated
o proliferate in the pr	esence of soluble F23	.1, IL-2, and acc	cessory cells.
nder the same condition	s, L3T4 <sup>+</sup> naive T cell	s were unresponsi	ive. These findings
hus demonstrated a diff	erence in the activat	ion requirements	of T cell sub-
opulations triggered th	rough T cell receptor	determinants.	specific targeting
i the i cell receptor t	ti-Ta antibody were	in contrast cap	able of activating
oth $Lyt2^+$ and $L3T4^+$ T c	ell subpopulations.	The nature of act	tivation signals
rovided under these div	erse conditions is cu	rrently under stu	udy. In particular,
he function of endogeno	us lymphokines is bei	ng analyzed. Par	rameters of T cell
esponse including speci	fic gene activation a	nd exocytosis of	cytoplasmic
ranules in response to	diverse stimuli have	been evaluated.	



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC	HEALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PR	OJECT	Z01 CB 09206-01 I
PEBIOD COVERED			
October 1, 1986 to Sept	tember 30, 1987		
TITLE OF PROJECT (80 cheracters or less.	. Title must fit on one line between the b	orders.)	
In Vivo Treatment With	Monoclonal Anti T Cel	I Receptor Antib	odies
PI: J. A. Blueston	ne Senior Investig	ator (Neme, title, labore) ator	tory, and institute affiliation) IB, NCI
Others: R. Hirsch D. H. Sachs	Medical Staff H Chief, Transpla	ellow ntation Biology (	IB, NCI Section IB, NCI
LAB/BRANCH			
Immunology Branch			
SECTION			
Transplantation Biolog	gy Section		
NCI. NIH. Bethesda. Mai	ryland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
4	3	1	· · · · · · · · · · · · · · · · · · ·
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	(b) Human tissues	$\Box_{\mathbf{x}}(c)$ Neither	В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space pro	vided.)	
SUMMARY OF WORK (Use standard unred Monoclonal antibodies a in vivo in an attempt of foreign transplantatior against the CD3 delta of have profound immunosup in vivo. We have devel CD3 epsilon chain of th CD3 counterpart, it car Animals treated with sn skin graft rejection by anti-T3 treated mice an class I and class II. vivo treatment with ant HVG responses.	used type. Do not exceed the space pro against T cell surface to delete T cells and n antigens. One such chain of human T cell ppressive effects on t loped a hamster monocl he murine T cell recep n significantly effect mall quantities of the y as much as three wee re unresponsive to a v Future studies will b ti T3 on bone marrow e	wided.) markers have bee allow for subseque monoclonal antibue receptor complex ransplantation re onal (145-2C11) of tor complex. Lift transplantation anti-T3 antibody ks. In addition ariety of alloand e designed to exa ngraftment and al	en used experimentally lent tolerence to ody OKT3, directed has been shown to ejection responses directed against the ce its anti human responses in vivo. y exhibit prolonged , cells removed from figens including both amine the role of in progation of GVH and

PROJECT NUMBER



	ND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PRO	JECT	Z01 CB 09207-01 I
PERIOD COVERED			
October 1, 1986 to Septe	ember 30, 1987		
T Cell Immune Deficiency	y in Mice and Humans Wi	th Autoimmune Di	sease
PRINCIPAL INVESTIGATOR (List other pro PI: G. M. Shearer	fessional personnel below the Principal Inv Senior Investigat	astigator.) (Name, titla, labora OT	tory, and institute effiliation) IB, NCI
Other: C. S. Via	Medical Staff Fel	low	IB, NCI
G. C. Tsokas	Senior Investigat	or	ARB, NIADDKD
			•
COOPERATING UNITS (if any)			
LAB/BRANCH Immunology Branch			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mary	/land 20892	1	
0.3	0.5	0.2	
CHECK APPROPRIATE BOX(ES)           Image: Check appropriate box(es)           Image: Check approximate box(es)	(b) Human tissues	C (c) Neither	В
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-de DNA antibodies and of su helper cell function.	uced type. Do not exceed the spece provi or mice gradually devel pendent which is concom appressor cells that se Fhis observation contra	med.) op a loss of L31 itant with the a lectively suppressts with Mrl +/4	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1) function that is age-dep DNA antibodies and of so helper cell function. The none of the above during the (NZBxNZW)F1 autoimmu	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom uppressor cells that se This observation contra g the same time period. une strain.	Med) op a loss of L31 itant with the a lectively suppre sts with Mrl +/4 Similar result	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit is were observed in
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. The none of the above during the (NZBxNZW)F <sub>1</sub> autoimmut Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom uppressor cells that se Chis observation contra g the same time period. one strain.	Med) op a loss of L31 itant with the a lectively suppre sts with Mrl +/4 Similar result ctive loss of CL	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. The none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel pendent which is concom appressor cells that se This observation contra g the same time period. ane strain. exhibit a similar sele	Med) op a loss of L3T itant with the a lectively suppre sts with Mrl +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-de DNA antibodies and of so helper cell function. To none of the above during the (NZBxNZW)F <sub>1</sub> autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom appressor cells that se This observation contra g the same time period. ane strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively suppre sts with Mrl +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit is were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. To none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom appressor cells that se this observation contra g the same time period. ane strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively suppre sts with Mrl +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. The none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel pendent which is concom appressor cells that se This observation contra g the same time period. one strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively suppre sts with Mr1 +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1) function that is age-de DNA antibodies and of so helper cell function. The none of the above during the (NZBxNZW)F1 autoimmut Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom appressor cells that se This observation contra g the same time period. ane strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively suppre sts with Mrl +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit is were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. To none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom appressor cells that se this observation contra g the same time period. one strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively supprests with Mr1 +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. The none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel pendent which is concom appressor cells that se This observation contra g the same time period. one strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively supprests with Mr1 +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1) function that is age-de DNA antibodies and of so helper cell function. The none of the above during the (NZBxNZW)F1 autoimmut Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom uppressor cells that se This observation contra g the same time period. une strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively supprests with Mrl +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit is were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-dep DNA antibodies and of su helper cell function. T none of the above during the (NZBxNZW)F1 autoimmu Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel bendent which is concom uppressor cells that se this observation contra g the same time period. one strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively supprests with Mr1 +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell
SUMMARY OF WORK (Use standard unred Spleen cells from Mrl-1 function that is age-de DNA antibodies and of su helper cell function. The none of the above during the (NZBxNZW)F1 autoimmut Human patients with SLE function.	uced type. Do not exceed the spece provi or mice gradually devel pendent which is concom uppressor cells that se this observation contra g the same time period. une strain. exhibit a similar sele	Med) op a loss of L31 itant with the a lectively supprests with Mr1 +/4 Similar result ctive loss of CI	24 <sup>+</sup> T helper cell appearance of anti- ess only L3T4 <sup>+</sup> T - mice that exhibit as were observed in 04 T helper cell



DEPARTMENT OF HEALTH A	NO HUMAN SERVICES - PUBLIC HE	TH SERVICE	PROJECT NUMBER	
	BANUDAL DESEARCH BRO	ECT	701 CB 00208-01 T	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	201 CB 09200-01 1	
PERIOD COVERED	1 00 1007			
October 1, 1986 to Septe	ember 30, 1987			
TITLE OF PROJECT (80 cheracters or less Regulation of Human T Ca	. Title must fit on one line between the borde 211 Responses by Adheren	t Cells		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principel Inves	tigator.) (Name, title, lebore r	tory, and institute affilietion)	T
	benier interessuer.	-	15, 10	
COOPERATING UNITS (if any)				
LAB/BRANCH				
Immunology Branch				
SECTION				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Mary	yland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
	0.5	0.5		
(a) Human subjects	□ (b) Human tissues 🗵	(c) Neither		
(a1) Minors				
(a2) Interviews				В
Depletion of human perin	oheral blood leukocytes	a) (PBL) of Leu M3	+ cells by adherence	ce
to plastic and sephadex	G10 results in the abrog	gation of proli	ferative ( <sup>3</sup> H) and	
cytotoxic T lymphocyte (	(CTL) responses to influe	enza A virus (H	'LU), but in an	
elevation of <sup>5</sup> H and CTL	responses to HLA alloant	tigens (ALLO).	This loss of the	
whereas the elevation of	the ALLO response was	shown to be due	to a suppressor	
cell (or a suppressor in	nducer cell) that is con	tained in the I	eu M3 <sup>+</sup> adherent	
cell population. Suppre	essor activity was inact:	ivated by cultu	ring either un-	
fractionated PBL or adhe	erent cells with viruses	, including inf	luenza A, measles	
and mumps viruses.				



DEPARTMENT OF HEALTH AN NOTICE OF INTE	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER ZO1 CB 09209-01 I
PERIOD COVERED October 1, 1986 to Sept	ember 30, 1987	
TITLE OF PROJECT (80 characters or less. Homologous Peptides fro	Title must fit on one line between the borders.) om HIV gp41 and HLA Class II Bind	CD4 on Human T Cells
PRINCIPAL INVESTIGATOR (List other profe PI: H. Golding	essional personnel below the Principal Investigator.) (Name, title Visiting Associate	e, laboratory, and institute affiliation) IB, NCI
Others: D. Singer F.A. Robey B. Golding	Senior Investigator Senior Investigator Senior Investigator	IB, NCI NIDR DBP, FDA
COOPERATING UNITS (if any)		
LAB/BRANCH		
Immunology Branch SECTION		
INSTITUTE AND LOCATION	1 1 00000	
NCI, NIH, Bethesda, Mar TOTAL MAN-YEARS:	PROFESSIONAL: OTHER:	
1	1	
(a) Human subjects [ (a) Alimons (a) Interviews	☐ (b) Human tissues 🛛 (c) Neither	В
The CD4 molecule has be Recently, the natural 1 tively localized to the ws postulated that the similar conserved regio high degree of homology DQ. Both the HIV and M tion of these peptides, 37°C for 45 min resulte and Leu3) to the cells. be blocked in the prese against other surface a tides. The temperature that the peptides induc mediated endocytosis. chicken albumin conjuga cells, but not to a CD4 could be partially inhi bodies. Therefore, the and MtC Class II, which of AIDS virus and MtC C serum and murine mAb sp intact inactivated viri	<pre>nide nide access the space provided ) en identified as the receptor for igand for CD4 on antigen presenti: N-terminal domain of the beta ch. MHC Class II and HIV bind the non- ns. A hydrophilic septamer was id- between gp41 of HIV and the beta HC Class II derived sepatmers were but not control peptides, with C d in reduced binding of anti-CD4 d This peptide mediated reduction nce of chloroquine. The binding of ntigens, were unaffected by pre-in requirement and the sensitivity d ed partial modulation of the CD4 d In addition, flow cytometry showed tes of the peptides can bind dired negative CEM mutant or to B cell bited in the presence of mouse mous e findings suggest that the homo. we have identified, may be the s: lass II antigens to CD4 on human d ecific for the HIV derived peptide </pre>	HIV envelope protein. ng cells has been tenta- ain of MHC Class II. It -polymorphic CD4 via dentified displaying a -l domain of HLA-DR and - e synthesized. Incuba- D4 positive cells at antibodies (OKT4, OKT4a of binding to CD4 could of antibodies directed ncubation with the pep- to chloroquine suggest molecules via receptor d that biotinylated ctly to CD4 bearing CEM lines. This binding noclonal anti-CD4 anti- logous regions of HIV ites involved in binding T cells. Rabbit anti- e were found to recognize lass II molecules on B



			PROJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLI	C HEALTH SERVICE	
NOTICE OF IN	FRAMURAL RESEARCH P	ROJECT	ZO1 CB 09210-01 I
October 1 1986 to Sen	tember 30 1987		
TITLE OF PROJECT (80 characters or les	s. Title must lit on one line between th	borders.)	
Induction of Class I M	dC Gene Expression by	Ethanol	
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Principa	I Investigator.) (Name, title, labo	pretory, and institute effiliation)
PI: D. Singer	Senior	Investigator	IB, NCI
Others: M. Kolber	Medical	Staff Fellow	IB, NCI
L. Parent	Guest R	esearcher	IB, NCI
K. Wall	Guest R	esearcher	G.W.U. Hospital
COOPERATING UNITS (if any)			
			······································
LAB/BRANCH			
SECTION			
SECTION			
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Man	vland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
0.25	0.25		
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
(a1) Minors			В
SUMMARY OF WORK (Use standard unre	suced type. Do not exceed the space j	novided.)	
Ethanol enhances expres	sion of cell surface	class 1 MHC anti	gens in a variety of
treatment of L colla of	yourc cert fine, thi	s increase is up	to 10-rold. Ethanol
gens with a concomitar	t increase in stoady	cell surface exp	PNA This offost is
promoter dependent and	restricted since no	-state revers or	te are elevated The
effective ethanol conce	entration (1%) is phy	siologically atta	inable. In a study of
chronic alcoholics, it	was found that the la	evels of Class I	MHC antigens on their
PBL was significantly h	igher than in normal	controls.	
-			
1			
-			
3			



			PROJECT NUM	BER
DEPARTMENT OF HEALTH A	AND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	ZO1 CB	09211-01 I
PERIOD COVERED				
UCCODET 1, 1980 LO DEC	Ember 30, 1987			
Cell Type Specific Reg	sulation of the T Cell R	ecentor & Chain		
PRINCIPAL INVESTIGATOR (List other pro	diacional personnel below the Principal Inva	stigator ) (Name title labora	tony and institute	affiliation
PI: K. Kelly	Iab Leader	ingator.) (Haine, title, labore	nory, and msinule	TR N
				12,
Others: M. Kearns	Guest Researcher			IB, NO
COOPERATING UNITS (if any)				
Immunology Branch				
SECTION				
SECTION 1				
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Ma	ryland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
1.25	1.25			
CHECK APPROPRIATE BOX(ES)		<u> </u>		
(a) Human subjects	(b) Human tissues	x(c) Neither		
(a1) Minors				В
(a2) Interviews				
SUMMARY OF WORK (Use standard unrac	duced type. Do not exceed the space provide	əd.)		
The genetic regulatory	mechanisms that govern	tissue specifi	c expressi	ion of the 1
cell receptor $\beta$ chain	have been investigated u	itilizing an in	vitro mod	del of cell
type specificity. A	transient expression sys	stem has been u	sed to ass	say the
transcription of a gen	iomic TCF $\beta$ chain gene (i	including 5 kb	5' of a re	earranged
V <sub>B1</sub> -J-C clone) in T ce	lls, fibroblasts, and a	variety of hem	atopoietio	c tumor
cells. DNA sequencing	; of the $V_{\beta 1}$ leader and a	an additional 4	00 bp 5',	in con-
junction with Sl nucle	ase protection assays, h	has identified	the start	site of
transcription. Also,	a putative regulatory he	examer, CTTTCT,	that is o	conserved in
several human and muri	ne $v_{\beta}$ genes has been 1de	entitied approx	imately 2	50 DD 5.
to the mRNA cap site.	Transfection efficience	les were normal	ized by de	stermining
the mRNA levels of a t	runcated histone gene co	ontained within	the plasm	ald vector
as a tissue nonspecifi	c control. Unlike immu	logiobuiin gene	s, express	sion of a
that T calls show a mi	rimum of a 3 fold profes	certial overcos	, IL was the	o C chain ac
compared to fibroblast	and monocytic calls	Furthermore a	15 kb da	eletion in
the 5' region of the I	intron does not a	reclude & chai	n express	ion
in T cells or fibrobla	$\beta_{I} \circ \beta_{I}$ Tissue specific r	gulation of T	cell recen	ntor & chair
expression does not an	pear to require gene set	wences within	this regio	on of the
intron, but may be inf	luenced by a conserved i	region of the g	ene 5' to	the promoto
				retuited



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CB 03200-18 LCBGY

PERIOD COVERED						
October 1, 1986 through TITLE OF PROJECT (80 characters or lass	September 30, Title must fit on one line	1987 between the border	rs.)			
Factors Influencing the PRINCIPAL INVESTIGATOR (List other pro	Induction, Gr	owth and R	epression of N	eoplasms	affiliation	
PI: L. W. Law	Second personner below	Chief, La	b. of Cell Bio	logy	LCB, NCT	
				87		
OTHER: E. Appella	o Tu	Medical 0	fficer (Res.)		LCB, NCI	
V. J. Hearin F A Robins	g, Jr.	Chomist	Biologist		LCB, NCI	
S. J. Ullric	h	Sr. Staff	Fellow		LCB, NCL	
W. D. Vieira		Microbiol	ogist		LCB, NCI	
					-	
COOPERATING UNITS (if any) Memorial Sloan-Ketterin	g Cancer Cente	r. New Yor	k NY			
Pittsburgh Cancer Insti	tute, Pittsbur	gh. PA	K, NI			
Frederick Cancer Resear	ch Facility, F	rederick,	MD			
LAB/BRANCH Laboratory of Cell Biol	nev					
SECTION	- 67					
Office of the Chief						
NCI, NIH, Bethesda, MD	20892					
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:			
3	1		2			
CHECK APPROPRIATE BOX(ES)	(b) Human tiss		(c) Neither			
(a) Human subjects		sues La				
(a2) Interviews				В		
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed	the space provide	d.)			
Class I (restricted)	and Class	II (cross	reacting) tun	nor antig	ens of t	he
trans-plantation reject	on type (TATA)	, and of t	umor antigens	(TA) ass	aved by	in
vivo and in vitro techr	iques and of t	he immune	responses they	v evoke ha	ve receiv	ved
major emphasis. As a co	orollary to thi	s study, t	the biologic p	propertie	s <u>in vit</u>	ro
and in vivo of alien hi	stocompatibili	ty (H-2) a	antigens and of	variant	antigens	in
several neoplasms are un	ider study. Pu	rification	of TATAs are	under inv	estigati	on
with the ultimate purp	ose of definit	ig these me	embrane and cyt	cosol anti	gens, art	ter
partication, in physica	Jenemical, 0101	logic and n	norecurar cerma	•		
		(11				



				PROJECT	NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES	PUBLIC HEA	ALTH SERVICE		
NOTICE OF IN	TRAMURAL RESEAR	RCH PROJI	ECT	ZO1 CB	03229-18 LCBGY
PERIOD COVERED October 1, 1986 throug	h September 30,	1987			
TITLE OF PROJECT (80 characters or les Structural Analysis of	s. Title must fit on one line be Histocompatibil	tween the borde ity and I	rs.) Cumor Antigens	and T-	cell Receptors
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the	Principal Inves	tigetor.) (Name, title, labo	ratory, and ins	stitute affiliation)
ri: E. Appe	118	Medical	Ufficer (Res.	)	LCB, NCI
OTHER: M. J. D.	arsley	Visiting	g Fellow		LCB, NCT
S. K. M	oore	Sr. Staf	f Fellow		LCB, NCI
E. A. R	obinson	Chemist			LCB, NCI
S. J. U.	llrich	Sr. Staf	f Fellow		LCB, NCI
K. Ozat	0	Res. Mic	robiologist		LDMI, NICHD
E. D. Ko	orn	Chief, L	Lab. Cell Biol	•	LCB, NHLBI
Weizmann Institute of	Sci Rehovot T	eraol			
ENEA-Euratom Immunogene	etics. Lab. of Pa	athology.	C.R.E., Casa	ccia. Ro	me. Italy
		, ,,	000000000000000000000000000000000000000		Juc, Itury
LAB/BRANCH					
Laboratory of Cell Bio	logy				
SECTION					
Chemistry					
NCL. NIH. BETHESDA. MD	20892				
TOTAL MAN-YEARS:	PROFESSIONAL:		OTHER:		
5	5		0		
CHECK APPROPRIATE BOX(ES)					
(a) Human subjects	(b) Human tissu	es 🖾	(c) Neither		
(a1) Minors (a2) Interviews					В
SUMMARY OF WORK (Use standard unre	duced type. Do not exceed the	e space provide	d.)		
The major area o	f our research	involve	s the molecul	lar stru	cture of histo-
compatibility antigens,	T cell suppres	ssor rec	eptors and to	umor an	tigens using a
combination of prot	ein and DNA se	equencin	g in conjunc	tion wi	th peptide and
nucleotide synthesi	s. Site dire	cted mu	tagenesis an	nd rec	ombinant DNA
constructs were used	to elucidate t	ne contr	ibution of ind	iividuai	amino actus as
well as of the individu	al 1/2 domains	, or cras	s i antigens	Loward	com ormacional
The complete cDN	A sequence of th	ne and	chains of th	ne T cel	1 receptor of a
T supressor clone was determined and was found to use the same bool of gene seg-					
ments used in T-helper and cytotoxic cells. These clones will be used to					
investigate the role of these genes in conferring suppressor activity.					
Residues 105-120 of hen egg lysozyme were found to correspond to the immuno-					
dominant epitope recognized by I-E <sup>q</sup> restricted T cell hybridomas. By using					
various synthetic peptides, individual amino acids involved in antigen/1-cell					
A tumor-specific translantation antigen was identified as a heat shock					
a tumor-specific translatation antigen was identified as a near shock					
multigene families dispersed on several chromosomes. Complete nucleotide sequence					
of one isoform and partial nucleotide sequence of the second isoform were deter-					
mined and genomic clones for both isoforms have been isolated. The regulation of					
the synthesis of three isoforms were examined in normal and transformed cells at					
the transcriptional and translational level. Further analysis should permit					
identification of the molecular changes in these antigens which elicit cell					
mediated immunity.					
DNA sequences predicted to have aberrant helices with hairpin stems and loops					
have been crystallized and preliminary X-ray structures have been solved.					



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT PROJECT NUMBER

## Z01 CB 09100-4 LCBGY

PERIOD COVERED					
October 1, 1986 through September 30, 1987					
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)					
Immunogenicity of Melanoma					
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute	affiliation)				
PI: Vincent J. Hearing, Jr. Research Biologist	LCB, NCI				
Other: Lloyd W. Law Chief, Lab. of Cell Biology	LCB, NCI				
Ettore Appella Medical Officer (Res.)	LCB, NCI				
Mercedes Jimenez-Atienzar Visiting Associate	LCB, NCI				
Koichiro Kameyama Visiting Fellow	LCB, NCI				
Columbia University, New York, NY					
Georgetown University Medical Center, Washington, D.C.					
Pittsburgh Cancer Institute, Pittsburgh, PA					
LAB/BRANCH					
Laboratory of Cell Biology					
SECTION					
Chemistry					
INSTITUTE AND LOCATION					
NCI, NIH, Bethesda, MD 20892					
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:					
4 3 1					
CHECK APPROPRIATE BOX(ES)					
(a) Human subjects (b) Human tissues (c) Neither					
	В				
This project is aimed at characterizing: (1) the host immune response	to malignant				
melanoma, and the role it plays in the progression of tumor growth and metastation					
spread; (2) tumor specific proteins produced by melanoma cells in	vivo and in				
vitro, to determine the mechanism of their formation, to examine th	e impact of				
their expression on tumor growth, and to study the feasibility of uti	lizing their				
specificity for the immunoassay and immunotherapy of melanoma; (3)	the role of				
cell surface proteases in the cascade of events leading to metastat	ic spread of				
tumors; (4) the control mechanisms involved in the regulation	of pigment				
production in normal and in transformed melanocytes. The results i	ndicate that				
various murine melanomas (of spontaneous, ultraviolet light induced, and					
chemically induced origin) share common cell surface antigens which are capable of					
eliciting tumor rejection (TSTA); these antigens have a specificity restricted to					
melanoma cells. One murine melanoma however (S91) has a unique TSTA, and studies					
are underway to characterize its antigen(s). We have shown that imm	unized mice				
produce high titers of melanoma-specific cytotoxic antibodies, and	that this B				
cell response may account for the observed tumor rejection, since we have been					
unable to demonstrate any I cell response, thus far. We have found that					
purrace unokinase activity significantly affects the metastatic potential of					
metastatic sequence. We have produced and utilized monoclonal antibodies specific					
for the melanocyte specific enzyme, tyrosinase to examine cellular control					
mechanisms functional in the response of melanocytes to varying environmental					
stimuli which affect pigmentation, such as melanocyte stimulating hormone.					



			PROJECT NUMBER	
DEPARTMENT OF HEALTH AND	HUMAN SERVICES - PUBLIC HEAL	TH SERVICE		
NOTICE OF INTRA	MURAL RESEARCH PROJEC	т		
			Z01 CB 08525-11 LTB	
PERIOD COVERED				
October 1, 1986 to Septer	mber 30, 1987			
TITLE OF PROJECT (80 cheracters or less Tit	le must fit on one line between the borders.	}		
Immunotherapy of Primary	Autochthonous Cancer			
PRINCIPAL INVESTIGATOR (List other profess	sional personnel below the Principal Investig	ator.) (Name, title, Jabora	tory, and institute affiliation)	
		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
PI: B. Zbar	Chief, Cellular Immur	ity Section	LIB NCT	
T. Borsos	Chief, Laboratory of		LIB NCI	
	Immunobiology		410 1101	
OTHER: G. Glenn	Medical Staff Fellow		LIB NCI	
T. Yano	Visiting Fellow		LIB NCI	
COOPERATING UNITS (if any)				
B. Szende	Semmelweis Medical Ur	iversitv.		
	Budapest, Hungary	,,		
LAB/BRANCH				
Laboratory of Immunobiolo	ogy			
SECTION				
Cellular Immunity Section	a			
INSTITUTE AND LOCATION				
NCI-FCRF, NIH, Frederick,	Maryland 21701			
TOTAL MAN-YEARS: PF	ROFESSIONAL:	OTHER:		
2.5	2.5	0		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects	(b) Human tissues $X$	c) Neither		
(a1) Minors				
(a2) Interviews			В	
SUMMARY OF WORK (Use standard unreduce	d type. Do not exceed the space provided.)			
The primary objective of	this project was to eva	luate the the	erapeutic	
efficacy of various biolo	ogic response modifiers	in animals wi	th primary	
cancer as a guide for tre	eatment of human cancer.	This projec	t has	
been terminated.				



DEPARTMENT OF HEALTH AND HUMAN SERVICES . DURING HEALTH SERVICE	PROJECT NUMBER			
NOTIOE OF INTRAMURAL PERSTADAL PRO FOR				
NOTICE OF INTHAMURAL RESEARCH PHOJECT	701 GD 00500 11 177			
	201 CB 08528-11 LIB			
October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)				
Mechanisms of Delayed Hypersensitivity and Tumor Graft Reject	ion			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principel Investigator.) (Name, title, labore	tory, and institute affilietion)			
PI: B. Zbar Chief, Cellular Immunity Section	on LIB NCI			
COOPERATING UNITS (in any)				
J. Iaimadge Program Kesources Inc., NCI-FCF	E Markan			
D. netwen opjonn rnarmaceutical, Kalamazo	o, michigan			
LAB/BRANCH				
Laboratory of Immunobiology				
SECTION				
Cellular Immunity Section				
NCT_ECOR NTH Erodorick Monster 21701				
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:				
0.5 0.5	)			
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects (b) Human tissues 🙀 (c) Neither				
(a1) Minors				
	В			
oommenti or morni jose standard amadabed type. Do not exceed the space provided.)				
The goals of this project are to analyze the genetic mechanic	ms by which			
immunogenic tumors escape host immune responses and the genet	ic basis of			
transplantation antigens of chemically-induced tumors.				



					PROJECT NUMBER
DEPA	DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE				
	NOTICE OF INT	RAMURAL RESE	ARCH PROJ	ECT	
					Z01 CB 08552-21 LIB
PERIOD COVE	1 1096 ha Card				
UCEOBER TITLE OF PBC	I, 1900 LO Sept	Title must fit on one line	between the borde	(5)	
Mechanie	am of Complement	Fixation and	Action		
PRINCIPAL IN	VESTIGATOR (List other pro	fessional personnel below	the Principal Invest	tigator.) (Name, title, labor	atory, and institute affiliation)
PI:	T. Borsos	Office	of the Chi	ef	LIB NCI
OTHER:	A. Circolo	Visiti	ng Associat	e	LIB NCI
	M. Kirschfink	Visiti	ng Fellow		LIB NCI
	S. Hosoi	Visiti	ng Fellow		LIB NCI
000050470					
COOPERATING	G UNITS (Ir eny)				
Dopanta	ant of Picchomic	terr IIndromada			
Departme	ent of blochemis	cry, universit	ry or Lausa	nne	
LAB/BRANCH					
Laborato	ry of Immunobic	logy			
SECTION					
Office c	of the Chief				
INSTITUTE AN	D LOCATION				
NCI, NIH	I, FCRF, Frederi	ck, MD 21701			
TOTAL MAN-Y	EARS:	PROFESSIONAL:		OTHER:	
	3.5		2.5		1.0
CHECK APPRO	OPRIATE BOX(ES)	(h) Human tia			
	Minore		sues X	(c) Neither	
	) Interviews				
	WORK (Use standard unred	duced type. Do not exceed	the space provide	d )	В
				u.)	
This is	a long-range pr	oiost invosti	nating the	machaniam of	amplement
fivation	a long lange pl	n particular t	the interac	tion of antib	dy-antigen
complexe	e with the fire	t component of	E complement	t and the real	it of this
interact	ion on the othe	r componente of	ro invocti	gated The rest	lation
hetween	antibody action	and complements	t activati	on is also over	lared
Finally.	the significan	ce of compleme	nt in the	humoral immune	defense
mechanis	m is studied.	tee or comprend	ine in ene	numorar immune	Gerense
			(05		

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			PROJECT NUMBER		
DEPARTMENT OF HEALTH	DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE				
NOTICE OF IN	ITRAMURAL RESEARCH PRO	JECT			
			Z01 CB 08577-02 LIB		
PERIOD COVERED					
October 1, 1986 to Se	ptember 30, 1987				
TITLE OF PROJECT (80 characters or la	ss. Title must fit on one line between the bol	ders.)			
Restriction fragment	length polymorphisms in	normal and neop	lastic human tissues		
PRINCIPAL INVESTIGATOR (List other p	rofessional personnel below tha Principal Inv	estigator.) (Name, title, labora	atory, and institute affiliation)		
PI: B. 2Dar	Chief, Cellular Im	munity Section	LIB NCI		
OTHER. H Brauch	Viciting Follow		LTD NOT		
T Yano	Visiting Fellow		LIB NCI		
M Lorman	Funct		LIB NOL		
G. Glenn	Medical Staff Fell	OH	LIB NCI		
M. Linehan	Surgery Branch	0w	DCT NCI		
int armenum	ourgery prunen		bor nor		
COOPERATING UNITS (if any) John	Minna N	avy Medical Once	ology Unit, NCT		
Bern	ard J. Poiesz	UNY Health Scien	nces Center, Syracuse		
Geor	ge D. Sorenson	artmouth Medica	1 School		
Pete	r Schwartz Y	ale University	School of Medicine		
LAB/BRANCH					
Laboratory of Immunob	iology				
SECTION					
Cellular Immunity Sec	tion				
INSTITUTE AND LOCATION					
NCI-FCRF, NIH, Freder	ick, Maryland 21701				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
4.5	2.5		2.0		
CHECK APPROPRIATE BOX(ES)					
🔲 🔲 (a) Human subjects	(b) Human tissues	x (c) Neither			
(a1) Minors					
(a2) Interviews			В		
SUMMARY OF WORK (Use standard unr	educed type. Do not exceed the space provi	ded.)			
The primary objective	of this project is to c	ompare restricti	ion fragment		
length polymorphisms	(RFLPs) in DNA extracted	from normal and	d neoplastic		
human tissues. The i	nitial study will focus	on renal cell ca	arcinoma and		
small cell lung cance	r. We will look for evi	dence of deletio	on of specific		
chromosomal loci (cha:	nge in RFLP from heteroz	ygosity to homoz	zygosity).		


DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT	701 OD 00575 15 170
PERIOD COVERED	201 CB 08575-15 LIB
October 1, 1986 to September 30, 1987	
Inflammation	
PRINCIPAL INVESTIGATOR (List other professional personnal below the Principal Investigator.) (Name, title, labore	atory, and institute affiliation)
PI: E. Leonard Chief Immunopathology Section	ITP NOT
in solution offer, immunopathology section	LIB NCI
OTHER: Antal Rot Visiting Fellow	LIB NCI
Terzo fosnimura Guest Researcher	LIB NCI
COOPERATING UNITS (it any)	
L. Henderson Litton Bionetics Basic Research Pro	gram, FCRF
LAB/BRANCH	
Laboratory of Immunobiology	
Immunopathology Section	
INSTITUTE AND LOCATION	
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:	<u> </u>
4.0 2.3 1.0	
(a) Human subjects (a) Human subjects (b) Human tissues (c) Neither (a2) Interviews	
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)	<u> </u>
Investigations in the Immunonathology Section are on chemotac	tic and
other immune effector responses of leukocytes. The emphasis	is on
chemotaxis, a mechanism by which cells are attracted to infla	mmatory
includes chemistry and biology of bacterial derived chemotact	ic factors,
characterization of a serum protein that modulates macrophage	motility,
and definition of functional subpopulations of blood monocyte	S•

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DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH PROJ	JECT	ZO1 CB 05190-07 LTIB
PERIOD COVERED October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less Monoclonal Antibodies D	. Title must fit on one line between the bord efine Carcinoma Associa	ted and Differe	ntiation Antigens
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inve	stigator.) (Name, title, labora	atory, and institute affiliation)
Jeffrey Schlom	Chief	LTIB, DCBD,	NCI
Patricia Horan Hand	Chemist	LTIB, DCBD,	NCI
Jean Simpson	Medical Staff Fellow	LTIB, DCBD,	NCI
Ricardo Parker	BTP	LTIB, DCBD,	NCI
Shashi Shrivastav	Visiting Fellow	LTIB, DCBD,	NCI
Masahide Kuroki	Visiting Associate	LTIB, DCBD,	NCI
Alfredo Molinolo	Visiting Fellow	LTIB, DCBD,	NCI
Kai Chang	Visiting Fellow	LTIB, DCBD,	NCI
COOPERATING UNITS (if any)		·····	
P. Noguchi, Bureau of B	iologics, FDA		
W. Johnston, Dept. of P	athology, Duke Univ.		
LAB/BRANCH			
Laboratory of Tumor Imm	unology and Biology		
SECTION			
Experimental Oncology S	ection		
INSTITUTE AND LOCATION			
NCI, NIH, Bethesda, Mar	vland 20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
6.3	4.3	2.0	
CHECK APPROPRIATE BOX(ES)	· · · · · · · · · · · · · · · · · · ·		
(a) Human subjects	🖄 (b) Human tissues	(c) Neither	
(a1) Minors			В
(a2) Interviews			-
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provid	led.)	:
			1

These studies involve the generation and utilization of monoclonal antibodies (MAbs) to identify and characterize human carcinoma associated antigens and differentiation antigens of mammary and colonic epithelium. These MAbs are being used to better understand the cell biology and pathogenesis of human carcinomas, and to provide reagents for use in several aspects of the management of human carcinomas. These include: detection of occult tumor cells; further defining the degree of differentiation of "normal", dysplastic, and carcinoma cell populations; serum antigens assays; and radiolocalization of primary and metastatic carcinoma lesions in situ (and potentially therapy) using radiolabeled monoclonal immunoglobulins and fragments., These studies are divided into four areas of investigation: (I) The generation and characterization of an MAb that defines a novel tumor associated antigen (TAG-72); (II) The development and characterization of MAbs to a repertoire of epitopes on carcinoembryonic antigen (CEA) which are differentially expressed among carcinoma cell populations; (III) The generation and characterization of MAbs to proteins associated with metastatic cell populations, and (IV) The definition and characterization of breast and colon differentiation antigens.



			PROJECT NUMBER
DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	
NOTICE OF INT	TRAMURAL RESEARCH PROJE	CT	
			ZO1 CB 09009-06 LTIE
PERIOD COVERED			
October 1, 1986 to Sept. TITLE OF PROJECT (80 characters or less	ember 30, 1987 s. Title must fit on one line between the border	s.)	
Augmentation of Tumor A PRINCIPAL INVESTIGATOR (List other pro	ntigen_Expression ofessional personnel below the Principal Investi	igator.) (Name, title, lebora	tory, and institute effiliation)
John W. Greiner	Cancer Expert	LTIB, DCH	BD, NCI
Fiorella Guadagni	Visiting Fellow	LTIB, DCE	BD, NCI
Jeffrey Schlom	Chief	LTIB, DCE	BD, NCI
COOPERATING UNITS (if any)			
D. S. Pestka, Institute	of Molecular Biology, Ho	ffman La Roche	, Nutley, NJ;
Dr. P. Fisher, Columbia	University, New York, NY	;	
Dr. P. Noguchi, Bureau	of Biologics, FDA		
Laboratory of Tumor Imm	unalogy and Rialogy		
SECTION	anorogy and brorogy		
Experimental Oncology Selection	ection		
NCT NTU Pathagia Mar	-1		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
3.4	2.4	1.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	(b) Human tissues	(c) Neither	
	· · · · · · · · · · · · · · · · · · ·		
SUMMABY OF WORK (lise standard unre	duced type. Do not exceed the space provideo		B
		••7	
Antigan hataroganaity W	ithin human tumor coll no	pulations can	be attributed
somewhat to the intrins	ic ability of the cells t	o modulate the	level of
expression of certain t	umor antigens by: 1) cel	1 cycle kineti	cs 2) clonal
variability and 3) cell	-to-cell communication in	three-dimensi	onal organoids.
Studies were carried ou	t to establish that exoge	nously adminis	tered biological
response modifiers, suc	h as the recombinant huma	n interferons,	can overide
the intrinsic modulation	n of these antigens resul	ting in an inc	rease in the
percent of the cell pop	ulation expressing the mo	noclonal-antit	oody (MAb) defined
tumor antigen as well as	s increasing the amount o	t antigen expr	essed per cell.
Utilizing eight differe	nt human breast tumor cel	I lines, it wa	is shown that
were effective in augme	nting several MAb-defined	cell surface	tumor antigens In
addition, alpha interfe	ron was shown to increase	the expression	on of TAG-72 on human
breast tumor cells isol.	ated from a patient's ple	ural effusion.	Additional studies
demonstrated that the in	n vivo administration of	recombinant le	ukocyte (clone A)
interferon was effective	e in increasing the amoun	t of tumor ant	igen expressed by a
human colon xenograft i	n situ and also augmented	the localizat	ion of a radiolabeled
MAb to the tumor site.	Thus, these studies may	lead to the ne	w strategies designed
to use recombinant inte	rieron as an adjunct for	MAD-Dinding to	numan carcinoma
cerr population.			



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT	NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT				
			Z01 CB	05233-06 LTIB
PERIOD COVERED October 1, 1986 to Septe	mber 30, 1987			
TITLE OF PROJECT (80 cheracters or less Purification of and Radi	. Title must fit on one line between the borde .oimmunoassays for Human	<sup>ws.)</sup> Carcinoma Asso	ciated	Antigens
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and ins	stitute affiliation)
David Colcher	Supv. Microbiologist	LTIB, D	CBD. NO	CI
Donald Sheer	STP Fellow	LTIB, D	CBD, NO	CI
Jeffrey Schlom	hief	LTIB, D	CBD, NO	CI
Patrizia Ferrone	/isiting Fellow	LTIB, D	CBD, NO	CI
COOPERATING UNITS (if any)				
LAB/BRANCH Laboratory of Tumor Immu	nology and Biology			
SECTION Experimental Oncology Se	ection			
NCI, NIH, Bethesda, Mary	rland 20892			
TOTAL MAN-YEARS: 1.7	PROFESSIONAL: 1.7	OTHER: 0		
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors	🖄 (b) Human tissues 🗌	(c) Neither		
(a2) Interviews	· · · · · · · · · · · · · · · · · · ·	A		
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	d.) r associated an	tigen	(termed
TAG $-72$ ) identified by mo	onoclonal antibody B72.3	has been estab	lished	The
distribution of TAG-72 i	n human tissues has been	h shown to be h	ighly s	specific for
carcinomas with no signi	ficant reactivity to not	rmal tissues.	The RIA	A was used
to examine sera from pat	ients with colorectal ca	arcinomas, othe	r malig	gnancies and
normal sera. A mean of	2.2 units/ml of TAG-72 v	was found in th	e norma	al sera. When
a cut-off level of 3 sta	indard deviations above t	the mean level	of TAG-	-72 found in
normals is used, no path	ent with inflammatory d	Lsease or other	benigi	n colon
advanced colon cancer pa	tients and patients with	other carcino	mas we	re positive
for TAG-72. A second RI	A using a solid-phase ma	atrix to establ	ish a r	multi-
determinant assay using	radiolabeled B72.3 was a	also establishe	d. Th:	is assay
detected significant (>IOU/ml) in approximately 60% of patients with colo-				
rectal carcinomas. Comparison of the TAG-72 levels in sera with antigens				
recognized by the monocl	onal antibodies current.	ly used to scre	en sera	a of carci-
noma patients clearly de	monstrated that TAG-72 :	is different fr	om the	other
by the commercially avai	lable MAb RIAs.	sera where no a	neigen	is delected
TAC-72 has been purified	from extracts of a hum	an color corcin	oma voi	nograft in
athymic mice using molecular has an apparent molecular	ular sieving and antiboder weight of $\geq 10^6$ dalton	dy affinity chr ns, and has man	omatog: y prope	raphy. It erties
similar to mucins.				



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC H	EALTH SERVICE	PROJECT NU	IMBER	
NOTICE OF INT	TRAMURAL RESEARCH PRO	JECT			
25000 0015050			Z01 CB 0	9008-06 LTIB	
October 1, 1986 to Sept.	ember 30, 1987				
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the bor	rders.)		ntibodios	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inv	vestigator.) (Name, title, labora	tory, and institu	ute affiliation)	
			lory, and monta		
David Colcher S	upv. Microbiologist	LTIB,	DCBD, N	CI	
Mario Roselli V	lsiting rellow	LTIB,	DCBD, N		
Patrizia Ferrone V	isiting Fellow	LIID, LTIB	DCBD, N		
			<i>bobb</i> , N		
COOPERATING UNITS (if any)	cology DCT NCL				
A. Keenan and S. Larson	, Department of Nuclear	Medicine, CC. N	IH:		
J. Carrasquillo, Departs	ment of Nuclear Medicin	e, CC, NIH	·,		
LAB/BRANCH Laboratory of Tumor Immu	unclogy and Biology				
SECTION					
Experimental Oncology Se	ection				
INSTITUTE AND LOCATION NCI. NIH. Bethesda, Mary	vland 20892				
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:			
2.5	2.0	0.5			
CHECK APPROPRIATE BOX(ES)					
(a) Human subjects	(b) Human tissues	(c) Neither	٨		
(a2) Interviews					
SUMMARY OF WORK (Use standard unred	duced type. Do not exceed the space provi	ded.)			
Monoclonal antibody B72	.3 binds to human breas	t and colon tumo	r associ	ated	
antigens. 1gG was purit	fied and radiolabeled w	ith 1-125, and I	-131 and	In-111	
into athymic mice bearing	activity. The radioial	an colon tumors	or an an	tigen-	
negative melanoma as a r	negative control. With	iodinated B72.3	IgG act	ivity in	
the tumor rose for the t	first 2 days and remain	ed constant over	the 19	day	
period of study. Tumor-	-to-normal tissue ratios	s rose over this	period	of time	
with ratios of approxima	ately 18:1 for liver, s	pleen and kidney	at 7 da	ys. At	
19 days approximately 40	0% of the radiolabeled	B72.3 IgG was fo	und in t	he tumor.	
IgG and radiolabeled wit	A, SUN-BZ-EDIA and SUN	biodistribution	tached t	o B/2.3	
were performed using al	1 four chelates showed	that the tumor u	ntake of	radio-	
label expressed as a per	rcentage of the injecter	d dose per gram	was very	similar	
when three of the chelat	tes were ligated to the	B72.3 IgG (30%	ID/g).	The	
uptake by normal organs,	uptake by normal organs, especially the liver, was greater when MA-DTPA, CA-DTPA,				
and SCN-Bz-EDTA chelate-	-B72.3 IgG was used in	comparison to th	at found	with	
B72 3-SCN-BZ-DIPA	Tumor to liver ratios	rose over time w ly 5.1 by 72b	The ture	In-111-	
liver ratios for the oth	her MAb-chelate complexi	es, on the other	hand. r	anged	
from only 1.3:1 to 2.5:1	1. Tumors could easily	be identified i	n scinti	graphic	
images with all the chel	trom only 1.3:1 to 2.5:1. Tumors could easily be identified in scintigraphic				
lation of activity in th	late-antibody complexes	<ul> <li>However, a pr</li> </ul>	ogressiv	e accumu-	
seen with the MA-DTPA, (	he abdominal organs, pro	<ul> <li>However, a pr edominantly in t</li> </ul>	ogressiv he liver	e accumu- , was	
seen with the MA-DTPA, CA-DTPA and SCN-Bz-EDTA chelate-antibody complexes.				e accumu- , was xes.	
This uptake was very pro	he abdominal organs, pro- CA-DTPA and SCN-BZ-EDTA ominent with these chela diected with B72.3-SCN-1	<ul> <li>However, a pr edominantly in t chelate-antibod ate-MAb complexe Bz-DTPA.</li> </ul>	ogressiv he liver y comple s but wa	e accumu- , was xes. s virtual-	



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE				
NOTICE OF INTRAMURAL RESEARCH PROJECT				
			Z01 CB 09018-03 LTIB	
PERIOD COVERED				
October 1, 1986 to Septe	ember 30, 1987			
Clinical Trials with Pa	intermustrit on one line between the border	s.)		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Invest	gator.) (Name title lebora	fory and institute affiliation)	
		geteri) (H2Het, Hite, H20H2		
Jeffrey Schlom	Chief	LTIB, DCH	3D, NCI	
David Colcher	Supv. Microbiologist	LTIB, DCH	BD, NCI	
Jean Simpson	Medical Staff Fellow	LTIB, DCH	3D, NCI	
Mario Roselli	Visiting Fellow	LTIB, DCH	3D, NCI	
Alfredo Molinolo	Visiting Fellow	LTIB, DCH	3D, NCI	
COOPERATING UNITS (if any)				
S. Larson, Chief, Nuclea	ar Medicine, NIH			
W. Sindelar, Chief, Cold	orectal Surgery, Surgery	Branch, NCI		
G. Bryant, Laboratory of	F Pathology, NCI			
LAB/BRANCH				
Laboratory of Tumor Imm	inology and Biology			
SECTION				
Experimental Uncology Se	ection			
NCL. NIH. Bethesda Mary	and 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
2.8	1.8	1.0		
CHECK APPROPRIATE BOX(ES)				
(a) Human subjects	(b) Human tissues	(c) Neither		
(a1) Minors	,	A		
		()		
Accurate detection and	anatomic localization of	both primary a	and metastatic	
lesions remains one of t	the major problems in the	management of	most human	
carcinomas. We have red	cently initiated clinical	trials at the	NIH Clinical	
Center to detect and loc	calize colorectal carcino	ma lesions usi	ng radiolabeled	
monoclonal antibody (MA)	b) B72.3. Parameters that	t are being sy	stematically	
investigated concerning	both the efficiency of M	Ab localizatio	on and the	
efficiency of gamma scar	nning of carcinoma lesior	s include: (a)	effect of	
MAb dose and specific ac	ctivity of radionuclide of	oupled MAb; (b	) comparison	
of the use of intact lg(	$f_{i}$ , $f(ab')_{2}$ , and $Fab'; (c)$	choice of rad	lionuclide;	
of the tumor mass such a	as antigen content: (f) t	he presence of	circulating	
antigen: (g) the present	e and/or absence of huma	n anti-murine	Ig antibodies:	
(h) metabolism of MAb ar	d fragments; (i) combina	tions of MAbs.	It is hoped	
that these studies will	also aid in establishing	a rational ba	sis for the	
subsequent therapeutic u	use of a particular MAb,	either coupled	to toxins,	
via effector cell-mediat	ed or complement-mediate	d mechanisms,	or using MAbs	
radiolabeled with one of	a variety of isotopes.	This latter g	oal can be	
accomplished by direct a	analyses of biopsy materi	al (both tumor	and normal	
ization index" or action	receiving radiolabeled MA	(i a the ret	te radiolocal-	
amount of MAb bound furi	compl per gram of tumor	tissue to that	bound per	
gram of normal tissues).	. cpmj per gram or cdmor	crosue co cilat	bound per	



PROJECT NUMBER DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT Z01 CB 09012-04 LTIB PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Monoclonal Antibodies to Detect Occult Carcinoma Cells PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) Jean Simpson Medical Staff Fellow LTIB, DCBD, NCI Noriaki Ohuchi Visiting Fellow LTIB, DCBD, NCI Alfredo Molinolo Visiting Fellow LTIB, DCBD, NCI Kai Chang Visiting Fellow LTIB, DCBD, NCI Jeffrey Schlom Chief LTIB, DCBD, NCI COOPERATING UNITS (if any) Drs. W. Johnston and C. Szpak, Department of Pathology, Duke Univ., Durham, NC: Dr. F. Gorstein, Department of Pathology, Vanderbilt Univ., Nashville, TN LAB/BRANCH Laboratory of Tumor Immunology and Biology SECTION Experimental Oncology Section INSTITUTE AND LOCATION NCI, NIH, Bethesda, Maryland 20892 TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 1.2 1.2 0 CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors A (a2) Interviews SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Monoclonal antibodies (Mabs) have been utilized with immunohistochemical methods for the (a) detection of occult carcinoma in surgical and cytology preparations. (b) phenotyping of malignant cell populations, (c) differentiation of histologic tumor types, and (d) identification of various cellular products. Mabs with selective reactivity against tumor-associated antigens have specifically been adapted for use with cytologic preparations including cytospins, membranes, and fine needle aspiration biopsies (FNAB) for the detection and differentiation of carcinomas from benign cell types and other cancerous lesions.



DEPARTMENT OF HEALTH		I PPO IECT NI IMPED
	H AND HUMAN SERVICES - PUBLIC HEAL	TH SERVICE
NOTICE OF I	NTRAMURAL RESEARCH PROJEC	ст
		701 CB 09021-01
ERIOD COVERED		
October 1, 1986 to	September 30, 1987	
TLE OF PROJECT (80 characters or I	less. Title must fit on one line between the borders.	)
Molecular Cloning o	f Tumor Associated Antigens	
RINCIPAL INVESTIGATOR (List other	professional personnel below the Principal Investig	ator.) (Name, title, laboratory, and institute affiliation)
Judy Venter	Europet	
Rosette Tran	Visiting Follow	LTIB, DCBD, NCI
Jian Xiang	Visiting Fellow	LIIB, DOBD, NOI
Shannon Dixon	Microbiologist	LTIB, DCBD, NCI
	0	, 2022, NOT
OPERATING UNITS (if any)		
B/BRANCH		
Laboratory of Tumor	Immunology and Biology	
Experimental Uncolo	gy Section	
NCI NIH Bethesda	Maryland 20802	
TAL MAN-YEARS:	PROFESSIONAL:	DTHER:
2.0	1.5	0.5
ECK APPROPRIATE BOX(ES)		
(a) Human subjects	🗌 (b) Human tissues 🗵	(c) Neither
(a) Human subjects (a1) Minors	☐ (b) Human tissues 🛛	(ç) Neither
(a) Human subjects (a1) Minors (a2) Interviews	☐ (b) Human tissues 🗵	(ç) Neither
(a) Human subjects (a1) Minors (a2) Interviews (a2) OF WORK (Use standard units)	(b) Human tissues I	(ç) Neither
(a) Human subjects (a1) Minors (a2) Interviews (A2) Interviews (MMARY OF WORK (Use standard un	(b) Human tissues	(c) Neither
(a) Human subjects (a1) Minors (a2) Interviews (A3) Interview	(b) Human tissues irreduced type. Do not exceed the space provided, all antibody technology has at is a feature of burgers.	allowed the identification and
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>MMARY OF WORK (Use standard un The use of monoclona partial characteriz, differentiation and the standard st</li></ul>	□ (b) Human tissues weduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as ation of human carcinoma-as	allowed the identification and sociated antigens as well as
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un The use of monoclona partial characteriz differentiation ant powerful tools for	□ (b) Human tissues inveduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnostic and ma	allowed the identification and sociated antigens as well as epithelium. MAbs provide
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews MMARY OF WORK (Use standard un The use of monoclona partial characteriz differentiation ant powerful tools for the They have been used	□ (b) Human tissues weduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic nurposes for the detection
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un partial characteriz differentiation ant powerful tools for They have been used of tumor associated	(b) Human tissues → weduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio-
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews MMARY OF WORK (Use standard un partial characteriz differentiation ant powerful tools for They have been used of tumor associated localization of prin	(b) Human tissues → reduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews MMARY OF WORK (Use standard un partial characteriz differentiation ant powerful tools for They have been used of tumor associated localization of prin radiolabeled monocle	□ (b) Human tissues weduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un partial characteriz differentiation ant powerful tools for They have been used of tumor associated localization of prin radiolabeled monoclo regime is being deve	□ (b) Human tissues weduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped.	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un partial characteriz: differentiation ant: powerful tools for un They have been used of tumor associated localization of prin radiolabeled monoclo regime is being deve	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped.	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy
<ul> <li>(a) Human subjects         <ul> <li>(a1) Minors</li> <li>(a2) Interviews</li> </ul> </li> <li>MMARY OF WORK (Use standard un partial characteriz, differentiation ant powerful tools for they have been used of tumor associated localization of printradiolabeled monocloreregime is being development.</li> </ul>	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul	allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the
<ul> <li>(a) Human subjects</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>MMARY OF WORK (Use standard un partial characteriz, differentiation ant; powerful tools for of They have been used of tumor associated localization of prin radiolabeled monoclo regime is being deve</li> <li>The overall goal of genes that encode the</li> </ul>	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul he tumor associated antigen	x) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un partial characteriz differentiation ant: powerful tools for They have been used of tumor associated localization of prin radiolabeled monocld regime is being deve The overall goal of genes that encode the recently initiated standard standard standard and the standard stand	(b) Human tissues ■ Inveduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnostis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul the tumor associated antigen studies for the cloning of	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have IAG-72. These studies
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews MMARY OF WORK (Use standard un The use of monoclone partial characterized differentiation ant: powerful tools for n They have been used of tumor associated localization of prin radiolabeled monoclo regime is being deve The overall goal of genes that encode the recently initiated as include: 1) the co	(b) Human tissues → reduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosts and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul ne tumor associated antigen studies for the cloning of onstruction of cDNA librari.	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have FAG-72. These studies es from LSI74 mRNA in several
(a) Human subjects          (a1) Minors         (a2) Interviews         MMARY OF WORK (Use standard under the standard und	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosts and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul this project is to molecul thus for the cloning of onstruction of cDNA librari. aryotic expression vectors.	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have TAG-72. These studies es from LSI74 mRNA in several 2) the cotransfection
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard un partial characterized differentiation ant: powerful tools for monoclour They have been used of tumor associated localization of print radiolabeled monoclour regime is being deve The overall goal of genes that encode th recently initiated as include: 1) the component prokaryotic and euka of LS174 tumor DNA was	(b) Human tissues → reduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosts and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul ne tumor associated antigen studies for the cloning of onstruction of cDNA libraria aryotic expression vectors. with plasmids carrying drug	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have TAG-72. These studies es from LS174 mRNA in several 2) the cotransfection selectable markers into
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews MMARY OF WORK (Use standard un partial characterized differentiation ant: powerful tools for to They have been used of tumor associated localization of print radiolabeled monocle regime is being deve The overall goal of genes that encode the recently initiated so include: 1) the co prokaryotic and euka of LS174 tumor DNA to mammalian cells. 3)	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosts and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul he tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug ) the construction of olig	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have FAG-72. These studies es from LS174 mRNA in several 2) the cotransfection selectable markers into omeric probes to the
(a) Human subjects (a1) Minors (a2) Interviews (a2) Interviews (a2) Interviews (a2) Interviews (a2) Interviews (a2) Interviews (a3) (a2) (a3) (a3) (a3) (a3) (a3) (a3) (a3) (a3	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnostis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul he tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug ) the construction of olig TAG-72 for use as hybridiz.	Ac) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have FAG-72. These studies es from LS174 mRNA in several 2) the cotransfection selectable markers into omeric probes to the ation probes.
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard under the search of monoclonary partial characterized differentiation ant: powerful tools for the the search of t	(b) Human tissues → reduced type. Do not exceed the spece provided, al antibody technology has ation of human carcinoma-as igens of mammary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul ne tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug ) the construction of olig TAG-72 for use as hybridiz.	Ac) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have TAG-72. These studies es from LSI74 mRNA in several 2) the cotransfection selectable markers into omeric probes to the ation probes.
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard under the search of monoclonary partial characterized differentiation anterpowerful tools for the the search of t	(b) Human tissues → reduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mamary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr eloped. this project is to molecul ne tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug ) the construction of olig TAG-72 for use as hybridiz. have recently been initiate plon and breast tumor cell	Ac) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have IAG-72. These studies es from LSI74 mRNA in several 2) the cotransfection selectable markers into omeric probes to the ation probes. d to study the regulation of lines after interferon
(a) Human subjects (a1) Minors (a2) Interviews MMARY OF WORK (Use standard under the second secon	□ (b) Human tissues weduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mamary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr aloped. this project is to molecul the tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug the construction of olig TAG-72 for use as hybridiz. NA probes have heen devel	Ac) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have FAG-72. These studies es from LS174 mRNA in several 2) the cotransfection selectable markers into omeric probes to the ation probes. d to study the regulation of lines after interferon poed to use in Northern blot
(a) Human subjects          (a1) Minors         (a2) Interviews         MMARY OF WORK (Use standard under the standard und	(b) Human tissues → reduced type. Do not exceed the space provided, al antibody technology has ation of human carcinoma-as igens of mamary and colon use in the diagnosis and ma for screening and diagnost antigens in blood serum as mary and metastatic carcino onal immunoglobulins and fr aloped. this project is to molecul ne tumor associated antigen studies for the cloning of onstruction of cDNA librari. aryotic expression vectors. with plasmids carrying drug ) the construction of olig TAG-72 for use as hybridiz. have recently been initiate blon and breast tumor cell DNA probes have been devel selected mRNA from these ce	(c) Neither allowed the identification and sociated antigens as well as epithelium. MAbs provide nagement of human carcinomas. ic purposes for the detection says, and for the radio- ma lesions in-situ. Using agments, a powerful therapy arly clone and identify the s TAG-72 and CEA. We have TAG-72. These studies es from LS174 mRNA in several 2) the cotransfection selectable markers into omeric probes to the ation probes. d to study the regulation of lines after interferon oped to use in Northern blot 11 lines.



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	I HOULDEN	
NOTICE OF INT	RAMURAL RESEARCH PRO.	JECT		
			Z01 CB 09017-03 LTIB	
PERIOD COVERED				
October 1, 1986 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the bord	lers.)		
Oncogene Expression in 1	Human Carcinomas			
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inve	stigator.) (Name, title, lebora	tory, and institute affilietion)	
D todađa Name Nasl				
Patricia Horan Hand	Chemist	LTIB	, DCBD, NCI	
Jeirrey Schlom	Chier	LTIB	, DCBD, NCI	
Norlaki Unuchi	Visiting Fellow	LTIB	, DCBD, NC1	
COOPERATING UNITS (if any)				
LAB/BBANCH				
Laboratory of Tumor Imm	unalogy and Biology		-	
SECTION	Indidgy and Bidiogy	······································		
Experimental Oncology Se	ection			
INSTITUTE AND LOCATION	section			
NCT NIH Bethesda Mary	vland 20802			
TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:		
4 /5	2 3	2.2		
CHECK APPROPRIATE BOX(ES)	2•5	2.02		
(a) Human subjects	(b) Human tissues	(c) Neither		
(a1) Minors	- (-,	- (-)		
(a2) Interviews				
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provid	ed.)		
Several distinct and his	sh-conserved genes comp	rise the ras ge	ne family of rodents	
and humans, i.e., rodent	t Harvey and Kirsten, at	d human Harvey	Kirsten and neuro-	
blastoma. Transformatic	on either by a point-mu	itation resulti:	, distant and heuro	
amino acid of the 21 kD	a ras gene product (p21)	or by increase	and expression of rac	
n21 has been demonstrat	ted to be mediated by my	mbors of this	sed expression of ras	
reported the development	t of direct binding light	id competition	radioimminoaccauc for	
the detection and quant:	itation of the ras oncou	tene and proto-	programe products	
Using these radioimmuno:	accave and rac p21 purif	ied from Feche	richia coli contain-	
ing the full-length T24	mutant human Harvoy rad	gano protoin	reduct as a standard	
we have defined the act	an amount of ras p21 p	er ug of total	cellular protein or	
per cell, in various ray	s transformed and "norm:	al" mammalian c	all lines. Absolute	
levels of Ha-ras p21 has	ve also been determined	in human breast	t and colon carcinomas	
benign lesions, and/or t	their respective normal	tissues using	the radioimmunoassays.	
Enhanced Ha-ras expressi	ion was documented in 60	5% of breast and	1 100% of colon car-	
cinomas as compared with	b their normal counterpart	arte with level	le in breast carcin-	
canonas as compared with their normal counterparts, with levels in Dreast carcin-				
of the breast and colon	also contained elevated	Ha-ras n21.	Relative levels of	
Harras p21 expression	detected by competition	RIA correlate	d with percent Ha-ras	
n21 positive colle co de	etermined by immunchiet	chemical account	e. Heing liquid	
competition RTA and imm	inobistochemical accave	it has been of	hown that levels of	
ras p21 expression did .	not always correlate bet	ween primary of	nd metastatic colon	
lesions of the same nati	ient. The use of the a	antitativo RTA	and semiquantitative	
immunohistochemical acc	ave in concert with an	VA probes for i	dentification of	
specific ras pointmitat	ad oncogones or protoon	A PLODES TOL I	a provide the means	
for definitive quantitat	tive analyses of rac protocold	in human care	inomae and bonign	
lesions.	ive analyses of ias p2	L III Human Care.	rnomas and benign	



	PROJECT NUMBER				
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SEI	RVICE				
NOTICE OF INTRAMURAL RESEARCH PROJECT					
	201 CB 08226-11 LTIB				
October 1, 1986 to September 30, 1987					
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Hormones and Growth Factors in Development of Mammary	y Glands & Tumorgenesis				
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (N	ame, title, laboratory, and institute affiliation)				
B.K. Vonderhaar Research Chemist	LTIB, DCBD, NCI				
C. Dati Visiting Fellow	LTIB, DCBD, NCI				
E. Ginsburg Biologist	LTIB, DCBD, NCI				
COOPERATING UNITS (# any) Dr. Kathleen Antol, Clarke College Dr. Sandra Haslam, Michigan State University, East La Dr. Randy Whitcomb, Developmental Endocrinology, NIC	, Dubaque, IA ansing, MI HD				
Dr. Susan Bates, Pediatrics Branch, NCI					
LAB/BRANCH Laboratory of Tumor Immunology and Biology					
SECTION Experimental Oncology Section					
NSTITUTE AND LOCATION NCI, NIH Bethesda, Maryland 20892					
TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 0+6 O+35	0.25				
CHECK APPROPRIATE BOX(ES) X □ (a) Human subjects ⊠ (b) Human tissues □ (c) Ne □ (a1) Minors □ (a2) Interviews	either B				
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)					
This project is designed to understand the role of hormones and growth factors in normal mammary gland development and differentiation and in development growth and maintenance of mammary tumors. Studies include: 1) examination of the role of epidermal growth factor and mammary gland-derived growth factors in lobuloalveolar development of the mouse mammary gland, 2) defining the roles of estrogen and progesterone in priming the mammary tissue prior to whole organ culture to determine their effects on induction of EGF receptors, mammary gland-derived growth factor receptors and the production of growth factors by the animals, 3) examine the hormonal conditions <u>in</u> <u>vitro</u> which induce production of autocrine growth factors by normal mammary tissue and breast cancer cell lines, 4) examine the effect of sialadenectomy on mammary tumor incidence and growth in mice as well as production of pre- neoplastic hyperplastic alveolar modules.					
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DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEALTH	SERVICE PROJECT NUMBER		
NOTICE OF INT	RAMORAL RESEARCH PROJECT	701 CB 08274-06 ITTB		
PEBIOD COVERED		201 0b 002/4 00 HIID		
October 1, 1986 to Ser	tember 30, 1987			
TITLE OF PROJECT (80 cheracters or less	Title must fit on one line between the borders.)			
Regulation of Lactoger	ic Hormone Receptors in Mam	mary Tissue		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Investigator.	) (Name, title, laboratory, and institute affiliation)		
		· · · · · · · · · · · · · · · · · · ·		
B.K. Vonderhaar	Research Chemist	LTIB, DCBD, NCI		
Suzanne Ziska	Staff Fellow	LTIB, DCBD, NCI		
Ratna Biswas	Visiting Fellow	LTIB, DCBD, NCI		
Claudio Dati	Visiting Fellow	LTIB, DCBD, NCI		
Erika Ginsburg	Biologist	LTIB, DCBD, NCI		
COOPERATING UNITS (if any)				
Dr. Rhoda Maneckjee, M	ledical Oncology Branch, NCI	, Bethesda, MD		
Dr. Anthony Capuco, US	DA, Beltsville, MD			
LAB/BRANCH	muncleary and Picleary			
Laboratory of lumor in	munology and Biology			
Experimental Oncology	Section			
	Section			
NTH NCT Bethesda Ma	ryland 20802			
TOTAL MAN YEARS		50.		
2.4	1.9	0.5		
CHECK APPBOPBIATE BOX(ES)		0.5		
(a) Human subjects	$ \overline{X} $ (b) Human tissues $\Box$ (c)	Neither		
(a1) Minors				
(a2) Interviews	/	В		
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provided.)			
This project is design	ed to evaluate the nature of	E lactogenic hormone		
receptors and the fact	ors (including other hormone	es) which affect binding		
of the hormone to this	molecule. Studies include	1) purification of the		
receptor from human ti	ssue and preparation and cha	aracterization of an		
antibody against it; 2	) examination of the nature	of the subunits of the		
receptor, 3) character	ization of the nature of the	e interaction of Tamoxifen		
with membrane bound re	ceptors related to the lacto	ogen receptor, and 4)		
define the relationshi	p of monoclonal antibody B6.	.2 to human lactogenic		
hormone receptors.				
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DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBL	IC HEALTH SERVICE	PROJECT NOMBER
NOTICE OF IN	TRAMURAL RESEARCH	PROJECT	
			Z01 CB 09022-01 LTIB
PERIOD COVERED	ember 30, 1987		
TITLE OF PROJECT (80 characters or les	s. Title must fit on one line between ti	he borders.)	
Cytoskeletal Proteins i	n Oncogenic Transfor	mation and Human Ne	eoplasia
PRINCIPAL INVESTIGATOR (List other pr	ofessional personnel below the Princip	pal Investigator.) (Nama, title, labore	tory, and institute affiliation)
Harbart I Cooper	Chief Coll & Moles	Phys. Section 1	
Basudev Bhattacharva	Visiting Fellow	Inys, section 1	LTIB, DCBD, NCI
			iiib, bobb, noi
COOPERATING UNITS (if any)	· · · · ·		
Laboratory of Tumor Imm	unology and Biology		
SECTION			
Cellular & Molecular Ph	ysiology Section		
INSTITUTE AND LOCATION	1 1 00000		
NCI, NIH, Bethesda, Mar	yland 20892		
2.2	1.7	0.5	
CHECK APPROPRIATE BOX(ES)	1	0.5	
(a) Human subjects	🖾 (b) Human tissues	(c) Neither	
(a1) Minors			В
		and the state	
SUMMARY OF WORK (Use standard unre-	uuced type. Do not axceed the space	provided.)	
Studies have continued	on the role of tropo	myosin (TM) suppres	sion in
neoplastic transformati	on. The mechanism o	f suppression of Th	1 synthesis by
retroviral oncogene exp	ression is being exp	lored. We have obt	ained evidence
that IM suppression in	fibroblasts transfor	med by retroviral o	oncogenes is
querce of oncogene expr	ession. In mouse ma	win factor produced	l as a conse-
tutively expressing act	ivated c-Ha-ras, Tm	synthesis was not a	suppressed, but
accumulation of newly s	ynthesized TM was su	ppressed, apparent]	ly due to
accumulation of actin a	nd TM in abnormal ra	tios in the cytoske	eleton. TM
expression was also stu	died in a panel of e	stablished human bu	east cancer
observed in the tumor of	case abnormalities 1	n tropomyosin expre	of TM ovpros-
sion may be a frequent	event in human neopl	asia.	of in expres-
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	•		
	685		



DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PUE	BLIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT			
			201 CB 09006-05 LTIB
October 1, 1986 to Septe	mber 30, 1987		
TITLE OF PROJECT (80 characters or less	Title must fit on one line between	the borders.)	rosolin
PRINCIPAL INVESTIGATOR (List other pro	ofessionel personnel below the Princ	upal Investigator.) (Name title I	aboratony and institute attiliation)
	of Coll and Malas	Phys. Cost. I	
Richard Braverman Che	er, cell and molec	. Phys. Sect. L	TIB, DCBD, NCI
			, ,
COOPERATING UNITS (if any)			
Laboratory of Tumor Imm	mology and Biology		
SECTION Cellular & Molecular Phy	vsiology Section		
NCI, NIH, Bethesda, Mary	/land 20892		
TOTAL MAN-YEARS: 1 • 8	PROFESSIONAL: 0.3	OTHER:	5
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects			<b>.</b>
(a2) Interviews			В
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the spac	ce provided.)	
Studies have continued o	on the unique phosp	hoprotein, pp17,	which undergoes
rapid phosphorylation in	HL60 promyelocyti	c leukemia cells	in response to
phorylated form of this	protein as a major	cytosolic protei	n of Mr 18.4K,
pI 5.9, and have named :	it 'prosolin'. With	hin 15 min of tre	atment of
HL60 cells with TPA near	ly 50% of pre-exis	ting prosolin is most significant	phosphorylated, biochemical
changes resulting from 2	TPA treatment in HL	-60 cells. Studi	es with
peripheral blood lympho	cytes and malignant	lymphoid cell li	nes suggest that
cells, while phosphoryla	associated with r.	apid growin of ne av be associated	with rapid cell
responses associated with	ch reduction of DNA	synthesis and ex	pression of
genes involved in differ	centiated cell func	tion. Amino acid	l sequencing and
cowa croning or prosorri	i ale in progress.		



DEPARTMENT OF HEALTH	ND HUMAN SERVICES - PUB	LIC HEALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH	PROJECT	
			Z01 CB 04848-16 LTIB
October 1, 1986 to Septe	ember 30, 1987		
TITLE OF PROJECT (80 cheracters or less RNA Tumor Viruses: Rep	Title must lit on one line between lication, Transformation	the borders.) ation, and Inhib:	ition in Cell Cultures
PRINCIPAL INVESTIGATOR (List other pro R. Bassin K. Yanagihara G. Tortora (half time) H. Cooper D. Salomon	dessional personnel below the Princ. Chief, Biochem. of Visiting Fellow Visiting Fellow Chief, Cell. and M Research Biologist	ipal Investigator.) (Nama, lutle, f Oncogenes Sect 101. Phys. Sect.	<pre>leboratory, and institute effiliation) LTTB, DCBD, NCI LTIB, DCBD, NCI</pre>
COOPERATING UNITS ( <i>if any</i> ) Dr. C. Lechene, Harvard Dr. S. Egan, University Dr. L. Benade, American	University, Boston, of Manitoba, Winnig Type Culture Collect	, Mass. Deg, Canada ction, Rockville	, MD.
LAB/BRANCH Laboratory of Tumor Immu	inology and Biology		
SECTION Biochemistry of Oncogene	es Secion		
INSTITUTE AND LOCATION NCI, Bethesda, Maryland	20892		-
TOTAL MAN-YEARS: 4 • 5	PROFESSIONAL: 2.0	OTHER: 2.5	
CHECK APPROPRIATE BOX(ES) (a) Human subjects (a1) Minors (a2) Interviews	🖾 (b) Human tissues	🗌 (c) Neither	В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space	e provided.)	
We are continuing to inv transformation by specifi and study of resistant of mutagens and new selecti resistant cell lines with do not block v-ras mRNA the transformation event worked out as have new s more resistant cells usi We are studying a new mu	vestigate the proper ic retroviral oncog cells have been deve ve procedures. Fol th Ha-MuSV, dot blot synthesis but must t. New methods for selective agents. We ang these methods.	tties of cells re genes. New metho eloped. This ind tlowing re-infect : analysis shows be altered at so developing resis We are currently duces solid tumon	esistant to ods for the selection cludes the use of new tion of the original that resistant cells ome point closer to stant cells have been trying to isolate
have worked with this is appears to be defective. is related to v-Ha- <u>ras</u> .	olate in cell cultu Initial dot blot	ire where it trat analysis indicat	nsforms cells and es that this isolate
			•



		U TU OFDUIOF	PROJECT NUMBER
DEPARTMENT OF HEALTH A	IND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	
NOTICE OF INT	RAMURAL RESEARCH PROJ	ECT	<b>FOI CD CO CO C C C C</b>
			201 CB 09003-05 LTIB
PERIOD COVERED October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or less Alpha Transforming Grow	. Title must lit on one line between the borde th Factors in Rodent and	Human Mammary	Carcinomas
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Inves	tigator.) (Name, title, labora	tory, and institute affiliation)
David Salomon	Supv. Kes. Biologist	LT.	LB, DCBD, NCI
Fortunato Clardiello	Visiting Fellow	LT	LB, DCBD, NCI
Repart Persia	Chief, Cell Cycle Reg.	Sec. LT.	LB, DCBD, NCI
Robert Gallabar	Chief, Biochemistry Un	cogenes Sec.LT	LB, DCBD, NCI
Kobert Callanan	Chief, Oncogenetics Se	C. LT	LB, DCBD, NCI
Herbert Cooper	Chief, Cellular and Mo	lecular LT	LB, DCBD, NCI
-Due	Physiology Sec.		
COOPERATING UNITS (if any) Dr.	Marc Lippman, Medicine B	ranch, NCI	
Dr. James lam, Dept. or	Blochemistry, Kockerell	er Univ., New	fork, NY
Dr. Kyk Derynck, Dept.	of Molecular Blology, Ge	nentech, inc.,	San Francisco, CA
Dr. Mary Lou McGeady, O	tsuka Pharmaceutical Co.	, Rockville, M	)
LAB/BRANCH Laboratory of Tumor Imm	unology and Biology		
SECTION Biochemistry of Oncogen	es Section		
INSTITUTE AND LOCATION NCI, NIH, Bethesda, Mar	yland 20892		·
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
3.0	2.0		1.0
CHECK APPROPRIATE POV(ES)			
CHECK AFFROFRIATE DUX(E3)			
(a) Human subjects	🗵 (b) Human tissues	(c) Neither	
(a) Human subjects (a1) Minors	🗵 (b) Human tissues	(c) Neither	
(a) Human subjects (a1) Minors (a2) Interviews	⊠ (b) Human tissues	(c) Neither	В
(a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred	(b) Human tissues	(c) Neither	B
(a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being contractions of the standard standard the standard standard the stand	(b) Human tissues	(c) Neither	B and role of alpha
Check Arrhoniate Subjects (a) Human Subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being c transforming growth fac mammary epithelial cell	(b) Human tissues	<ul> <li>(c) Neither</li> <li>d)</li> <li>e distribution</li> <li>nd malignant ro</li> <li>(a) anthracene</li> </ul>	B and role of alpha odent and human
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CHECK AFFROMINE BOLIES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unred Experiments are being co transforming growth fac mammary epithelial cell nitrosomethylurea (NMU) mare biologically active	(b) Human tissues Juced type. Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin a and immunoreactive αTG	<ul> <li>(c) Neither</li> <li>a)</li> <li>c) distribution</li> <li>nd malignant re</li> <li>(α) anthracene</li> <li>(</li></ul>	B and role of alpha odent and human (DMBA) and hree to seven-fold antable DMBA-I
CHECK AFFROMME BOALES)  (a) Human subjects (a1) Minors (a2) Interviews  SUMMARY OF WORK (Use standard unrec Experiments are being co transforming growth fac mammary epithelial cell nitrosomethylurea (NMU) more biologically activy	(b) Human tissues Huced type Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive αTG Moreover a spacific 5	<ul> <li>(c) Neither</li> <li>distribution</li> <li>nd malignant ra</li> <li>(α)anthracene</li> <li>omas possess the space</li> <li>Fs than transpice</li> </ul>	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ion could be determ
Check AFFROMATE BOJES (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being co transforming growth fac mammary epithelial cell nitrosomethylurea (NMU) more biologically activy and NMU-II carcinomas.	(b) Human tissues Waved type Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcine and immunoreactive αTG Moreover, a specific 5. and NUL tymore following	<ul> <li>(c) Neither</li> <li>a)</li> <li>b) distribution</li> <li>nd malignant ration</li> <li>(α) anthracene</li>     &lt;</ul>	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec-
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<pre>CHECK AFFORMATE DUBJECS (a) Hurnan subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being contransforming growth fac mammary epithelial cell: nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT </pre>	(b) Human tissues weed type. Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive αTG Moreover, a specific 5. and NMU tumors followin GF CDNA probes but not i	<ul> <li>(c) Neither</li> <li>a)</li> <li>c) distribution</li> <li>nd malignant re</li> <li>(α) anthracene</li> <li>(</li></ul>	B and role of alpha odent and human (DMBA) and nree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA c NMU-II tumors.
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<pre>Check Arrhoniate bolics) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being cd transforming growth fac mammary epithelial cell. nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epithelial epithelial </pre>	☑ (b) Human tissues Indeed type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been the tot the tot the tot the tot the tot the tot tot the tot tot the tot tot the tot tot tot the tot tot tot tot tot tot tot tot tot to	<ul> <li>(c) Neither</li> <li>a)</li> <li>a) distribution</li> <li>nd malignant responses</li> <li>a) anthracene</li> <li>a) anthracene</li> <li>b) mas possess the</li> <li>Fs than transposed</li> <li>Fs than transposed</li> <li>g hybridization</li> <li>n the DMBA-I or</li> <li>se in the level</li> <li>ss in the expression</li> <li>transformed with</li> </ul>	B and role of alpha odent and human (DMBA) and bree to seven-fold lantable DMBA-I les could be detec- n of poly A(+) RNA r NMU-II tumors. L of αTGFs in the ession of αTGF ith a point-mutated
Check Arrhonate boddes) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being co transforming growth fac mammary epithelial cell nitrosomethylurea (NMU) more biologically activ and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epi c-Ha-ras proto-oncogene	(b) Human tissues Waved type Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive αTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMuMG/ras <sup>H</sup> cells, beco	<ul> <li>(c) Neither</li> <li>distribution</li> <li>nd malignant ra</li> <li>(α)anthracene</li> <li>(α)anthr</li></ul>	B and role of alpha odent and human (DMBA) and bree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. I of aTGFs in the ession of aTGF ith a point-mutated o the growth promo-
Check Arrhon Bubjects (a) Human Subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being c transforming growth fac mammary epithelial cell. nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epi c-Ha-ras proto-oncogene ting effects of EGF bec.	(b) Human tissues Waved type Do not exceed the space provide onducted to determine th tors (αTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive αTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMuMG/ras <sup>H</sup> cells, beco ause these cells have an	<ul> <li>(c) Neither</li> <li>a)</li> <li>b) distribution</li> <li>nd malignant ration</li> <li>(α) anthracene</li>     &lt;</ul>	B and role of alpha odent and human (DMBA) and pree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. l of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize
<ul> <li>Check AFFNORTE DUBJECS</li> <li>(a) Human subjects</li> <li>(a1) Minors</li> <li>(a2) Interviews</li> <li>SUMMARY OF WORK (Use standard unred Experiments are being currents are being currents are being currents are being currents and primary epithelial cells nitrosomethylurea (NMU)</li> <li>more biologically active and NMU-II carcinomas.</li> <li>ted in the primary DMBA to a human and mouse aT</li> <li>Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epithelian</li> <li>c-Ha-ras proto-oncogene ting effects of EGF beca</li> <li>aTGF mRNA. Human breast</li> </ul>	★ (b) Human tissues Auced type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMUMG/ras <sup>H</sup> cells, beco ause these cells have an t cancer cell lines are	(c) Neither a) e distribution nd malignant ray (α) anthracene of a string of a str	B and role of alpha odent and human (DMBA) and nree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. l of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess
Check AFFNARE Subjects (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being currents are being currents are being currents are being currents and prime biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aTr Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epic-Ha-ras proto-oncogene ting effects of EGF bec. aTGF mRNA. Human breas aTGF mRNA. In MCF-7 ce	★ (b) Human tissues Auced type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMuMG/ras <sup>H</sup> cells, beco ause these cells have an t cancer cell lines are lls, the level of produc	(c) Neither a) e distribution nd malignant responses (α) anthracene (α) anthracene (α) anthracene b than transpipe 0 kb mRNA spec: g hybridization n the DMBA-I or se in the leve ss in the leve transformed with me resistant to increased capa also producing tion of αTGF at	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA c NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize aTGF and possess and TGFα mRNA
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Check AFFORMATE BOLLES) (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being c transforming growth fac mammary epithelial cell. nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aTI Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epi c-Ha-ras proto-oncogene ting effects of EGF beca aTGF mRNA. Human breas: aTGF mRNA. In MCF-7 cell monoclonal antibody agai cells in vitro. Elevato	(b) Human tissues	(c) Neither a) e distribution nd malignant regression (α) anthracene omas possess the second sec	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I les could be detec- n of poly $A(+)$ RNA r NMU-II tumors. l of $\alpha$ TGFs in the ession of $\alpha$ TGF lth a point-mutated b the growth promo- acity to synthesize $\alpha$ TGF and possess and TGF $\alpha$ mRNA strogens. In addition tibody or with a lt the growth of these IGF mRNA can be
CHECK AFFORMATE DUBJECS (a) Hurnan subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being currents transforming growth fac mammary epithelial cell. nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epi c-Ha-ras proto-oncogene ting effects of EGF bec. aTGF mRNA. Human breas: aTGF mRNA. In MCF-7 cell monoclonal antibody again cells in vitro. Elevated detected in approximate	E (b) Human tissues	(c) Neither a) e distribution nd malignant re (α) anthracene (α) anthracene o mas possess the stanspille 5 than transpille 0 kb mRNA spector g hybridization n the DMBA-I or se in the level ss in the level ss in the level ss in the level transformed with me resistant to increased capa also producing tion of αTGF are cked by anti-es -human TGFα are tor will inhibitive αTGF and α' breast carcinor	B and role of alpha odent and human (DMBA) and pree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NU-II tumors. l of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess nd TGFα mRNA strogens. In addition ntibody or with a lit the growth of these IGF mRNA can be mas. There is a
Check AFFORMATE DUBJECS          (a) Human subjects         (a1) Minors         (a2) Interviews         SUMMARY OF WORK (Use standard unred Experiments are being currents and primary epithelial cells in itrosomethylurea (NMU)         more biologically active and NMU-II carcinomas.         ted in the primary DMBA to a human and mouse aT         Ovariectomy produced a primary DMBA tumors whimRNA. Mouse mammary epitheliag effects of EGF becatGF mRNA. Human breas: aTGF mRNA. In MCF-7 cells arGF mRNA. In MCF-7 cells in vitro. Elevate detected in approximate strong positive correlation of the primare strong positive correlation.	★ (b) Human tissues Auced type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMUMG/ras <sup>H</sup> cells, beco ause these cells have an t cancer cell lines are lls, the level of produc ced by estrogens and blo s with a polyclonal anti inst the human EGF recep ed levels of immunoreact ly 65% of primary human tion between the presenc	(c) Neither a) e distribution nd malignant ray (α) anthracene of omas possess the stans possess the stans transpoor of the DMBA-I or search of the DMBA-I or search the DMBA-I or search the expression of a TGF and the transformed will inhibitive a TGF and a discrete of a TGF mRNA	B and role of alpha odent and human (DMBA) and nree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess and TGFα mRNA strogens. In addition ntibody or with a it the growth of these GGF mRNA can be mas. There is a and the presence
Check AFFNARE SUBJECTS (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being currents and primery pithelial cells nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aTr Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epic c-Ha-ras proto-oncogene ting effects of EGF bec. aTGF mRNA. In MCF-7 cells monoclonal antibody agai cells in vitro. Elevate detected in approximate strong positive correlar	★ (b) Human tissues Auced type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decrea ch was preceeded by a lo ithelial which have been , NMuMG/ras <sup>H</sup> cells, beco ause these cells have an t cancer cell lines are lls, the level of produc ced by estrogens and blo s with a polyclonal anti inst the human EGF recep ed levels of immunoreact ly 65% of primary human tion between the presenc receptors in a subset of	(c) Neither a) e) distribution nd malignant ray (a) anthracene (a) anthracene (a) anthracene (b) mRNA spec: g) hybridization n the DMBA-I or se in the leve ss in the leve ss in the leve ss in the leve cransformed with transformed with transformed with to arGF and control of arGF and control breast carcinone e of arGF mRNA these tumors.	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess and TGFα mRNA strogens. In addition tibody or with a it the growth of these IGF mRNA can be mas. There is a and the presence These results sug-
Check AFFNARE SUBJECS (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being c transforming growth fac mammary epithelial cell: nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epi c-Ha-ras proto-oncogene ting effects of EGF bec: aTGF mRNA. Human breas: aTGF mRNA. In MCF-7 cell: monoclonal antibody aga: cells in vitro. Elevato detected in approximate strong positive correla: of functional estrogen gest that TGFa may funct	★ (b) Human tissues Inceed type Do not exceed the space provide onducted to determine th tors (aTGFs) in normal a s. Primary dimethylbenz rat mammary adenocarcin e and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decreation of the two to three-fold decreation of the two to three fold decreations are the spece of the set of the se	(c) Neither (d) Neither (a) addistribution (a) anthracene (a) anthracene (a) anthracene (b) mRNA spec: (c) kb man specific mRNA specific man specif	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA c NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess and TGFα mRNA strogens. In addition tibody or with a lt the growth of these TGF mRNA can be mas. There is a and the presence These results sug- a subset of rodent
Check AFFNARE Subjects (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unred Experiments are being c. transforming growth fac mammary epithelial cell: nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aT Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epic-Ha-ras proto-oncogene ting effects of EGF bec. aTGF mRNA. Human breas: aTGF mRNA. In MCF-7 cell: monoclonal antibody again cells in vitro. Elevated detected in approximate strong positive correlation of functional estrogen gest that TGFa may functional	E (b) Human tissues	(c) Neither a) e) distribution nd malignant restribution (α) anthracenes omas possess the second	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA c NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess and TGFα mRNA strogens. In addition ntibody or with a lit the growth of these TGF mRNA can be mas. There is a and the presence These results sug- a subset of rodent ad that the acti-
Check AFFNARE Subjects (a) Human subjects (a1) Minors (a2) Interviews SUMMARY OF WORK (Use standard unrec Experiments are being c. transforming growth fac mammary epithelial cell nitrosomethylurea (NMU) more biologically active and NMU-II carcinomas. ted in the primary DMBA to a human and mouse aTI Ovariectomy produced a primary DMBA tumors whi mRNA. Mouse mammary epic-Ha-ras proto-oncogene ting effects of EGF bec: aTGF mRNA. Human breas: aTGF mRNA. In MCF-7 cells monoclonal antibody again cells in vitro. Elevated detected in approximate strong positive correla of functional estrogen gest that TGFa may funct and human mammary tumor	E (b) Human tissues	(c) Neither a) e) distribution nd malignant responses (α) anthracenes omas possess to Fs than transpipe 0 kb mRNA species g) hybridization n the DMBA-I or se in the level ss in the expression transformed with transformed wi	B and role of alpha odent and human (DMBA) and hree to seven-fold lantable DMBA-I ies could be detec- n of poly $A(+)$ RNA of NMU-II tumors. I of $\alpha$ TGFs in the ession of $\alpha$ TGF ith a point-mutated the growth promo- acity to synthesize $\alpha$ TGF and possess at TGF and possess at GFG mRNA strogens. In addition hibody or with a it the growth of these TGF mRNA can be has. There is a and the presence These results sug- a subset of rodent at the acti- crol the level of
Check AFFORMETE SUBJECTS (a) Hurnan subjects (a2) Interviews SUMMARY OF WORK (Use standard unreaded to the standard unre	★ (b) Human tissues Indeed type Do not exceed the space provide onducted to determine that tors (aTGFs) in normal as primary dimethylbenz rat mammary adenocarcin as and immunoreactive aTG Moreover, a specific 5. and NMU tumors followin GF cDNA probes but not i two to three-fold decreat ch was preceeded by a lo ithelial which have been the space cells have and t cancer cell lines are lis, the level of product ced by estrogens and blo s with a polyclonal anti inst the human EGF recepted levels of immunoreact ly 65% of primary human tion between the present receptors in a subset of tion as an autocrine grocells which are estrogen of a ras proto-oncogen	(c) Neither a) e distribution nd malignant r (α) anthracene (α) anthracene o mas possess the stanspion b kb mRNA spectors g hybridization n the DMBA-I or see in the level ss in the exprasional stansport of the second secon	B and role of alpha odent and human (DMBA) and pree to seven-fold lantable DMBA-I ies could be detec- n of poly A(+) RNA r NMU-II tumors. I of αTGFs in the ession of αTGF ith a point-mutated o the growth promo- acity to synthesize αTGF and possess nd TGFα mRNA strogens. In addition ntibody or with a lit the growth of these TGF mRNA can be mas. There is a and the presence These results sug- a subset of rodent nd that the acti- trol the level of



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH	SERVICE
NOTICE OF INT	RAMURAL RESEARCH PROJECT	
		Z01 CB 05148-08 LTIB
PERIOD COVERED		
October 1, 1986 to Sep	tember 30, 1987	
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borders.)	
Mammary Tumorigenesis	in Inbred and Feral Mice	1/Alomo title laboration of the second
	assional parsonnal below the Fincipal Investigator.	.) (Name, life, laboratory, and institute amiliation)
Robert Callahan	Chief, Oncogenetics	Section LTTB, DCBD, NCT
Gilbert Smith	Microbiologist	LTIB, DCBD, NCI
COOPERATING UNITS (if any)		
Dr. Christine Kozak, L	VD, NIAID, NIH	
Dr. Michael Potter, LG	, DCBD, NCI, NIH	
Dr. John Silver, LVD,	NIAID, NIH	
LAB/BRANCH	man la ma di Dita la ma	
SECTION	nunology and Blology	
Oncogenetics Section		
INSTITUTE AND LOCATION		· ·
NCI, NIH, Bethesda, Ma	ryland 20892	
TOTAL MAN-YEARS:	PROFESSIONAL: OTH	ER:
	1.5	1.0
(a) Human subjects	$\Box$ (b) Human tissues $\sqrt{\Box}$ (c)	Neither
(a1) Minors		B
(a2) Interviews		
SUMMARY OF WORK (Use stendard unrad	uced type. Do not exceed the space provided.)	
We have identified a n	ew common integration locus	(designated int-3) for
the mouse mammary tumo	c virus (MMTV) in MMTV (CZEC	CHII) induced mammary
tumors. Our current d	ita show that 8 out of 44 C2	ZECHII tumor DNAs con-
found to induce a fib	at this site. MMIV integra	ation at int-3 has been
ribed 2.4kb RNA species. Both RNAs correspond to DNA sequences adjacent		
to the int-3 locus. In 10 out of the 44 CZechII tumor DNAs the int-1		
locus was found to be occupied by an MMTV genome. One of these tumor		
DNAs also had an insert	tion of the int-2 locus. Ar	nalysis of the int loci
in tumor DNAs from CZE	CHII mice infected with anot	ther strain of MMTV as well
as other strains of MM	IV infected mice shows that	the frequency of int
activation is a function	on of the virus strain as we	ell as the genetic background
of he host. In other	work we have found that MMTV	V infected CZECHII mice
develop mammary gland hyperplastic aveolar nodules (HAN). Currently hyper-		
plastic outgrowth (HOG	) lines are being developed	rrom MMTV intected CZECHII.

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		11.0551.055	PROJECT NUMBER
DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE			
NOTICE OF INTRAMURAL RESEARCH PROJECT			
			Z01 CB 04829-13 LTI
PERIOD COVERED			
October 1, 1986 to Septemb	er 30, 1987		
TITLE OF PROJECT (80 characters or less. The m	ust fit on one line between the borders.)		
The_Identification_and_Cha PRINCIPAL INVESTIGATOR (List other professiona	racterization of Humar Personnel below the Principal Investigat	tor.) (Name, title, labora	iated with Neoplasia
Debent Callebar	Chief Operating	Soution	LTTP DOPD NOT
Tabal Ali	Visiting Associate	Section	LTIB, DCBD, NCI
Renato Mariani-Costantini	Visiting Associate		LTIB DCBD NCI
Georgio Merlo	Visiting Fellow		LTIB, DCBD NCI
Danielle Liscia	Visiting Associate		LTIB, DCBD, NCI
COOPERATING UNITS (if any)			
Dr. Carlo Croce, Wistar In	stitute, Philadelphia	, PA	
Dr. Rosette Lidereau, Rene	Huguenin Centre, St.	Cloud, Franc	e
LAB/BBANCH			
SECTION	Logy_and_Biology		
Oreception Contion			
INSTITUTE AND LOCATION			· · · · · · · · · · · · · · · · · · ·
NCI NIL Pothorda Maryla	nd 20802		
TOTAL MAN-YEARS: PROFE	SSIONAL: 0	THER:	
4.0	4.0	0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects (b)	)Human tissues 🗌 (c	c) Neither	
(a1) Minors			
(a2) Interviews			В
SUMMARY OF WORK (Use standard unreduced typ	be. Do not exceed the space provided.)		
We have continued our effo	rts to identify and ch	naracterize f	requent genetic
changes associated with pr	imary human breast tur	nor DNAs. In	20% of the
tumor DNAs (n=56), heteroz	ygosity of multiple lo	oci on chromo	some llp was lost.
The somatic loss of these	sequences has a signi:	ficant correl	ation with histo-
pathological grade III tum	or (P<.006), estrogen	and progeste	rone receptor
negative tumors (P<.02 and	P<.002, respectively	) and patient	s which develop
distalmetastasis (P<.05).			
Our data augreets that the	most froquently dala	tod rogion li	as between the
B Clobin and PTH loci	n eitu RNA.RNA hybrid	ization on fr	ozen sections
of primary breast and colo	n carcinomas was used	to examine of	myc and cHras-1
expression. In the breast	carcinomas high level	is of cmvc RN	A expression:
with few exceptions: corre	lates with amplificat	ion of the ge	ne. The expression
of cmyc and cHras-1 in col	on carcinomas is aber	rantly regula	ted in several
cases. Their expression i	s not a function of th	he proliferat	ive capacity
of the tumor. In addition	no genetic alteration	ns of these g	enes could be
detected which explain the patterns of expression observed.			



DEPARTMENT OF HEALTH	AND HUMAN SERVICES - PUBLIC HEA	LTH SERVICE	A NOTECH NOWBER
NOTICE OF INT	FRAMURAL RESEARCH PROJE	ECT	
			201 09023-01 LTIB
October 1, 1986 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 cheracters or les. Cloning of Immunoglobul	s. Title must fit on one line between the border in Genes	rs.)	
PRINCIPAL INVESTIGATOR (List other pre	ofessionel personnel below the Principel Invest	igator.) (Name, title, labore	itory, and institute affiliation)
Syed Kashmiri Ex	pert	LTIB,	DCBD, NCI
Robert Callahan Ch	ief, Oncogenetics Section	n LTIB,	DCBD, NCI
Jeffrey Schlom Ch	lef	LTIB,	DCBD, NCI
COOPERATING LINITS (# any)			
	•		
LAB/BRANCH	upology and Biology		
SECTION			-
Oncogenetics Section	· · · · · · · · · · · · · · · · · · ·		
NCI, NIH, Bethesda, Mar	yland 20892		
TOTAL MAN-YEARS: 2.2	PROFESSIONAL: 1.2	OTHER: 1.0	
CHECK APPROPRIATE BOX(ES)			
(a) Human subjects	L (b) Human tissues	(c) Neither	
(a2) Interviews			В
SUMMARY OF WORK (Use standerd unred	fuced type. Do not exceed the space provided	(.) chimeric antii	bodies
of defined specificity.	Such immunoglobin mole	cules which co	uld be ideal
for radiotherapy and ra	dioimaging will include of	chimeric antibo	odies with
murine variable region	and human constant region	Additional	ly, we plan
We will also attempt to	manipulate antibody gene	nonocional ant: es that may le	ad to a change
in Fc fragment of the a	ntibody molecule resultin	ng in a desiral	ble change in
the biological effector	function. Our plans als	so include gen	eration of
pared down antibody mol-	ecules (Fab 2, Fab and F	V). Such mole	cules can be
desirable variants of a	ntibody molecules that we	will attempt	to generate
by gene manipulation will include, a) antibodies with improved affinity for			
the target, b) molecules with altered carbohydrate content, and c) antibody			
molecules that can spec	ifically bind to certain	enzymes or to:	xic substances.
To attain our objective	s we will initially atter	npt to clone th	ne cDNA
copies of messages for	light and heavy chain ger	nes of immunog	lobulin
synthisized by hybridom	as against tumor associat	ed antigens.	We will
structs by inserting th	es and will attempt expre	ession of the constant	DNA con-
construct into myeloma cells. Subsequently, we will attempt to clone the			
rearranged genomic DNA segments encoding heavy and light chain genes of			
hybridomas.			
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		PROJECT NUMBER	
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PROJECT		
		Z01 CB 05216-16 LTIB	
PERIOD COVERED			
October 1, 1985 to Sept	ember 30, 1987		
TITLE OF PROJECT (80 characters or lass	. Title must fit on one line between the borders.)		
CAMP Receptor Protein 1	n Cancer Growth Control		
Y S Cho-Chung	Chief Cellular Biochemistry Secti	Doretory, and Institute affiliation)	
T. Clair	Chemist	LTIB DCBD NCI	
P. Tagliaferri	Visiting Fellow	LTIB DCBD NCI	
D. Katsaros	Visiting Fellow	LTIB, DCBD, NCI	
G. Tortora	Visiting Fellow	LTIB, DCBD, NCI	
S. Ally	Guest Worker	LTIB, DCBD, NCI	
		,,,	
COOPERATING UNITS (if any)			
Dr. W.R. Miller, U. of	Edinburgh Dr. L. Neckers	, LP, DCBD, NCI	
Dr. S.O. Doskeland, U.	of Bergen, Norway		
Dr. R.K. Robins, Nucle	i Acid Research Institute, Costa Mes	sa, CA	
LAB/BRANCH			
Laboratory of Tumor Imm	unology and Biology		
SECTION			
Cellular Biochemistry S	ection		
INSTITUTE AND LOCATION	1 1 00000		
NCI, NIH, Bethesda, Mar	PROFESSIONAL		
DIAL MAN-TEARS.	PROFESSIONAL. OTHER:		
	2.0		
(a) Human subjects (a1) Minors	$\Box$ (b) Human tissues $\chi \Box$ (c) Neither	В	
(a2) Interviews	•		
SUMMARY OF WORK (Use standard unred	uced type. Do not exceed the space provided.)		
Cyclic AMP (cAMP) in ma	mmalian cells functions by binding t	o cAMP receptor	
protein, the regulatory	subunit of cAMP-dependent protein k	cinase. The cAMP	
receptor protein has tw	o different cAMP binding sites, and	cAMP analogs that	
specifically bind to ei	ther one of the two binding sites an	e known as Site 1-	
selective (C-2 and C-8	analogs) and Site 2-selective (C-6 a	nalogs), respec-	
tively. Further the Si	te 1- and Site 2-selective analogs i	n combination	
produce synergistic enh	ancement of the binding to cAMP rece	ptor protein and	
protein kinase activation in vitro.			
Application of these in	witro findings to demonstrate sAMP	analog-modiated	
response in vivo in in	tact calls or tissues has been scare	Moreover	
virtually all next studies of sAMP-regulation of call growth employed a few			
early known cAMP analo	as which are weakly active for prote	in kinase and ef-	
factive only at uphyciological high my concentrations. The site-selective			
camp analogs which are manu-fold more active for protein kinase have never			
been tested for their growth regulatory effect.			
We, therefore, investig	ated the growth regulatory effect of	site-selective	
cAMP analogs on a spect	rum of human cancer cell lines nd t	the in vivo growth	
of rodent mammary tumor	s. The analog effect on the cell gr	owth will be	
correlated with the response of cAMP receptor protein present in the			
cancer cells. The goal of this study is to elucidate the growth regu-			
latory mechanism of cAMP analogs which can be extrapolated to the treatment			
of human cancer.			



DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HE	ALTH SERVICE	PROJECT NUMBER	
NOTICE OF INT		EOT		
NOTICE OF INT	RAMORAL RESEARCH PROJ	ECT	701 CB 09291-05 ITTB	
PERIOD COVERED			LOT OD OOZOT-OJ LIIB	
October 1, 1985 to Sept	ember 30, 1987			
TITLE OF PROJECT (80 characters or less	. Title must fit on one line between the borde	ərs.)		
The Regulatory Mechanis	m of Oncogene Expression	n		
PRINCIPAL INVESTIGATOR (List other pro	fassional personnel below the Principal Inves	stigator.) (Name, title, labora	itory, and institute affiliation)	
Y.S. Cho-Chung	Chief Cellular Biochem	istry Section	LTTB DCBD NCT	
T. Clair	Chemist	ibery beceiven	LTIB, DCBD, NCI	
P. Tagliaferri	Visiting Fellow		LTIB, DCBD, NCI	
D. Katsaros	Visiting Fellow		LTIB, DCBD, NCI	
G. Tortora	Visiting Fellow		LTIB, DCBD, NCI	
R. Bassin	Chief, Biochemistry Once	ogenes Section	LTIB, DCBD, NCI	
COOPERATING UNITS (if any)				
Dr. J.D. Corbin, Howard	Hughes Medical Inst. L	ab., Vanderbilt	U., Nashville, TN	
Dr. R.K. Robins, Nuclei	c Acid Research Inst.,	Costa Mesa, CA	,,,	
Dr. H. Fan, University	of California, Irvine,	CA		
LAB/BRANCH				
Laboratory of Tumor Imm	unology and Biology			
Cellular Biochemistry	Section			
INSTITUTE AND LOCATION				
NCI, NIH, Bethesda, Mar	yland 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
2.5	2.0	0.5		
(a) Human subjects	(b) Human tissues	(c) Neither	n	
$\square$ (a) Minors			D	
(a2) Interviews	· · · · · · · · · · · · · · · · · · ·			
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the space provide	ed.)		
In spite of the relativ	ely large body of inform	mation concerni	ng the molecular	
structure of retrovirus	oncogenes and their sp	ecific protein	products, little is	
known about the mechani	sms by which they trans	torm cells. Mc	reover, protoonco-	
genes, the cellular cou	ion is low and the mech	oncogenes, have	low expression is not	
known. It is conceivab	ble that substances that	increase tumor	development by ap-	
parently increasing cel	lular proliferation do	so by altering	the quantitative or	
temporal expression of	cellular oncogenes. Und	erstanding the	cellular mechanisms	
governing the expression	n of both viral and cel	lular oncogenes	would therefore pro-	
vide an insight into th	e mechanism of neoplast	ic cell growth	and tumor development.	
Occasionally, tumor cells differentiate spontaneously and then regress completely.				
tion of pooplastic coll	nat CAMP may be linked	with the morpho	vith dibuturul cAMP	
control neoplastic certs since treatment of some tumor certs with dibutyly care, prostal and in $F_{i}$ and inbibitors of cMP-phospholastorase induces irreversible				
morphological differentiation. That this differentiation may be a reversion of				
malignancy is supported by the observation that no tumor is produced when these				
treated cells are inocu	lated into animals.			
To investigate factors	that affect phenotypic	reversion of tr	ansformed cells, we	
have chosen a cell line	transfected with trans	forming ras ger	ne of Ha-MuSV,	
clone 13-3B-4 of NIH 37	3 cells. The effect of	cAMP on the tr	anscriptional	
activities of the wild type and deleted M-MuLV LTRs was also studied. We also				
used human cancer cell lines. The goal of this study is to investigate the				
and growth factors on the expression of cellular oncogenes.				



		PROJECT NUMBER	
DEPARTMENT OF HEALTH A	ND HUMAN SERVICES - PUBLIC HEALTH SERVI	CE	
NOTICE OF INT	RAMURAL RESEARCH PROJECT		
		Z01 CB 08280-04 LTIB	
PERIOD COVERED			
October 1, 1985 to Sept	ember, 30, 1987		
TITLE OF PROJECT (80 charecters or less	. Title must fit on one line between the borders.)		
Enhancement of Oncogene	Expression and Mammary Cancer		
PRINCIPAL INVESTIGATOR (List other pro	fessional personnel below the Principal Investigator.) (Name	e, title, leboretory, and institute affiliation)	
Y.S. Cho-Chung Ch	nief, Cellular Biochemistry Sect	ion LTIB, DCBD, NCI	
T. Clair Ch	nemist	LTIB, DCBD, NCI	
S. Ally Gu	lest Researcher	LTIB, DCBD, NCI	
D. Katsaros Vi	isiting Fellow	LTIB, DCBD, NCI	
COOPERATING UNITS (if any)			
Dr. W.R. Miller, U. of	Edinburgh, Scotland		
Dr. B.E. Haley, U. of V	yoming, Dept. of Biochemistry,	Laramie, Wyoming	
Dr. H. Abou-Issa, Ohio	State U., Dept. of Surgery, Col	umbus, Ohio	
LAB/BRANCH			
Laboratory of Tumor Imm	nunology and Biology		
SECTION			
Cellular Biochemistry S	bection		
NGT NTU Detheede Mer			
TOTAL MAN YEARS	PROFESSIONAL OTHER		
0.7	2.0	0.7	
CHECK APPROPRIATE BOX(ES)	2.0	D	
(a) Human subjects	(b) Human tissues (C) (c) Neith	ner D	
(a) Minors			
(a2) Interviews	· · · · ·		
SUMMARY OF WORK (Use standard unreg	uced type. Do not exceed the space provided.)		
Over twenty distinct tr	ansforming genes have been iden	tified in the genomes	
of oncogenic retrovirus	ansiothing genes have been iden	a homologue in the	
chrosomal DNA of a vert	abrate species Current eviden	ce indicates that	
this highly sensoryed a	et of gopog may play a wital re	le in coll proliferation	
and/or differentiation	In addition inappropriate on	procession of some of	
these genes has been in	in addition, inappropriate ex	pression of some of	
is that dependentian of	ipricated in the genesis of cand	er. Our hypothesis	
is that deregulation of	tion of nonlogic in humans	ossible general	
mechanism for the induc	lular handlague of the rea gone	the encourage corried	
by Harvey and Vinator	initial homorogue of the fas gene	, the oncogene carried	
by harvey and Kristen S	arcoma viruses. In this study	t and human manager	
che fole of fas gene ex	pression in the induction of ra	c and numan manmary	
carcinomas. In a study	of more than 200 numan breast	carcinomas, we have	
observed elevated expression of c-rash in /0% of estrogen and progesterone			
receptor positive tumors and 40% of estrogen and progesterone receptor			
negative tumors. Whereas, an amplified or rearranged c rash gene has not			
been detected in numan mammary carcinomas. Inus, the mechanism by which c-			
rash gene expression is deregulated in these tumors remain to be determined.			
To study the mechanism of the enhanced c-rash gene expression, we will			
acreating the c-rash ex	determine the c-rash expression in growing and growth-arrested human breast		
cancer cells (MCF-/), growing vs regressing rat mammary tumors, hormone-			
dependent vs normone-in	idependent tumors, and the mamma	ry grand or rodents	
during normal development and chemical or viral carcinogenesis. The goal			
of this proposal is to provide us a fundamental basis for better understanding			
and growth.	. sheegened involved in the neop	Lastie actorophene	



DEPARTMENT OF HEALTH	AND HUMAN SERVICES . BURLIC HE		PROJECT NUMBER	
DEPARTMENT OF HEALTHY	DAMURAL BEOFAROU PRO	ALTH SERVICE		
NOTICE OF INT	RAMURAL RESEARCH PRO.	JECT		
REBIOD COVERED			Z01 CB 08249-07 LTIB	
October 1 1986 to Ser	tember 30 1987			
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the bord	lers.)		
Hormonal Control of Gro	wth of Normal and Neopl	astic Mammary C	ells	
PRINCIPAL INVESTIGATOR (List other pro	ofessional personnel below the Principal Inve	stigetor.) (Name, title, labora	atory, and institute affiliation)	
William R. Kidwell	Chief, Cell Cycle Reg	ulation Sect.	LTIB, DCBD, NCI	
David Salomon	Supv. Res. Biologist		LTIB, DCBD, NCI	
Sanjeeva Mohanam	Visiting Fellow		LTIB, DCBD, NCI	
Sue Liu	Bio. Lab. Tech		LTIB, DCBD, NCI	
Brunella SanFilippo	Visiting Fellow		LTIB, DCBD, NCI	
COOPERATING UNITS (if any)				
Rick Dervnck	Genentech			
Richard Grosse	Akadamie der Wissensc	haffen der DDR		
· · · · · · · · · · · · · · · · · · ·				
LAB/BRANCH				
Laboratory of Tumor Imm	unology and Biology			
Coll Crole Devilation				
INSTITUTE AND LOCATION	ection			
NCL. NIH Bethesda, Mary	land 20892			
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:		
2.5	0.5	2		
CHECK APPROPRIATE BOX(ES)		7		
(a) Human subjects	(b) Human tissues	(c) Neither	В	
(a1) Minors				
	durand turns. Do not expected the energy provide	lod 1		
SUMMAN OF WORK USS Standard United				
Mechanisms for the esca	pe of breast cancer cel	ls from normal	growth controls	
are being evaluated, bo	th in human and rodent	tumor model sys	tems. Two growth	
promoting and two growt	h inhibiting activities	, present in an	d made by mammary	
tissues, have been dete	cted. One of these, MD	GF1, a human fa	ctor, was found	
to be secreted into the	growin medium by prima	ry cultures of	normal, benign	
and mailgnant numan mam	mary epithelium. On av	erage, the mail	gnant cells made	
about three times as mu	ch MDGFI as did the nor	mai cells. A s	econd growth pro-	
colle and by correiners	in oitu In modert tio	was also made	by both normal	
production wad found an	in situ. In rodent tis	sues, a change	n iGra	
production was found as a function of the stage of progression of the tumors.				
adenocarcinomas was sig	nificantly more In th	a most advanced	tumore those	
with high metastatic po	tential TCFg productio	n was nearly ze	ro These	
results were confirmed	both by radioimmunoassa	v and hy Northe	rn blot analysis	
of poly A+ mRNA. In vivo and in viro studies demonstrated that estrogens				
regulated the production of TCFG by rodent mammary adenocarcinomas				
finding consistent with the depletion of TGFG mRNA following ovariertomy. TGF8				
one growth inhibitor made by mammary tissues, was found by bioassay				
and by Northern blot hybridization to be produced in equivalent amounts by				
both normal and malignant rodent and human mammary epithelium. A second				
inhibitor, a 13 Kd acidic protein, was found to be high in normal but low in				
malignant mammary cells. This factor has been purified about 5000 fold and				
partial sequence determined. Nanogram amounts inhibit normal and malignant				
mammary cell growth in vitro and also dramatically lower the production of				
extracellular matrix proteins.				
	oteins.	arr) 10001 000	production of	



			PROJECT N	UMBER
DEPARTMENT OF HEALTH AND HUMAN	SERVICES - PUBLIC HEA	LTH SERVICE		
NOTICE OF INTRAMURAL	RESEARCH PROJE	CT	Z01 CB	08212-13 OD
PERIOD COVERED	0 1007			
October 1, 1986 to September 3	0, 1987			
From Gene to Protein: Structu	re Function and	Control in Euk:	arvotic	Cells
PRINCIPAL INVESTIGATOR (List other professional perso	nnel below the Principal Invest	igetor.) (Name, title, labore	tory, and insti	tute effiliation)
PI: Shelby L. Berger	Res	earch Chemist		OD DCBD NCI
Other: William H. Eschenfeldt	Sen	ior Staff Fello	w	OD DCBD NCI
Marc S. Krug	Sta	ff Fellow		OD DCBD NCI
Alvaro Leone	Vis	iting Fellow		OD DCBD NCI
COOPERATING UNITS (# any)				
LAB/BRANCH				
OD, DCBD				
SECTION				
INSTITUTE AND LOCATION				
NCI, NIH, Betnesda, MD 20892	141	071157		
TOTAL MAN-YEARS: PROFESSION	AL: / 0			
	4.0	0.0		
(a) Human subjects (b) Hu	man tissues	(c) Neither		
(a1) Minors			n	
a2) Interviews	1		В	
SUMMARY OF WORK (Use standard unreduced type. Do	not exceed the space provided	1.)		
Clones for human prothymosin a l	nave been identif	ied in cDNA li	braries	from staphy-
lococcal enterotoxin A-stimulat	ed normal lympho	ocytes and fro	m simia	n virus 40-
transformed human fibroblasts.	The 1198-base-	pair fibrobla	st clo	ne has been
sequenced. The encoded protein	n is highly aci	dic and share	s great	er than 90%
sequence homology with rat pro	thymosin $\alpha$ . The second seco	ne peptide "ho	rmone"	thymosin al
appears at positions 2-29 of the prothymosin $\alpha$ amino acid sequence. There is no				
signal peptide. Prothymosin a m	is inducible and	enjoys broad	tissue	specifi-
City. In two systems, the mitogen stimulated resting lymphocyte and the serum				
deprived NiH 3.3 cell upon serum restitution, an increase in the level of pro-				
of which have been isolated from cosmid libraries. There is no evidence that				
prothymosin G serves as a precursor for secreted thymic peptides or that its				
function specifically involves modulation of the immune system. Rather, pro-				
thymosin $\alpha$ appears to play a rol	e in cell prolif	eration.		, , ,



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE Z01 CB 05526-19 NOTICE OF INTRAMURAL RESEARCH PROJECT PERIOD COVERED October 1, 1986 to September 30, 1987 TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) P53: A Common Protein in Embryonic Differentiation and in Cellular Transformation. PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: Supervisory Chemist Peter T. Mora OD DCBD NCI Other: C. Dale Smith Visiting Associate OD DCBD NCI M. John Louis Visiting Fellow OD DCBD NCT V. W. McFarland Chemist OD DCBD NCI K. Chandrasekaran Visiting Scientist OD DCBD NCT COOPERATING UNITS (# any) Pierre May, CNRS, Villejuif, France; Frank Hetrick, University of Maryland: Anton Jetten, National Institute of Environmental Health Sciences; David Winterbourne, St. George's Hospital, University of London LAB/BRANCH OD, DCBD SECTION INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892 TOTAL MAN-YEARS: PROFESSIONAL: OTHER: 0.0 4.2 4.2 CHECK APPROPRIATE BOX(ES) (b) Human tissues (c) Neither (a) Human subjects (a1) Minors В (a2) Interviews SUMMARY OF WORK (Use standard unreduced type. Do not exceed the spece provided.) A sequence homologous to the mammalian "oncogene", p53 was detected in fish showing great evolutionary conservation. During the embryonal development of the chicken the decrease of this nuclear phosphoprotein was traced to a posttranscriptional step in the mRNA processing, eventually accounting for the decline in the steady state level of the protein. Similar declines in p53 mRNA were found in two different types of induced differentiation in culture of the rabbit tracheal epithelial cells. This together with earlier experiments on retinoic acid induced differentiation of embryonal carcinoma cells, indicates that the decline of p53 mRNA is a common correlate of the cellular differentiation processes. Upon stimulation of adrenergic receptors with isoprotenerol a very rapid and great increase in p53 (and also of c-fos and c-myc) mRNA was observed in rat parotid acinar cells. Numerous SV40 transformed murine and human cell lines were found in which a stable p53 is not in complex with the T antigen or with any other protein, demonstrating that other, yet unknown mechanisms can result in the stability and thus elevated level of the p53 protein. In spontaneous transformation of mouse cells the elevated level of p53 and its half life was unrelated to the cellular tumorigenicity as it was the mRNA levels of p53 and also of all the major hitherto recognized proto-oncogenes. However, in the spontaneous transformation a very significant (10/10) correlation was recognized between spontaneous tumorigenecity and a specific change in the heparan sulfate structure. The same heparan sulfate change was recognized before in SV40 transformation of cells. The clonal analysis of the cell systems and the method of selection we present for variant cells for their ability to colonize in the host could be invaluable by allowing a systematic analysis of the natural evolution of tumors. 723 GPO 914-918

PROJECT NUMBER



DEPARTMENT OF HEALTH AND HUMAN SERVICES . PUBLIC HEALTH SERVICE	PROJECT NUMBER			
	701 CD 000/1 01 1-			
NOTICE OF INTRAMURAL RESEARCH PROJECT	ZUI CB 00941-31 OD			
PEBIOD COVERED				
October 1, 1986 to September 30, 1987				
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)				
Genetic and Other Factors Affecting Marrow Transplantation or	n Irradiated Mice			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Neme, title, laboretory, and institute attiliation) PI: Delta S. Uphoff Research Biologist OD DCBD NCI				
COOPERATING UNITS (if any)				
None				
LAB/BRANCH				
OD, DCBD	-			
SECTION				
INSTITUTE AND LOCATION NCI, NIH, Bethesda, MD 20892				
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:				
2.0 1.0 1.0				
CHECK APPROPRIATE BOX(ES) (a) Human subjects (b) Human tissues (c) Neither (a1) Minors	В			
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.) Successful marrow transplantation requires not only genetically compatible donors but the elimination of normal or malignant hematopoietic cells of the recipient without destruction of other vital tissues. Procedures for irradiating experi- mental animals were recommended by the International Commission on Radiological Units and Measures. The investigation of physical factors affecting successful marrow transplantion in inbred mice has demonstrated that the ICR recommendations were obsolete and other basic concepts of radiation biology were invalid. Ex- posure-rate effects and exposure-rate + absorption significantly altered the repair capabilities of normal and malignant hematopoietic cells. Repair was initiated only-during exposure and the pattern of repair required only 10 min. to become established. Successful repair of hematopoietic cells interfered with establishment of the marrow graft resulting in partial chimerism or complete re- versal to recipient genotype. Significant differences in results occurred with simultaneous 2 direction, dorsal, ventral and reciprocal alternate dorsal + ventral and ventral + dorsal exposures to X-rays. Similar effects are being found using gamma radiation from Ces 137. Cellular repair has usually been in- vestigated using tissue culture system rather than intact animals which gave new incite into this phenomenon. There must be changes in the way physical factors are reported when dealing with biological systems to insure reproduci- bility of experimental data. In addition the universal practice of converting roentgens as calibrations in air to Grays as absorbed tissue doses should be abandoned in all cases were exact measurements are impractical.				



DEPARTMENT OF HEALTH AND HUMAN SERVICES , BUDUIC HEALTH SERVICE	PROJECT NUMBER		
NOTICE OF INTRAMURAL RESEARCH PROJECT	ZO1 CB 08901-3 OD		
PERIOD COVERED			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Studies of Animal Cell Adhesion			
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, lebo	etory, and institute affiliation)		
ri: Samuel W. Luborsky Chemist	OD DCBD NCI		
COOPERATING UNITS (IT any)			
Kenneth M. Yamada, Chief, Membrane Biochemistry Section, LMB	, DCBD, NCI		
OD. DCBD			
SECTION			
INSTITUTE AND LOCATION			
TOTAL MAN-YEARS: PROFESSIONAL: OTHER:			
1.0 1.0 0.0	)		
CHECK APPROPRIATE BOX(ES)			
$\Box$ (a) Human subjects $\Box$ (b) Human tissues $\Box$ (c) Neither			
(a) Interviews	В		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)			
Cells of most vertebrate species are anchorage dependent and	l undergo mitosis and		
their own adhesion proteins (a g fibrometin (FN)) when	cells often secrete		
adhesion to extracellular substrate surfaces or to other appropriate colle			
The mechanism of cell adhesion is little understood. Recently, synthetic peptides			
derived from the sequence of FN have been used for competitive inhibition of its			
functions in vitro. We have started to examine this system for the possible			
effects of homologous and heterologous peptide associations upon peptide func-			
by sedimentation equilibrium experiments in the analytical ultracentrifuge.			
determined that sedimentation equilibrium was achieved in an overnight centri-			
fugation run in phosphate buffered saline, pH 7.2. Such studies were carried			
out on these peptides and the percent dimer determined fo	r each peptide at a		
series of peptide concentrations. For such small peptides, the effects of changes in amino acid composition or sequence on pentide properties and percent			
dimer were significant and easily seen. We hope the result	ts of these studies		
will help us to better understand the mechanism of cell adhes	sion.		



DEPARTMENT OF HEALTH	NO HUMAN SERVICES - PUBLI	CHEALTH SERVICE	PROJECT NUMBER
NOTICE OF INT	RAMURAL RESEARCH P	ROJECT	ZO1 08903-1 OD
October 1, 1986 to Sep	tember 30, 1987		
TITLE OF PROJECT (80 characters or less	s. Title must fit on one line between the	borders.)	
The Structure of Thyro	id Hormone Precursors	5	
PI: Sidney Shifrin	tessional personnel below the Principa Chemist	I Investigator.) (Name, title,	laboratory, and institute effiliation) OD DCBD NCI
Evelyn F. Grollma	n		LBM NIADDK
Sonia Quatin Doi			LBM NIADDK
COOPERATING UNITS (if any)			
Richard Montali, D.V.M	., National Zoologica	al Park, Washin	gton, D. C.
LAB/BRANCH			
SECTION			
SECTION			
INSTITUTE AND LOCATION NIH, NCI, Bethesda, MD	20892		
TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:	
1.0	1.0	0	.0
(a) Human subjects     (a1) Minors     (a2) Interviews	🛛 (b) Human tissues	🗌 (c) Neither	В
SUMMARY OF WORK (Use standard unred	luced type. Do not exceed the spece p	provided.)	
The thyroid proteins is characterized by chemic extracted from a Bongo proteins in many of its	olated from FRTL cell al methods and by phy obtained from the Nat properties.	s and from a hu sicochemical mu ional Zoo resen	uman goiter are being ethods. The proteins mble the human goiter
r			







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