EPI-001

EPI-001 is the first experimental drug that is antagonist to the intrinsically disordered amino-terminus domain of the androgen receptor. EPI-001 is being developed by the pharmaceutical company ESSA Pharma Inc (Vancouver, Canada) for the treatment of castration-resistant prostate cancer and is currently in pre-clinical development.

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Discovery

EPI-001 was discovered by Dr. Marianne D Sadar at the British Columbia Cancer Agency and Dr. Raymond J Andersen at the University of British Columbia.

Mechanism of Action

EPI-001 is a mixture of four stereoisomers. EPI-001 binds to the activation function-1 (AF-1) region in the amino-terminus of androgen receptor (AR) as opposed to the antiandrogens that bind to the C-terminus ligand-binding domain (Sadar 2012). A functional AF-1 is essential for the androgen receptor to have transcriptional activity. If AF-1 is deleted or mutated, the androgen receptor will still bind androgen, but will have no transcriptional activity (Jenster et al., 1991). Importantly, if the androgen receptor lacks a ligand-binding domain, the receptor will be nuclear and constitutively active (Jenster et al., 1991). Constitutively active splice variants of the androgen receptor that lack ligand-binding domain are correlated to castration-resistant prostate cancer and poor survival (Guo et al., 2009; Hu et al., 2009, Sun et al., 2010; Haile & Sadar 2011; Hornberg et al., 2011; Zhang et al., 2011).

EPI-001 is the first and currently only inhibitor of constitutively active splice variant of androgen receptor that lack the C-terminal ligand-binding domain (Andersen et al 2010). Antiandrogens do not inhibit constitutively active variants of androgen receptor that have truncated or deleted ligand-binding domain.

In the absence of androgen, all known antiandrogens cause translocation of

androgen receptor from the cytoplasm to the nucleus (Clegg et al. 2012; Sadar 2011; Sadar 2012), whereas EPI-001 does not cause androgen receptor to become nuclear (Andersen et al., 2010). Binding of EPI-001 to the amino-terminus domain of the androgen receptor blocks protein-protein interactions that are essential for its transcriptional activity. Specifically, EPI-001 blocks androgen receptor interactions with CREB-binding protein, RAP74, and between the N-terminal domain and C-terminal domain (termed N/C interaction) required for antiparallel dimer formation of androgen receptor (Andersen et al., 2010). Unlike antiandrogens such as bicalutamide (Masiello et al., 2002; Clegg et al., 2012), EPI-001 does not cause androgen receptor to bind to androgen response elements on the DNA of target genes (Andersen et al., 2010).

Specificity and Efficacy

EPI-001 inhibits androgen receptor-dependent proliferation of human prostate cancer cells while having no significant effects on cells that do not require androgen receptor for growth and survival (Andersen et al., 2010). EPI-001 has specificity to the androgen receptor and has excellent antitumour activity in vivo with xenografts of castration resistant prostate cancer (Andersen et al., 2010).

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