Development of a small molecule inhibitors targeting androgen receptor (AR) mutations associated with resistance to current AR antagonists

Gilles Bignan, Ian Hickson, James Bischoff, Jonathan Branch, Janine Ondrus, **Charles Theuer,** Marco Gottardis.

Janssen Pharmaceuticals, Springhouse, PA**;** TRACON Pharmaceuticals, Inc., San Diego, CA

Background: Resistance to AR-targeted therapy is a challenge in the contemporary treatment of mCRPC, and single amino acid mutations of the AR ligand binding domain, including the F876L mutation, may mediate resistance to current second generation AR inhibitors, including enzalutamide, in approximately 10% of cases. The development of potent antagonists of wild-type (WT) AR as well as mutated AR, including F876L mutant AR is a priority.
Methods: Small molecule inhibitors were synthesized to bind WT AR and AR containing ligand binding domain mutations. Inhibitors were studied *in vitro* to determine affinity and quantify antagonism and possible agonism towards WT AR and mutated AR. Inhibitors were also studied *in vivo* in xenograft models of prostate cancer cell lines containing WT AR and F876L mutated AR.
Results: AR antagonists bound to WT AR with high affinity (Ki < 10 nM) and functioned as antagonists of WT AR and F876L, L701H, W741C,T877A, and H874Y mutant AR, without demonstrating significant agonist activity. AR antagonists potently inhibited nuclear translocation of WT and F876L mutant AR that was superior to the activity of enzalutamide and ODM-201. AR antagonists potently inhibited the growth of prostate cancer cell lines expressing WT AR, and, in contrast to enzalutamide, arrested the growth of prostate cancer cell lines expressing F876L mutant AR. These AR antagonists are orally bioavailability with favorable PK and drug-drug interaction profiles.
Conclusions: Potent antagonists of WT AR and AR mutations that generate resistance to current second generation AR inhibitors have been developed and are expected to begin clinical investigation.

This research was funded was by Janssen Pharmaceuticals

Conflict of Interest: Dr's Bignan, Hickson, Bischoff, Branch, Ondrus, and Gottardis are or were employees of Janssen Pharmaceuticals, and Dr. Theuer is an employee of TRACON Pharmaceuticals