Degradation is ideally suited for AR. AR PROTACs are effective against growth factor activated AR. AR PROTAC: 3.

AR degradation in... provides a novel mechanism for providing efficacious therapy for patients with prostate cancer. In summary, PROTACs designed to degrade AR are potent, specific, active in vitro and in vivo. AR PROTACs target AR irrespective of its mutational status and binding partners. This technology seems ideal for addressing competitive process, degradation is a progressive process. As such, it is less susceptible to increases in androgen ligand, target expression, or mutations in the target. Thus this technology seems ideal for addressing many mechanisms of AR resistance in patients with prostate cancer.

AR PROTACs were shown to degrade AR in LNCaP and VCaP cells, with low nM to pM potency, and had a >90% reduction in AR concentration (Dimas). Degradation was rapid, with 50% of AR lost in within 15 minutes and complete degradation observed by hours. The degradation process in cells was specific, as the PROTAC activity can be competed with excess E3 ligase and PROTACs with an inactive epitope did not degrade AR. AR PROTACs induced rapid apoptosis and cell death in VCaP cells. In LNCaP and VCaP cell systems, AR PROTACs were anti-proliferative under conditions in which enzalutamide was inactive, such as increasing concentrations of the AR agonists B1811 and cells containing the AR-F876L mutation. AR PROTACs typically exhibited good pharmacokinetic properties, with t1/2 values of several hours and bioavailability of >95% after po or sc injection. In mice, AR PROTACs demonstrated in vivo activity, including reduction of AR protein levels, prostate involution and tumor growth inhibition.

In summary, PROTACs designed to degrade AR are potent, specific, active in vitro and in vivo, and have cellular efficacy superior to enzalutamide. Targeted degradation of AR may provide a novel mechanism for providing efficacious therapy for patients with prostate cancer for whom current therapies have failed.

VHL recruiting Androgen Receptor (AR) PROTACs: potent, rapid, VHL specific and specific.

AR PROTACs induce rapid apoptosis and cell death in VCaP cells.

AR PROTAC retains potency in high androgen milieu and across AR mutations.

AR PROTACs exhibit favorable pharmacokinetic (PK) profile – representative curves shown.

AR PROTAC leads to mouse prostate involution.

Stereoselective activity of AR PROTACs in vivo.

Summary

The AR PROTACs demonstrate potent AR degradation efficacy and consistent functional activity in various in vitro and in vivo systems thought to represent the shortcomings of current prostate cancer treatment regimens.

Complete degradation of AR provides a novel mechanism to address mCRPC:

• Degradation is ideally suited for AR-activated mCRPC.
• AR PROTACs target AR irrespective of its mutational status and binding partners.
• Stereoselective activity of AR PROTACs is effective against growth factor activated AR.