Degradation is ideally suited for AR targeting. Technology developed by Prof. Craig Crews, Yale University. Since PROTACs only need to make a transient interaction with their targets, ARV-330 exhibits potent and specific AR degradation.

ARV-330: An Androgen Receptor PROTAC Degradator for Prostate Cancer
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Abstract

Patients with prostate cancer who progress on therapy often have enhanced Androgen Receptor (AR) signaling due to several mechanisms: increased androgen production, increased AR transcription, and increased AR expression and/or specific AR mutations that render current therapies ineffective. A novel approach to block AR signaling is to specifically target AR for degradation. To do this, we have created AR PROTACs (PROtein-Targeting Chimera), which inhibit functions of the AR binding moiety on one end and an E3 ligase recruiting element on the other end, which leads to AR ubiquitination and degradation. We have applied this technology to determine if it could address mechanisms of resistance to current therapy in prostate cancer models.

Our lead AR PROTAC, ARV-330, degrades AR in LNCaP and VCaP cells with 99% degradation concentration (DC90s) < 10 nM. AR degradation had functional consequences in cells, suppressing the AR target gene PSA, inhibiting proliferation, and potently inducing apoptosis in VCaP cells, with maximal apoptosis observed around 20 nM, versus 1 μM for enzalutamide. While both ARV-330 and enzalutamide block proliferation of VCaP cells in response to 0.1 μM of the AR agonist R1881, enzalutamide lacks antiproliferative potency with increasing R1881 concentrations, whereas ARV-330 maintained antiproliferative effects. In cells containing the ARWT mutation, enzalutamide was mediocre; however, ARV-330 maintained complete effectiveness. In mice, ARV-330 exhibited good pharmacokinetic properties, with ≥72 values of several hours and bioavailability of >80% after injection. Treatment of mice with ARV-330, at doses ranging from 0.3 to 10 mg/kg, resulted in reduced AR protein levels and prostate involution in normal mice and, in mice implanted with VCaP tumors, reduction in plasma PSA and blockade of tumor growth.

In summary, the AR PROTAC ARV-330 removes AR from prostate cancer cells in a potent manner and produces therapeutic effects as a result. This cellular efficacy has translated into preclinical effectiveness in animal models, and ARV-330 is now in preclinical development. Thus, targeted degradation of AR may provide a novel mechanism for providing efficacious therapy for patients with prostate cancer for whom current therapies have failed.