An oral androgen receptor PROTAC degrader for prostate cancer

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Abstract

Background: The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer during the transition from a localized to metastatic disease. Most patients initially respond to inhibitors of the AR pathway, but the response is often short-lived. The majority of patients progressing on enzalutamide or abiraterone exhibit genetic alterations in the AR locus, either in the form of amplifications or point mutations in the AR-gene. Given these mechanisms of resistance, our goal is to eliminate the AR protein using the PROTACology Targeting Chimera (PROTAC) technology. Further, we sought to make an orally bioavailable AR PROTAC.

Methods: Medicinal chemistry efforts yielded a small molecule AR PROTAC that simultaneously binds E3-ligase and AR, thus leading to ubiquitination and degradation of AR. This molecule has been characterized in vivo and in vivo preclinical studies.

Results: Our oral AR PROTAC ARCC4 degrades 90% of total AR in all cell lines tested, with a 50% degradation concentration (CD50) of 1 nM. AR degradation suppresses the expression of AR target gene PSA, PARP1, and cell proliferation, and induces apoptosis in VCAP cells. No activity is observed in AR-null cell lines, such as PC-3. While enzalutamide inhibits its activity in the presence of known androgens, the AR PROTAC maintains its antiproliferative activity. Further, the ARCC4 is able to degrade all clinically relevant mutant AR proteins. Overall, these properties are sufficient to enable robust oral bioavailability, resulting in dose dependent AR degradation in an oral-administered VCAP xenograft. Congruent with AR degradation, a tumor growth inhibition is observed in AR-dependent xenograft studies.

Conclusions: In summary, we report the first orally bioavailable AR PROTAC that robustly degrades AR in vitro and in vivo.

Characterization of ARCC4 – a potent AR PROTAC degrader

- AR PROTAC ARCC4 is a sub-nanomolar AR degrader
- Dose response of ARCC4 in VCAP cells
- Time course of AR degradation by AR PROTAC in VCAP cells
- ARCC4 induces apoptosis in VCAP cells
- ARCC4 degrades AR across common prostate cancer cell lines, yet AR PROTACs do not degrade Glucocorticoid Receptor (GR)

Functional characterization of ARCC4

- ARCC4 blocks PSA synthesis, inhibits AR-dependent cell proliferation, and causes apoptosis in VCAP cells
- Inhibition of PSA synthesis in LNCaP cells stimulated with 0.1 nM R1881
- Inhibition of LNCaP cell proliferation stimulated with 0.1 nM R1881
- Inhibition of cell proliferation in VCAP cells stimulated with 0.1 nM R1881
- ARCC4 treatment induces caspase-3 activation in VCAP cells

Orally bioavailable AR PROTAC ARCC4

- ARCC4 possesses robust oral bioavailability
- Dose dependent in vivo AR degradation observed in VCAP xenografts upon oral dosing of ARCC4, concurrent with inhibition of AR signaling

PROTAC: PROTACology Targeting Chimera

- Technology developed by Prof. Craig Crews, Yale University
- Platform licensed to Arvinas in 2013

Selected publications on PROTAC technology:

Summary

Orally bioavailable ARCC4 demonstrates AR-DMT degradation potency 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-stable mCRPC
- PROTAC targets AR irrespective of its mutational status and binding partner
- Since PROTACs only need to make a transient interaction with their targets, AR PROTACs retain efficacy in high androgen environment

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