An oral androgen receptor PROTAC degrader for prostate cancer

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Abstract #273
Board D13

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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 PROteolysis TArgeting Chimera (PROTAC) technology. Further, we sought to make an orally bioavailable AR PROTAC.

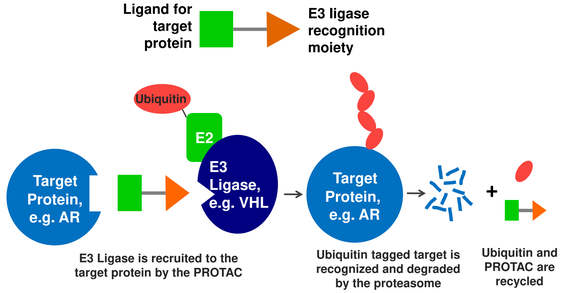
Methods: Medicinal chemistry efforts yielded a small molecule AR PROTAC that simultaneously binds E3-ubiquitin ligase and AR, thus leading to ubiquitination and degradation of AR. This molecule has been characterized in *in vitro* and *in vivo* preclinical studies.

Results: Our lead oral AR PROTAC degrades >90% of total AR in all cell lines tested, with a 50% degradation concentration (DC_{50}) < 1 nM. AR degradation suppresses the expression of AR-target gene PSA, inhibits cell proliferation, and induces potent apoptosis in VCaP cells. No activity is observed in AR-null cell lines, such as PC-3. While enzalutamide loses its activity in the presence of elevated androgens, the AR PROTAC maintains its antiproliferative activity. Further, the AR PROTAC is able to degrade all clinically relevant mutant AR proteins. Overall ADME properties are sufficient to enable robust oral bioavailablity, resulting in 95% AR degradation in AR-amplified VCaP xenografts at doses as low as 3 mg/kg. Congruent with AR degradation, a dose responsive 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*.

PROTAC: PROteolysis TArgeting Chimera

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

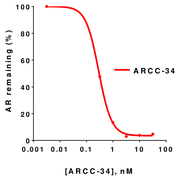


Selected publications on PROTAC technology:
1. PNAS. 2016 Jun 28;113(26):7124-9
2. Nature Chem Biology. 2015 Aug;11(8):611-7
3. Nature Reviews Drug Discov. 2017 Feb;16(2):101-114

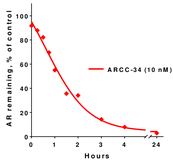
Characterization of ARCC-34 – a potent AR PROTAC degrader

- AR PROTAC ARCC-34 is a sub-nanomolar AR degrader and achieves Dmax by 4 hrs

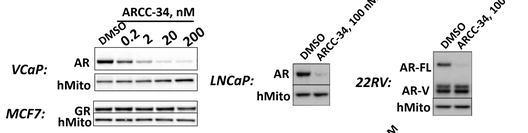
Dose response of ARCC-34 in VCaP cells:



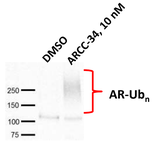
Timecourse of AR degradation by 10 nM ARCC-34 in VCaP cells:



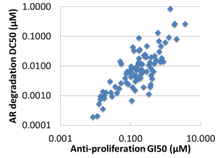
- ARCC-34 degrades AR across common prostate cancer cell lines, yet it does not degrade Glucocorticoid Receptor (GR)



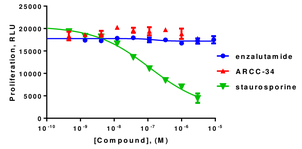
- ARCC-34 causes poly-ubiquitination of AR:



- There is a good correlation between AR degradation potency and the corresponding antiproliferative potency in VCaP cells:



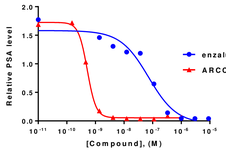
- ARCC-34 has no antiproliferative effect on AR-negative PC-3 prostate cancer cells:



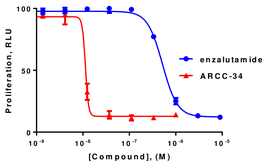
Functional characterization of ARCC-34

- ARCC-34 blocks PSA synthesis, inhibits AR-dependent cell proliferation and causes apoptosis in VCaP cells

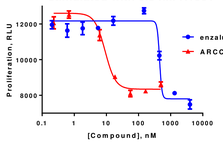
Inhibition of PSA synthesis in VCAP cells stimulated with 0.1 nM R1881



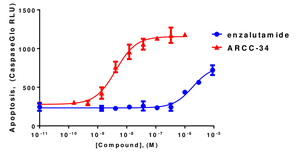
Inhibition of cell proliferation in VCaP cells stimulated with 0.1 nM R1881



Inhibition of LNCaP cell proliferation stimulated with 0.3 nM R1881

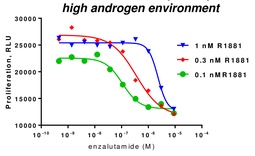


Apoptosis in VCaP cells stimulated with 0.1 nM R1881:

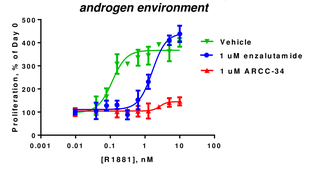


- ARCC-34 retains potency in high androgen milieu

Enzalutamide loses potency in high androgen environment

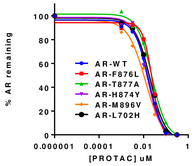


ARCC-34 retains potency in high androgen environment



- AR point mutations are amenable to AR PROTAC mediated degradation

AR mutation	agonist
F876L	Enzalutamide, ARN-509
T877A	Glucocorticoids, progesterone
H874Y	Glucocorticoids, progesterone
M896V	Bicalutamide
L702H	Glucocorticoids

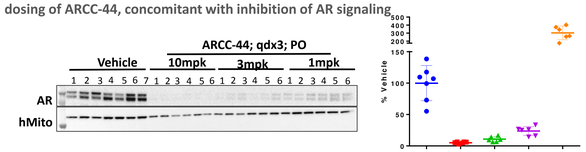


Orally bioavailable AR PROTACs ARCC-34 and ARCC-44

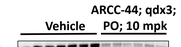
- ARCC-34 and ARCC-44 possess robust oral bioavailability

	Mouse Cl (mL/min/kg)	Mouse %F	AUC/Dose (μM*hr)/(mg/kg)	Vss (L/kg)
ARCC-34	4.8	55	2.3	1.9
ARCC-44	3.5	66	3.4	2.2

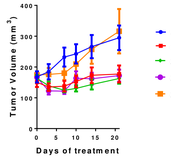
- Dose dependent *in vivo* AR degradation observed in VCAP xenografts upon oral dosing of ARCC-44, concomitant with inhibition of AR signaling

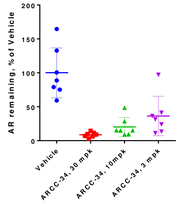


VCaP cells harbor TMPRSS2-Erg fusion, putting Erg under transcriptional control of AR:



- Antitumor activity observed with daily oral dosing of ARCC-34 in castrated VCaP model





Summary

Orally bioavailable AR PROTACs demonstrate pM AR 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-amplified mCRPC
- PROTACs target AR irrespective of its mutational status and binding partners
- Since PROTACs only need to make a transient interaction with their targets, AR PROTACs retain efficacy in a high androgen environment

Acknowledgements

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