BET PROTACs Are More Broadly Effective Than BET Inhibitors

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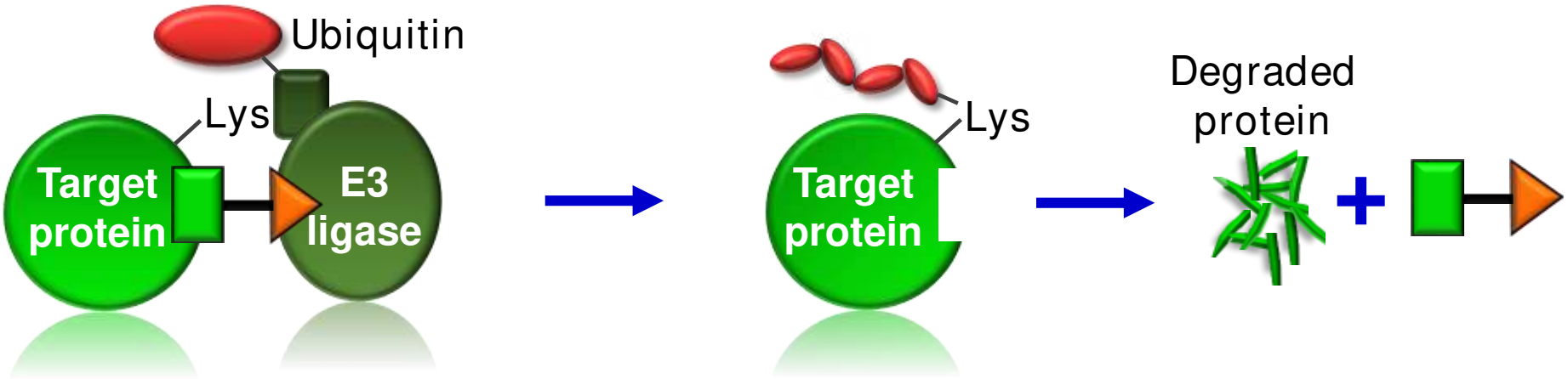
Disclosures

I am an employee of and have an equity stake in Arvinas

Arvinas: The Protein Degradation Company

- Private company, founded July 2013
  - Founder: Dr. Craig Crews
  - Licensed Technologies for Targeted Degradation of Proteins from Yale University

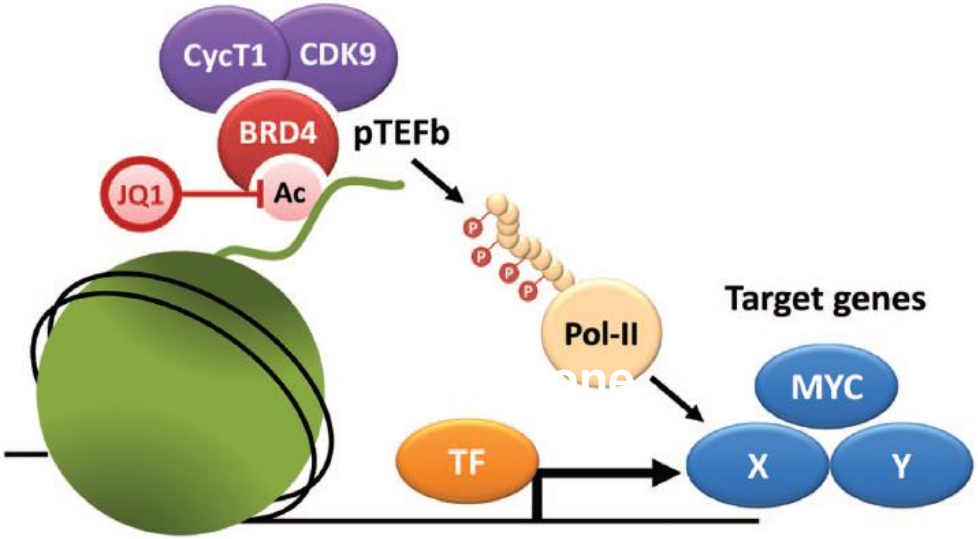
PROTACs Induce The Rapid Degradation Of Target Proteins



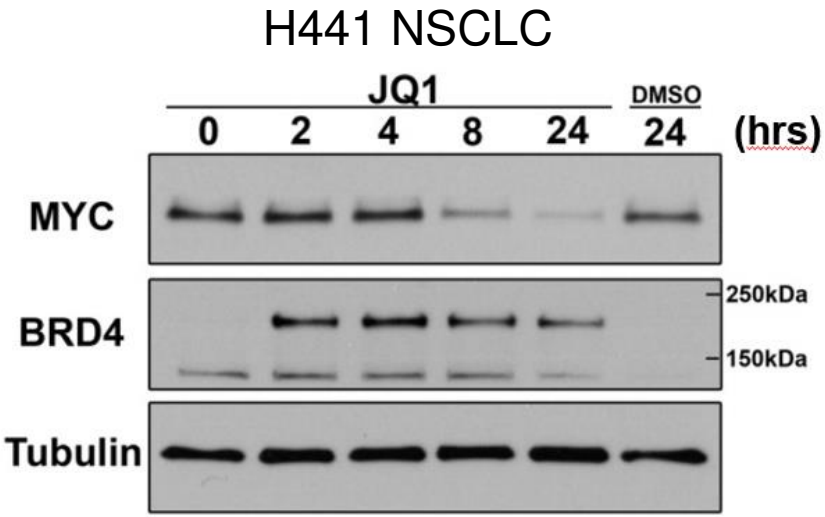
- PROTACs (Proteolysis-Targeting Chimera) are bifunctional chimeric molecules that recruit an E3 ligase to a target protein to induce its degradation
  - Have successfully degraded proteins using ligands that bind to several E3 ligases, including cereblon, IAP2, MDM2, VHL
- PROTAC technology is robust:
  - Have degraded >85% of proteins tested & potentially can degrade any unwanted protein
  - Degradation of unwanted proteins is fast (hours), durable (days), and potent (pM)
- PROTAC technology is broadly applicable across target classes & therapeutic areas

BRD4 Is An Important Cancer Epigenetic Regulator

- BRD4 is a member of the Bromodomain and Extra-Terminal motif (BET) family of proteins
- BRD4 is an epigenetic reader of acetylated histones and regulates gene transcription through the recruitment of other proteins to super-enhancer regions
- BET inhibitors selectively disrupt transcription of a number of important cell- and lineage-specific genes including oncogenes, i.e., MYC



Valent and Zuber (2014) Cell Cycle 13:689



Shimamura et al. (2013) Clin Cancer Res 19: 6183

ARV-825 Potently And Rapidly Degrades BRD4 In A Cereblon- And Proteasome-Dependent Manner

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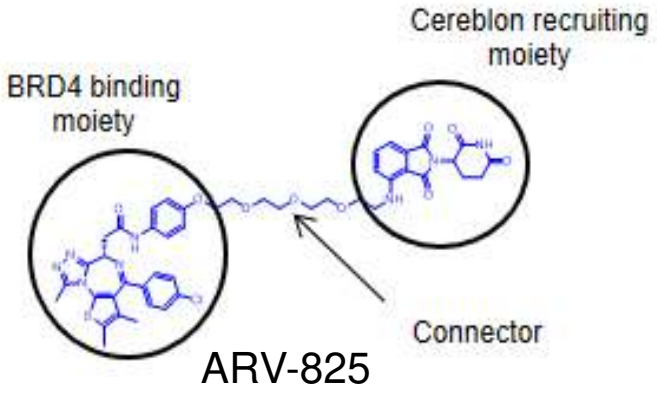
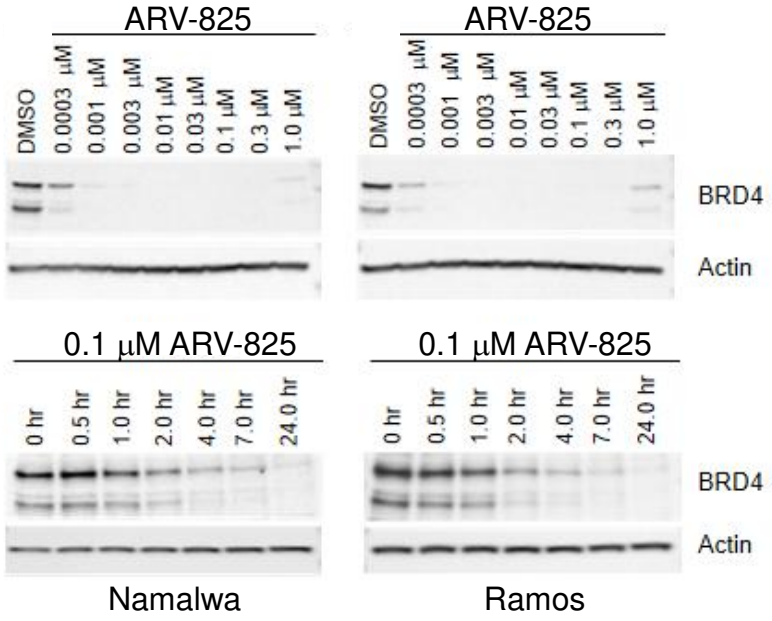
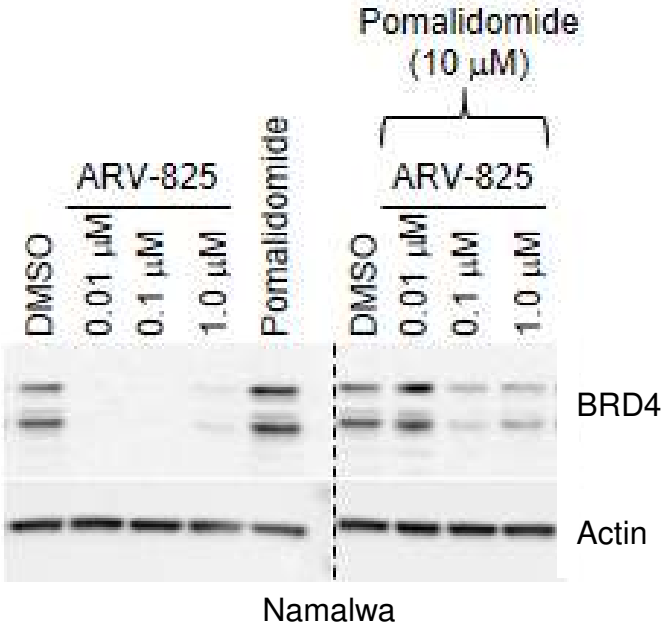
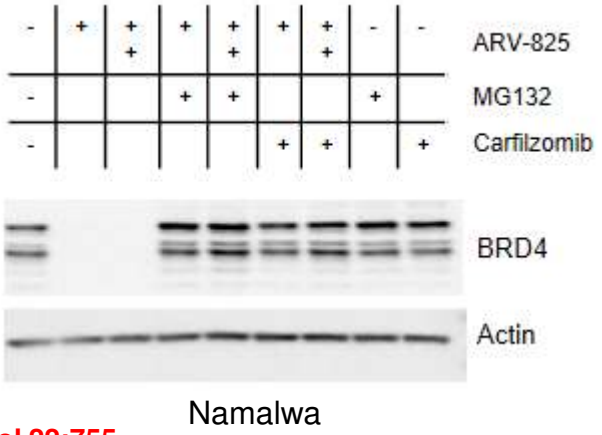




ARV-825 is a potent degrader of all BET family members





Lu et al. (2015) Chem. Biol 22:755

BET PROTACs Cause Prolonged BRD4 Degradation, MYC Suppression and Inhibition of Cell Proliferation

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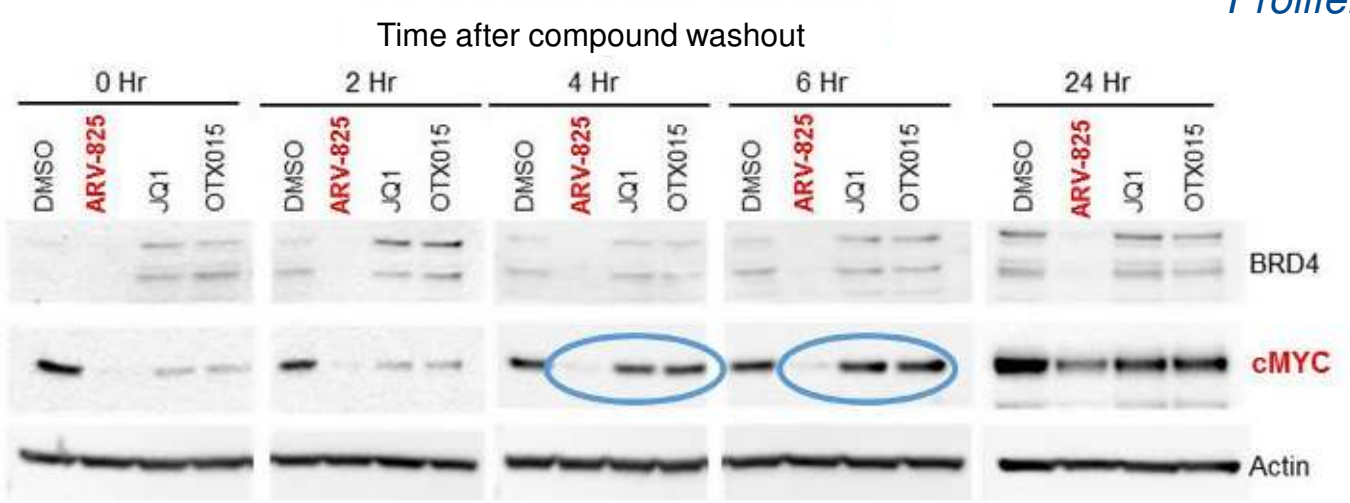
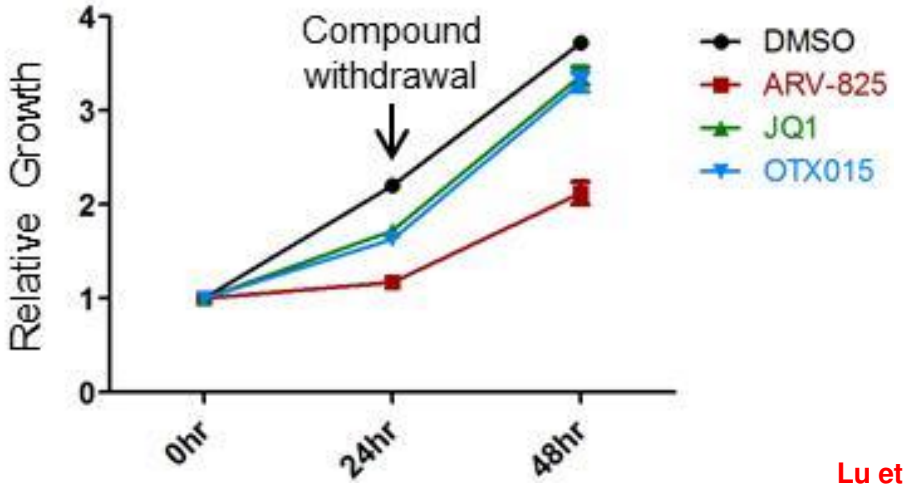
Burkitt's Lymphoma Namalwa cells → *Compound Incubation 12 h* → *Compound Washout* → *Immunoblot*; *Cell Proliferation*

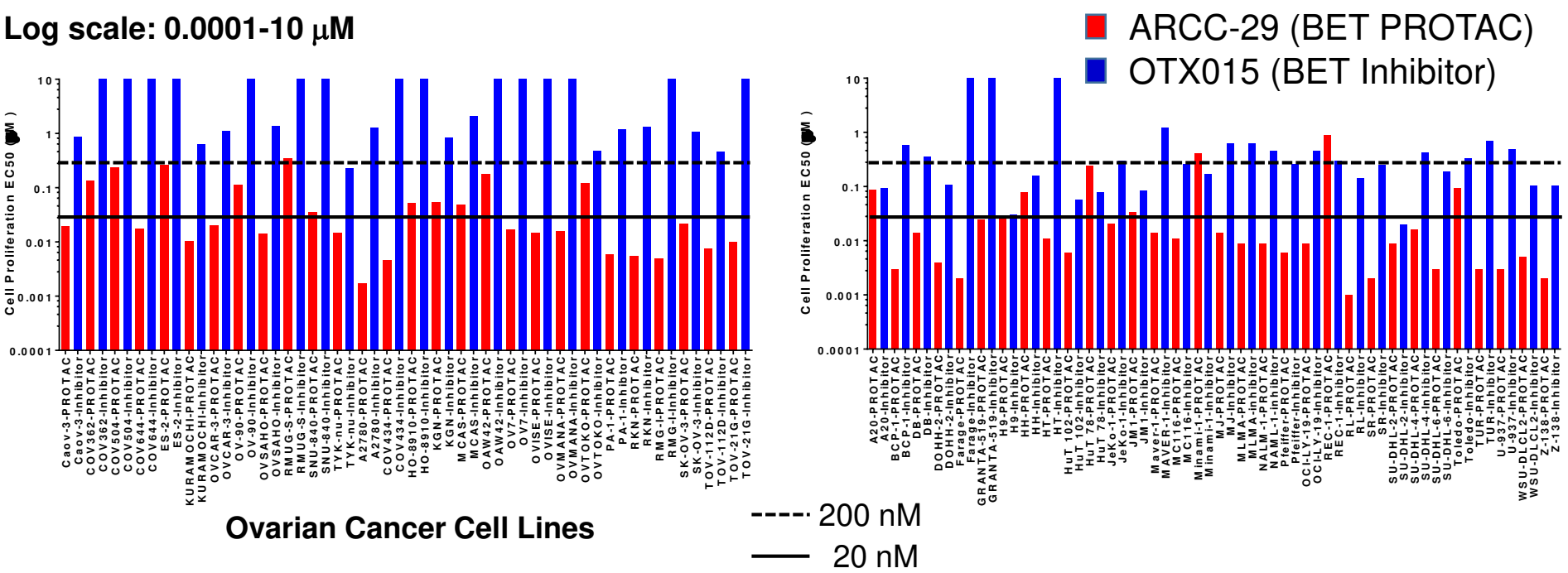




Lu et al. (2015) Chem. Biol 22:755

Tumor Cell Lines Are Consistently More Sensitive To BET Degradation Than To BET Inhibition

Log scale: 0.0001-10 μM

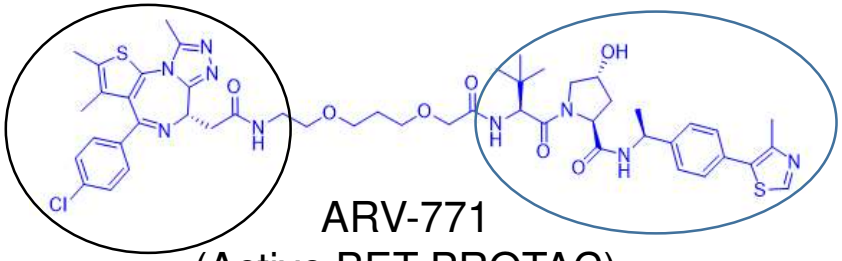


- Ovarian cancer cell lines are consistently more sensitive to BET protein degradation than they are to BET protein inhibition
- 54% of ovarian cancer cell lines are resistant to 10 μM OTX015
- Breast and NSCLC cell lines are similarly more sensitive to BET PROTACs compared to BET inhibitors
- Lymphoma cell lines are more sensitive to BET inhibition compared to ovarian, breast, and NSCLC cell lines
- Nevertheless, lymphoma cell lines are largely more sensitive to BET protein degradation than they are to BET protein inhibition

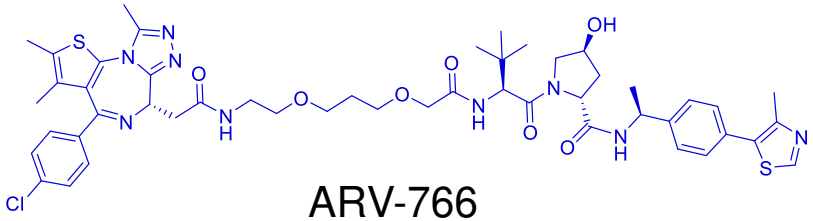
BET PROTACs Have Superior Anti-Proliferative Activity in DLBCL Cells Compared to BETi's

BRD4-binding moiety

VHL-binding moiety



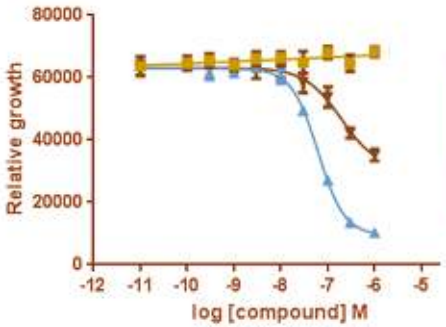
ARV-771
(Active BET PROTAC)



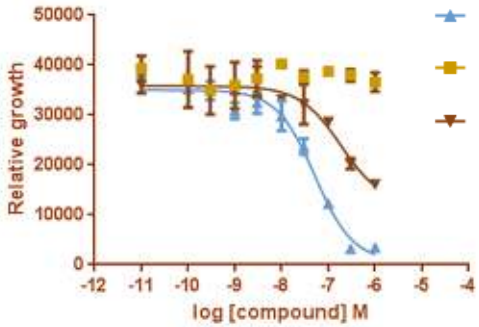
ARV-766
(Inactive diastereomer)

Raina et al. (2016) PNAS 113:7124

U2932

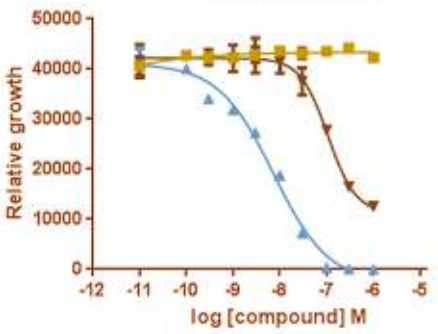


RI-1

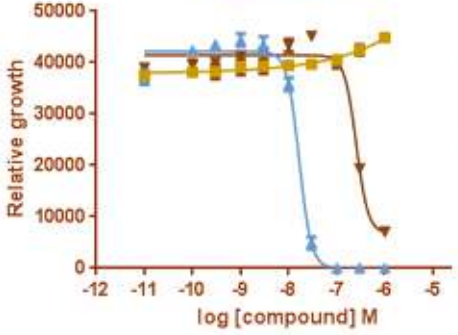


ARV-771
ARV-766
OTX015

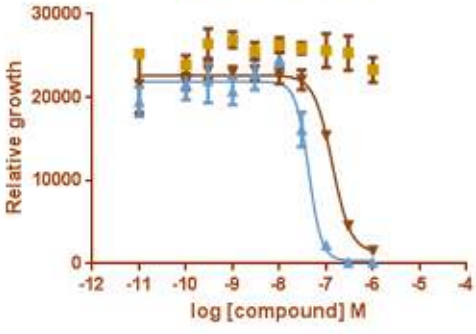
SU-DHL-6



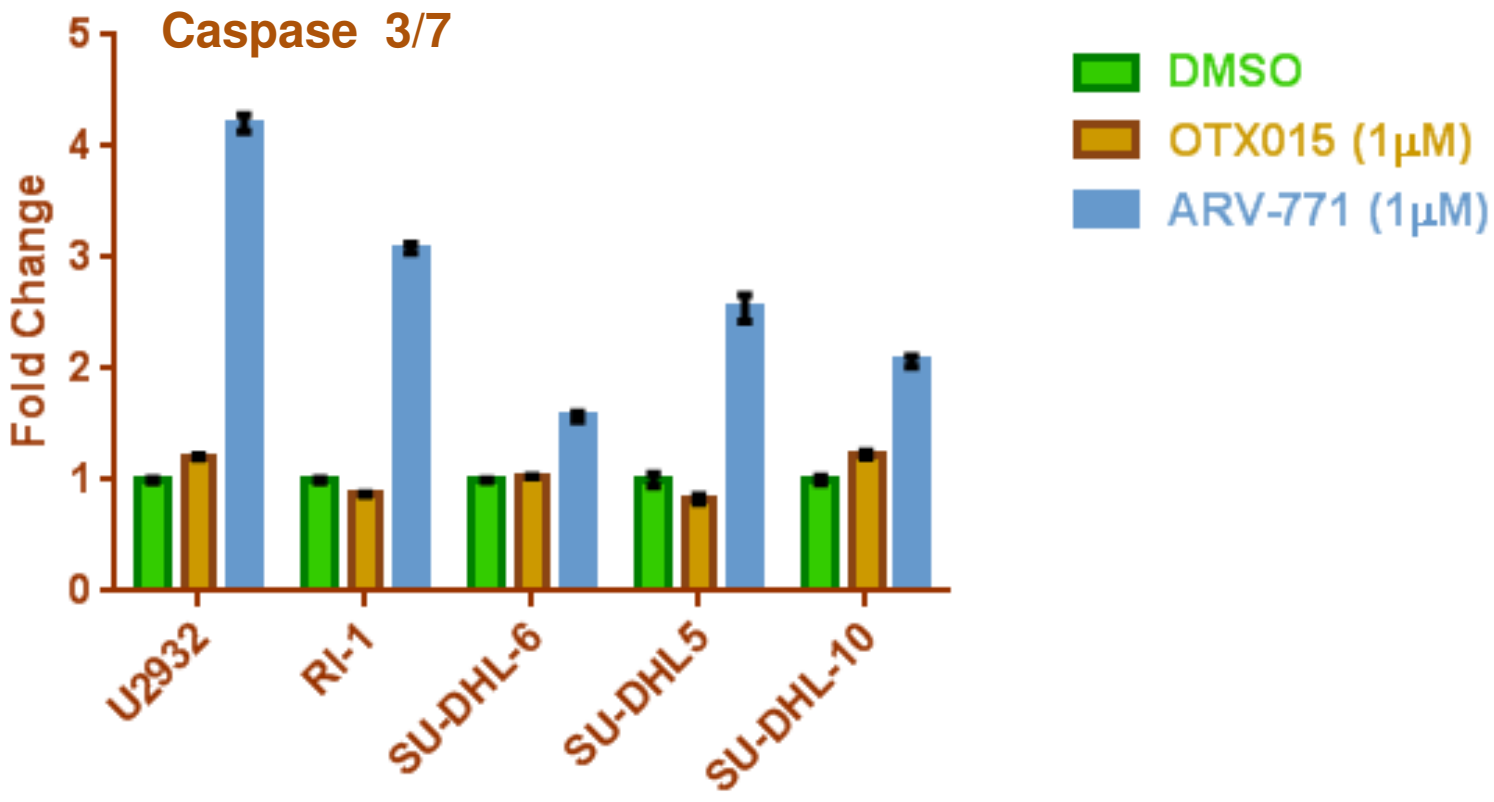
SU-DHL-5



SU-DHL-10

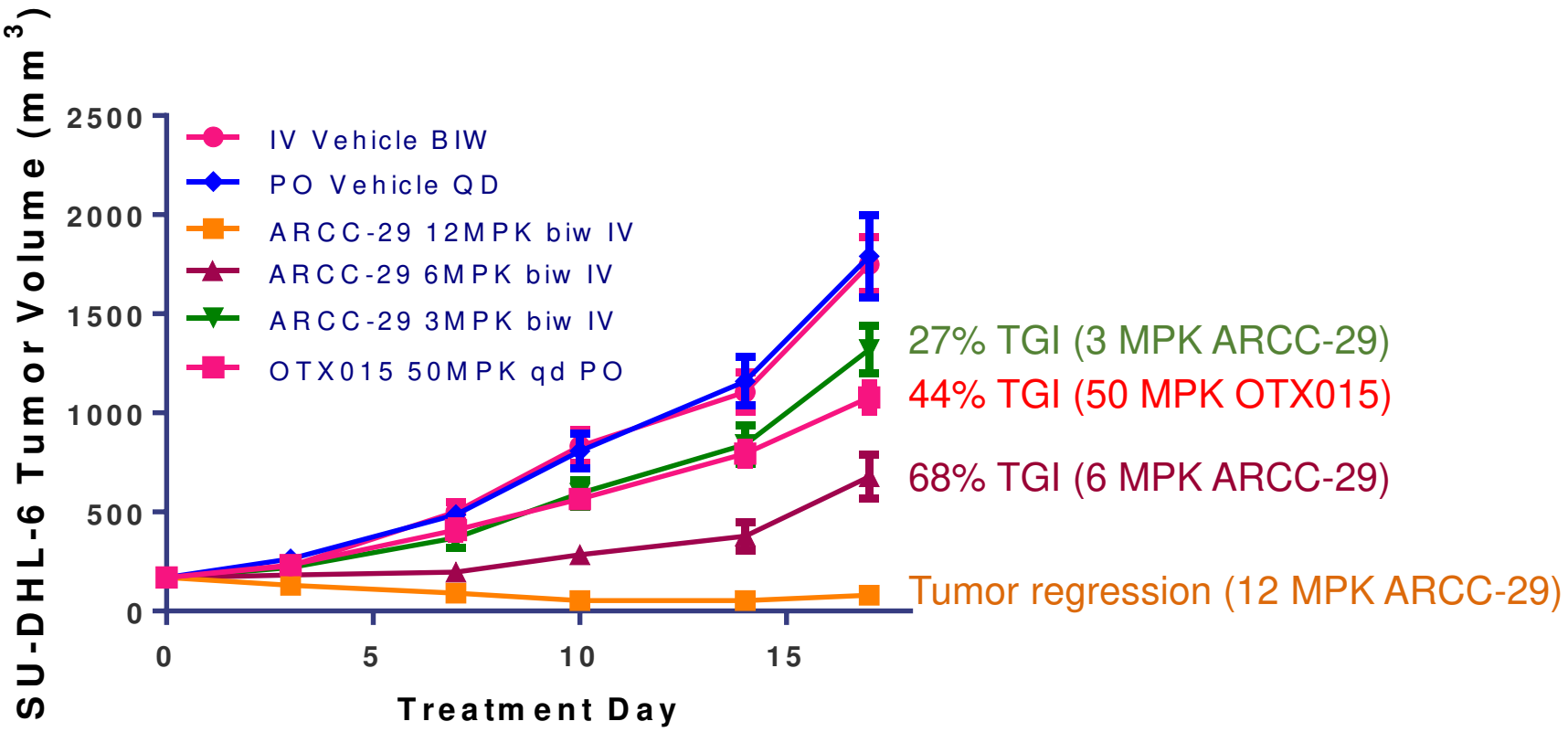


BET PROTACs Have Superior Apoptotic Activity In DLBCL Cells Compared to BET Inhibitors



- BET PROTACs have also been shown to have superior apoptotic activity than BET inhibitors in ovarian and prostate cancer cell lines

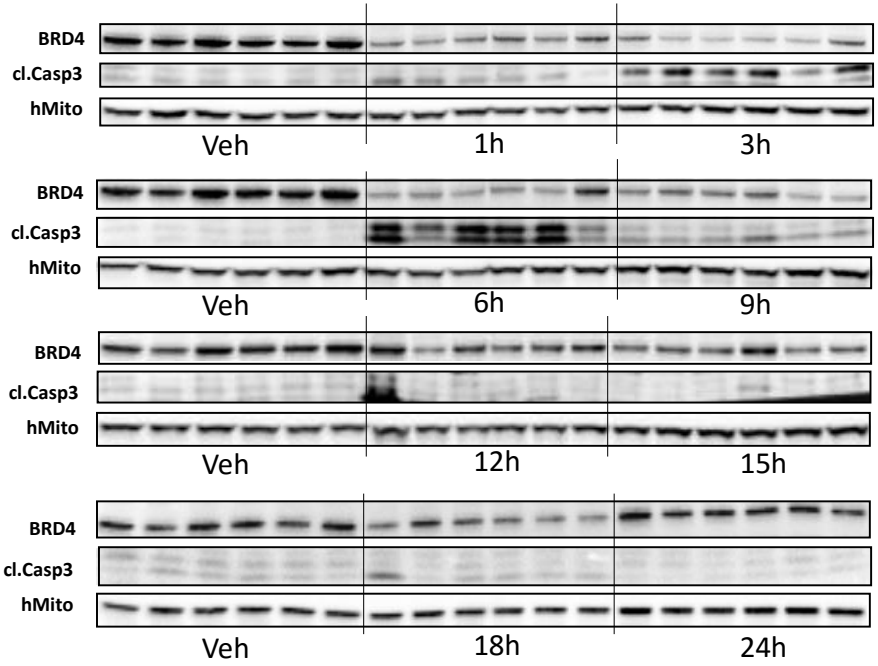
Intermittent Dosing Of The BET PROTAC ARCC-29 Causes Tumor Regression

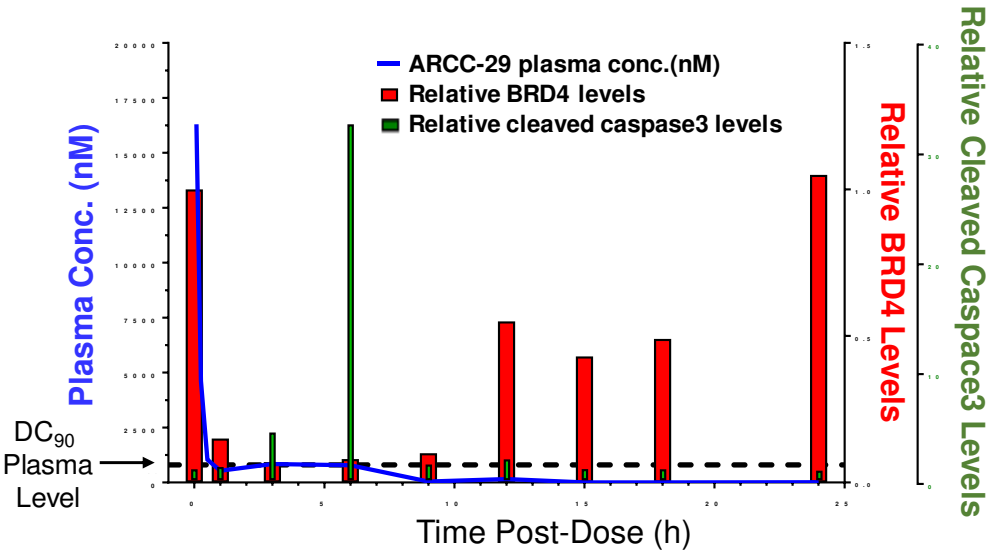


- Once-weekly dosing of the BET PROTAC ARCC-29 also results in tumor stasis or regression in human prostate and ovarian cancer xenograft models

The Bet PROTAC ARCC-29 Causes Rapid BRD4 Degradation And Caspase Activation

SU-DHL-6 DLBCL Xenograft Model





- Free fraction of ARCC-29 stays above the predicted plasma concentration required to achieve 90% BRD4 knockdown for ~ 6 hours
- Maximal BRD4 knockdown occurs at 3 hours followed by robust caspase activation at 6 hours
- BRD4 protein levels return to untreated levels 24 h post-dose

BET PROTACs Are More Broadly Effective Than BET Inhibitors

- BET PROTACs cause robust BRD4 degradation and more prolonged c-Myc suppression *in vitro* and have greater efficacy *in vivo* compared to BET inhibitors
- Tumor cell lines representing different tumor types are consistently more sensitive to BET protein degradation than BET protein inhibition
- BET PROTACs have superior anti-proliferative and apoptotic activity in DLBCL, prostate cancer, and ovarian cancer cells compared to BET inhibitors
- Intermittent dosing of BET PROTACs caused tumor regression or stasis in DLBCL, prostate cancer, and ovarian cancer xenograft models
- Arvinas' BET PROTAC is planned to enter the clinic in 2H17

Acknowledgements

Arvinas Biology

Kanak Raina

Jing Lu

Martha Altieri

Ann Marie Rossi

Deborah Gordon

Ryan Willard

Jim Winkler

Arvinas Chemistry

Yimin Qian

Xin Chen

Jing Wang

Hanqing Dong

Andy Crew

Yale University

John Hines

Craig Crews