Parabilis MEDICINES

October 25, 2025

Discovery of bifunctional ERG degraders using a ML-driven stapled peptide platform

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Disclosures

- I am a full-time employee of Parabilis Medicines

Presentation Overview

- Parabilis Medicines (formerly Fog Pharma) has built a drug discovery engine that combines wet bench and computational methodologies (AI/ML) to discover and optimize α-helically constrained peptide drugs (Helicons)

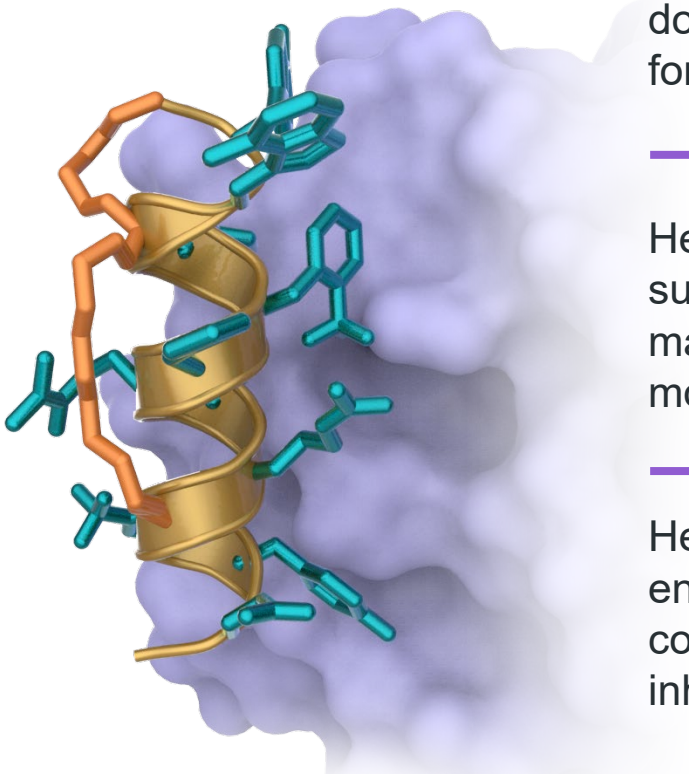
- Two key advantages of the Helicon modality are:
  1) ability to bind to protein target surfaces that are undruggable with traditional small molecule approaches (ie β-catenin, ERG)
  2) achieve intracellular exposures that allow modulation of intracellular targets where peptide drugs have historically failed

- The first drug derived from the platform is FOG-001, a direct binder and inhibitor of β-catenin
  - Preliminary safety, target engagement and efficacy of this drug have been observed in Phase 1 clinical trial; NCT05919264 first data released at ESMO, AACR-NCI-EORTC October 2025

- Bifunctional Helicon degraders of the ERG transcription factor have been discovered and optimized
  - with low nanomolar cell-based activity, in vivo validation studies using multiple xenograft models (CDX, PDX)

Helicon Peptides Allow Targeting of Challenging Intracellular and Extracellular Proteins

Helicons are able to bind flat surfaces



Many important targets do not have pockets for small molecules

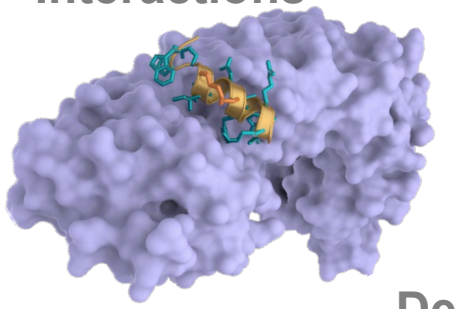
Helicons bind flat surfaces and can engage many proteins that small molecules cannot

Helicons can efficiently enter cells and achieve concentrations sufficient to inhibit abundant proteins

Utilize >1000 synthetic amino acid building blocks

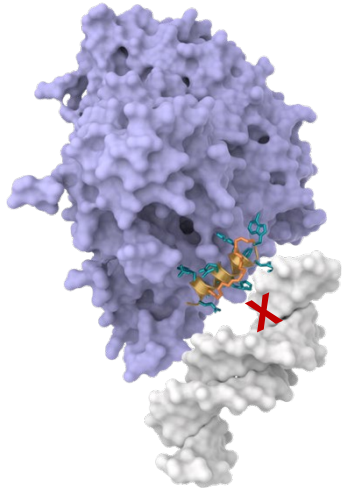
Enabling Multiple Modes of Action

Protein-Protein Interactions

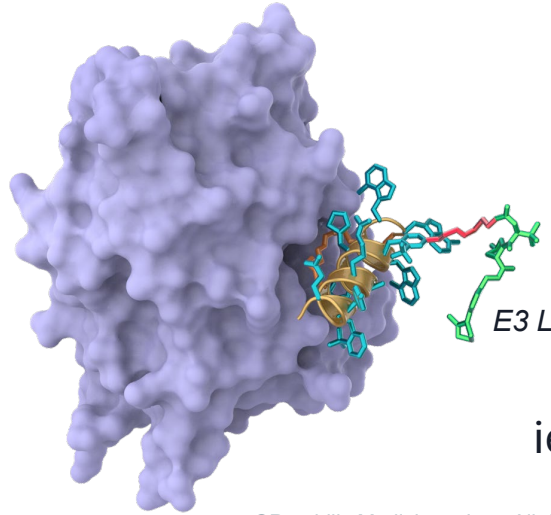


ie β-catenin

DNA-Protein Interactions



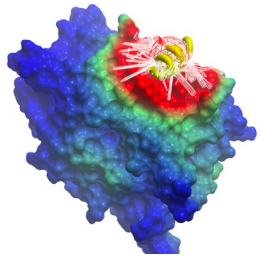
Degraders



ie ERG

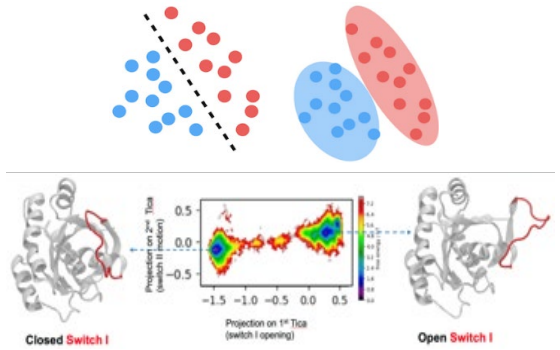
Integration of Bench Experimentation and Computation Enables Rapid Helicon Discovery and Optimization

Target Evaluation



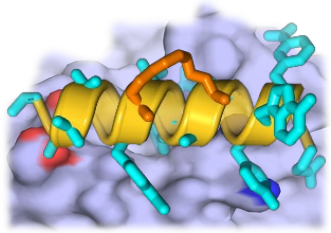
ML-Based Prediction of Helicon Binding Sites

Accurate for both positive and negative predictions



Foundational ML & Simulation Capabilities

Hit Discovery

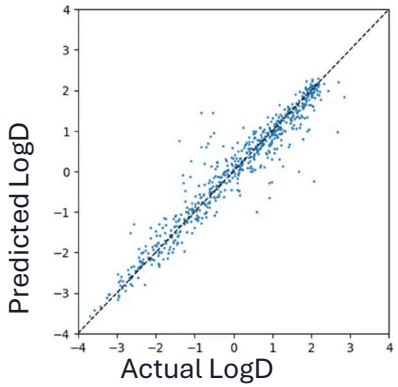


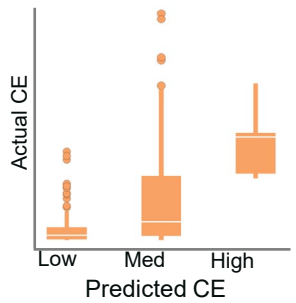
Highly-Parallelized Helical Phage & mRNA Display

Library sizes: 10^8 – 10^{12}
Targets screened: ~140
Target hit rate: >60%

In Silico De Novo Helicon Design

$>10^{45}$
14
>85%

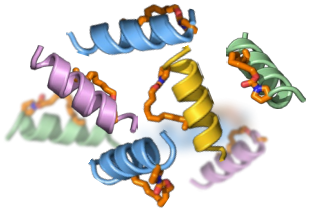




ML-Based Property Predictions to Inform Design

Built with in-house data collected across dozens of chemical series

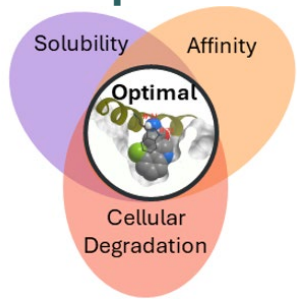
Hit-to-Lead



Multiplexed Mass Spec Library Screening

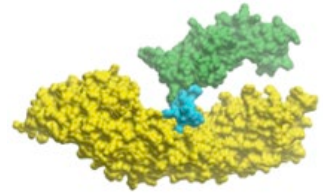
Library sizes: 10,000s
Helicons tested: >300,000
Total data points: $>10^6$

Lead Optimization



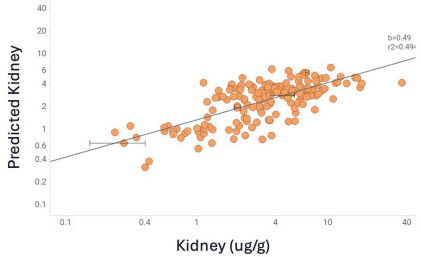
Generative Design

ML-driven multiparameter optimization



Degrader Simulations

Physics-based optimization



ADMET

ML and Helisite models

FOG-001 is the First Clinically Validated Direct β-catenin Inhibitor

And first proof of concept drug discovery program at Parabilis Medicines

Decades of WNT pathway drug discovery effort has not yielded direct β-catenin targeting agents

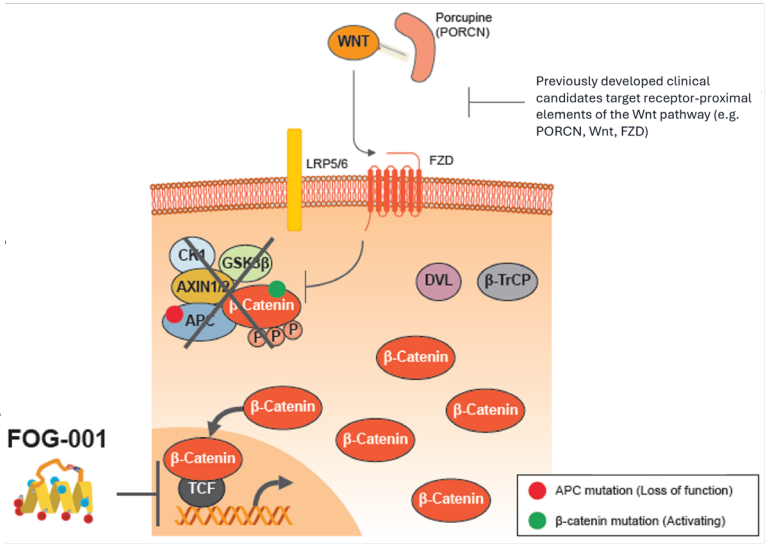
Early **1990's**: APC identified as a key early mutation in CRC*

2010's: Upstream Wnt/β-catenin inhibitors enter clinical trials: vantictumab (α-Fzd Ab), ipafricept (Fzd8-Fc), WNT974, RXC004, ETC159 (Porcupine inhibitors); definition of bone tox and management approach

2023: FOG-001 entered Ph1/2 clinical trial in solid tumors with WPAM

2025: Confirmation of β-catenin:TCF inhibition and activity in patients

FOG-001 mechanism of action

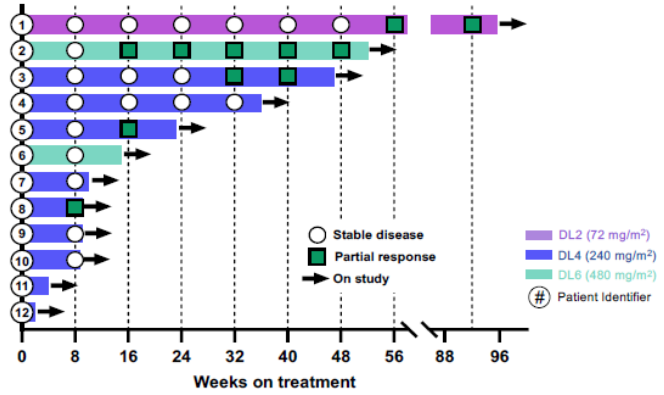


*Powell et al. Nature 359:235 1992
Madan et al Bone Res 6:17, 2018
Madan et al JCI 128:12, 2018
Kaur et al EMBO Mol Med 13: e13349 2021

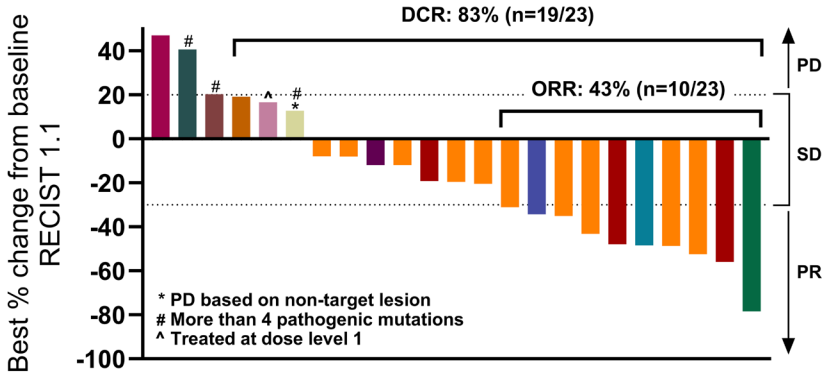
Broderick et al Prostate Can and Prostatic Dis 2025

Preliminary efficacy in patients with β-catenin-driven tumors (NCT05919264)

Desmoid patient cohort (Greg Cote, MGH)



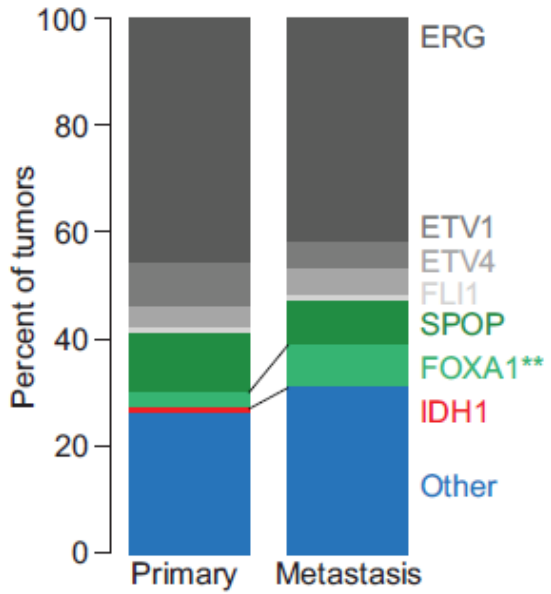
Solid tumor (non-CRC) RECIST Responses (Sam Klempner, MGH)



ESMO (Oct '25), AACR-NCI-EORTC (Oct '25)

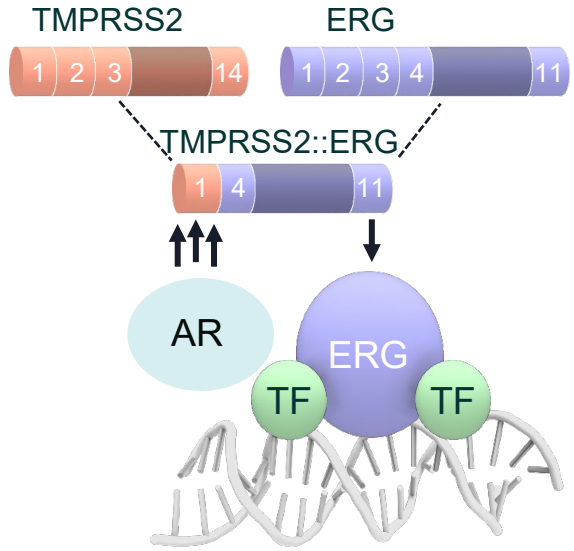
ERG is an Oncogenic Driver of Prostate Cancer

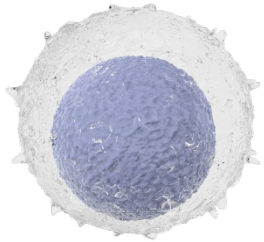
TMPRSS2:ERG fusion present in 40-50% of prostate cancer (PC) patients



Tomlins et al, Sci 2005, 310:644
TCGA Network, Cell 2015, 163:1011
Carver et al, Nat Gen 2009, 41:619
Haffner et al, Nat Gen 2010, 42:668

AR drives high levels of ERG expression via TMPRSS2 promoter





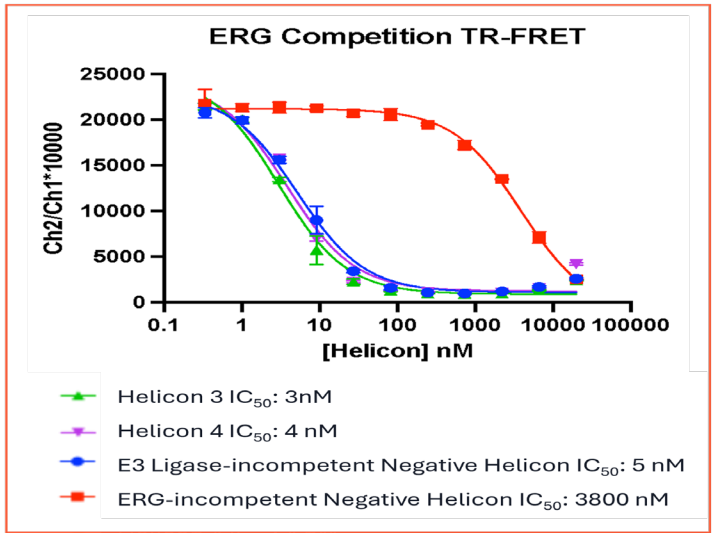
Proliferation
Angiogenesis
Anti-apoptosis
Cell migration
Differentiation
Invasion
Genomic instability

Goal: Develop a first-in-class ERG degrader with single agent and combination activity for treatment of prostate cancer

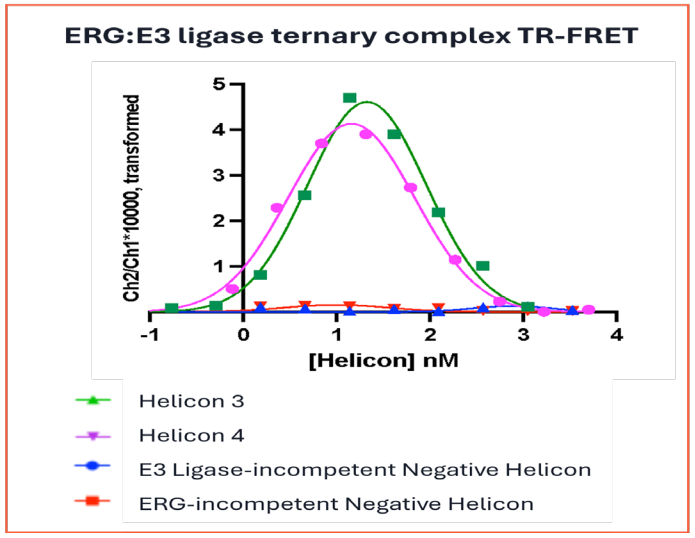
ERG Bifunctional Degrader Helicons Have High Affinity for ERG and Form Ternary Complexes in Biochemical Context

- Multiple phage display screens led to two distinct Helicon series that bind to two distinct ERG domains
- In lead optimization phase, helicons are routinely screened using :
  - SPR (direct binding of Helicon to ERG)
  - Competition TR-FRET (for competition against probe binding to ERG)
  - Ternary complex formation with E3 ligase complex using TR-FRET
    →both VHL and CRBN have been successfully employed
  - Co-crystal structures of ternary complex (ERG/E3 ligase/Helicon) are in hand

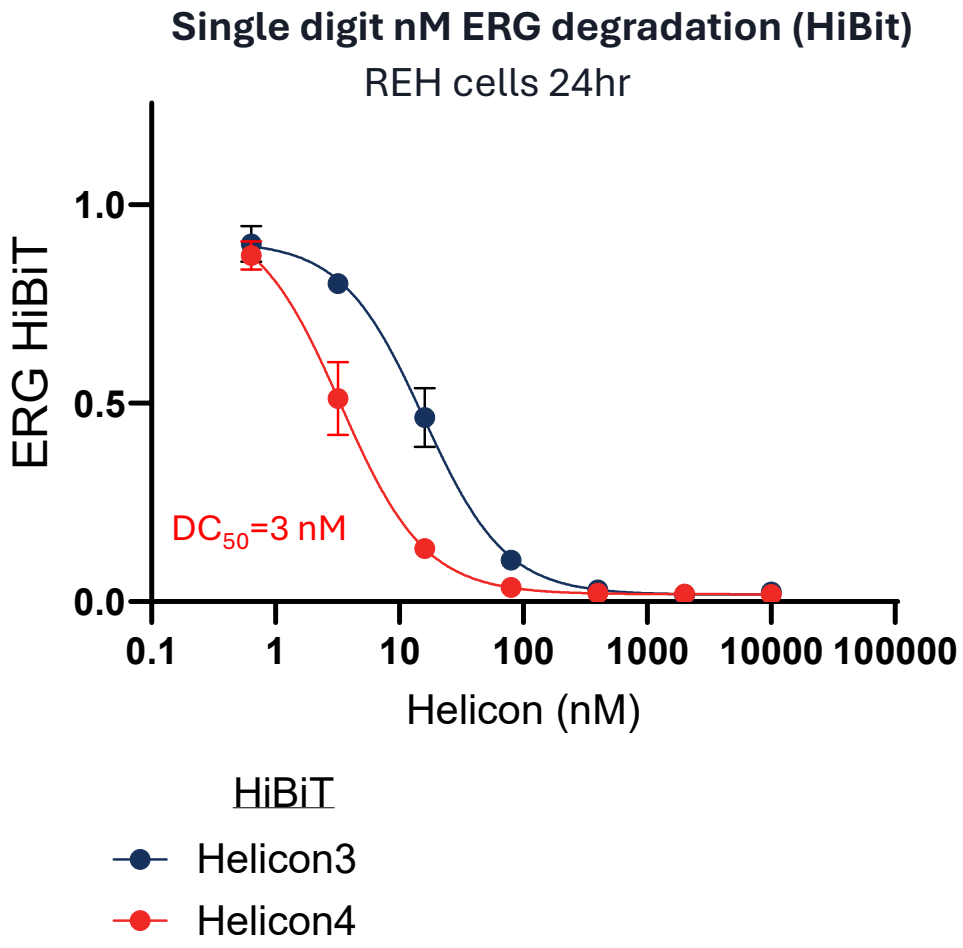
ERG Helicons compete for binding with PNT-domain specific probe with high affinity



Bifunctional ERG degrader Helicons form strong ternary complexes with E3 ligase

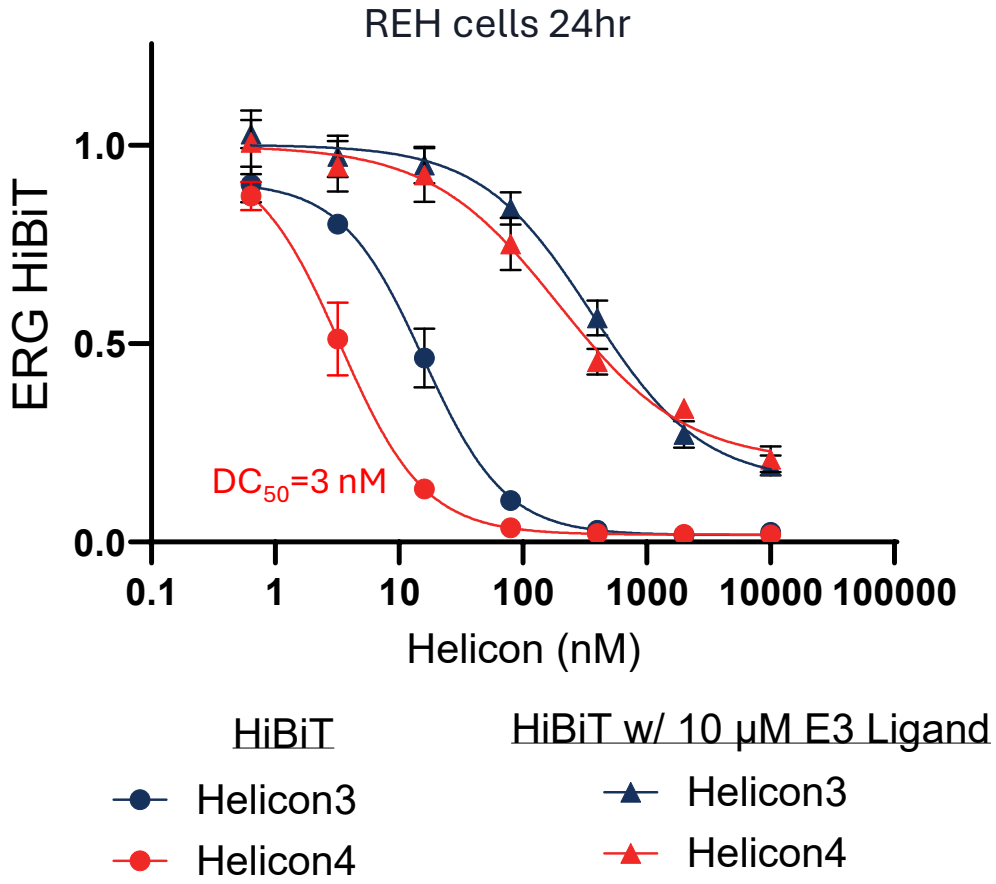


Proteasome and E3 Ligase-Dependent Degradation of ERG in Cell-based Assays



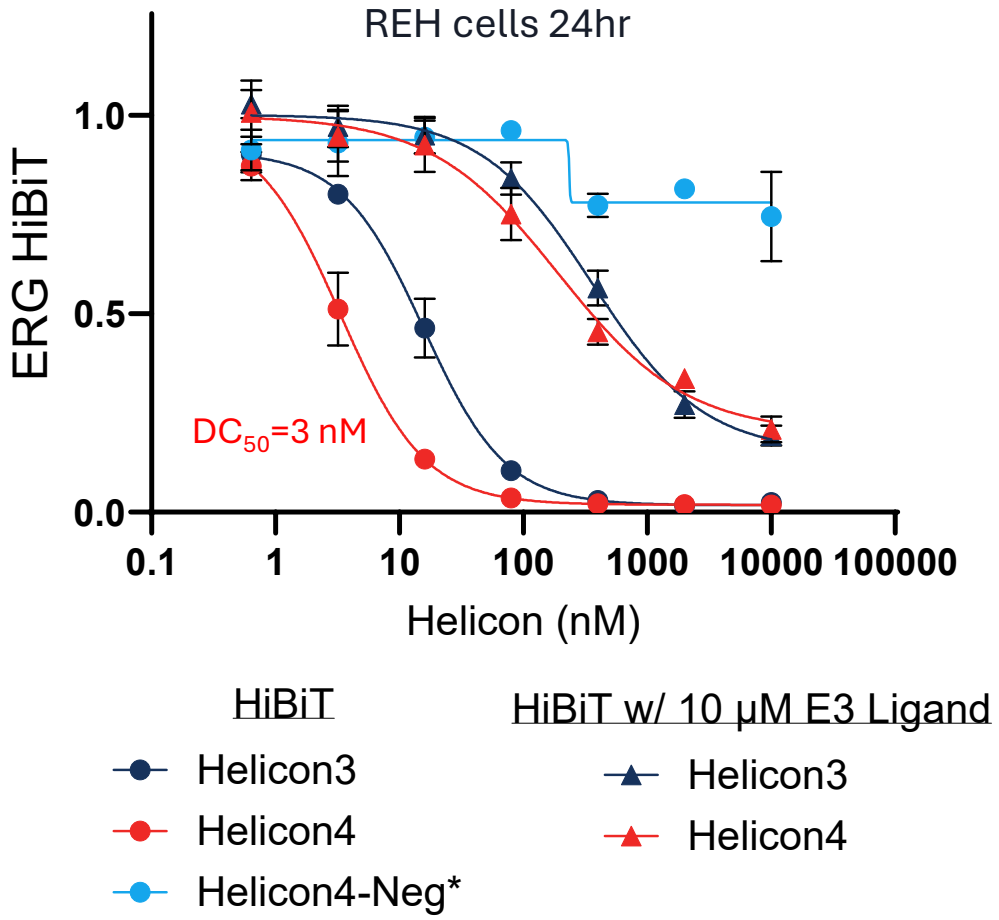
Potent Cell-Based Degradation of ERG: Proteasome and E3 Ligase Dependent

Soluble E3 ligand competes with degrader helicon for E3



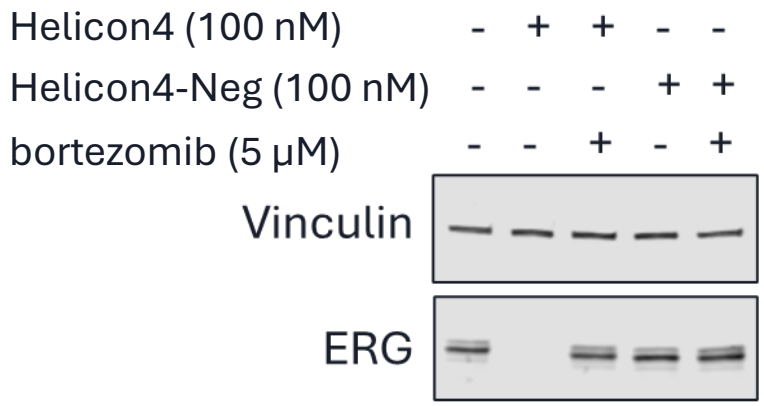
Potent Cell-Based Degradation of ERG: Proteasome and E3 Ligase Dependent

E3-incompetent Helicon does not degrade

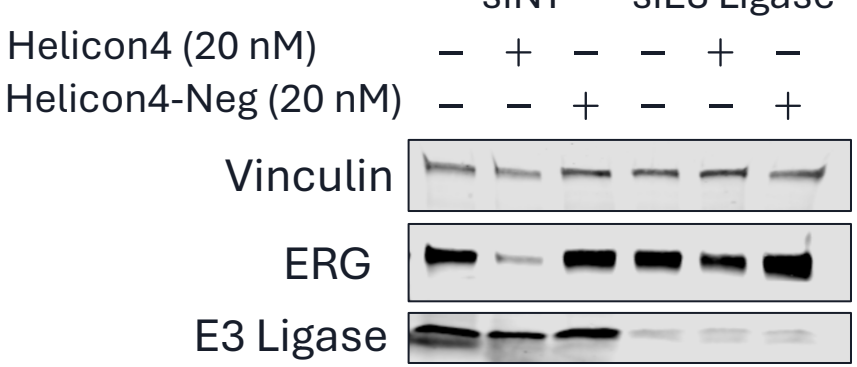


*E3 ligase incompetent modification of Helicon4

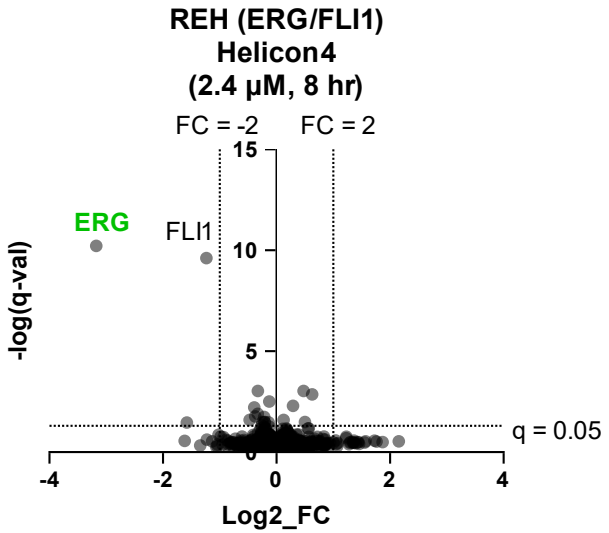
Proteasome Dependent Degradation



E3 Ligase Dependent Degradation

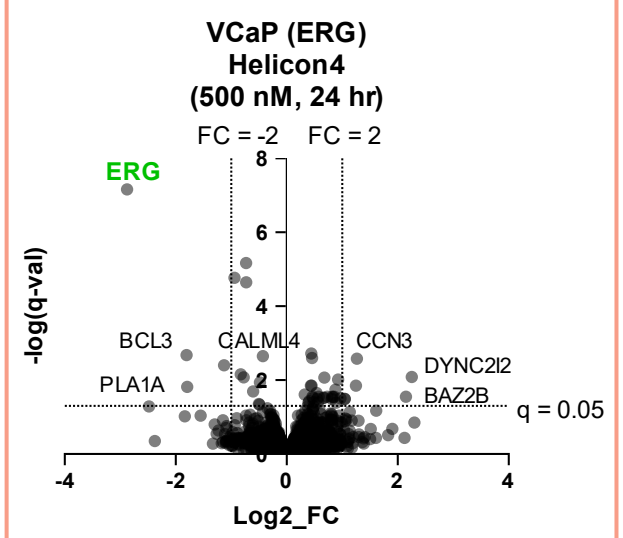


Highly Selective ERG Degradation Versus Off-target and FLI1 Proteins



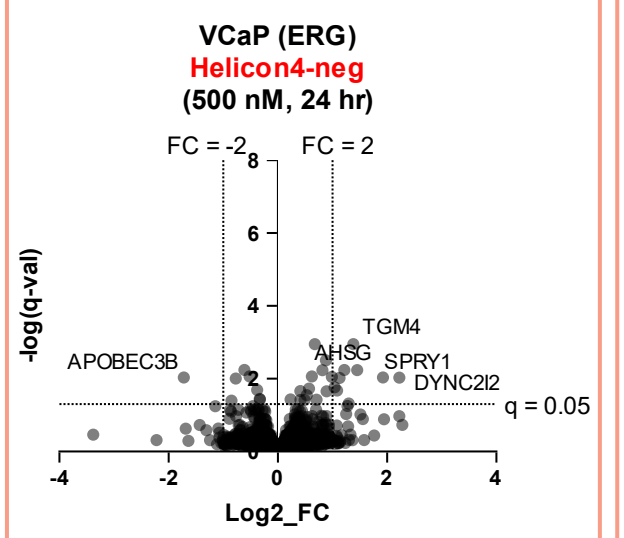
>6500 proteins identified

ERG is preferred substrate over FLI1 in REH cells, which contain both proteins.



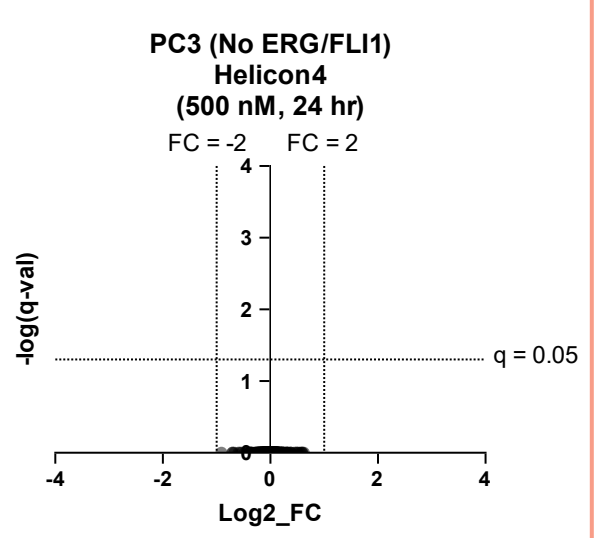
>7000 proteins identified

ERG and its target genes are the most highly downregulated proteins in VCaP at 24 hr treatment.



>7000 proteins identified

Null E3 matched negative control demonstrates minimal off-target protein changes in VCaP at 24 hr treatment.



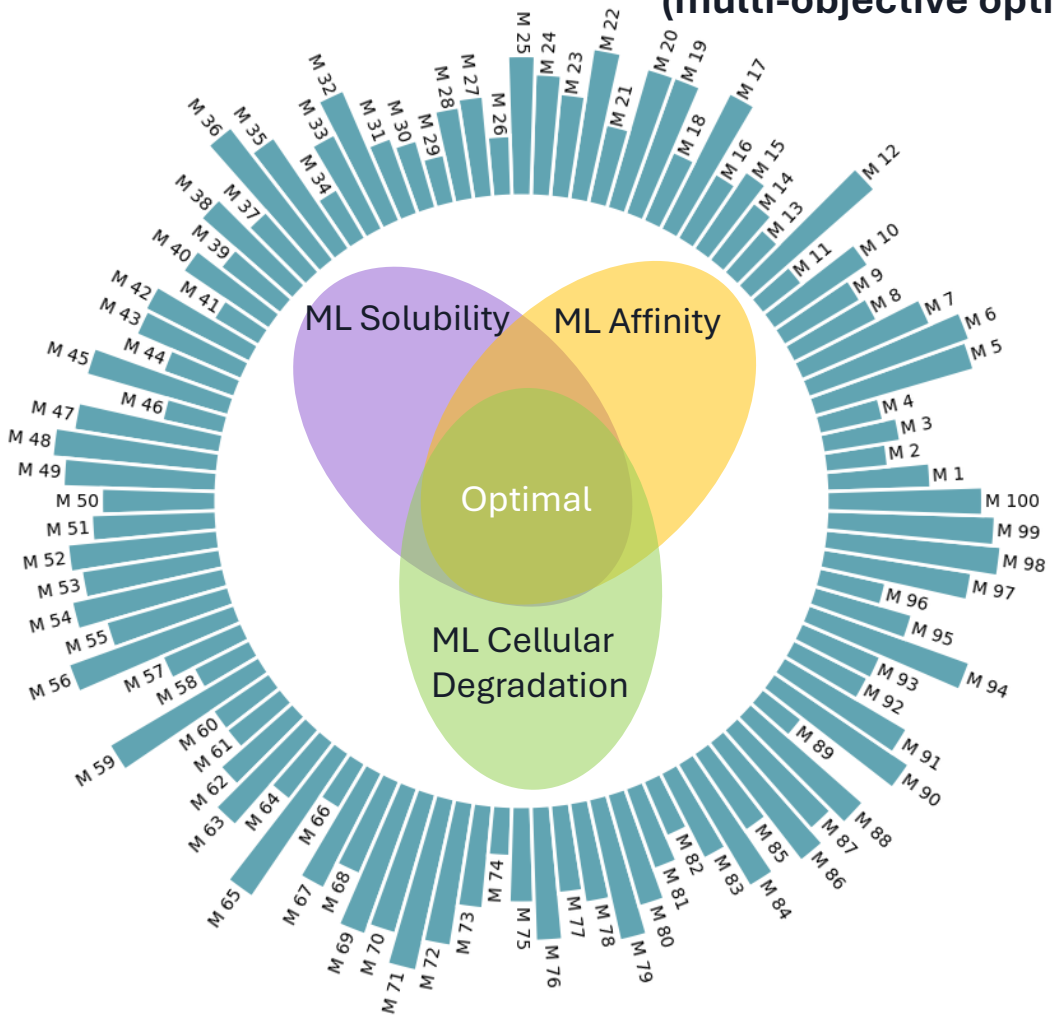
>7000 proteins identified

No proteins are significantly changed at 24 hr treatment in PC3, with Helicon2 or its null E3 matched negative control (not shown).

- Helicon4 has ~50X selectivity for ERG versus FLI1 in HiBit assays

Generative AI* Aids in the Identification of Novel Degraders with Improved Solubility and Cell-based Activity

Generative AI applied to ID novel Helicons bounded by ML models for solubility, affinity and degradation (multi-objective optimization from millions of possibilities)



48/48 designs with solubility >10uM;

5/48 with equivalent or better cell-based activity

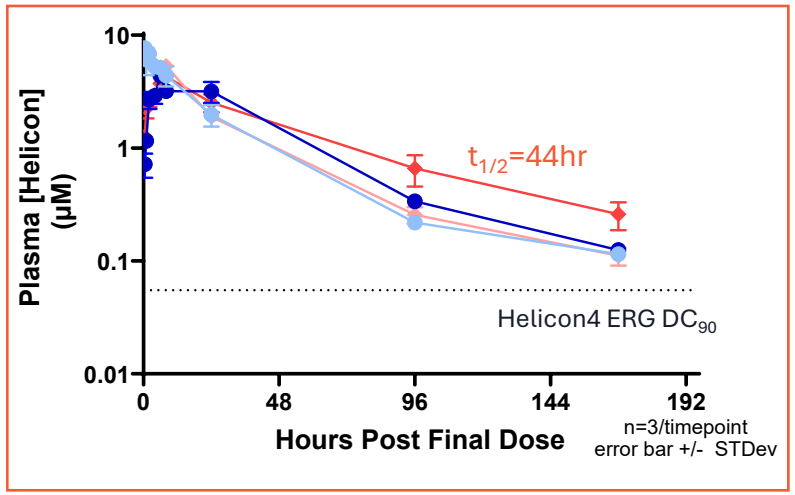
ID	Solubility (uM)	DC50 (nM)	#Mutation Sites
Parent	2	47	0
H76	50	29	2
H80	50	47	6
H64	50	49	5
H72	50	49	7
H66	50	50	6
H82	50	92	6
H74	50	139	6
H84	50	185	7
H62	50	194	6
H52	43	239	5
H58	16	192	5

M: probabilities of monomer occurrence from internal data create novel Helicons evaluated for fitness with ML models

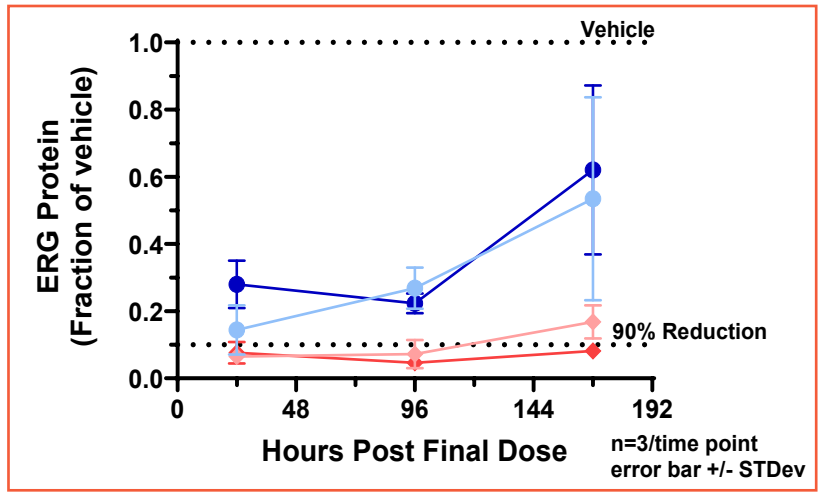
*Our scientists use Generative AI as one of many tools to discover and optimize degraders

Subcutaneous Dosing of Advanced Candidate Achieves Optimal PK and Prolonged Target Engagement

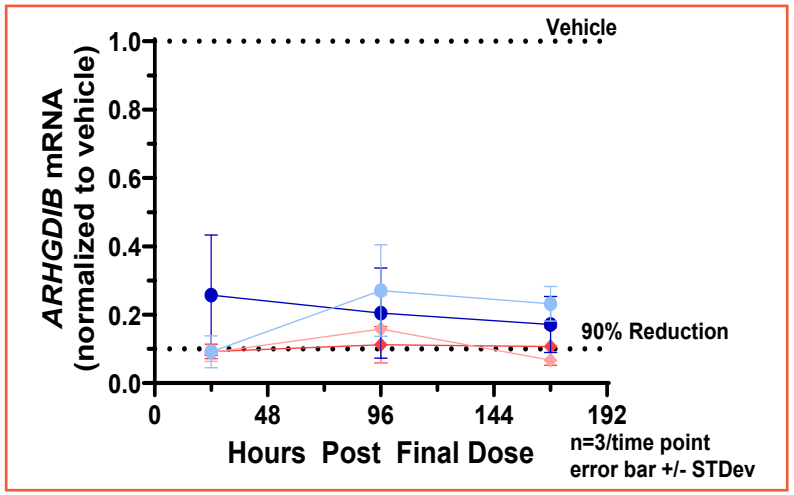
Subcutaneous Dosing of Lead Compound Minimizes C_{max}

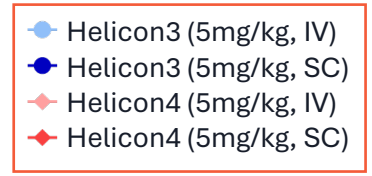


Deep and Durable Degradation of ERG Protein 7 Days Post 2nd Dose



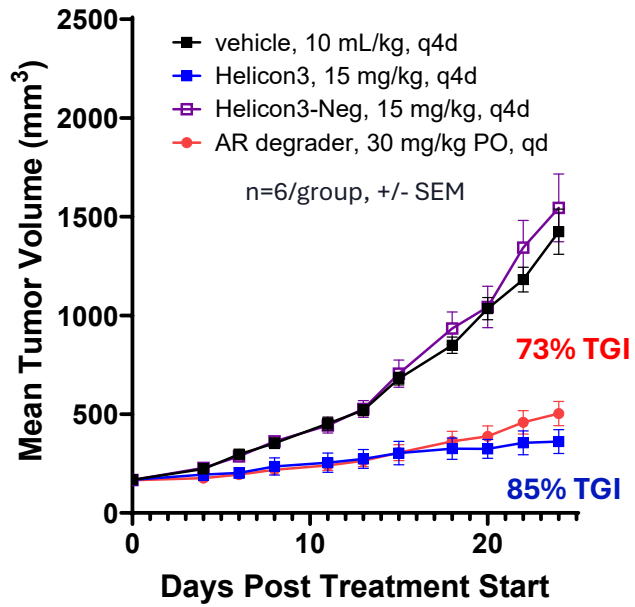
Deep and Prolonged Inhibition of ERG Transcription 7 Days Post 2nd Dose



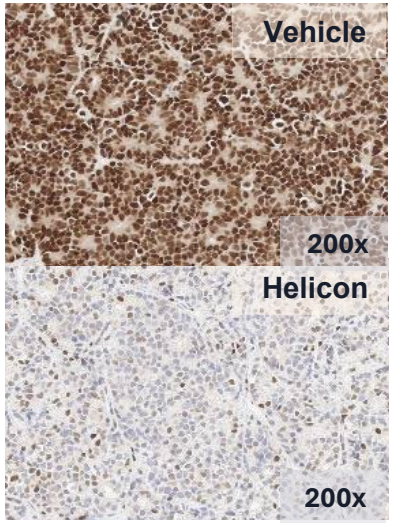


In Vivo Proof of Concept Efficacy for ERG Bifunctional Helicon Degraders: ERG Dependency in both CDX and PDX Models

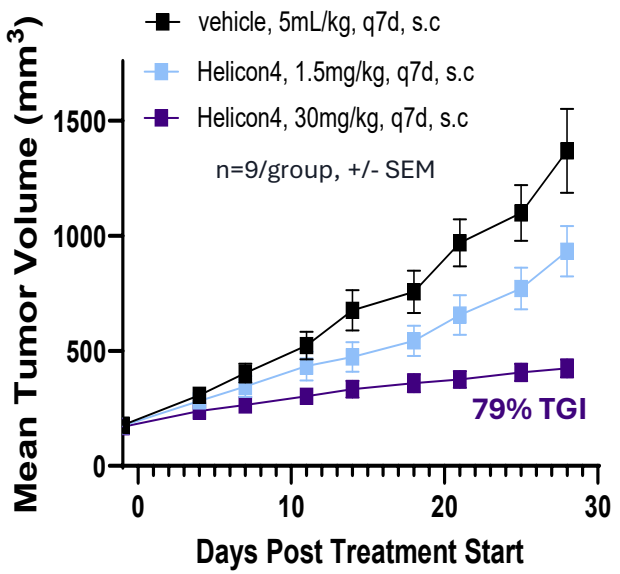
VCaP Xenograft Efficacy: ERG-fusion+, mCRPC AR amplified



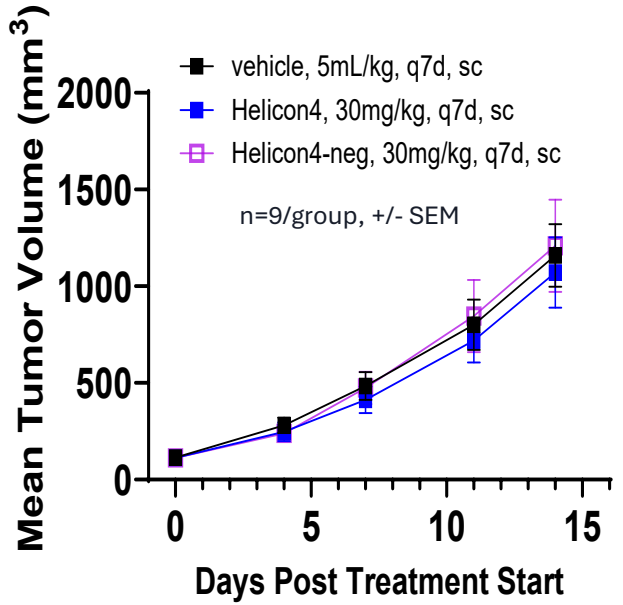
IHC-based ERG detection



Strong Anti-Tumor Activity in PDX#1 ERG-fusion+, mCRPC, AR amplified

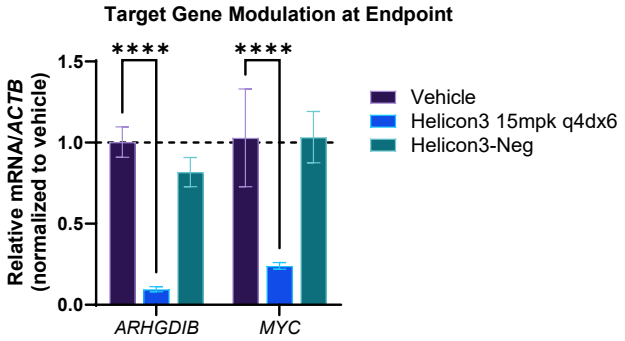


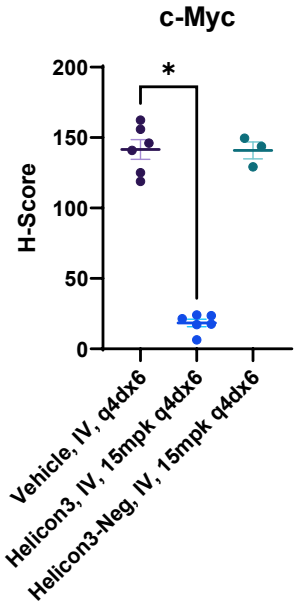
No activity in PDX#2 ERG-fusion+, ERG low, NE

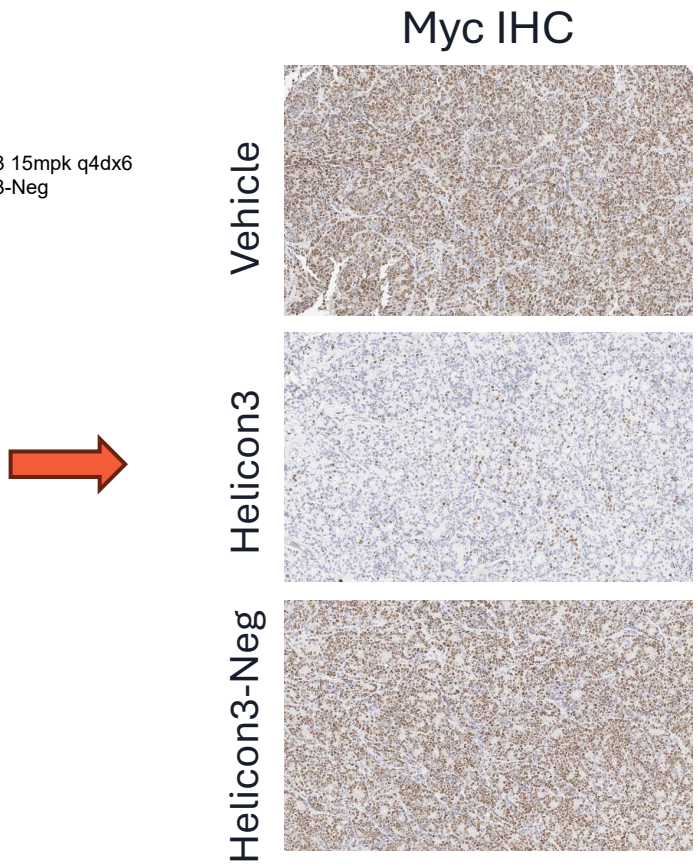


ERG Degradation in VCaP Tumors Leads to Down-regulation of MYC and Upregulation of Differentiation Markers

C-MYC RNA, Protein Levels and Downstream Program are Inhibited in VCaP Tumors Treated with ERG Degrader

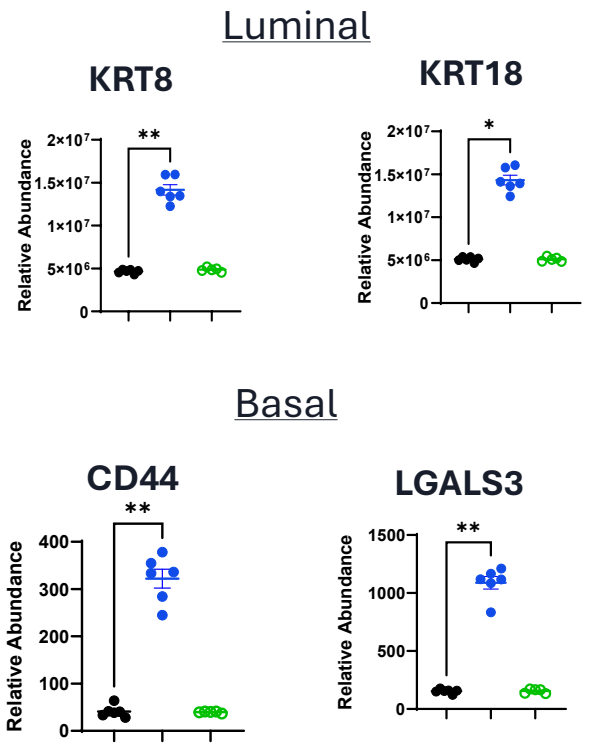






RNASeq: GeneSet	logFC	meta.q
HALLMARK:MYC_TARGETS_V1	-0.5199	0.00085
HALLMARK:MYC_TARGETS_V2	-0.6616	0.00085

Differentiation Markers are Up-regulated by ERG Degrader††



††Measured by proteomics

Note: Very low KRT5/14 in these samples

Summary

- ML-driven Helicon peptide drug discovery platform has yielded potent bifunctional degraders of ERG transcription factor
  - Low nM binding affinity for ERG (SPR)
  - Low nM DC_{50} for ERG in cell-based HiBit assay
- Long plasma $t_{1/2}$ (~2 days) with subcutaneous dosing route in animal models
- Suppression of tumoral ERG protein levels $\geq$ 90% for 7 days post dose in animal models
- Anti-tumor activity in VCaP CDX and multiple PDX models of mCRPC correlated with degree of ERG degradation
- Ongoing work to define sub-populations of ERG-fusion+ patients for clinical inclusion/exclusion, PD biomarker definition (circulating, digital pathology, tumor biopsy), combination strategies

Acknowledgments

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