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KRAS-Targeted PROTAC Degraders are Broadly Efficacious Against KRAS-Dependent Tumor Models

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I have the following relevant financial relationships to disclose:

Employee of: Arvinas Operations, Inc.

Stockholder in: Arvinas, Inc.

PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies

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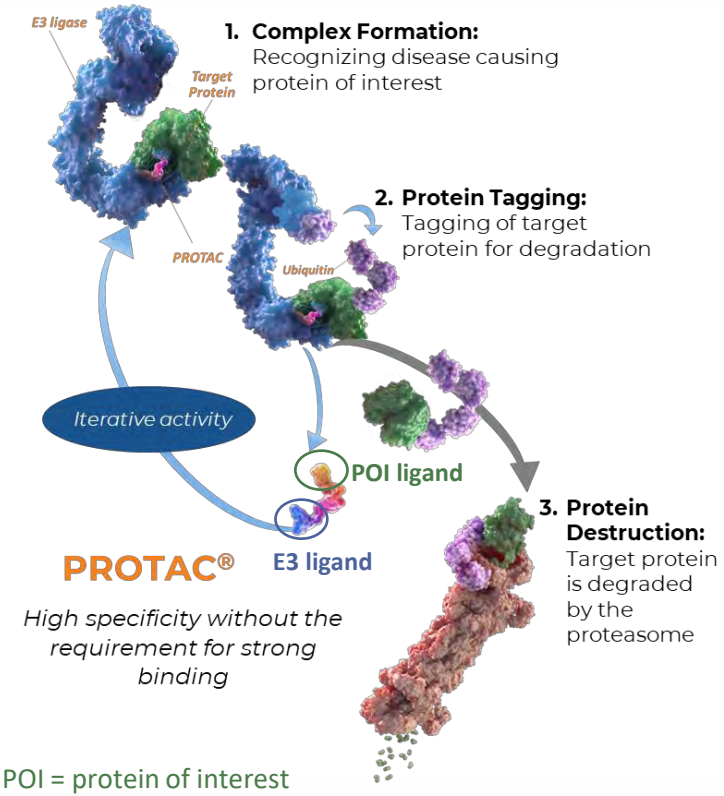

POI = protein of interest

Arvinas' proteolysis-targeting chimera (PROTAC®) degraders can:

- Eliminate (rather than inhibit) disease-causing proteins
- Disrupt scaffolding functions of target proteins
- Bind and degrade classically "undruggable" proteins
- Act iteratively (catalytically)
- Be delivered orally and achieve broad tissue distribution, including across the blood-brain-barrier

Why might a KRAS PROTAC degrader have advantages?

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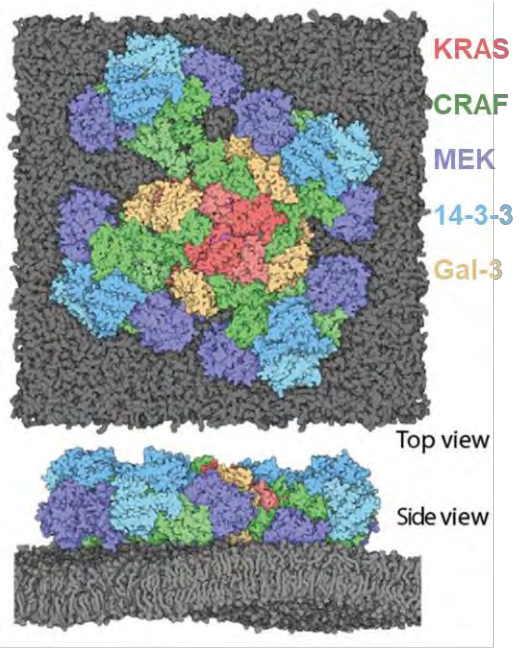
- KRAS biology (scaffolding role):
  - KRAS exists in a multi-protein complex at the membrane that may be disrupted by degradation
- Catalytic/durable pharmacodynamics (PD):
  - Slow resynthesis rate of KRAS
  - Extended exposure due to possible accumulation of PROTAC in the tumor

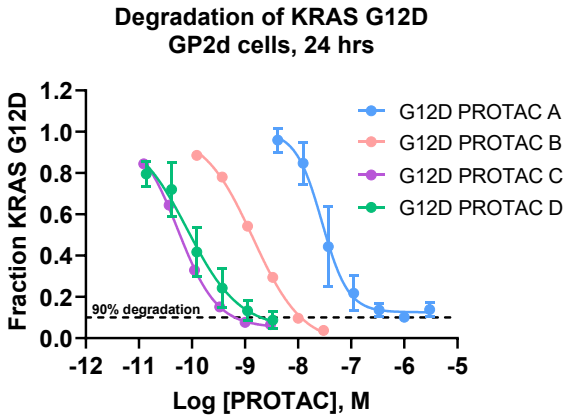
Focus on KRAS G12D for this talk

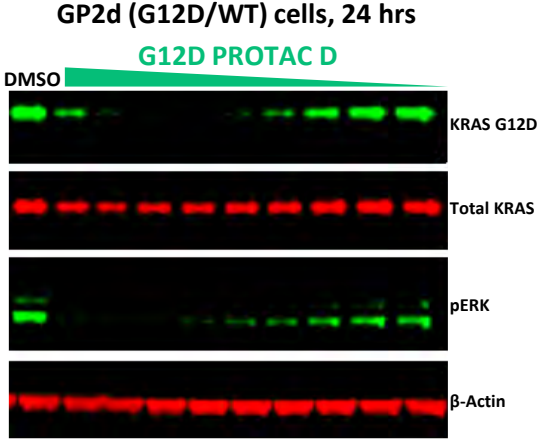


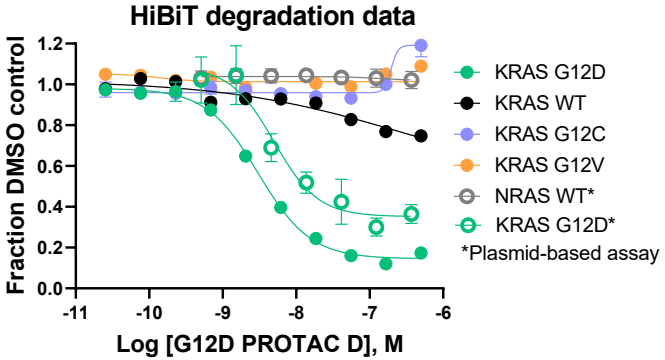
Mysore *et al.* Nat Struct Mol Biol, 2021

G12D PROTAC degraders have picomolar potency and high selectivity

- Optimized degraders exhibit DC_{50} <1 nM and Dmax >90% for G12D
- Potent pERK suppression
- Highly selective for KRAS G12D



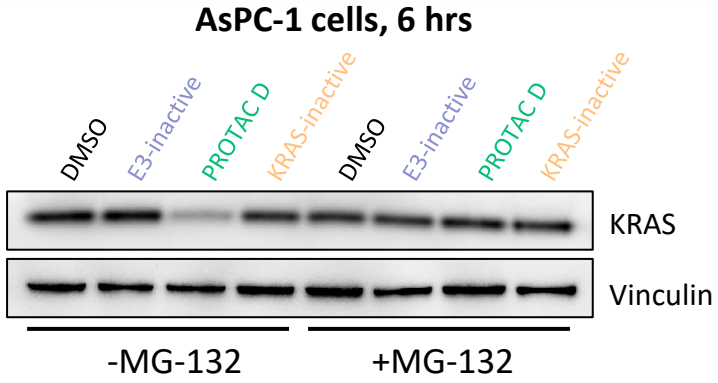


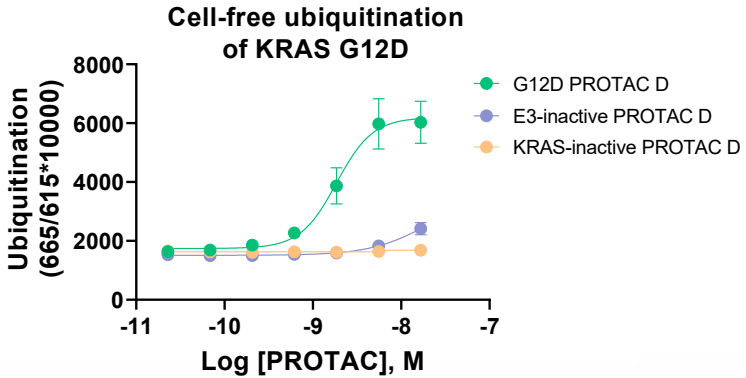


G12D PROTAC degraders are dependent on the Ubiquitin Proteasome System (UPS)

- Inactivating either the KRAS or E3 ligase ligand prevents degradation
- Inhibiting the UPS pathway rescues degradation
- G12D PROTAC leads to direct ubiquitination of KRAS G12D

Does degradation have advantages over inhibition?
Compare active PROTAC vs E3-inactive PROTAC
(same physiochemical properties)

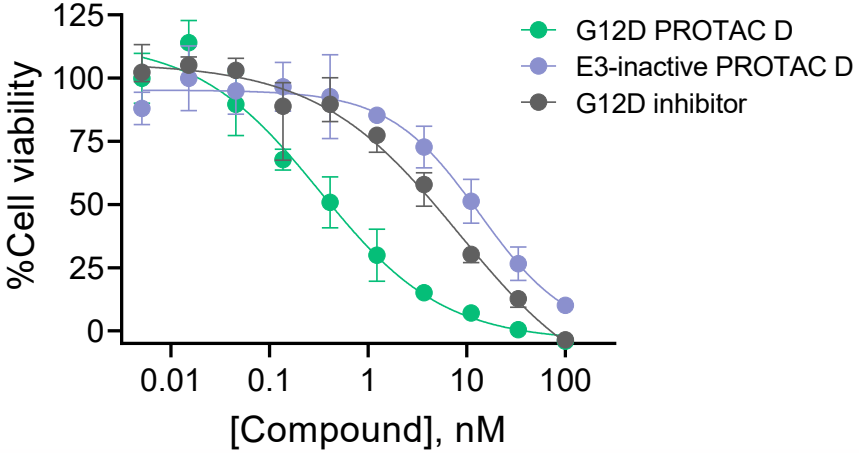




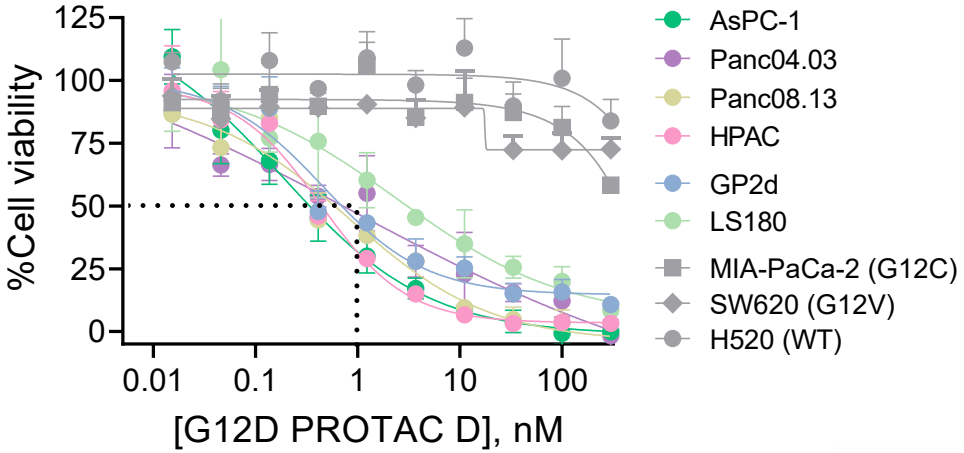
Degrader shows more potent anti-proliferative effect

- Active degrader >20-fold more potent at inhibiting proliferation in 3D
- Degrader displays GI_{50} < 1 nM in multiple G12D models

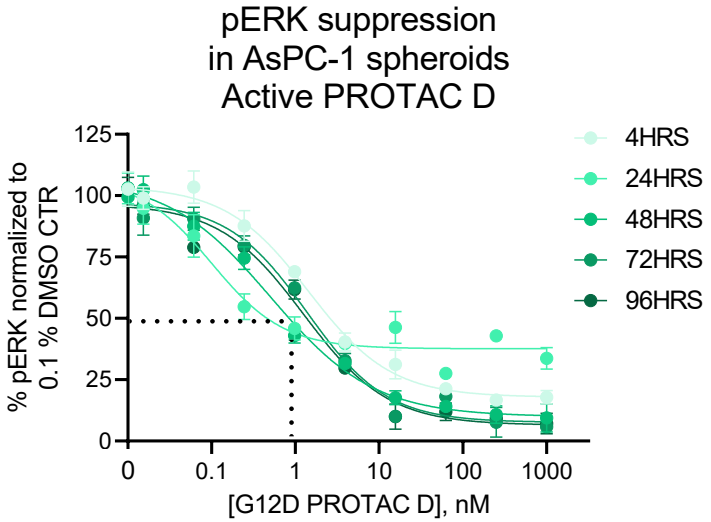
3D proliferation in AsPC-1 cells

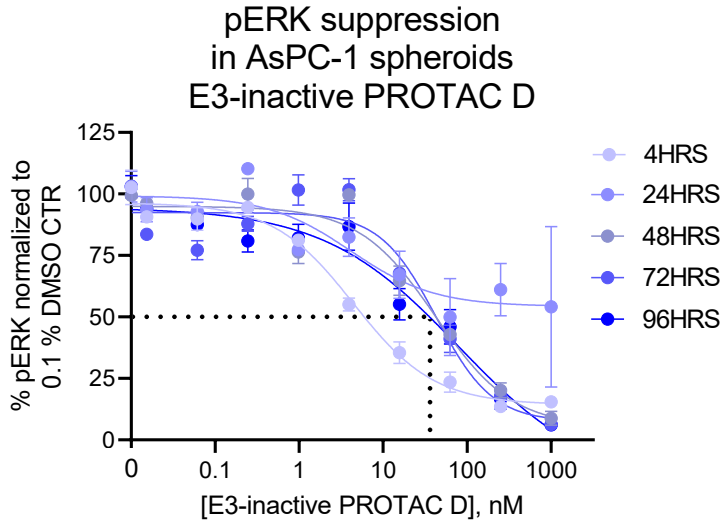


3D proliferation in multiple models



Degrader shows more potent signaling suppression

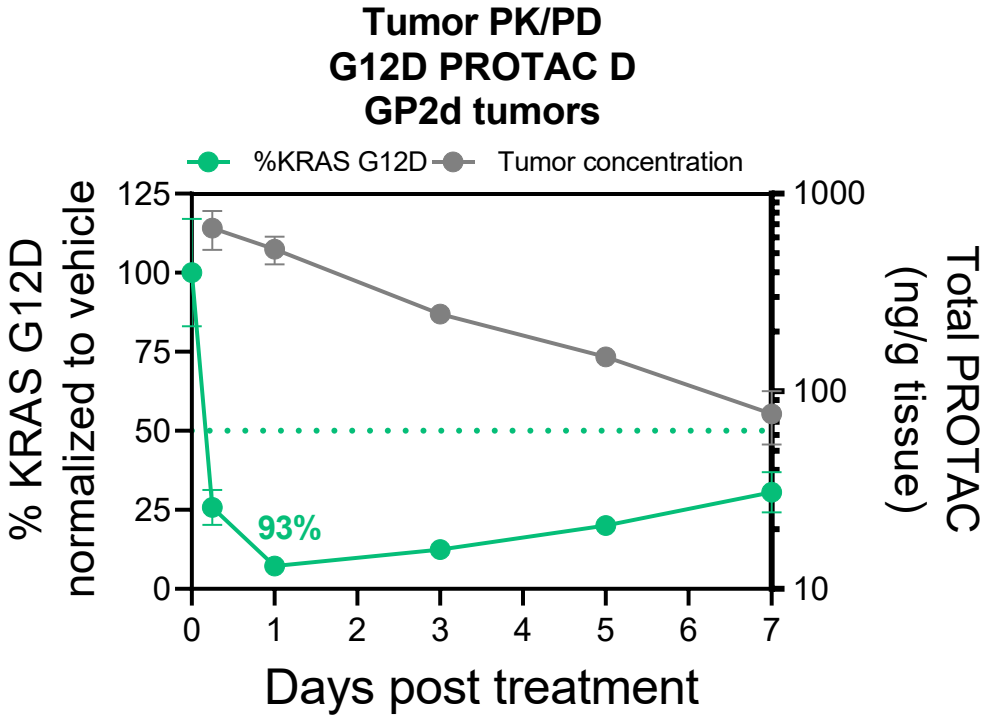




- MAPK (pERK) and AKT ($pS6^{240/244}$;data not shown) signaling more potently suppressed with active degrader

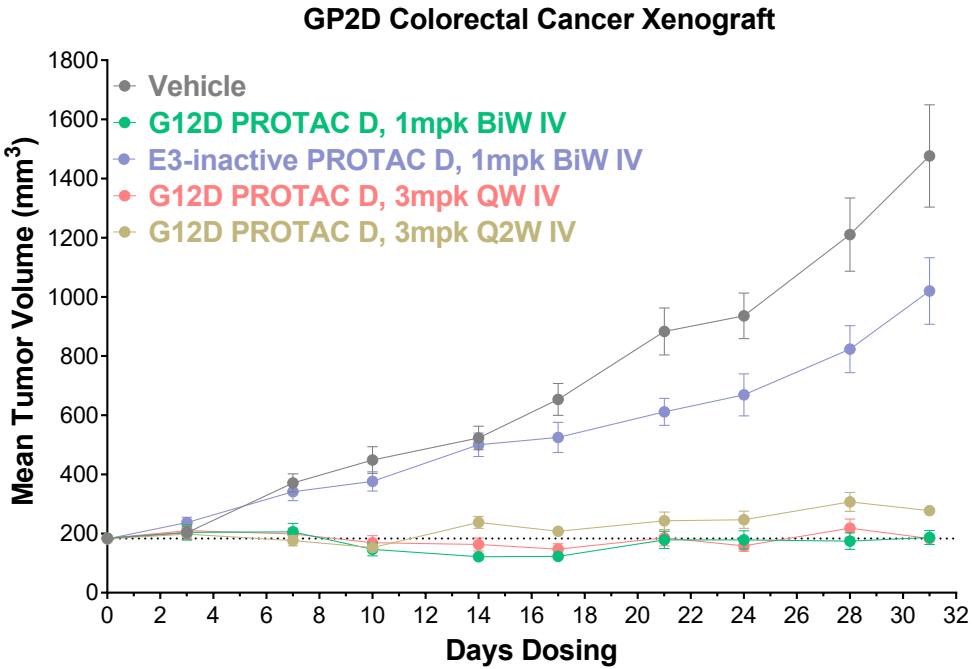
Single dose of G12D PROTAC suppresses KRAS levels for ≥7 days

- Single 3 mpk IV dose of PROTAC D administered
- Maximum degradation of >90% achieved at 24 hrs
- After 7 days, KRAS is still 70% degraded
- Prolonged exposure in tumor



Low, infrequent dosing of G12D PROTAC is efficacious *in vivo*

- PROTAC dosed at 1 mpk BiW or 3 mpk QW and Q2W demonstrates 93-100% TGI
  - Significantly more efficacious than E3-inactive
- No body weight effects



Summary

- KRAS G12D PROTAC degraders are potent and selective
- Degradation of KRAS G12D provides an advantage *in vitro* and *in vivo*
  - Potent signaling suppression, anti-proliferation and apoptosis induction (data not shown) *in vitro*
  - Single, low dose of PROTAC suppresses KRAS in tumors for ≥7 days
  - Extended *in vivo* PD correlates with ~100% TGI with intermittent dosing
  - Well tolerated in mice

Acknowledgements

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