Protein Translation Inhibitors (PTIs) Enable Next-Generation Antibody Drug Conjugates

Hexagon Bio

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Hexagon Bio, Menlo Park, CA, USA

Only Three Classes of ADC Payloads Are Approved More Are Needed

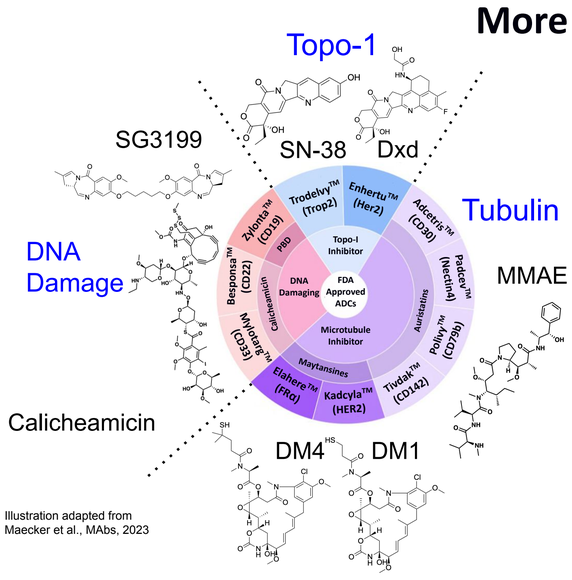
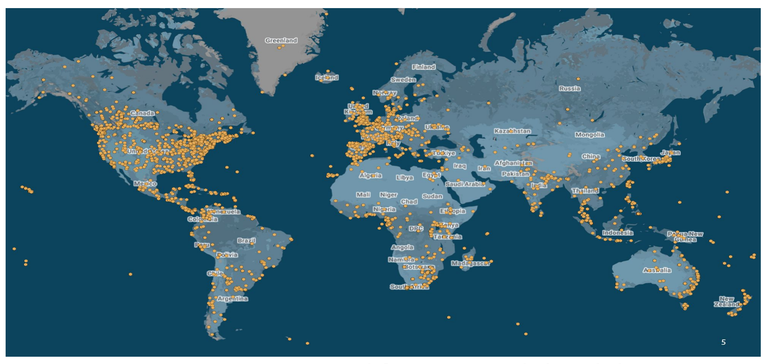


Illustration adapted from Maecker et al., MAbs, 2023

"The problem is, regardless of the antibody, there are sequencing issues when a tumor has already been exposed to a payload of similar class. **New payloads are desperately needed to advance ADCs forward."**
Patricia LoRusso, Yale School of Medicine, ASCO 2025

Hexagon's >100,000 Microbial Strains Are an Unparalleled Source for Novel Cytotoxic ADC Payloads



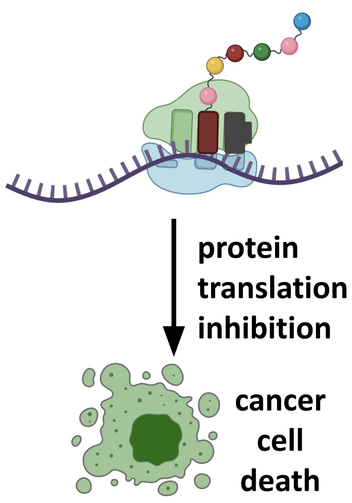
Strains were acquired from around the globe.
We have sequenced **over 80,000** genomes.
Approximately 400 putative mechanisms of action predicted.

Platform identifies mechanisms orthogonal to existing ADC payloads

~400 cytotoxic MoAs essential to cancer cell growth / survival:

- **DNA/RNA-associated pathways**
  - Nucleotide biosynthesis
  - mRNA splicing
  - tRNA, rRNA modification
- **Protein-associated pathways**
  - Protein biosynthesis: Initiation, elongation, termination
  - Sumoylation
- **Energy production**
  - Electron transport
  - Citric acid cycle
  - Glutamine metabolism
- **Fat/lipid synthesis**
  - Cholesterol, sphingolipid, triglyceride biosynthesis
- **Plus many other mechanisms**
  - Cell cycle, vacuolar protein sorting, and dozens more

Protein Translation is a Key Vulnerability in Cancer

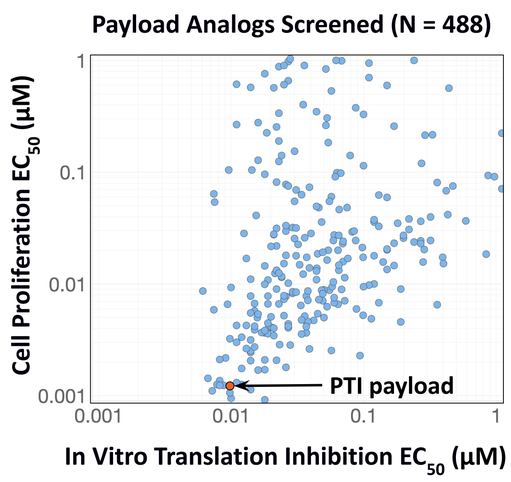


Tumor development and progression depends on continuous proteome remodeling and sustained production of oncogenic proteins.

Tumors likely to be most sensitive to protein translation inhibition are those that:

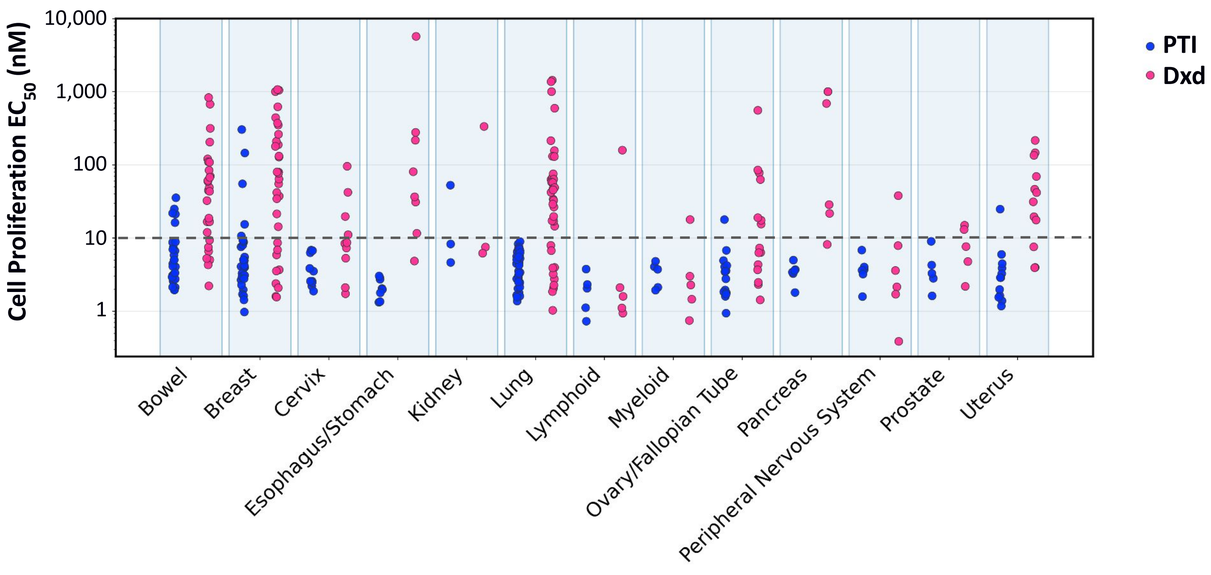
- Rely on continuous supply of oncogenic drivers
- Overexpress oncogenic proteins with short half-lives
- Express elevated levels of translational machinery

Generation of PTI Payload

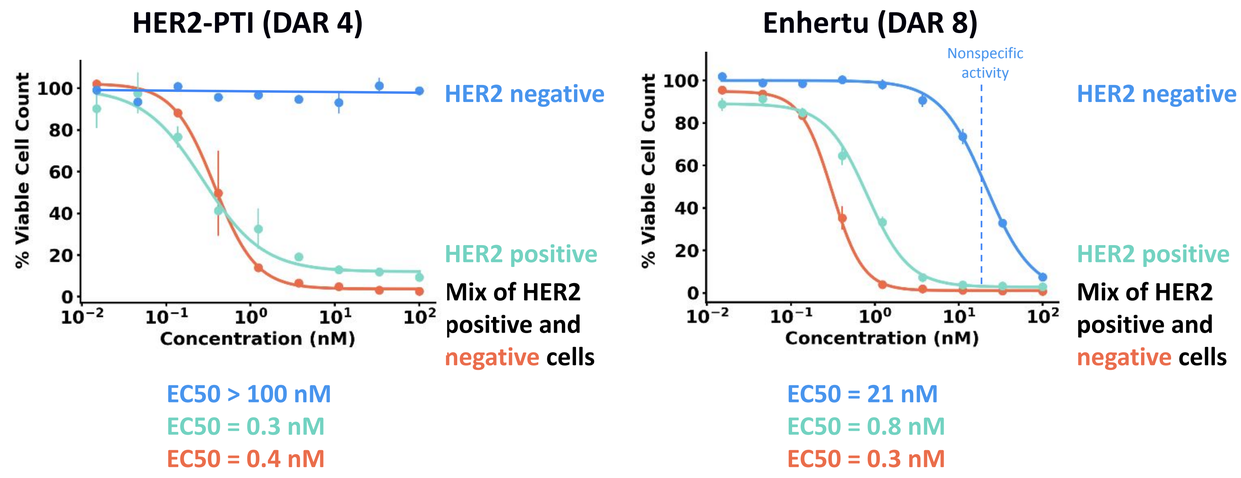


Assessment	PTI Payload
ALogP | ALogD(7.4)	2.3 | 2.2
Topological polar surface area	146 Å^2
Calculated pKa (%ionized at pH 7.4)	6.9 (24%)
Kinetic solubility (pH 7.4 PBS)	290 µM
In vitro translation EC50 (span)	14 nM (95%)
72 hr in vitro cell killing EC50 (geo mean)	1.4 nM
Permeability Caco-2 + elacridar	6.5 µcm/s

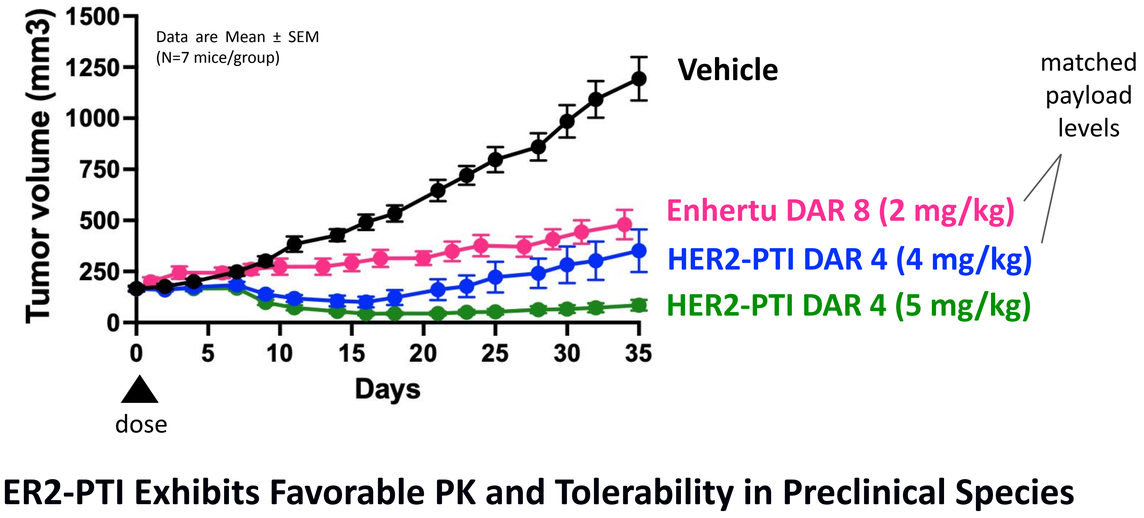
Hexagon's PTI Payload Inhibits 92% of Cell Lines with EC50 ≤ 10 nM Compared to 37% for Topo-1 Payload Dxd (N = 170)



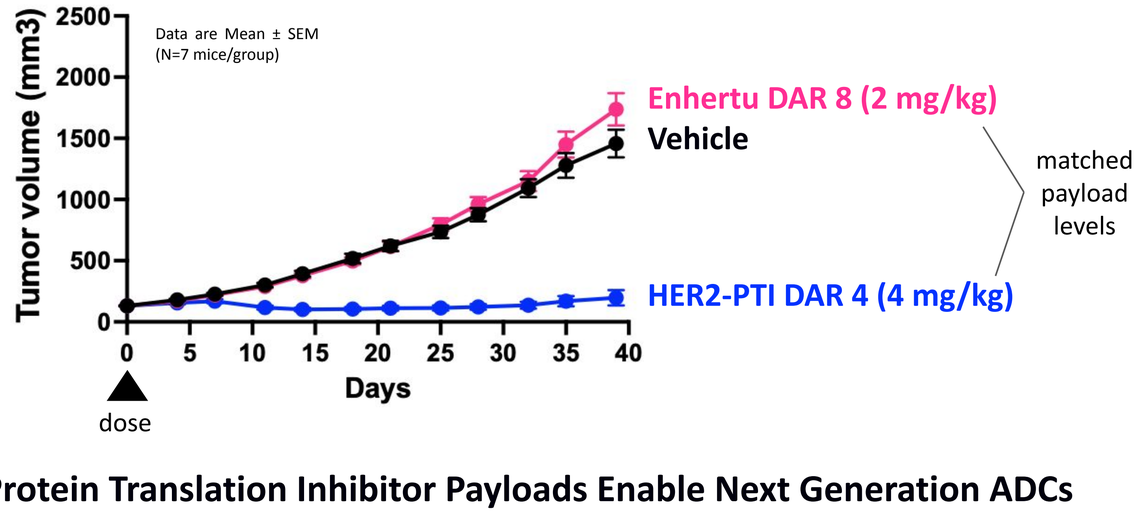
Trastuzumab ADC (HER2-PTI) Shows Antigen-Dependent Cancer Cell Killing and Bystander Killing



A Single Dose of HER2-PTI is Effective in NCI-N87 Gastric Model (HER2 High ~500k receptors/cell)



A Single Dose of HER2-PTI is Effective in an Enhertu Acquired Resistance NCI-N87 Gastric Model (HER2 Medium ~200k receptors/cell)



HER2-PTI Exhibits Favorable PK and Tolerability in Preclinical Species

Assessment	HER2-PTI Result
PK in Mouse	Total Antibody t1/2 = 264 h (matches Enhertu)
PK in Rat	Total Antibody t1/2 = 261 h (matches Enhertu)
PK in Cyno	Total Antibody t1/2 = 158 h (matches Enhertu)
Safety in Rat	Tolerated at 30 mg/kg
Safety in Cyno	Tolerated at 15 mg/kg Q3W x 2

Protein Translation Inhibitor Payloads Enable Next Generation ADCs

Payload Property	PTI
Mechanism is not used in SoC chemotherapy (i.e., no prior exposure)	✔
Low vulnerability to resistance related to target mutation or expression	✔
Low vulnerability to resistance related to drug efflux by BCRP	✔
Highly potent across a broad range of cancer cell lines	✔
Induction of immunogenic cell death markers	✔
Absence of classical ADC toxicities: hematologic, ocular, pulmonary	✔
First-in-class potential across validated tumor targets	✔