The Development Path of a HER2-Targeted Translation Inhibitor ADC: A Novel Payload and ADC to Address a Growing Clinical Need

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Only Three Classes of ADC Payloads Are Approved; More Are Needed

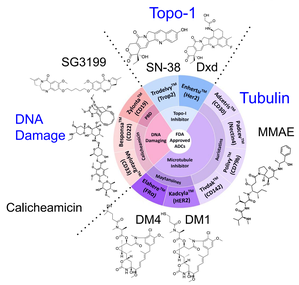


Illustration from Maecker et al., MAbs, 2023

There is a need for new ADC payload mechanisms due to:

- **Safety liabilities** with existing payloads
- **Resistance to existing payloads**: Tumors stop responding to existing ADC payloads

All approved ADC payloads are derived from natural products – they are cytotoxic agents optimized by evolution for potency and cell permeability

Clinical Problem: New ADC Payloads are Needed For Cancer Cures

1. Resistance to Existing ADC Payloads

>100k patients/yr treated with ADCs, but most tumors relapse:

ADC	mPFS
Enhertu (HER2)	13-29 mo
Kadcyla (HER2)	6-10 mo
Trodelvy (TROP2)	5-11 mo
Datroway (TROP2)	4-8 mo

Tumor relapse is often due to **payload resistance** *(Destiny-Breast 02, Huppert et al. NPJ Breast Cancer 2025)*

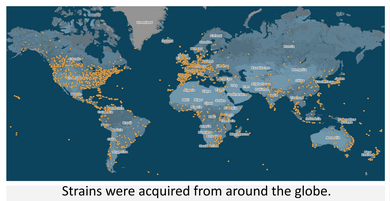
"The problem is, regardless of the antibody, there are sequencing issues when a tumor has already been exposed to a payload of similar class. **New payloads are desperately needed to advance ADCs forward."**
- Patricia LoRusso, Yale School of Medicine, ASCO 2025

2. Some tumor types don't respond to existing ADC payloads due to resistance against the same standard-of-care chemotherapy class

- Chemo standard of care (SOC) often leads to resistance against many current ADCs due to existing payloads using the same class/mechanism of action (MOA)
- Novel payloads with non-overlapping MOAs present large opportunities where current topo-based ADCs cannot effectively compete today

Patients urgently need ADC payloads with **mechanistically distinct and novel MOAs**

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.

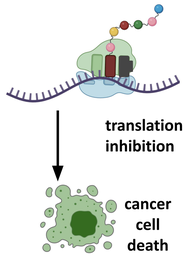
Platform identifies mechanisms orthogonal to existing ADC payloads

~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

HER2-TI payload was not identified using platform

Translation is a Key Vulnerability in Cancer

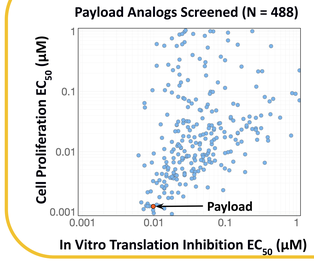


Tumor development and progression depends on continuous proteome remodeling and sustained production of oncogenic proteins.

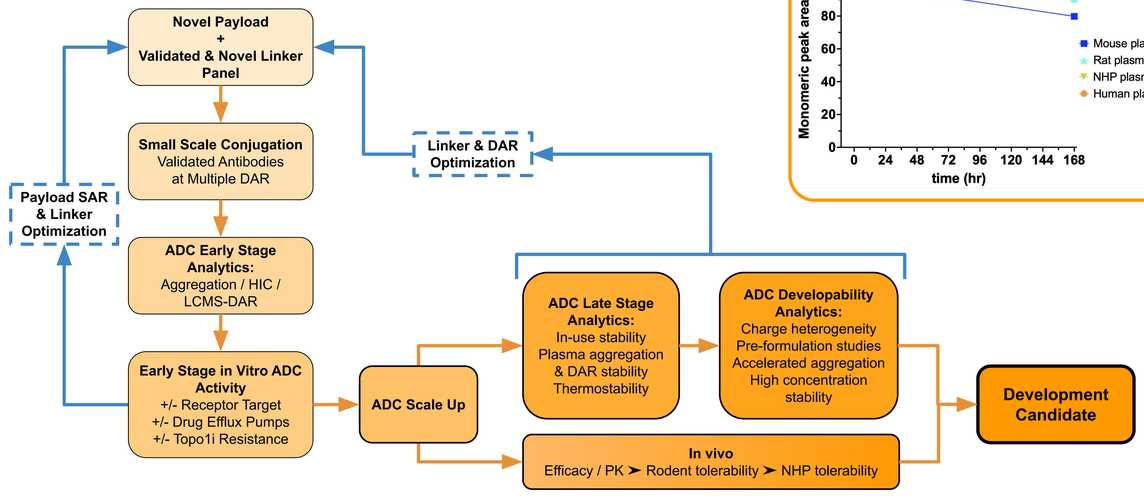
Tumors likely to be most sensitive to translation inhibition are those that:

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

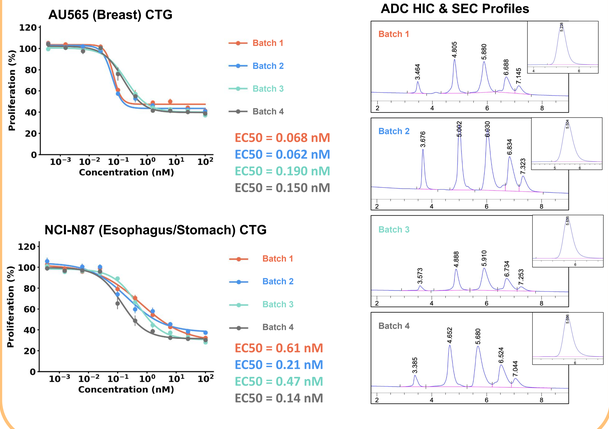
Generation of Translation Inhibitor Payload



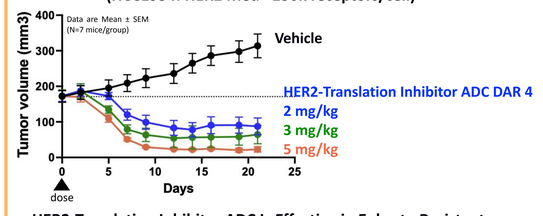
Assessment	Translation Inhibitor Payload
ALogP | ALogD(7.4)	2.3 | 2.2
Topological polar surface area	146 Å^2
Calculated pKa (%ionized at pH 7.4)	6.9 (24%)
Kinetic solubility (pH 7.4 PBS)	290 µM
In vitro translation EC50 (span)	14 nM (95%)
72 hr in vitro cell killing EC50 (geo mean)	1.4 nM
Permeability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



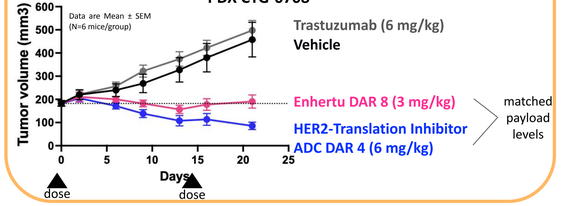
HER2-Translation Inhibitor ADC Batch-to-Batch Consistency For *in vitro* Assays and *in vivo* Studies



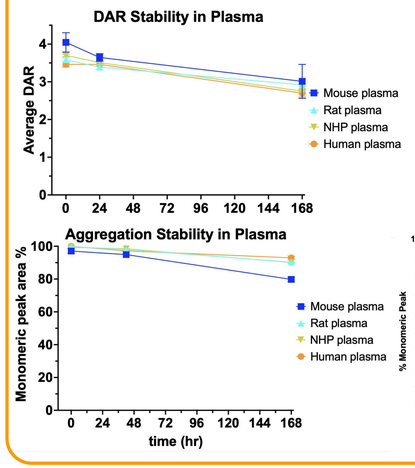
A Single Dose of HER2-Translation Inhibitor ADC Is Effective in Breast Cancer Model: MED <2 mg/kg (HCC1954: HER2 Med ~250k receptors/cell)

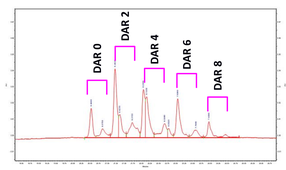


HER2-Translation Inhibitor ADC Is Effective in Enhertu Resistant PDX CTG-0708

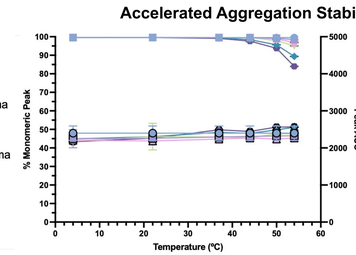


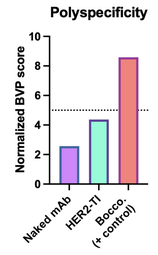
HER2-Translation Inhibitor ADC Shows Favorable Biophysical Properties





Peak	pI	% Area
DAR 0, Main	8.67	9
DAR 0, Acidic	8.57	5.1
DAR 2, Main	8.46/8.42	12.4
DAR 2, Acidic	8.31	10.6
DAR 4, Main	8.22 / 8.19	27.7
DAR 4, Acidic	8.04 / 8.00	9.9
DAR 6, Main	7.93	14.3
DAR 6, Acidic	7.77	4.1
DAR 8, Main	7.66	6.9

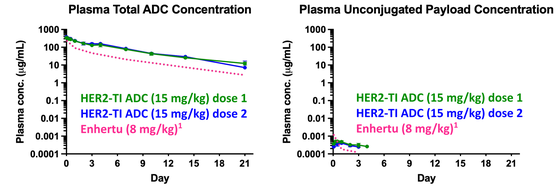




HER2-Translation Inhibitor ADC Exhibits Favorable PK in Preclinical Species

Assessment	HER2-Translation Inhibitor ADC 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 NHP	Total Antibody t1/2 = 158 h (matches Enhertu)

The PK Profile for HER2-Translation Inhibitor ADC in NHP Is Similar to Enhertu



HER2-Translation Inhibitor ADC Is Tolerated Up to 15 mg/kg in NHPs and 40 mg/kg in Rats With No Body Weight Loss or Mortality

	NHPs: 15 mg/kg (N=2)	Rats: 40 mg/kg (N=3)
Study design	Two doses (d0, d21) with 21 days recovery	Single dose (d0) with 14 days recovery
Mortality	No mortality observed	No mortality observed
Body weight	Stable body weight (+/-5% of baseline)	Stable body weight (+/- 10% of baseline)
Ophthalmic observations	Normal	No findings (histopathology)
Hematology & coagulation	No thrombocytopenia and no neutropenia. Reversible increase in fibrinogen	Mild to moderate increases in WBC ≥20 mg/kg
Clinical chemistry	Reversible increase in ALT, AST, CK Stable bilirubin	Mild hypoalbuminemia, reduction in cholesterol ≥30 mg/kg and increase in LDH ≥30 mg/kg
Necropsy observations	N=1 Thyroid gland (increased size) N=1 Liver (adhesion)	Skin erythema, scabbing
Histopathology	No TA-related findings	Skin hyperplasia of the epidermis and dermal inflammation