# Antibody Drug Conjugates With Novel Translation Inhibitor Payloads Exhibit Tumor Growth Inhibition in Solid Tumor Models

Hexagon Bio
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Hexagon Bio, Menlo Park, CA

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

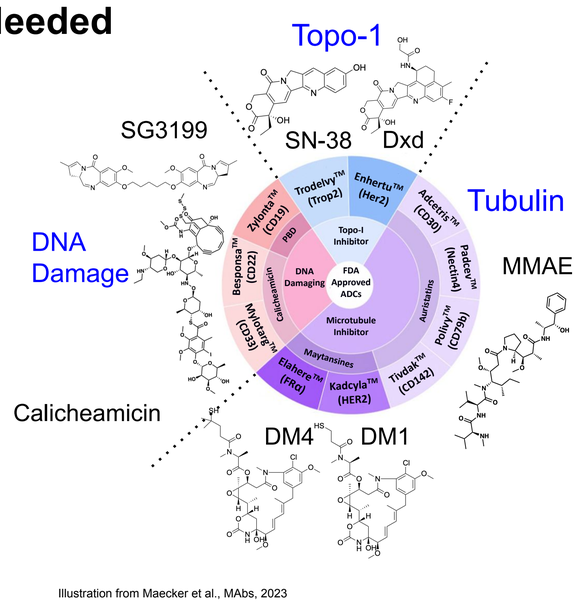


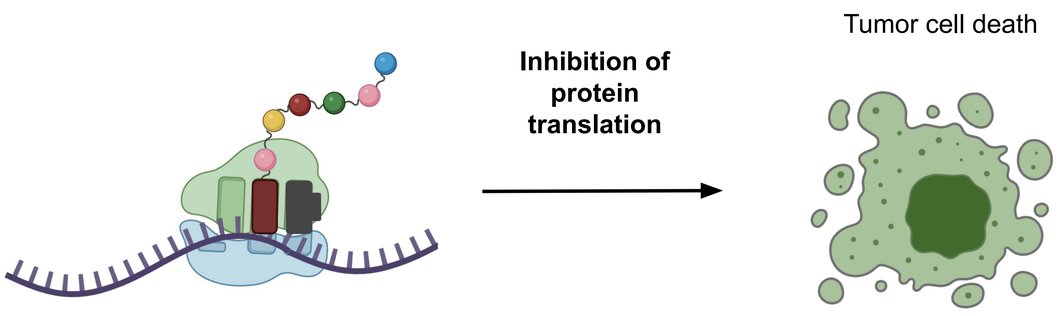

Illustration from Maecker et al., MAbs, 2023

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

## We Have Identified Inhibitors of Protein Translation, an MoA Orthogonal to Existing Classes of ADC Payloads

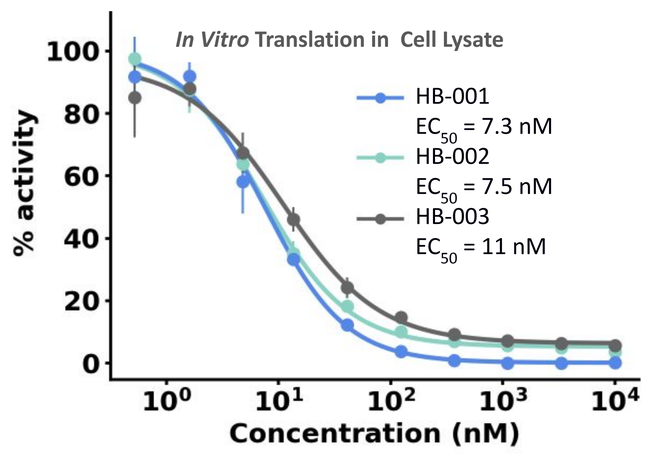



## Hexagon Has Designed Physicochemically Diverse Protein Translation Inhibitor (PTI) Payloads With a Range of Permeabilities

| Compound ID | Topological Polar Surface Area (Å$^2$) | Calculated AlogD (pH 7.4) | Calculated ALogP | Caco-2 Permeability, $P_{app}$, A->B, ($x10^{-6}$ cm/s) |
|---|---|---|---|---|
| HB-001 | 146 | 2.2 | 2.3 | 6.5 |
| HB-002 | 146 | 0.2 | 1.7 | <0.5 |
| HB-003 | 154 | -3.3 | 1.8 | <0.5 |

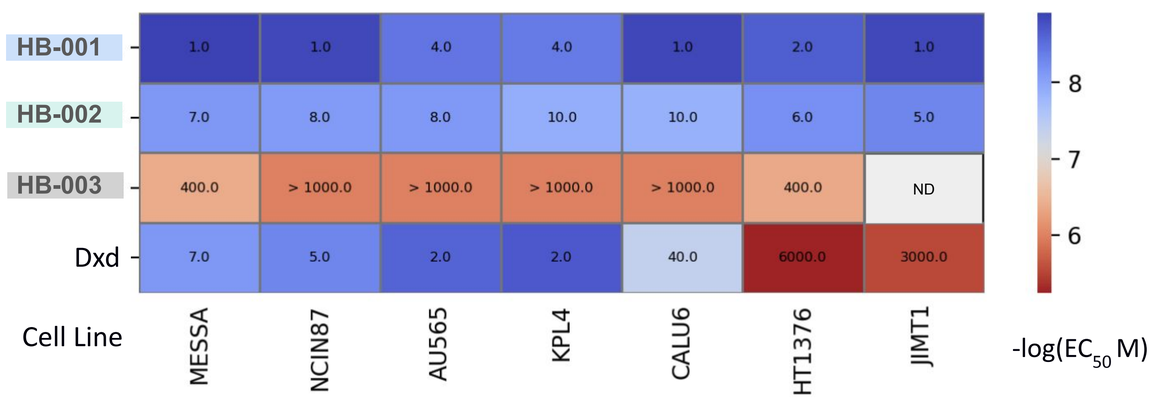
Caco-2 permeability assay run in the presence of 10 µM Elacridar

## Hexagon PTI Payloads Arrest Protein Translation *In Vitro*




Cell-free *in vitro* translation inhibition assays (IVT) measure translation of a luciferase reporter mRNA in cell lysate (1.5 hr reaction). Dose response curves were generated for 10 concentrations of each test compound and the half-maximal effective concentrations ($EC_{50}$) were calculated. Signals were normalized to vehicle (100% activity) and no mRNA controls (0% activity). Data are mean of 2-3 replicates.

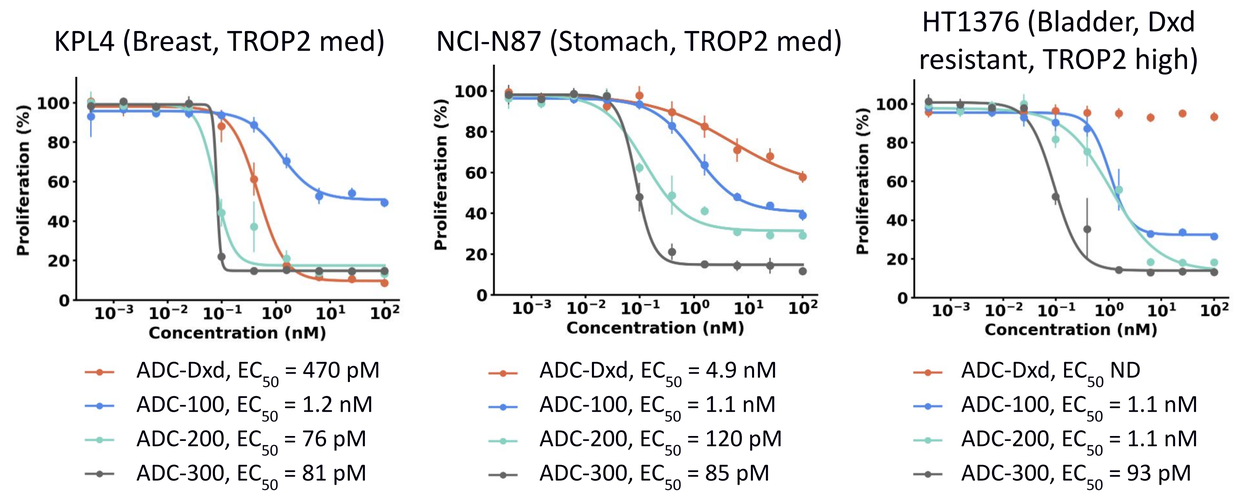
## Hexagon Protein Translation Inhibitor Payloads Are Cytotoxic Across Diverse Cell Types, Including Those Resistant to Dxd




CellTiter-Glo luminescent assay was performed to measure cell viabilities upon 72h treatment (N=2-3 biological replicate, N=2-3 technical replicates). Dose response curves were generated for 9 concentrations of each test compound and the half-maximal inhibitory concentration ($EC_{50}$) was calculated. Values are mean $EC_{50}$ (nM).

## Hexagon TROP2 ADCs Demonstrate Potent Cytotoxicity *In Vitro*, Including in Dxd-Resistant Cell Types

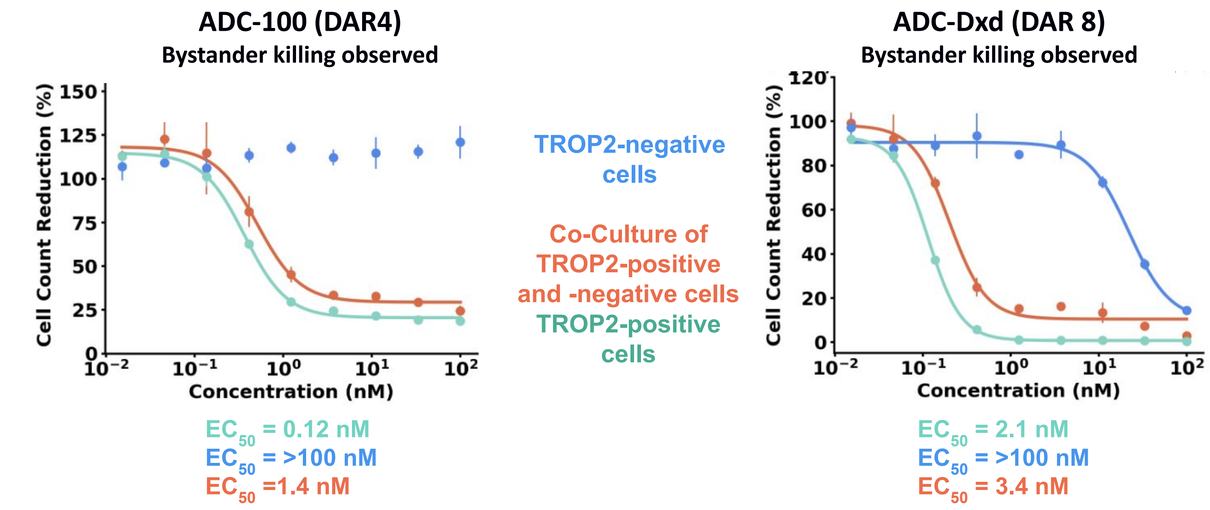
ADC potency is inversely correlated to payload permeability



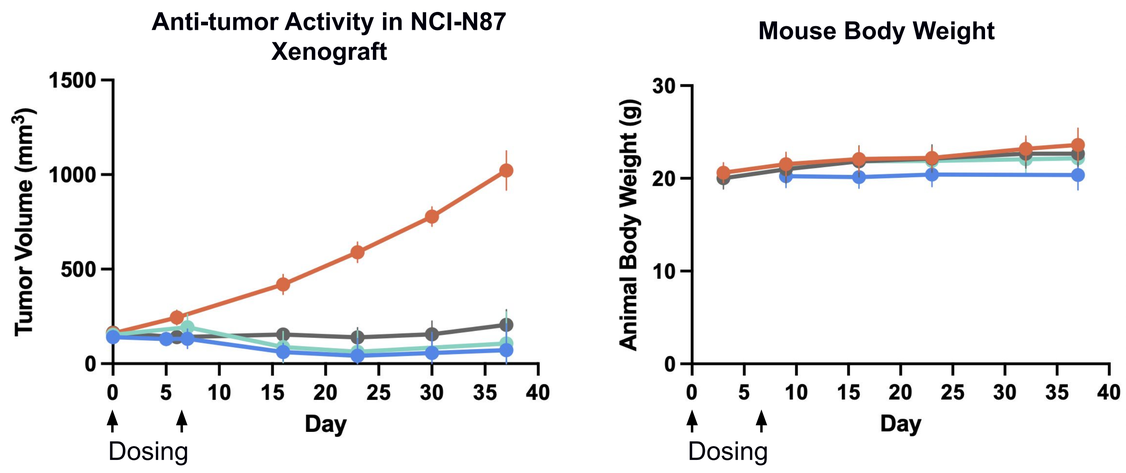

| ADC ID | Payload ID | DAR | mAb Antigen |
|---|---|---|---|
| ADC-Dxd | Dxd | 4 | TROP2 |
| ADC-100 | HB-001 | 4 | TROP2 |
| ADC-200 | HB-002 | 4 | TROP2 |
| ADC-300 | HB-003 | 4 | TROP2 |

CellTiter-Glo luminescent assay measured cell viabilities upon 120 h treatment. Dose response curves were generated for 10 concentrations of each test compound and the half-maximal effective concentrations ($EC_{50}$) were calculated. Data are mean of 2-3 replicates.

## Hexagon TROP2 ADC, ADC-100, with High Permeability Payload Induces Bystander Killing Similar to TROP2-Dxd Benchmark




## Hexagon TROP2 Protein Translation Inhibitor ADCs Demonstrate Antitumor Activity *In Vivo* in NCI-N87 Mouse Tumor Models With No Effect on Body Weight




The *in vivo* therapeutic efficacy of Hexagon TROP2 ADCs was evaluated in the treatment of the subcutaneous human gastric cancer xenograft model NCI-N87 in female BALB/c nude mice (N=7-8 mice/group). Mice were dosed with each test article at Day 0 when tumors reached a volume of 175 mm$^3$. A second dose was given 7 days later. Data are mean ± SEM.

## Hexagon TROP2 ADCs Exhibit Diverse Activity Profiles, Suitable to Address a Spectrum of Tumor Types

| | ADC-100 | ADC-200 | ADC-300 |
|---|---|---|---|
| Free Payload Permeability | +++ | + | – |
| Payload Bystander Killing Potential | +++ | + | – |
| ADC *In Vitro* Potency | + | ++ | +++ |
| ADC *In Vivo* Potency (NCI-N87 Model) | +++ | +++ | +++ |
| Potential Applications | Solid Tumors | Solid and Hematologic Tumors | Hematologic Tumors |