# Generation of a Panel of Differentiated Cytotoxic Payloads for Antibody Drug Conjugates

Hexagon Bio

Abstract 164
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## Only Three Classes of ADC Payloads Are Approved; More Are Needed

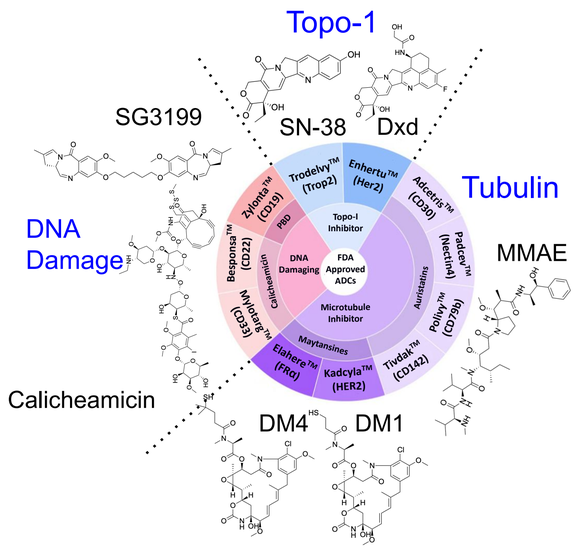



Illustration from Maecker et al., MAbs, 2023

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

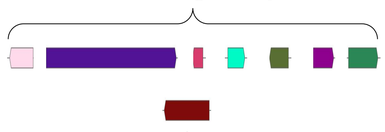
- **Safety liabilities** with existing payloads
- **Resistance to existing payloads**: Tumors stop responding

All approved ADC payloads are derived from natural products potentially because they have evolved for potency and cell permeability

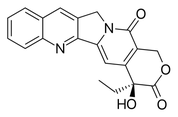
## Hexagon's Platform Uses DNA Sequencing to Identify Small Molecule Natural Products for Novel ADC Payloads

***Camptotheca acuminata***

**Genes encoding camptothecin**



**Topo-1 Resistance gene ("R-gene"):** Mutated topo-1 confers protection to camptothecin

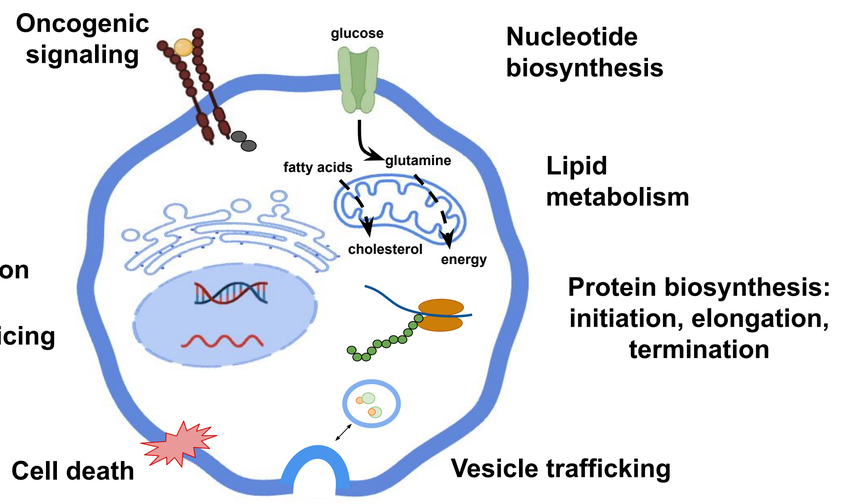


**Camptothecin** evolved to inhibit topoisomerase-1

**We applied this insight using AI to identify new ADC payloads**

## Platform Identifies ADC Payload Mechanisms Orthogonal to Existing Payloads

**Natural products tend to target essential tumor pathways that are orthogonal to existing ADC payload mechanisms**




## Translation Inhibitor as a Novel ADC Payload Mechanism

**MOA is orthogonal to existing payloads, with potential to treat resistant cancer types**

- **Demonstrated activity in >200 tumor cell lines, including lines resistant to available payloads**
- Active in multi-drug resistant cells
- Attractive physicochemical properties
- Amenable to semi-synthesis and medicinal chemistry
- *In vitro* and *in vivo* ADC activity demonstrated

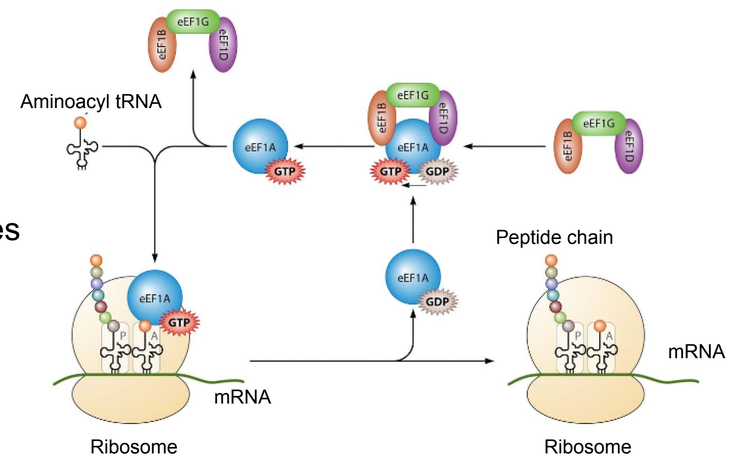
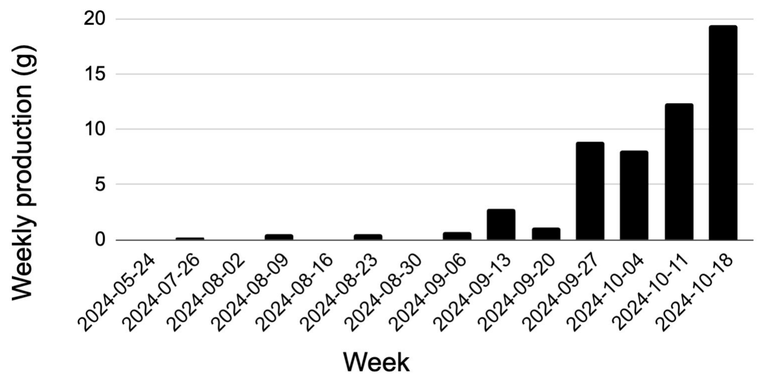


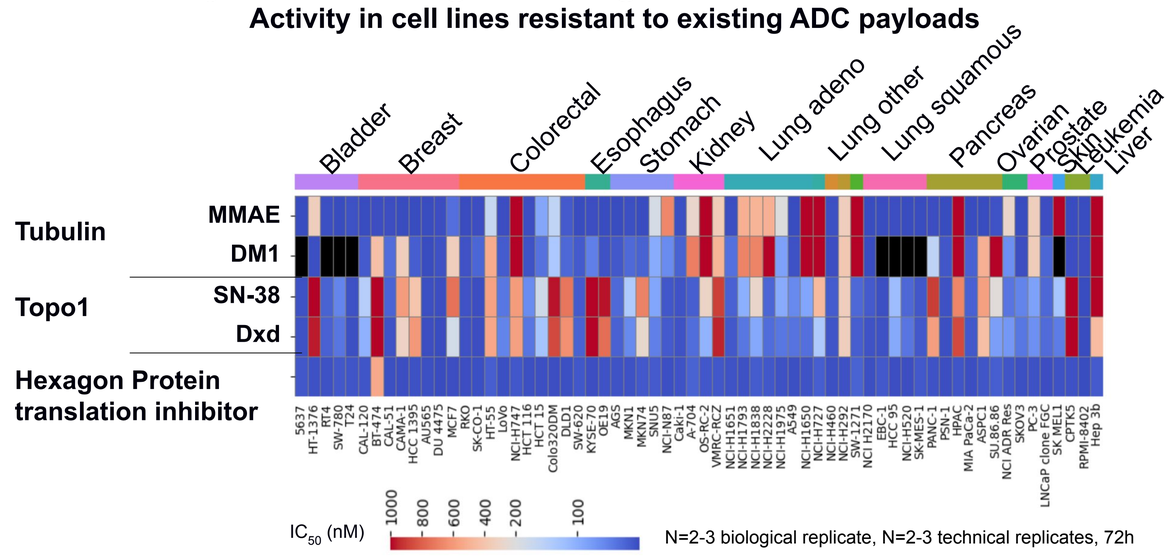

Illustration from Li et al., Microbiol and Mol Bio Rev, 2013

## All Payload Starting Materials Are Produced and Isolated Internally




## Payload Profiling of Hexagon Translation Inhibitor:

**Activity in cell lines resistant to existing ADC payloads**

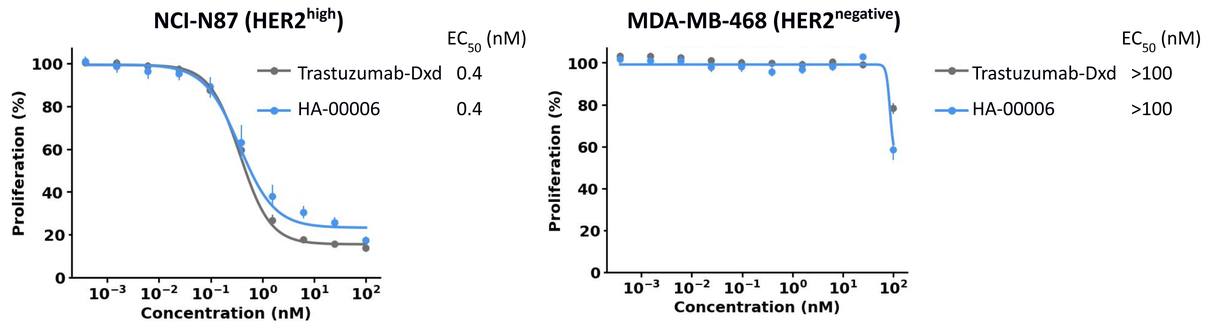



N=2-3 biological replicate, N=2-3 technical replicates, 72h

CellTiter-Glo luminescent assay was performed to measure cell viabilities upon 72h treatment. Dose response curves were generated for 9 concentrations of each test compound and the half-maximal inhibitory concentration (IC50) was calculated. The authors would like to thank Crown Bioscience for their OmniScreen cell based screening services to generate the profiling data above.

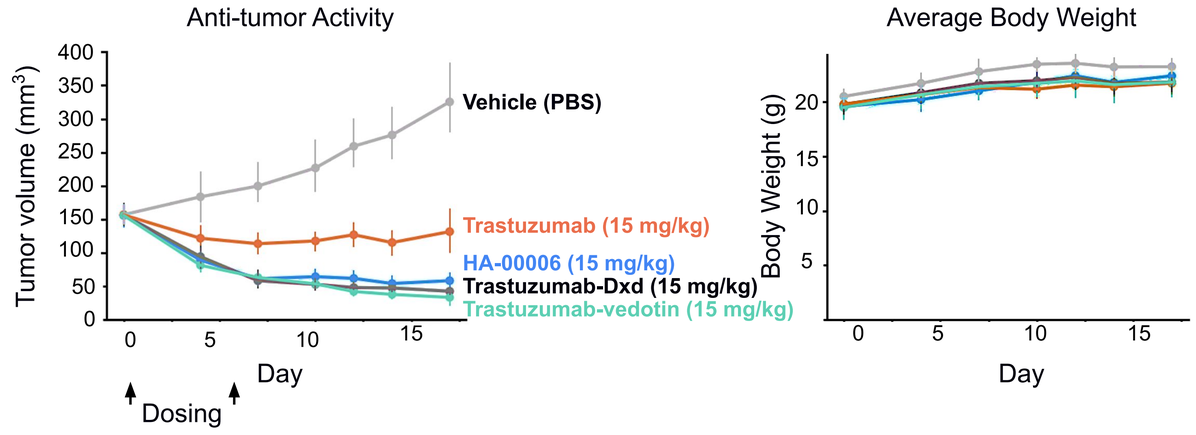
## Hexagon HER2 ADC With Translation Inhibitor Payload Demonstrates Antigen-dependent Cytotoxicity *in Vitro*

**HER2 + translation inhibitor payload ADC (HA-00006; DAR8) demonstrates antigen-dependent cell killing**




CellTiter-Glo luminescent assay was performed to measure cell viabilities upon 120 h treatment. Dose response curves were generated for 10 concentrations of each test compound and the half-maximal effective concentrations (EC50) were calculated.

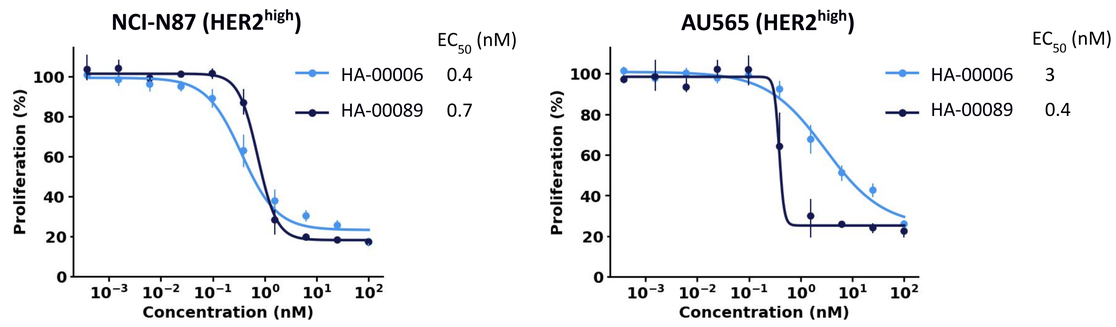
## Hexagon HER2 ADC With Translation Inhibitor Payload Demonstrates Antitumor Activity *in Vivo* in NCI-N87 Mouse Tumor Model With no Effect on Body Weight




The in vivo therapeutic efficacy of HER2 ADCs (HA-00006, Trastuzumab-Dxd and Trastuzumab-vedotin) was evaluated in the treatment of the subcutaneous human gastric cancer xenograft model NCI-N87 in female BALB/c nude mice (N=8 mice/group). Mice were dosed with each test articles at Day 0 when tumors reached a volume of 175 mm3. A second dose was given 7 days later. Data are Mean ± SEM.

## Optimization of Translation Inhibitor Yields Improved ADCs

**Medicinal chemistry campaign has produced new payloads with significantly improved ADC activity (HA-00006: original payload, HA-00089: improved analog)**




CellTiter-Glo luminescent assay was performed to measure cell viabilities upon 120h treatment. Dose response curves were generated for 10 concentrations of each test compound and the half-maximal effective concentrations (EC50) were calculated.

## Hexagon's Next-generation ADC Platform: Novel Payloads and Dual Payloads to Improve Patient Response