Abstract #2870 Enhancing Topo1i ADC efficacy: development of homogeneous dual-payload ADCs combining Topo1i with microtubule inhibitors (MTi) or PARP inhibitors

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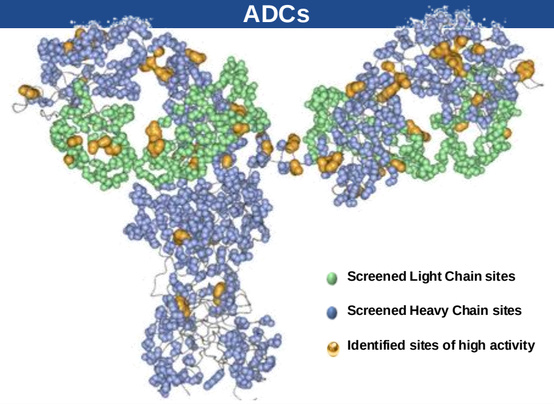
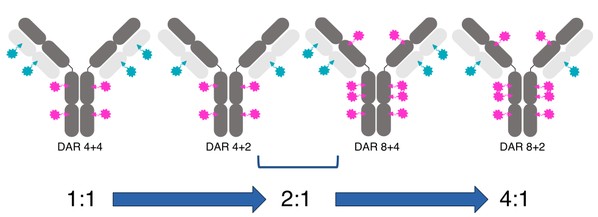
Introduction

- There is a critical need to safely enhance the potency of antibody-drug conjugates (ADCs) for targeting low-expression and heterogeneous tumors.
- Cancer cells often develop resistance to single-agent therapies and sequential treatment with similar payloads.
- Dual-payload ADCs combine two payloads with different mechanisms of action (MOA) into a single ADC, offering the potential to enhance ADC efficacy and overcome drug resistance.
- Key challenges in dual-payload ADCs: 1) tolerate a higher DAR while maintaining favorable physicochemical properties and 2) having the flexibility to optimize the stoichiometry between the payloads.
- Sutro Biopharma's cell-free platform enables the precise and efficient development of high-DAR, dual-payload ADCs.

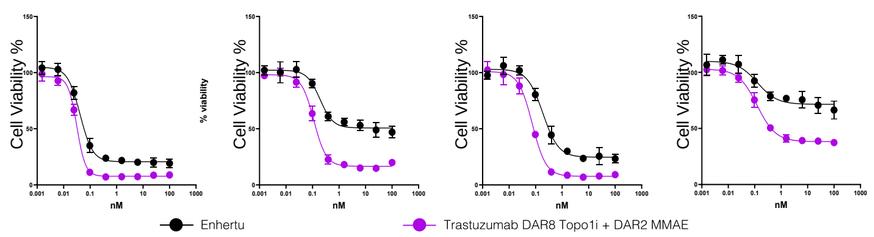
Sutro's XpressCF+® Platform Allows for Empirical Evaluation to Identify the Best Conjugation Site Combinations for Dual-Payload ADCs



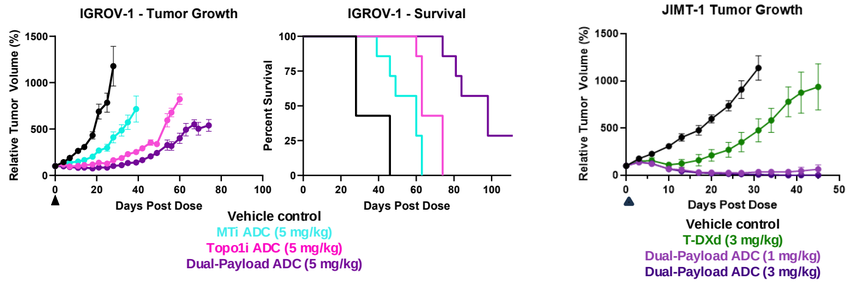
XpressCF+® Platform Facilitates Precise Tuning of the DARs and Ratio of Two Payloads Critical for Optimal Synergy of Two MOAs



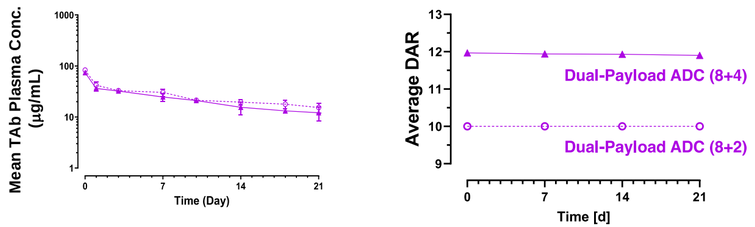
Dual-Payload ADC Case Study
Topo1i + MTi



Dual-payload ADCs have improved *in vitro* cell killing in comparison to Enhertu.

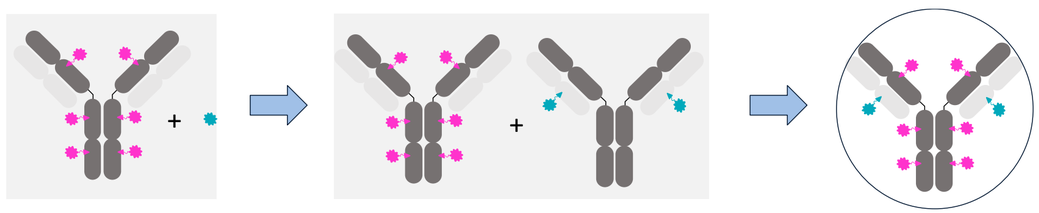


Dual-payload ADCs exhibit superior *in vivo* efficacy compared to single-payload ADCs and T-DXd.



Dual-payload ADCs show desirable PK and DAR profiles in a 21-day *in vivo* mouse study.

Dual-payload ADC Exhibits Advantages over ADC/Chemo or ADC/ADC Combination

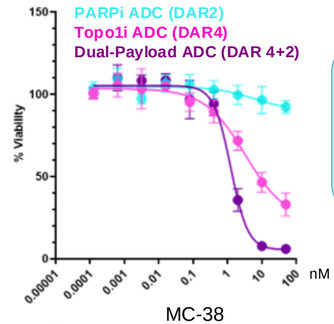


ADC + Chemo
- Lacks tumor-targeted delivery
- Increased toxicity
- Narrower therapeutic window

ADC + ADC
- Require separate:
  Pre-clinical & clinical dev.
  Manufacturing
  Regulatory
  Treatment regimen

Dual-payload ADC
- Focused tumor targeting
- Synergistic mechanisms
- Improved tumor delivery
- Streamlined manufacturing & clinical development

Dual-Payload ADC Case Study
Topo1i + PARPi



Dual-payload ADCs have improved cell killing compared to mono-payload ADCs.

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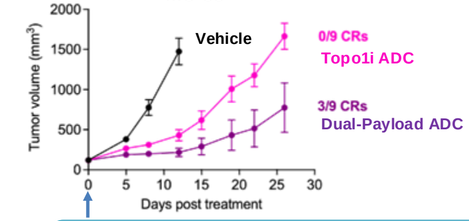
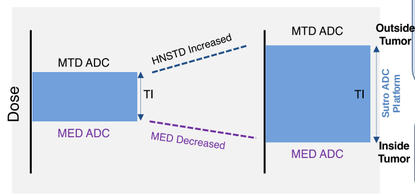


Dual-payload ADCs have improved in vivo efficacy in comparison to mono-payload ADCs.

Summary

The Sutro XpressCF+® Platform is ideal for the discovery and development of homogeneous dual-payload ADCs, offering:
- **Site-selective conjugation for two distinct linker-payloads**
- **Optimized stoichiometry between linker-payloads**
- **Favorable physicochemical properties**
- **Robust manufacturability**

Dual-payload ADCs, including Topo1/MTi and Topo1/PARP1i, demonstrate:
- **Enhanced in vitro and in vivo efficacy**
- **Favorable pharmacokinetics and stability**
- **Great potential to increase the therapeutic index**



- Payload potency
- Linker payload stability
- Linker cleavage specificity
- Fc effector function
- Physicochemical properties

- Higher DAR → target-low tumor
- Dual-payload ADC → MOA combination