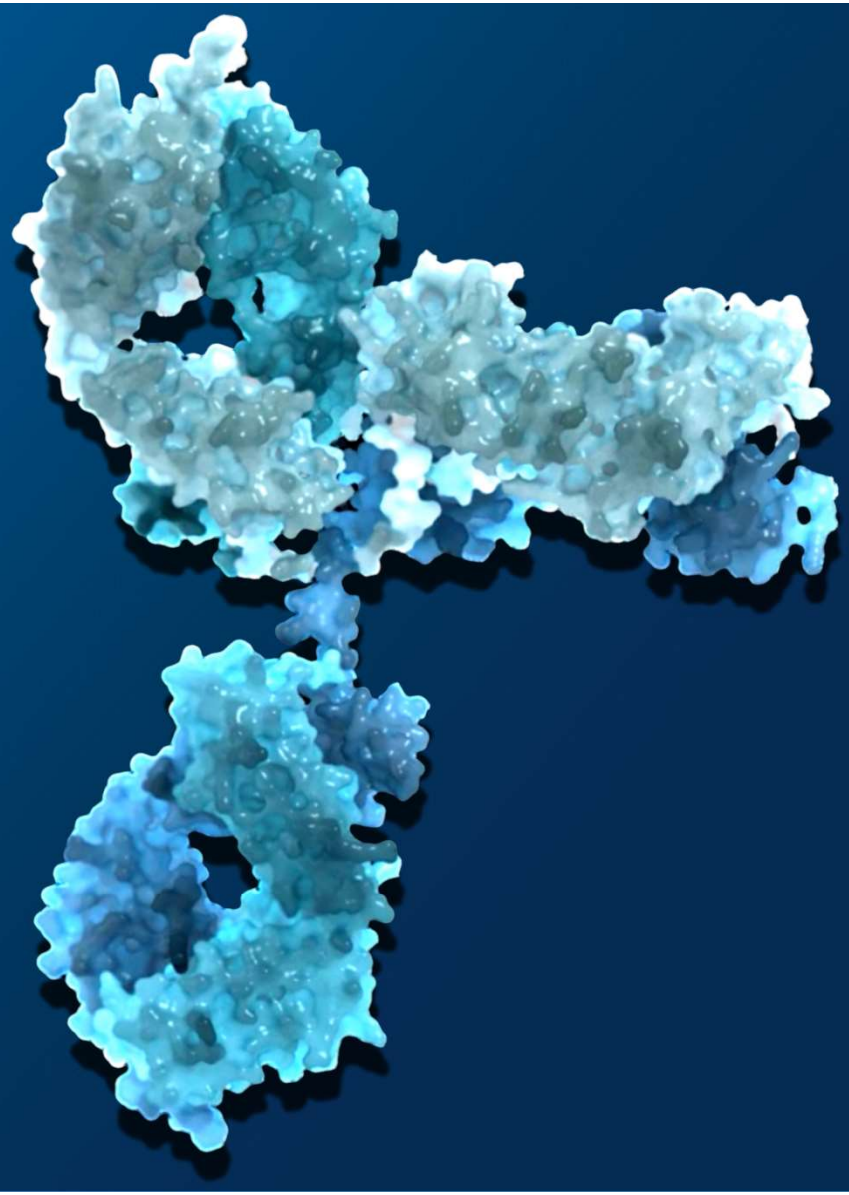
SUTRO BIOPHARMA

Development of Dual-Payload Antibody Drug Conjugates

Daniel Calarese

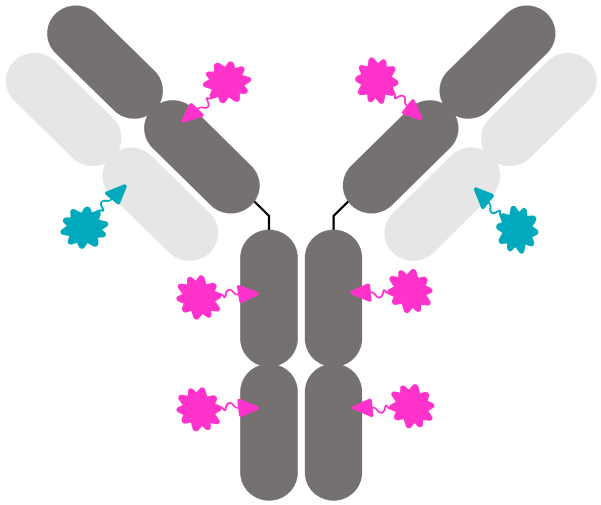
November 4th, 2024

15th ANNUAL WORLD adc SAN DIEGO 2024



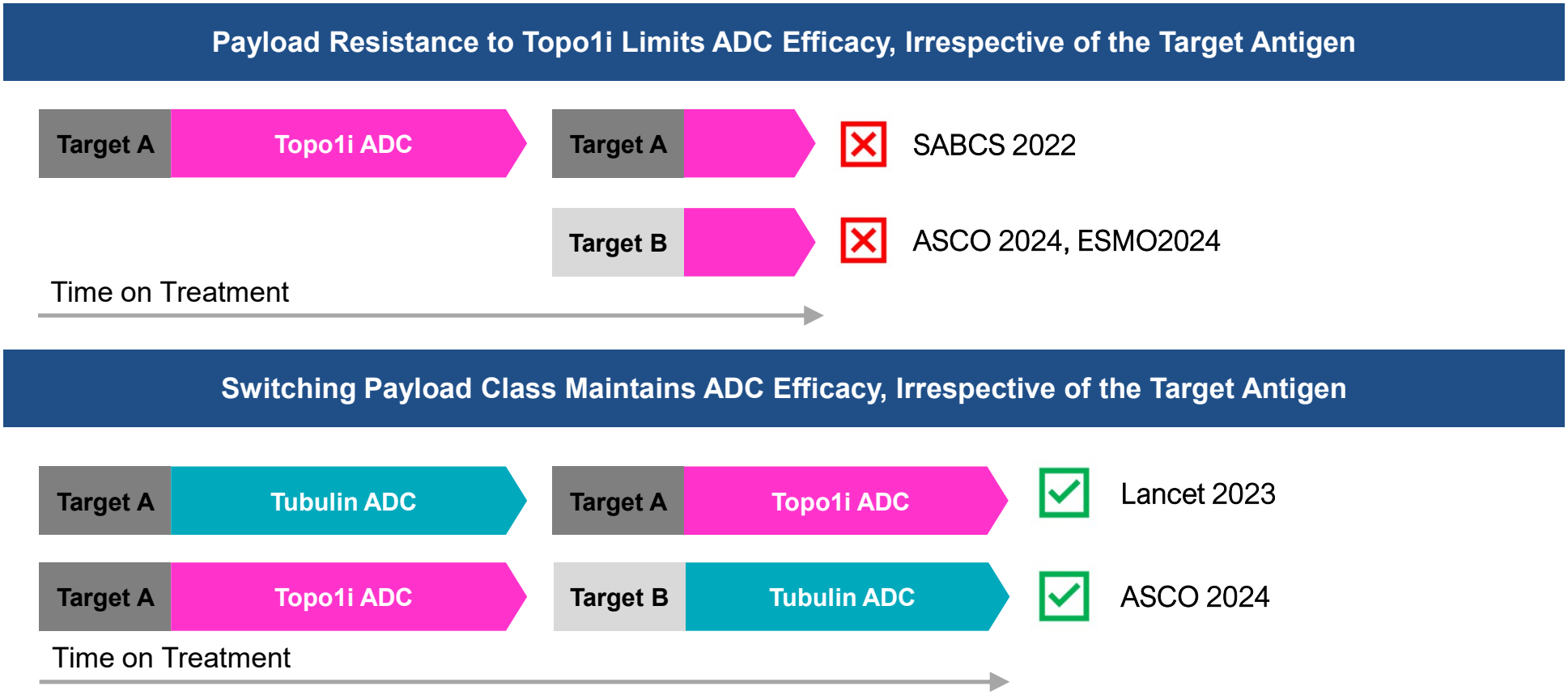
- Dual Payload ADC Advantages
- Cell-Free Production of Dual Payload ADCs
- Dual Payload Approach: Distinct Mechanisms of Actions
- Dual Payload Approach: Synergistic Payloads

Potential Advantages of Dual-Payload ADC Approach



- Reduced Toxicity
- Reduced Clinical Complexity
- Simultaneous Payload Delivery
- Overcome Resistance Mechanisms

Emerging Clinical Challenge: Payload Resistance Limits ADC Efficacy



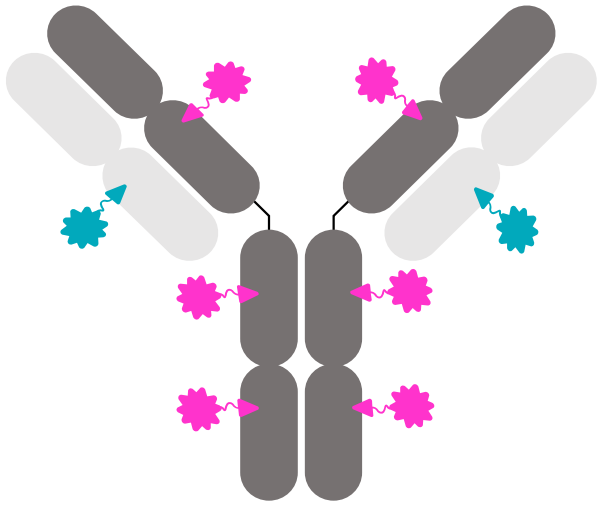
SABCS – San Antonio Breast Cancer Symposium; ASCO – American Society of Clinical Oncology

Emerging Clinical Challenge: Payload Resistance Limits ADC Efficacy

Payload Resistance to Topo1i Limits ADC Efficacy, Irrespective of the Target Antigen					
Indication	**ADC 1 (Topo 1)**	**ADC 2 (Topo 1)**	**Clinical Readout as First ADC**	**Clinical Readout as Second ADC**	**Ref**
TNBC	Prior Topo1 ADC	Dato-DXd (Trop2)		11.7% ORR	Krop, SABCS 2022
	No ADC		44 % ORR		
mBC	SG (Trop2)	T-DXd (Her2)	6.5 m PFS, 20.1 m OS	2.1 m PFS, 5.6 m OS	Huppert, ASCO 2024
	T-DXd (Her2)	SG (Trop2)	5.3 m PFS, 15.1 m OS	3.6 m PFS, 7.7 m OS	

Switching Payload Class Maintains ADC Efficacy, Irrespective of the Target Antigen					
Indication	**ADC 1 (Topo 1)**	**ADC 2 (Tubulin)**	**Clinical Readout as First ADC**	**Clinical Readout as Second ADC**	**Ref**
TNBC	SG (Trop2)	PADCEV (Nectin 4)		3 .5 m PFS	Giordano, ASCO 2024
	PADCEV (Nectin 4)		3.4 m PFS		

Potential Advantages of Dual-Payload ADC Approach



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Sutro's ADC Platform is Fundamentally Different: Manufacturing of Proteins in Cell-Free Extracts

DNA Vector Engineering → Genome Sequencing → Strain Engineering

Prokaryotic Cells

1977: Somatostatin
1978: Insulin
1979: HGH

1976

Genentech: Boyer (UCSF)
Purpose: Manufacture Protein Therapeutics

DNA - deoxyribonucleic acid; HGH – human growth hormone; UCSF – University of California, San Francisco

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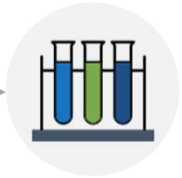

Enzymes
Proteases
Cytokines

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Purpose: Manufacture in Prokaryotic Cell Extract

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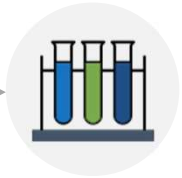

Enzymes
Proteases
Cytokines

Sutro Cell Free
2010: 100L CF demonstration
2011: mAbs
2013: nnAA incorporation and ADCs
2014: bsAb and ADC
2016: CF GMP manufacturing
2024: 4,000L GMP run

Advantages to Improve Therapeutic Index of ADCs
- Site Specific Conjugation
- Immune Stimulatory (iADC)
- High DAR (>8)
- Dual-Payload ADCs

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Purpose: Manufacture Protein Therapeutics

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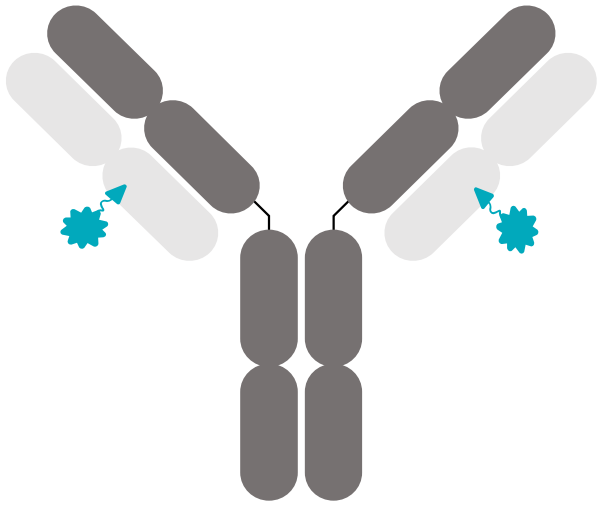
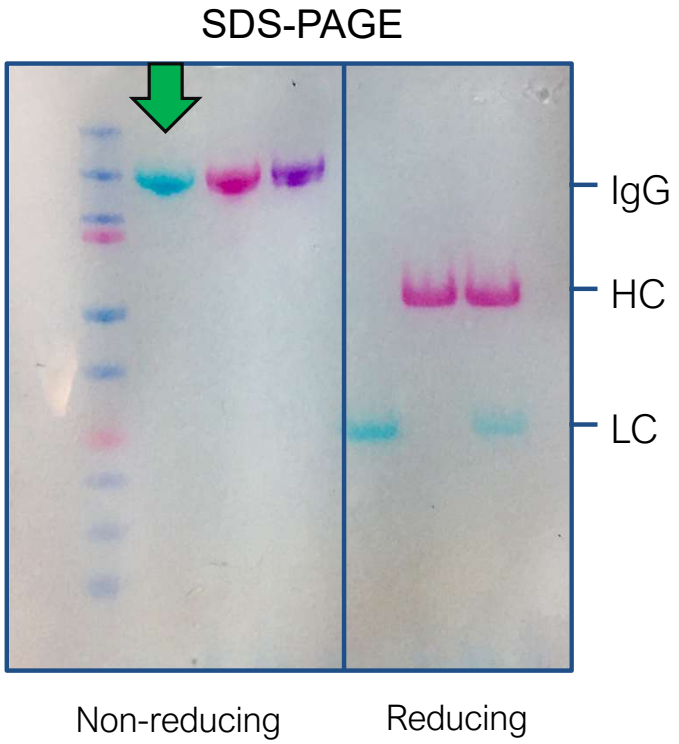
2024

Sutro Milestones
Manufacture Cheaper, Faster, Better

nnAA – non-natural amino acids; CF – cell-free; bsAb – bispecific antibody; GMP – good manufacturing practice

Sutro Cell-Free Platform Allows Precise Tuning of Linker-Payloads





SDS-PAGE – sodium dodecyl sulfate polyacrylamide gel electrophoresis; IgG – immunoglobulin G;HC – heavy chain; LC – light chain

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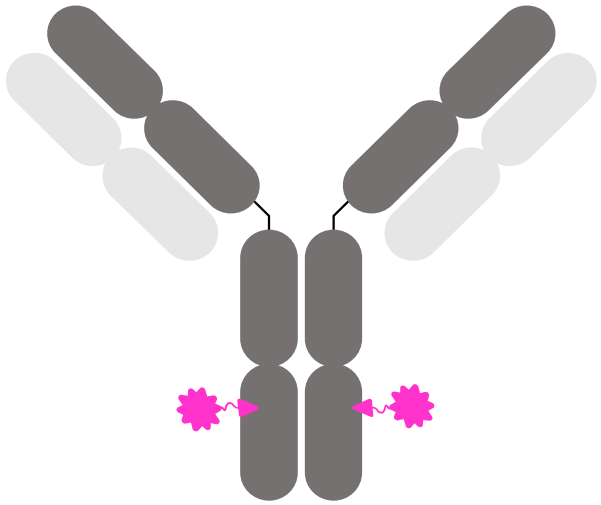

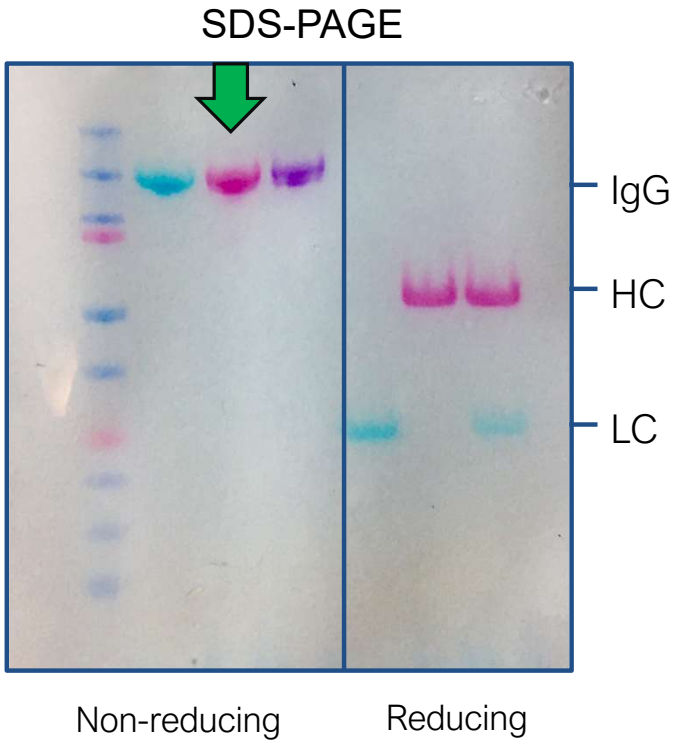

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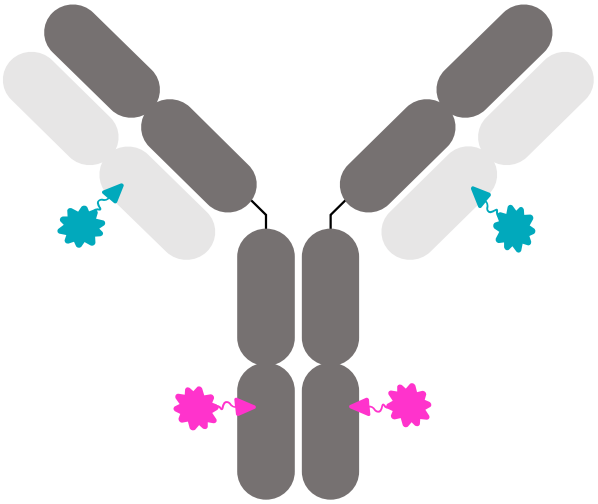

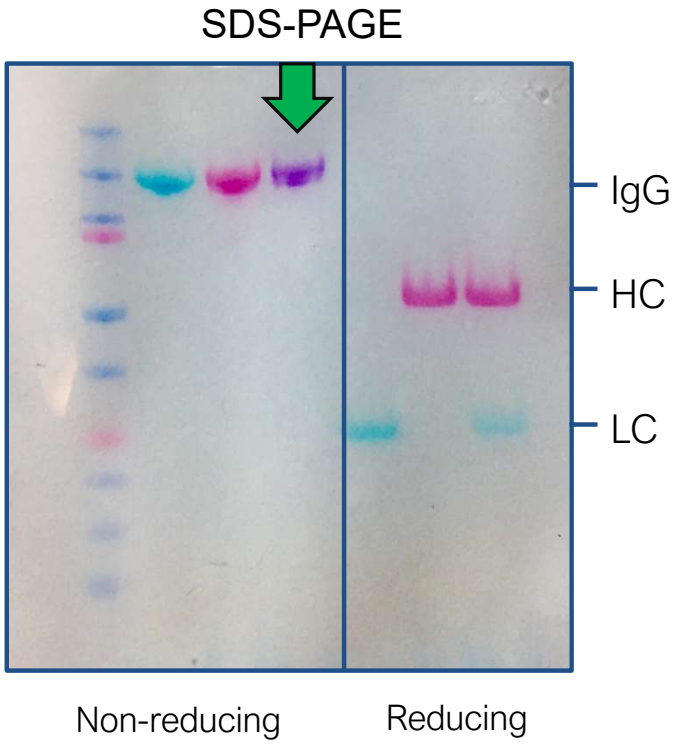

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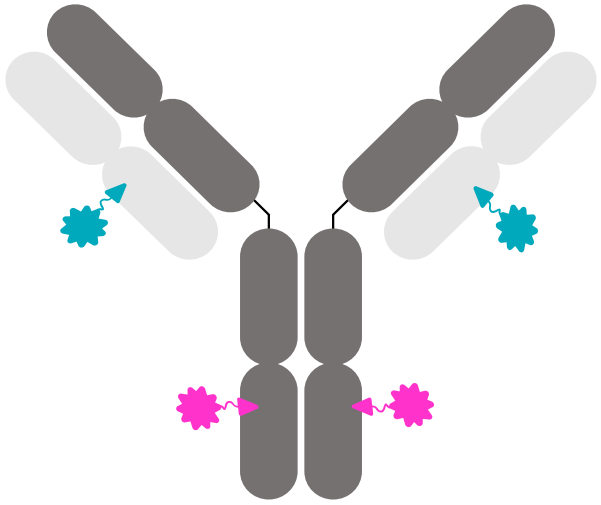
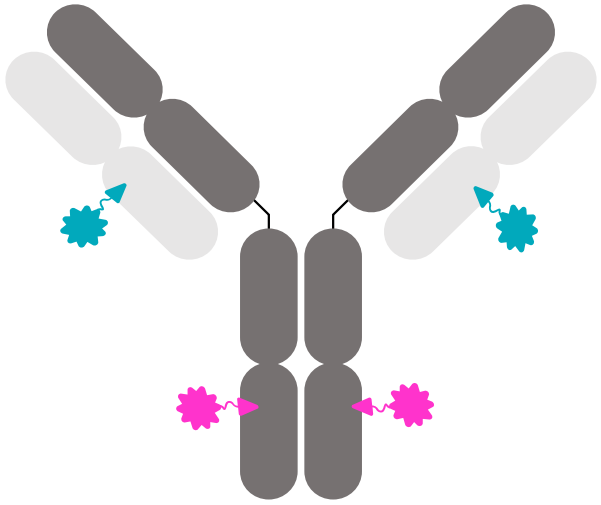


1:1

Sutro Cell-Free Platform Allows Precise Tuning of Linker-Payloads



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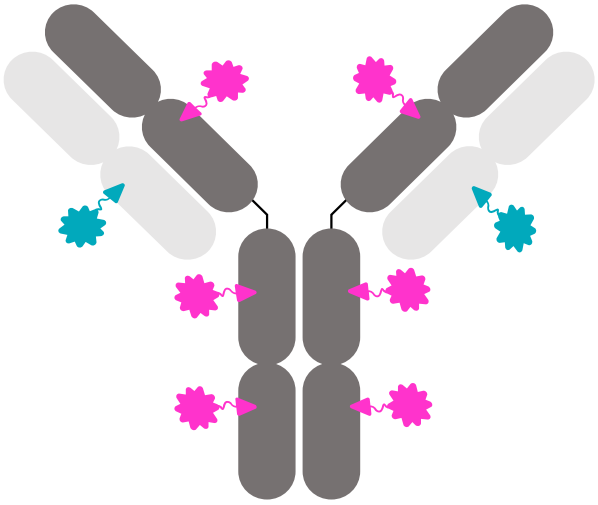

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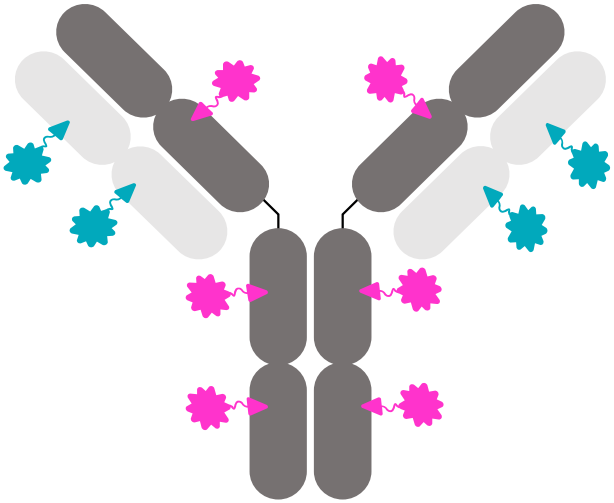
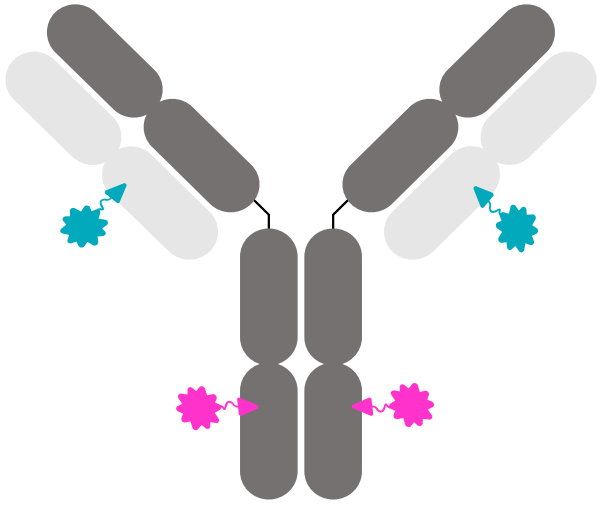


3:2

Sutro Cell-Free Platform Allows Precise Tuning of Linker-Payloads



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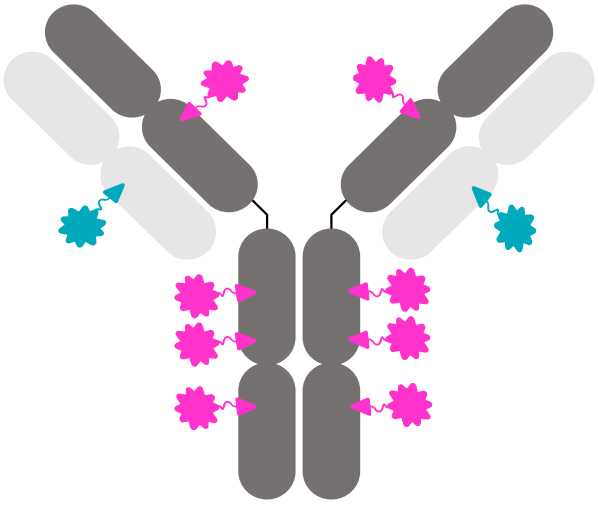

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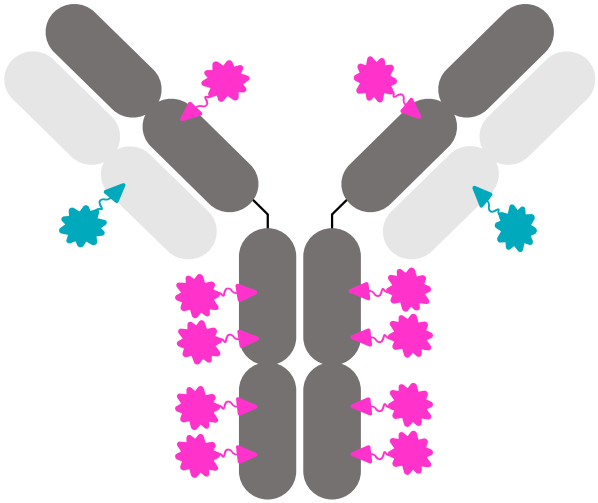

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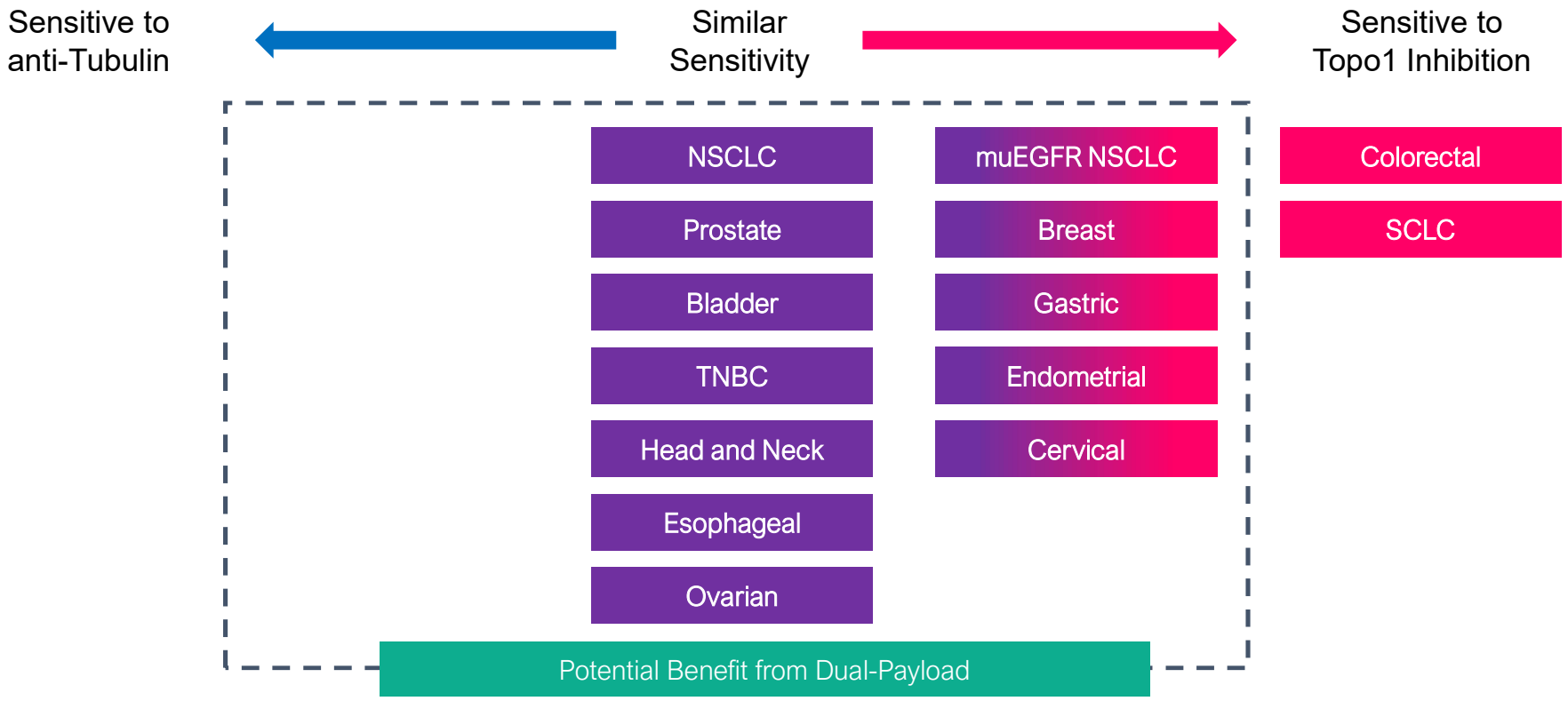
Topo1i + Anti-Tubulin Dual-Payload ADC Positioned to Address Broad Therapeutic Opportunity



Source: internal Sutro data
muEGFR – mutant epidermal growth factor; SCLC – small cell lung cancer

Topo1i + Anti-Tubulin Dual-Payload Clinically Validated by Trodelvy + Padcev Combination Study

ADC(s)	Developer(s)	Payload	DAR	Clinical Data			
				Trial	Median PLoT	N	ORR (%)
Sacituzumab Govitecan (Trodelvy)	Gilead	SN-38	7.6	TROPHYU-01[1,2]	3 (1-8)	87	29%
Enfortumab Vedotin (Padcev)	Seattle Genetics, Astellas	MMAE	4	EV-201[3]	3 (1-6)	89	51%
Trodelvy + Padcev	Gilead Seattle Genetics, Astellas	SN-38 MMAE	7.6 4	DAD[4]	≥ 2	21	70%

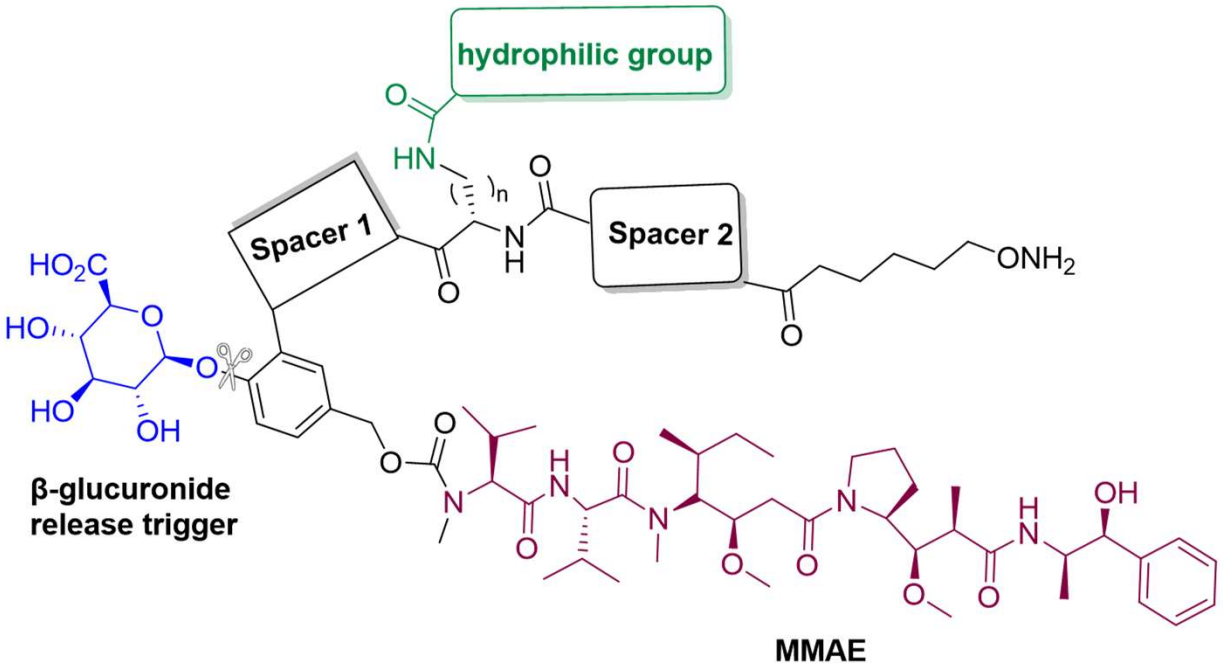
Non-overlapping toxicities of Tubulin and Topoisomerase 1 inhibitors[4]

Well-tolerated when dosed simultaneously[4]

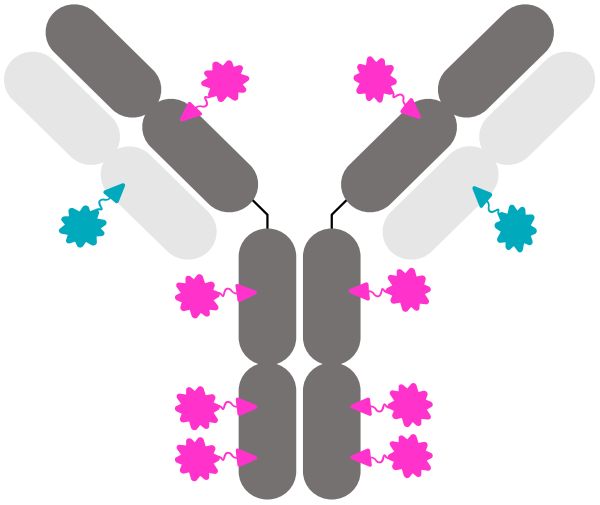
Clinical trial amended to include a "DAD-IO" arm to test the ADC combination with pembro[4]

[1]Loriot Y., et al. 2023 ASCO Annual Meeting Abstract Number 4579. [2]Loriot Y., et al. 2023 ASCO Annual Meeting Abstract Number 4514. [3]McGregor BA., et al. 2021 ASCO Annual Meeting Abstract Number 4524. [4]McGregor BA., et al. 2024 ASCO
PLoT – prior lines of therapy

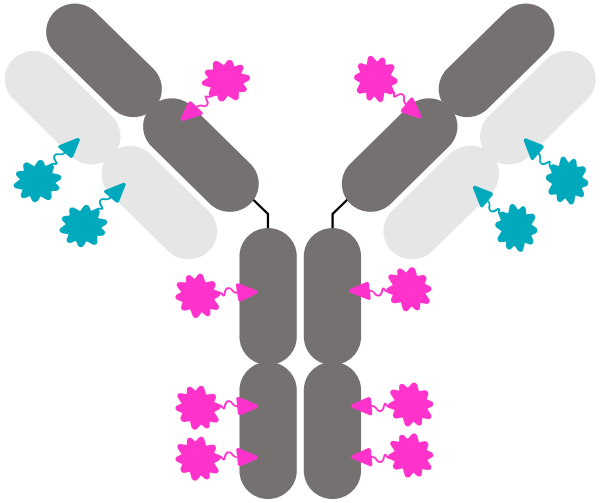
PEGylated β-glucuronidase Anti-Tubulin Linker-Payload Design



Optimization of Dual-Payload ADC Design (Topo1i + anti-Tubulin)



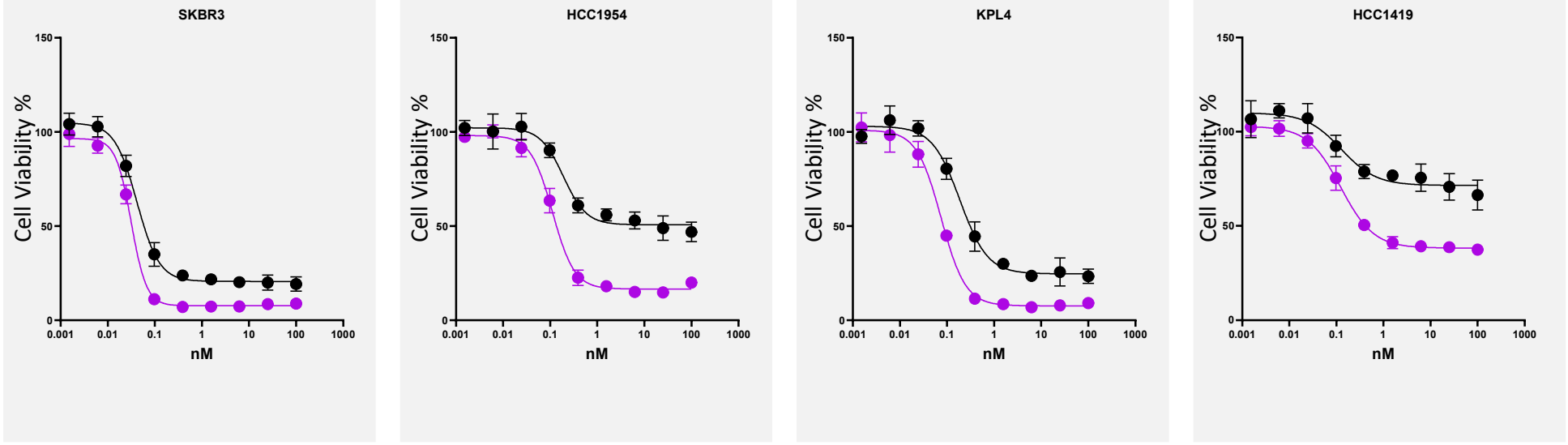
8+2



8+4

Improved *In Vitro* Activity of Dual-Payload ADC

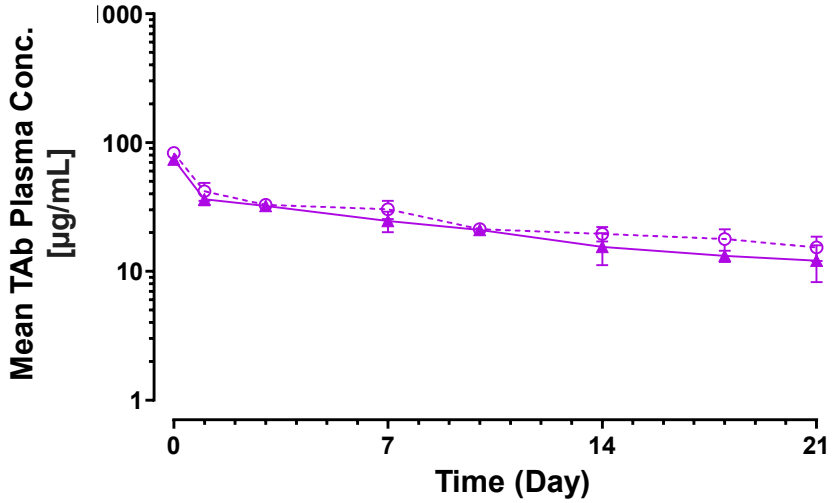
SKBR3	HCC1954	KPL4	HCC1419



Enhertu

Trastuzumab DAR8 Topo1i + DAR2 MMAE

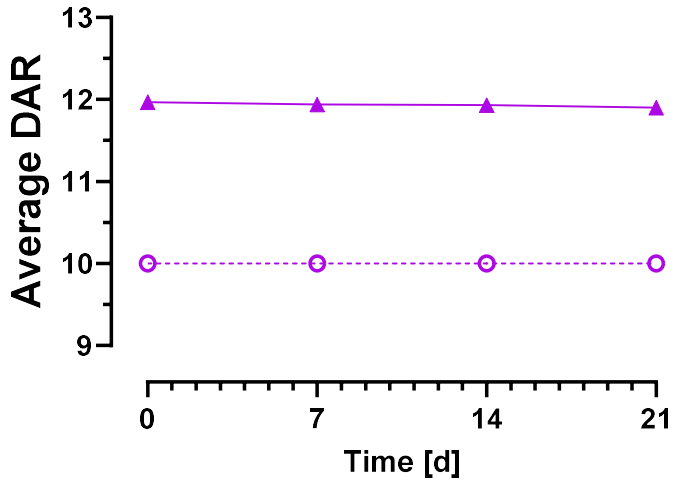
Dual-Payload ADC Displays Desirable Preclinical Mouse PK



	DAR		Cl_{obs} ($mL \cdot d^{-1}/kg$)	V_{ss} (mL/kg)	$t_{1/2}$ (days)
	Topo1i	MMAE			
-(--)-	8	2	3.3	75.8	16.3
-▲-	8	4	4.2	81.4	14

CLobs – observed clearance; Vss – volume of distribution at steady state; t1/2 – half-life

Dual-Payload ADC Has Solid *In Vivo* Stability

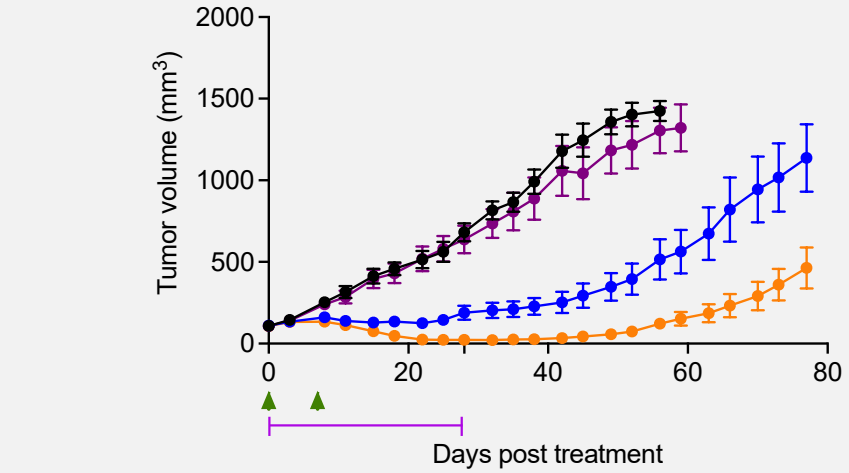


	DAR	
	Topo1i	MMAE
⊖	8	2
▲	8	4

Opportunity and Challenges in Combining PARP and Topoisomerase 1 Inhibitors: A Path Forward with Dual-Payload ADCs

- Well-established preclinical synergy
- PARP directly involved in Topoisomerase 1 inhibitor DNA damage repair

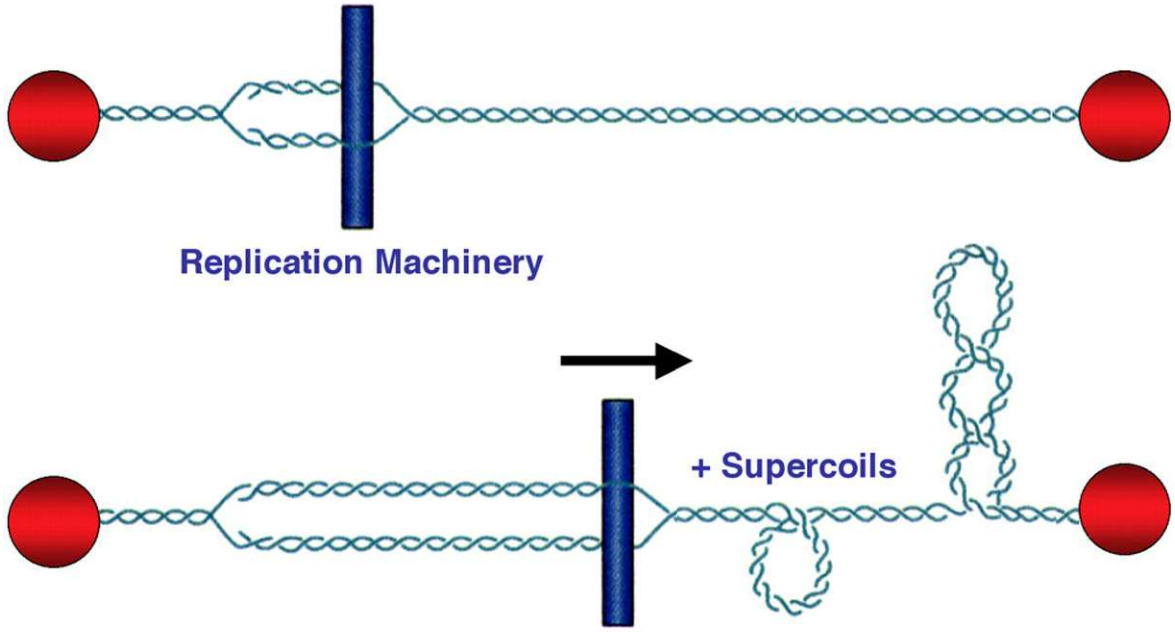
MDA-MB-231



	TGI (Day 56)
Vehicle	
Talazoparib (0.33 mpk)	9%
DAR4 Topo1i ADC (0.25 mpk)	69%
DAR4 Topo1i ADC (0.25 mpk) + Talazoparib (0.33 mpk)	99%

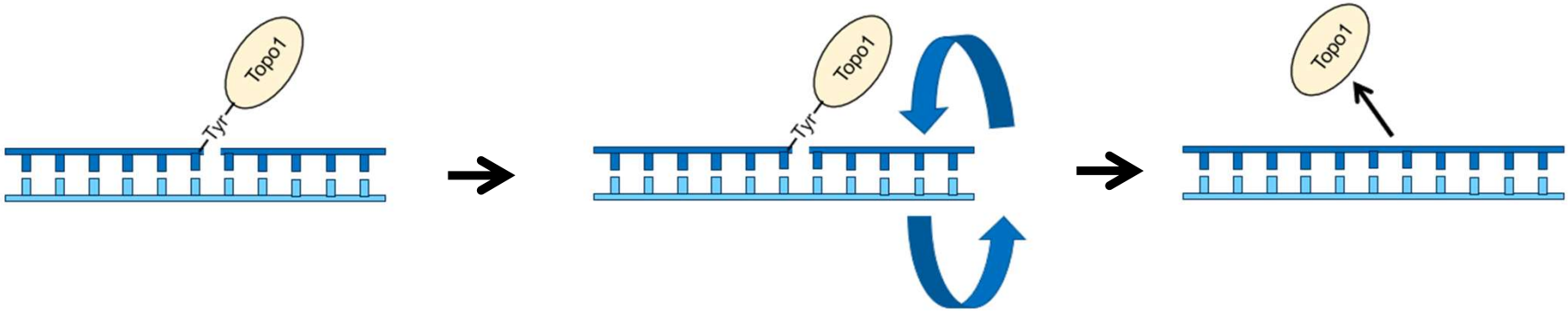
PARPi - Poly (ADP-ribose) Polymerase inhibitor; TGI – tumor growth inhibition

Supercoiled DNA Imposes a Barrier on the Progressing Replication Fork



Adapted from J.C. Wang, et al., Nat. Rev. Mol. Cell. Biol., 3 (2002), pp. 430-440

Topoisomerase 1 is an Unwindase That Can Relieve DNA Supercoiling

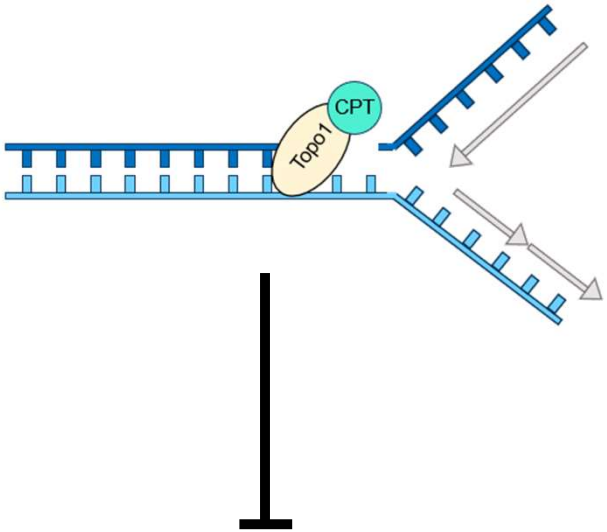


Topo1 nicks the dsDNA and covalently binds to a ssDNA

Supercoiled DNA is now free to unwind

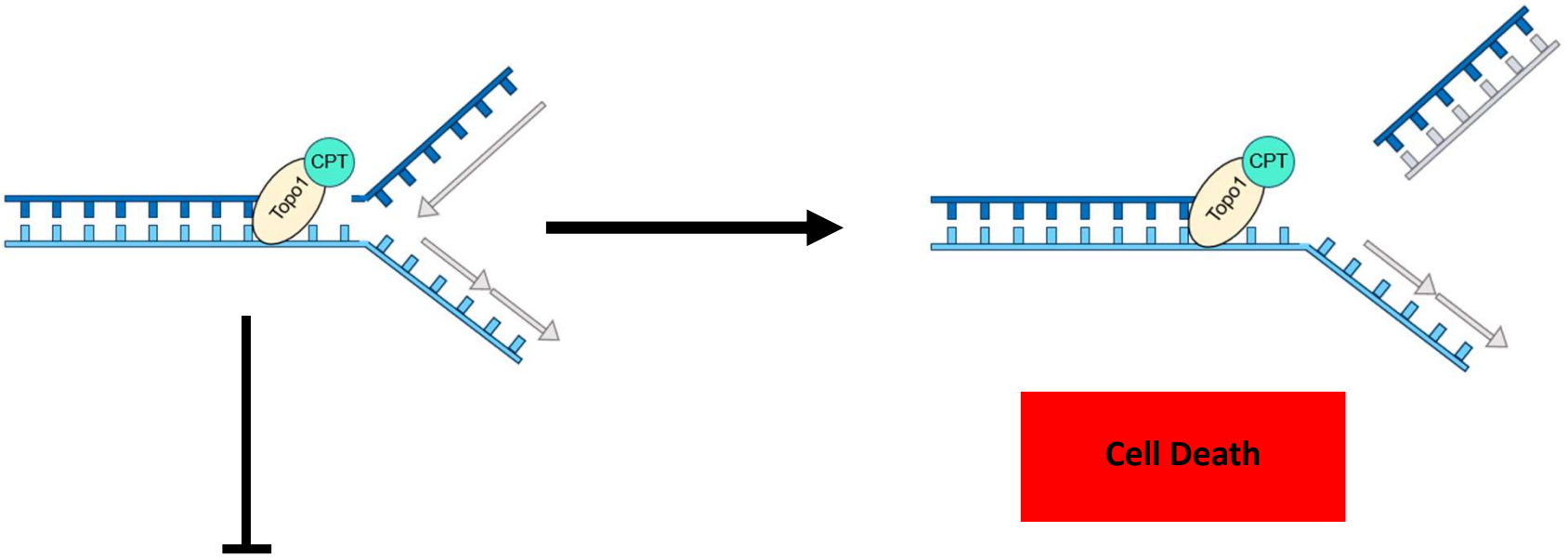
Re-ligation occurs once the DNA is in a more relaxed state

Topoisomerase 1 Inhibitors Trap Topoisomerase 1 and Prevent Re-Ligation

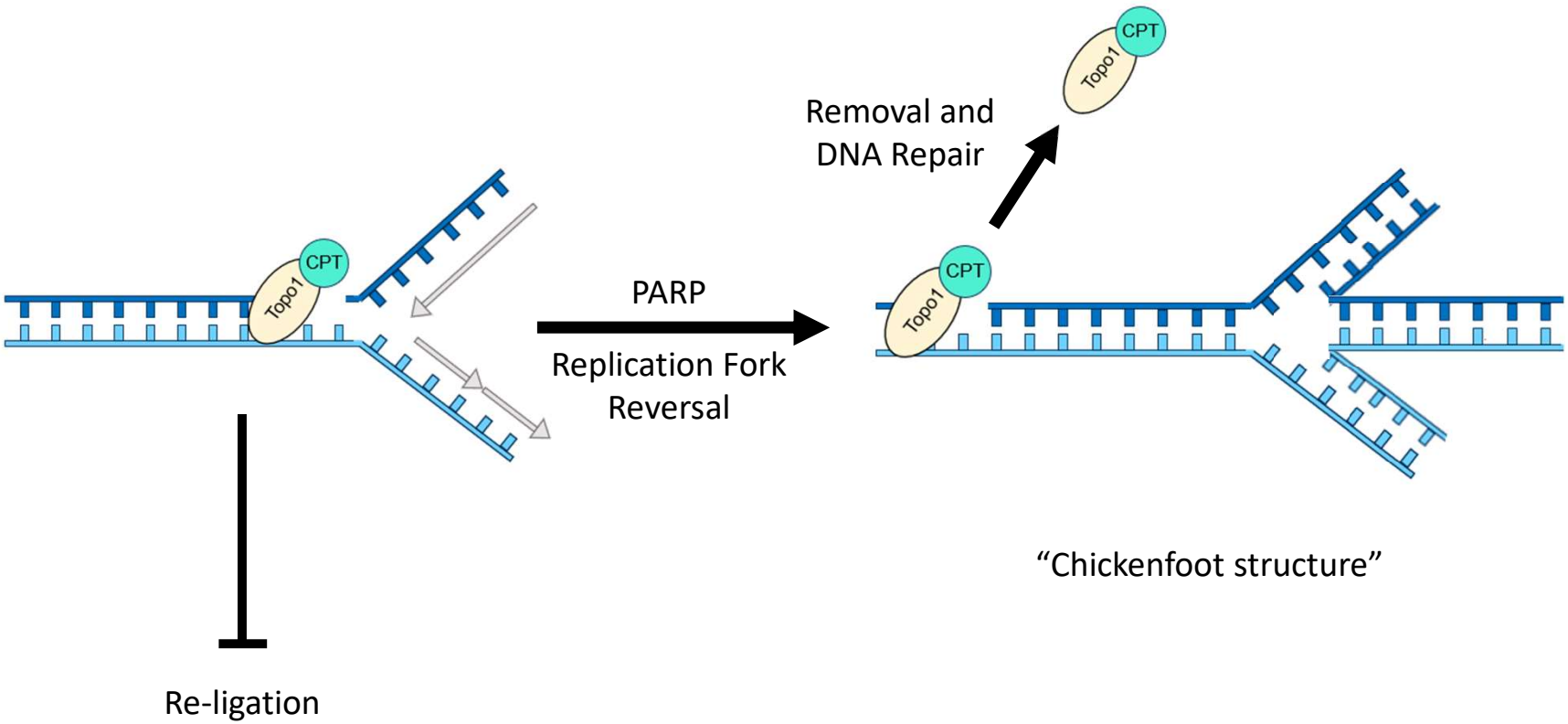


Camptothecin binds and traps the Topo1 covalent complex on the DNA (Top1cc)

Topoisomerase 1 Inhibitors Trap Topoisomerase 1 and Prevent Re-Ligation



PARP Mediates Replication Fork Reversal and DNA Damage Repair from Topoisomerase 1 Inhibition



A.R. Chaudhuri, et al., Nat. Struct. Mol. Biol., 2012; 19(4):417-423

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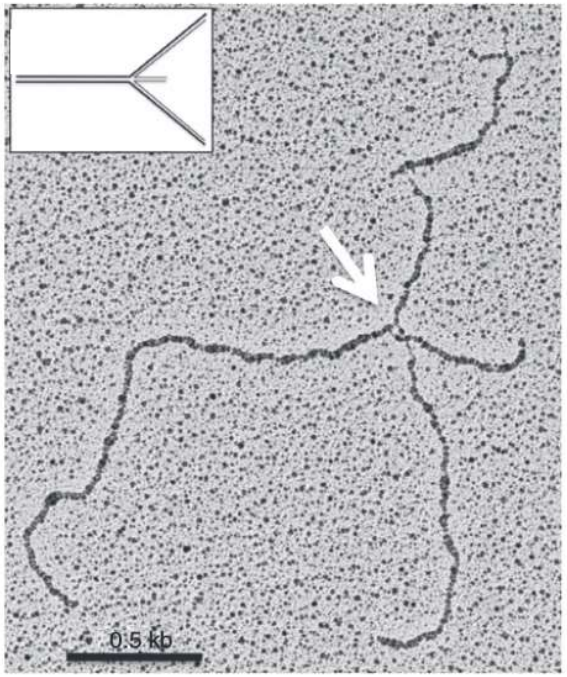

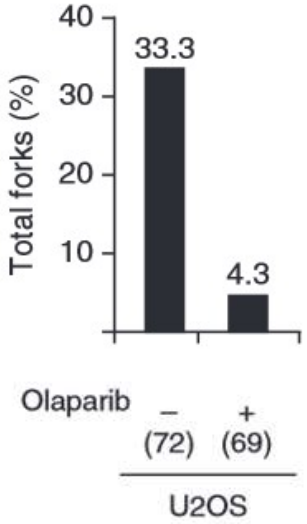

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Opportunity and Challenges in Combining PARP and Topoisomerase 1 Inhibitors: A Path Forward with Dual-Payload ADCs

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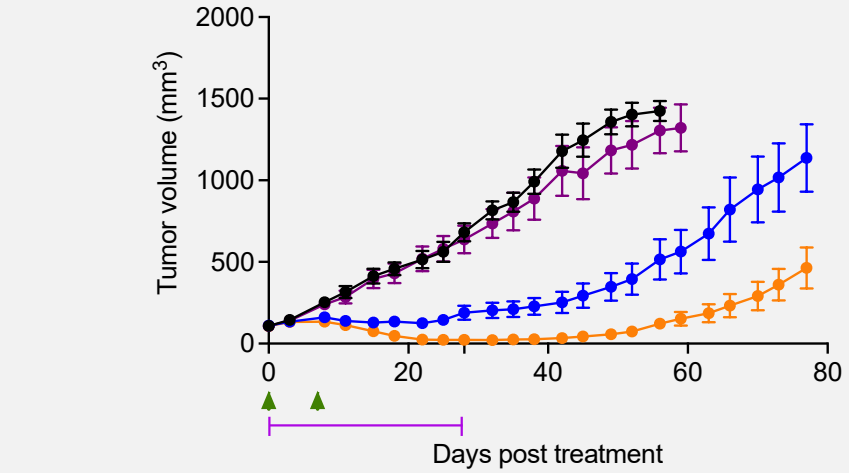
- PARP directly involved in Topoisomerase 1 inhibitor DNA damage repair
- Combo not realized in clinic due to toxicity
- ADC + PARPi under clinical investigation
- PARP inhibition toxicity

MDA-MB-231



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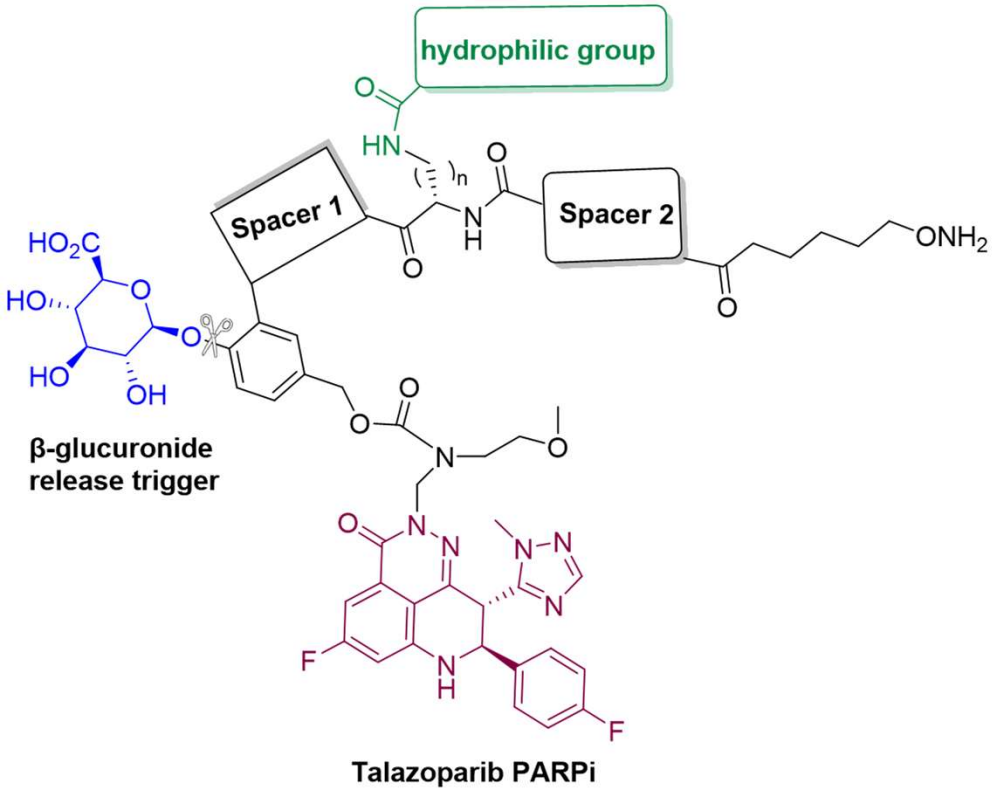
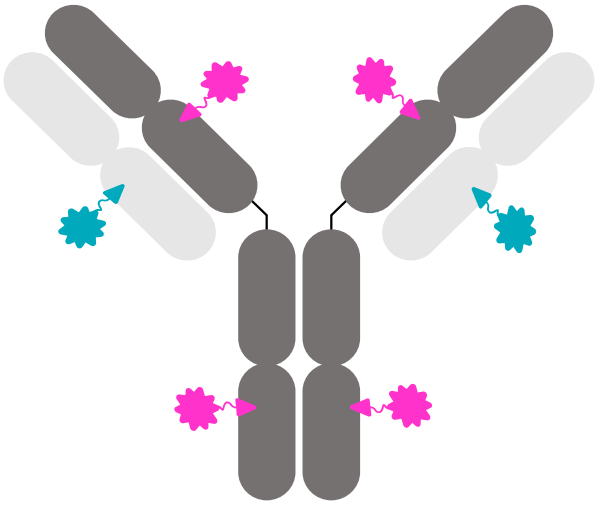
PEGylated β-glucuronidase PARPi Linker-Payload Design



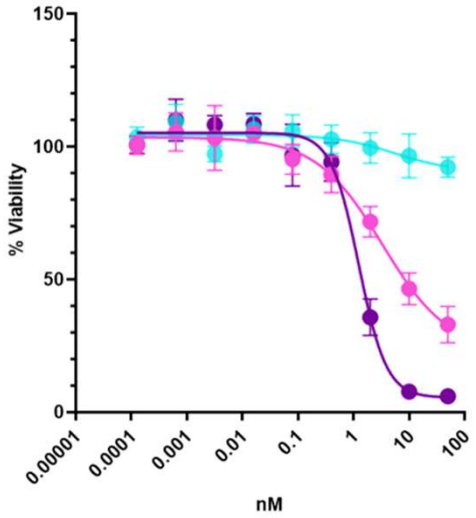
Optimization of Dual-Payload ADC Design (Topo1i + PARPi)



4+2

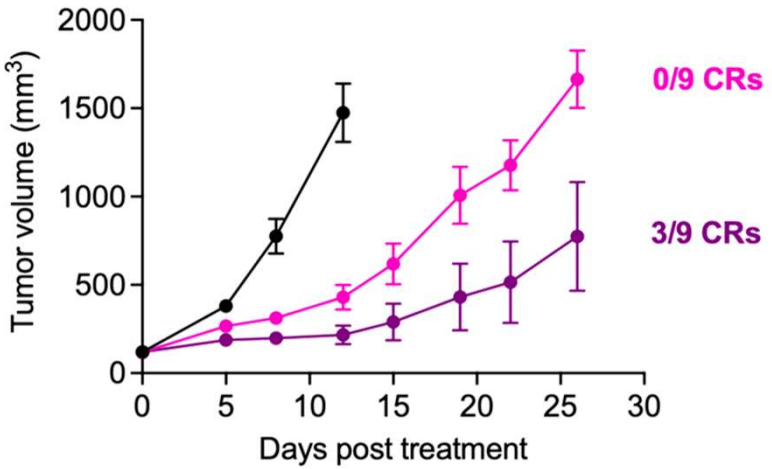
Dual-Payload Topo1i + PARPi ADC Shows Increased Activity Compared to Topo1i ADC

MC38-hTF *in vitro potency*



DAR2 PARPi ADC
DAR4 Topo1i ADC
DAR4 Topo1i + DAR2 PARPi ADC[2]

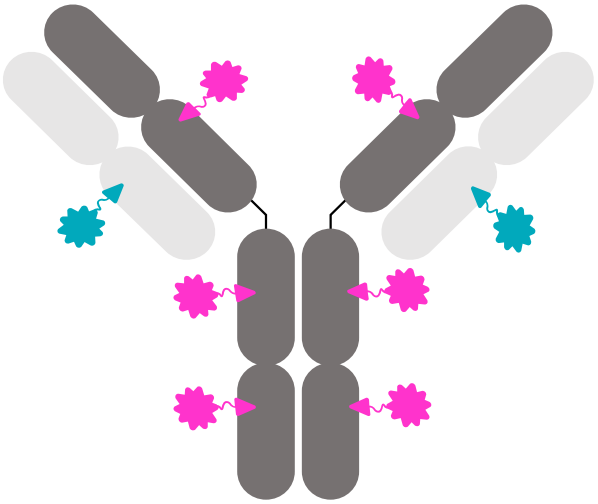
MC38-hTF *in vivo anti-tumor activity*



Vehicle (PBS)
5 mg/kg DAR4 Topo1i ADC
5 mg/kg DAR4 Topo1i + DAR2 PARPi ADC[2]

PBS – phosphate buffered saline

Our Focused R&D Strategy: Make ADCs Better Inside the Tumor with Dual-Payloads



- Multiple different dual-payload ADCs
- Best-in-class platform potential to optimize dual-payload ADCs
- Overcome resistance in clinic