DESIGNED

TO DELIVER

Dual Payload ADCs To Overcome Resistance

Hans-Peter Gerber, Ph.D.

CSO

World ADC 2026, February 25th

London, UK

SUTRO BIOPHARMA

Overcoming Resistance: Key Criteria for Next-Generation ADCs

Designing ADCs to Delay or Prevent Resistance

1

Increase ADC exposure

- Achieve higher payload delivery while reducing platform and on-target toxicity
- Exemplified by **STRO-004** and **STRO-006** programs

2

Combine payloads with complementary mechanisms of action

- Create dual-payload ADCs that integrate distinct MOAs (e.g., Topo1 + MMAE or Topo1 + STING) to extend the time to resistance
  - **STRO-227: Topo1 x MMAE dpADC**
  - **HER2-dpADC program: Topo1 x STING**
- Enhance the potency of Exatecan (Topo1 inhibitor) through combination with DNA DDRi

DDRi – Damage response inhibitors; dpADC – Dual-payload ADC; MMAE – Monomethyl Auristatin E (tubulin inhibitor); MOA – Mechanism of action; HER2 – Human epidermal growth factor receptor 2; Topo1 – Topoisomerase I inhibitor

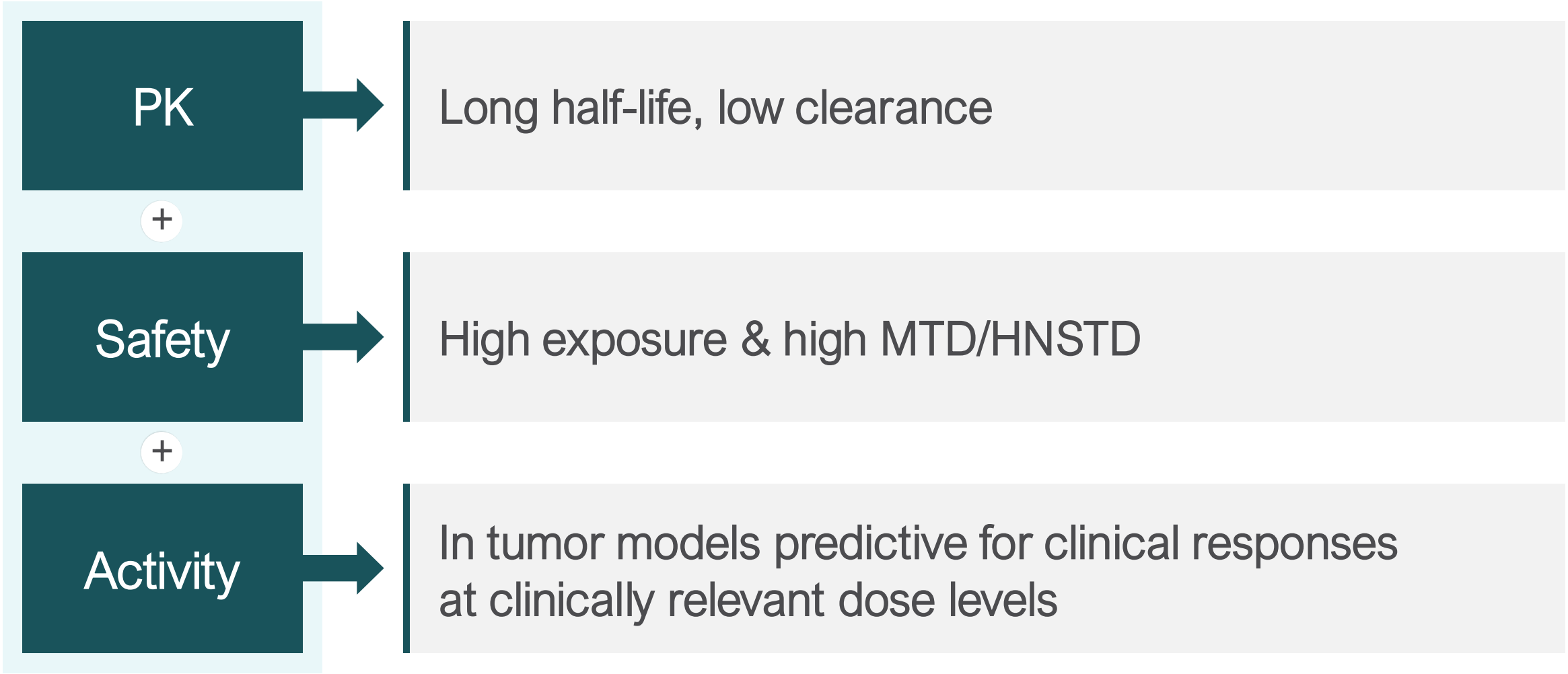
Topo1 Inhibitor ADC Payloads Demonstrate Improved Efficacy over Tubulin Inhibitors Across Indications and Targets

ADC Target	Indication	Program	Payload, DAR	ORR Gain (%)	PFS Gain (Months)
CEA	Colorectal	SAR408701	DM4, 3.9	0 → 31	1.8 → 5.1
		M9140	Topo1, 8	31	6.9
HER2	HER2+ Gastric	Kadcyla	DM1, 3.5	21 → 30	2.7 → 2.9
		Enhertu	Topo1, 8	51	5.6
	HER2+ Breast	Kadcyla	DM1, 3.5	37 → 42	7.2 → 21.8
		Enhertu	Topo1, 8	79	29
C-Met	wtEGFR NSCLC	Emrelis	MMAE, 3.1	29 → 19	5.7 → 1.2
		ABBV-400	Topo1, 6	48	6.9
	muEGFR NSCLC	Emrelis	MMAE, 3.1	11 → 52	4 → 6.9
		ABBV-400	Topo1, 6	63	10.9

Tubulin Inhibitor ADC Topo1 Inhibitor ADC

DM4, Ravtansine (tubulin inhibitor); DM1, Mertansine (tubulin inhibitor); TOPO1, Topoisomerase I inhibitor; MMAE, Monomethyl Auristatin E (tubulin inhibitor).
HER2+, Human Epidermal Growth Factor Receptor 2 positive; wt/muEGFR, wild type / mutant Epidermal Growth Factor Receptor; NSCLC, non-small cell lung cancer.
Source: Published data.

Pharmacology Attributes of “Winner” ADCs



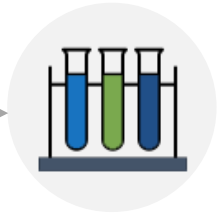
MTD: maximum tolerated dose

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



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
- High DAR (≥16)
- Multi-Payload ADCs

1976

Genentech: Boyer (UCSF)
Purpose: Manufacture Protein Therapeutics

2003

Sutro: Swartz (Stanford)
Purpose: Manufacture in Prokaryotic Cell Extract

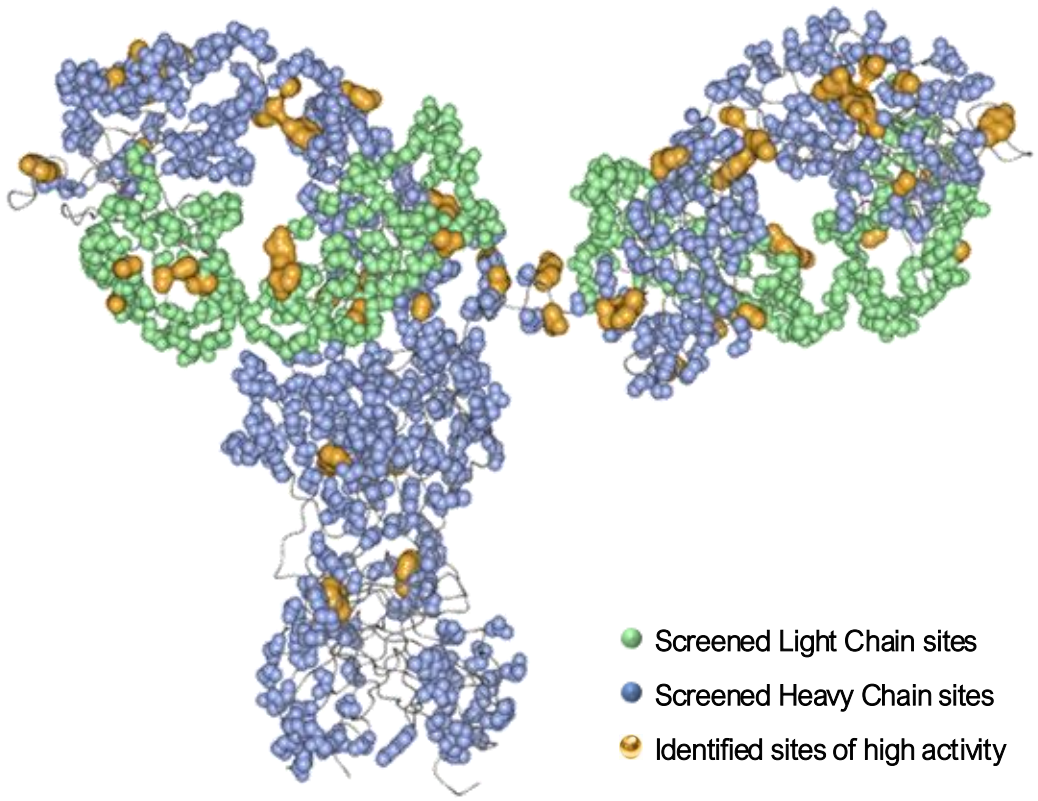
2024

Sutro Milestones
Manufacture Cheaper, Faster, Better

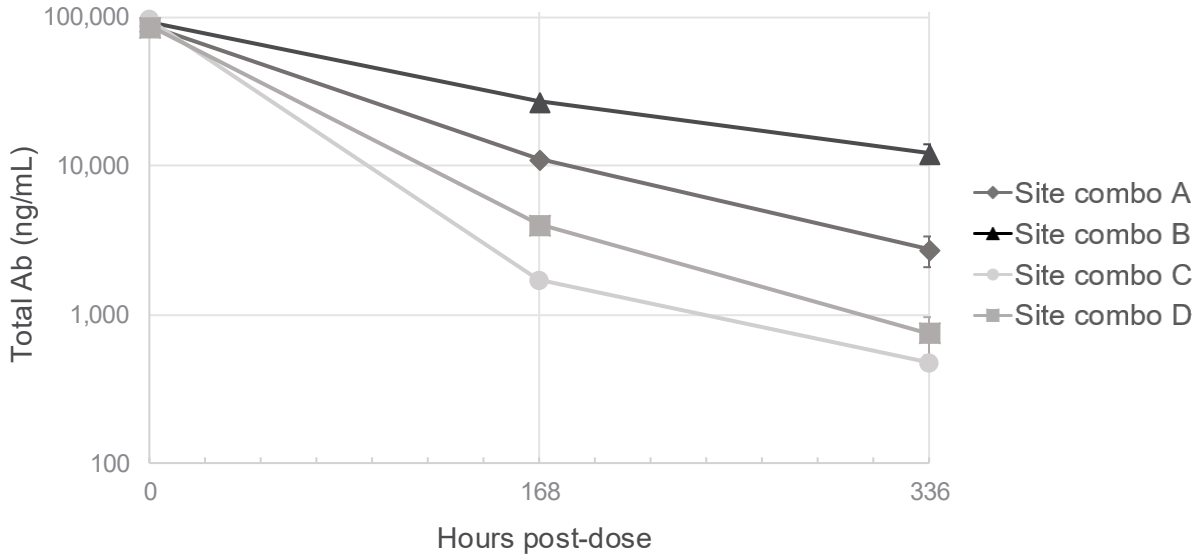
nnAA – non-natural amino acids; CF – cell-free; bsAb – bispecific antibody; GMP – good manufacturing practice

Sutro Cell-Free Manufacturing Platform Enables Site-Selective ADCs with Superior Exposure and Design Flexibility [1 of 2]

Surface Sites Screened on an IgG



DAR16 ADCs

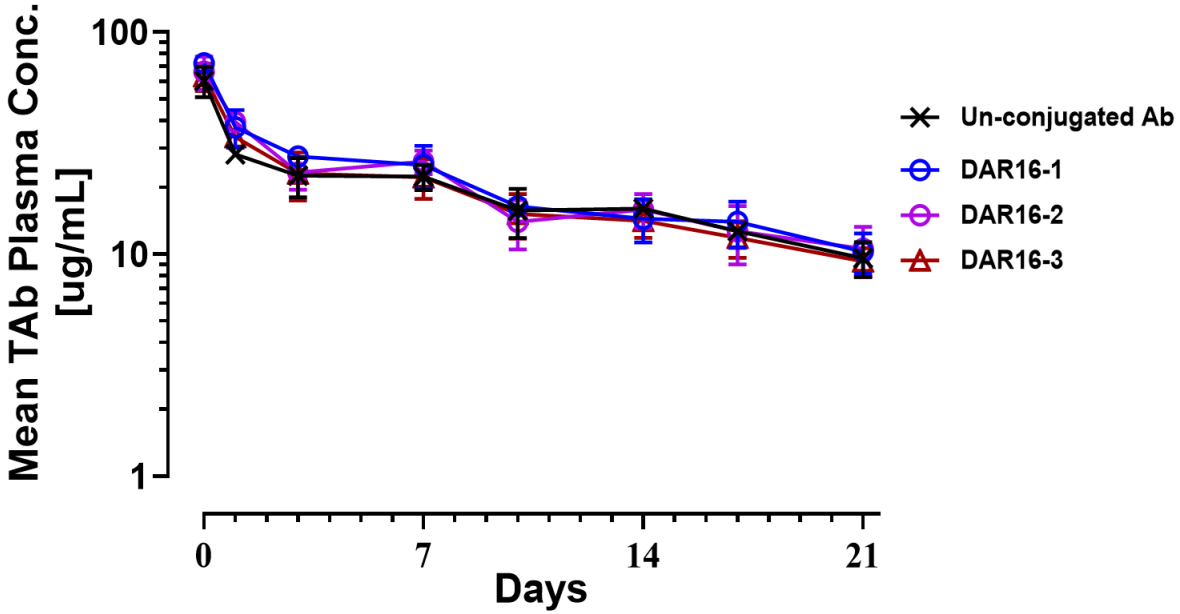


Choosing <u>the right combination</u> of sites can result in optimized pharmacokinetics

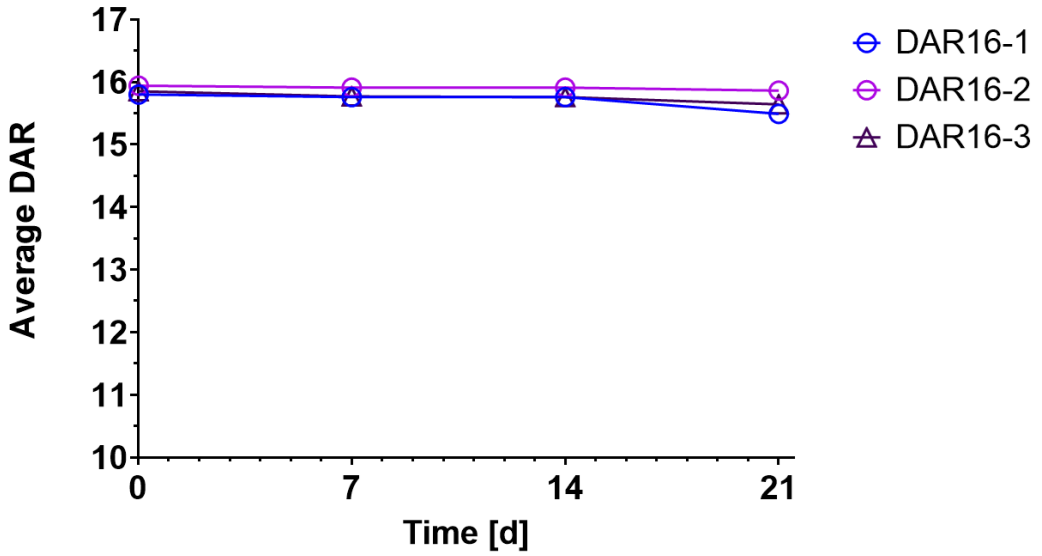
- Better PK
- Less ADC Clearance
- Less Systemic Toxicity

Sutro Cell-Free Manufacturing Platform Enables Site-Selective ADCs with Superior Exposure and Design Flexibility [2 of 2]

PK of DAR16 ADCs in C57BL/6 mice



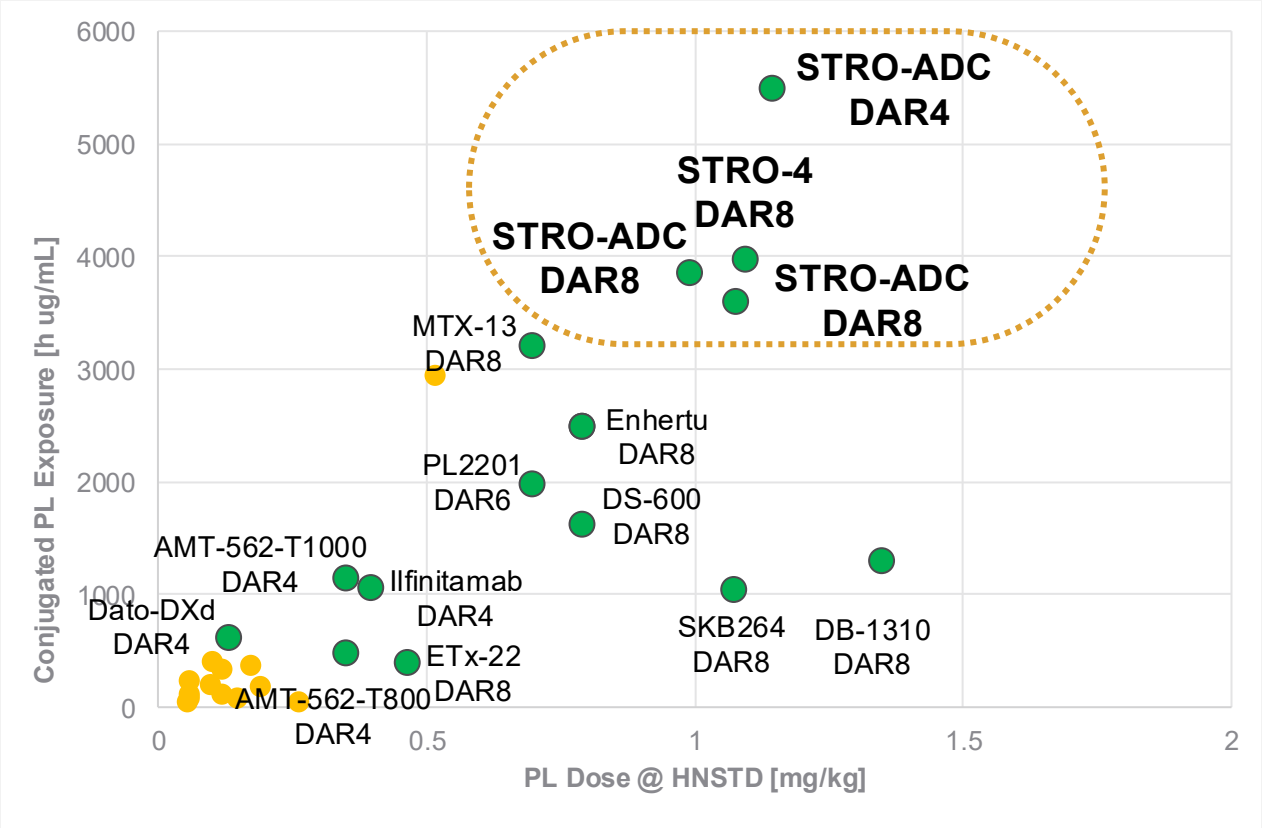
In Vivo DAR Stability



	DAR	$CL_{\_obs}$ ($mL \cdot d^{-1}/kg$)	$T_{1/2}$ (d)
Unconjugated Ab	0	5.07	14.6
DAR16-2	16	4.67	14.6

Sutro's ADC Platform Enables Industry-Leading ADC Exposure, Which Correlates with Better Safety

Comparison of Exposure Levels in NHPs at Highest Non-Severely Toxic Dose (HNSTD) Levels in DAR Equivalents

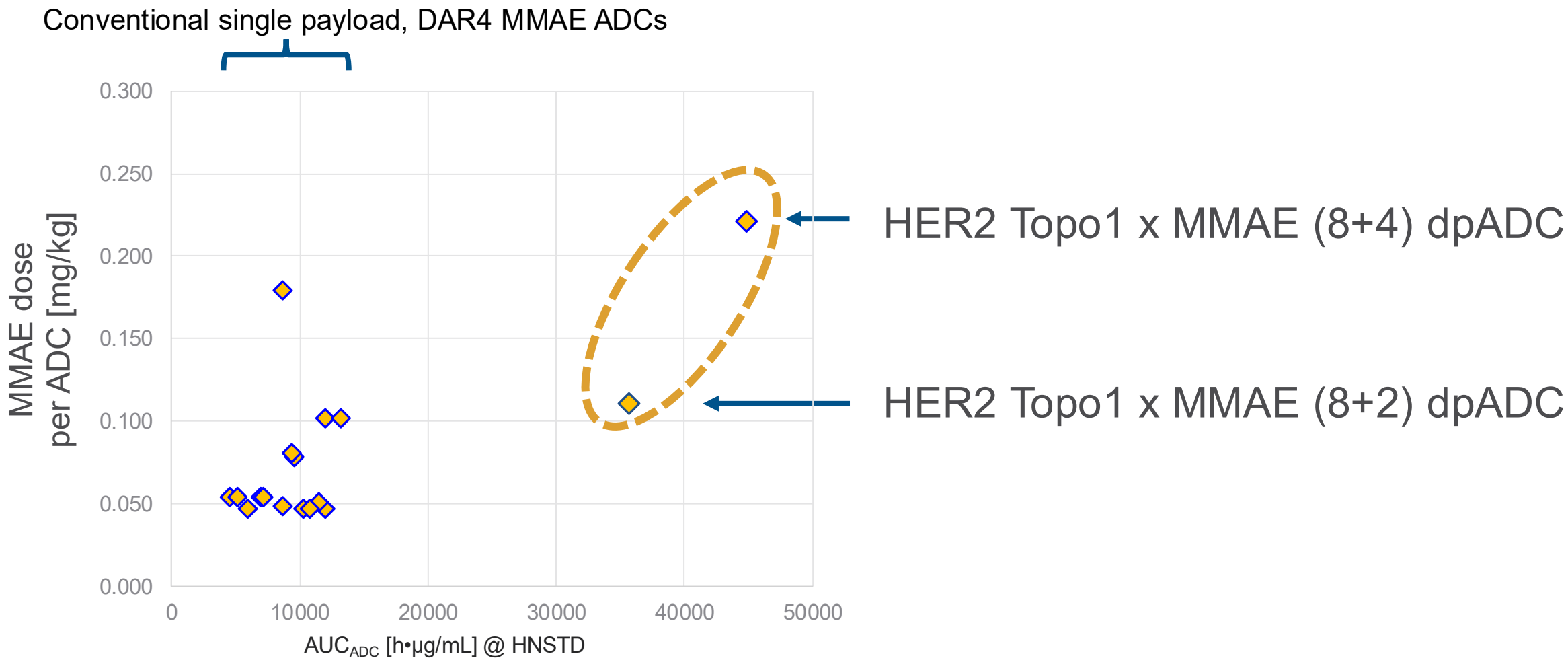


Why does it matter?

- For ADCs, exposure drives efficacy
- Based on PK data, our exatecan ADCs are positioned to be differentiated on safety and efficacy versus on-market ADCs

Exatecan/Topo1i ADCs Tubulin inhibitor ADCs

Industry Highest MMAE Exposure In Presence of 8 Exatecan Payloads



PK Benefit Is Transferable to Other Payload Classes (MMAE, STING, others)

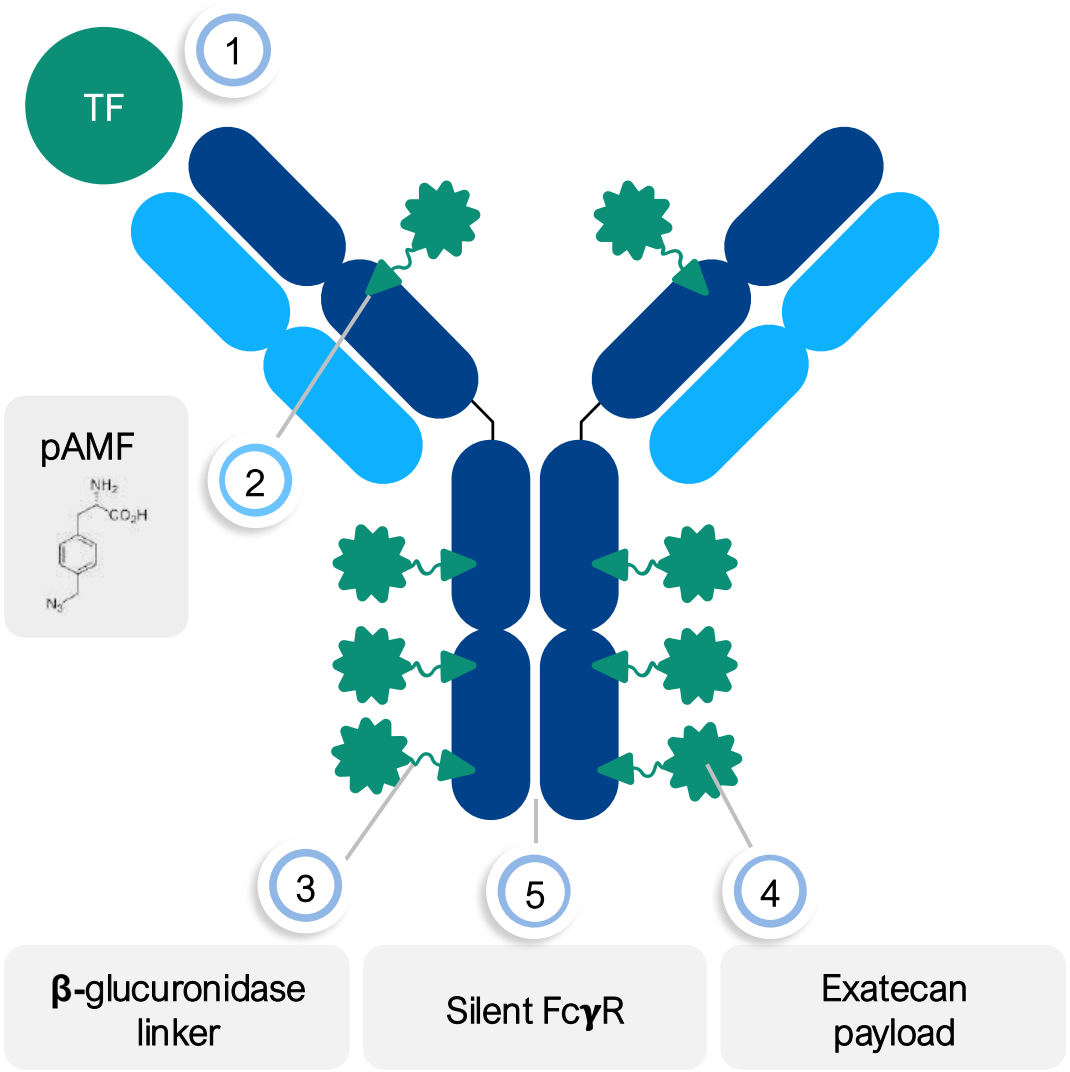
Platform Design, Not β-Glu Linker Alone, Drives PK and Stability

Platform	STRO		Exelixis	PFE/Seagen	Lilly	Merck/Seron o
Target	TF	ITGB6	TF	ITGB6	Nectin 4	CEACAM5
Conjugation Sites	**nnAA select sites**		Cys	Cys	Cys	Cys
Conjugation Chemistry	**Click**		HIPS	Maleimide	Maleimide	Maleimide
Linker	**β-Glu & PEG**		**β-Glu** & CatB	**β-Glu**	**β-Glu**	**β-Glu**
Payload	Exatecan		Belotecan	AMDCPT	Exatecan	Exatecan
DAR	8		8	8	8	8
HNSTD cyno (mg/kg)	50	25	40	N/A	20 (SD)	30
T ½ ADC in cyno (days)	**6.9**	**7.2**	**1.96-2.85**	**18% DAR8**	**3.73**	**4.72**
DN C_{max} (ng/mL)	**2.4**	**2**	NR	NR	**24.3**	**19.4**
Clinical Stage	Ph1	Preclin	Ph1	Ph1	Ph1	Ph1

DN C_{max}= Dose Normalized Free Payload Concentration: **Key driver of off-target platform toxicity in normal tissues**

T ½ ADC = ADC half-life; NR = Not Reported; DAR= Drug Antibody Ratio

STRO-004 Anatomy: Designed to Deliver Superior Safety and Efficacy

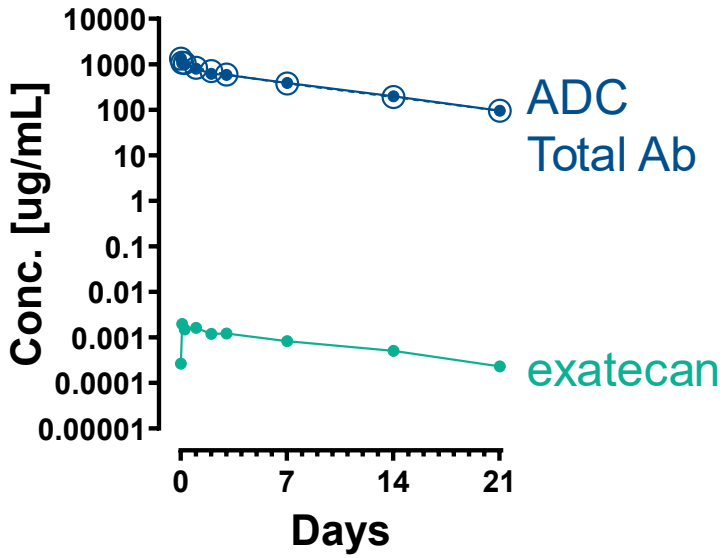


STRO-004 is a homogeneous antibody drug conjugate (ADC) with a drug-antibody ratio (DAR) of 8, targeting TF

1. Enhanced mAb with high affinity, internalization; **reduced bleeding risk**
2. Optimally positioned non-natural amino acids, p-azidomethyl-L-phenylalanine (pAMF), combined with ultra stable click chemistry results in **lowest levels of unconjugated payloads**
3. **β-glucuronidase cleavable linkers** with tumor selective cleavage, strong stability while in circulation, **and added hydrophilicity** led to **best-in-class PK**
4. **Exatecan payload causing DNA disruption** and potent tumor cell killing, with high bystander activity, and immunogenic cell death (ICD)
5. **Lack of FcγR interactions** limits uptake by alveolar macrophages, reducing risk of interstitial lung disease (ILD)

STRO-004 (TF-Topo1-DAR8): Well-Tolerated in NHP up to 50 mg/kg Designed for Enhanced Drug Exposure and Tumor Targeting

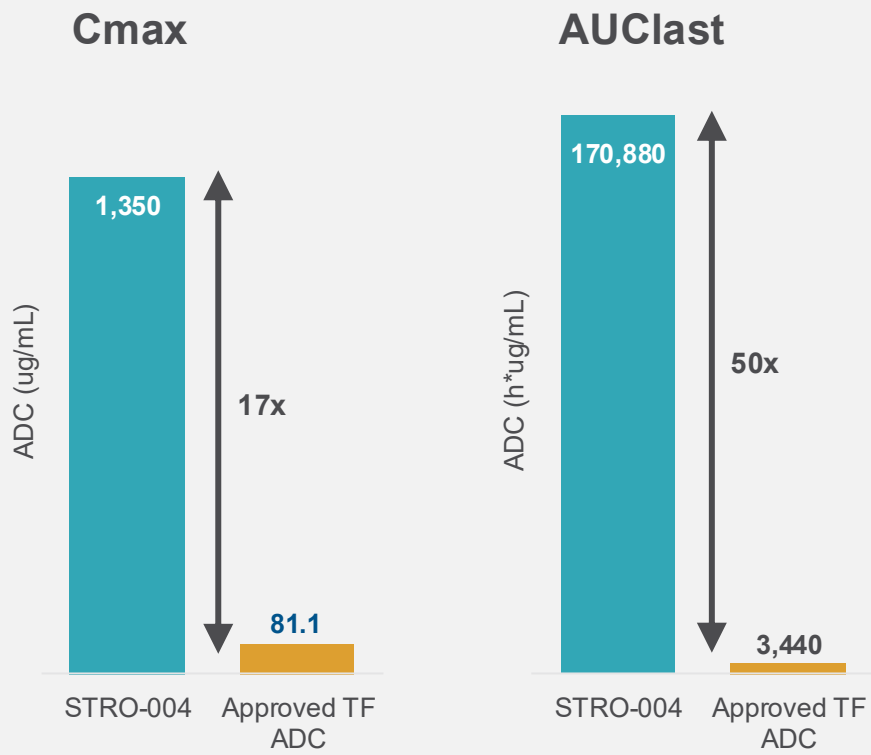
STRO-004 well-tolerated in NHP at 50 mg/kg



- STRO-004 well tolerated in NHP up to 50mg/kg
- Long circulatory half-life of the ADC, low free payload (~ng/mL)
- No significant heme toxicities
- no evidence of bleeding, eye toxicity; only mild skin toxicity

Study design: NHPs were administered 10, 25, or 50 mg/kg once every 3-weeks in a 6-week study (1M/1F per group)
NHP – Non-human primate; TAb – Total antibody; HNSTD – Highest non-severely toxic dose; MED: minimum effective dose

Increased Tolerability Leads to Enhanced Drug Exposure

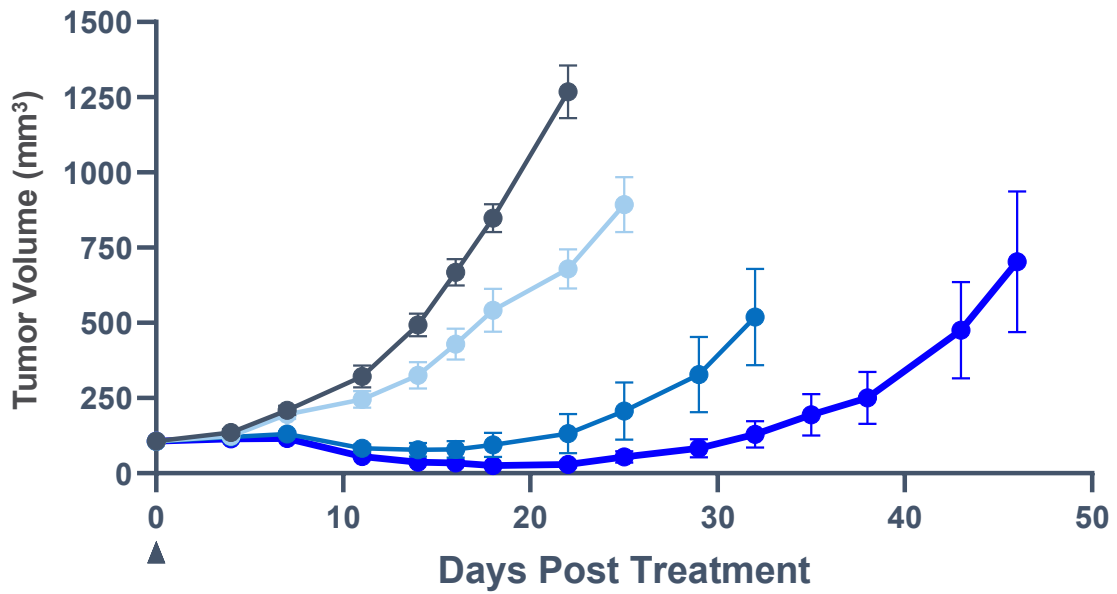


STRO-004, HNSTD ~ 50 mg/kg
Approved TF ADC, HNSTD ~ 3 mg/kg

STRO-004 DAR8 Exatecan Achieved Sustained Tumor Regressions in Xenograft Models of NSCLC and HNSCC at Low Doses

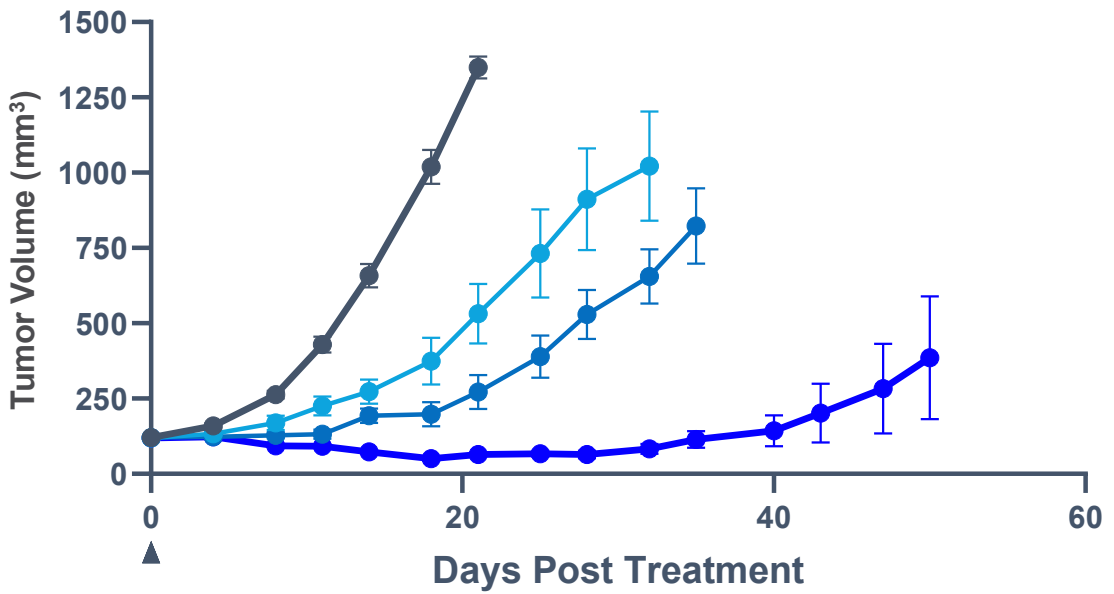
Lung (TF+++)

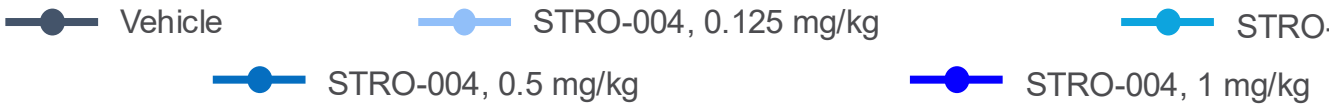
H1975 Growth Curves



Head and Neck (TF++)

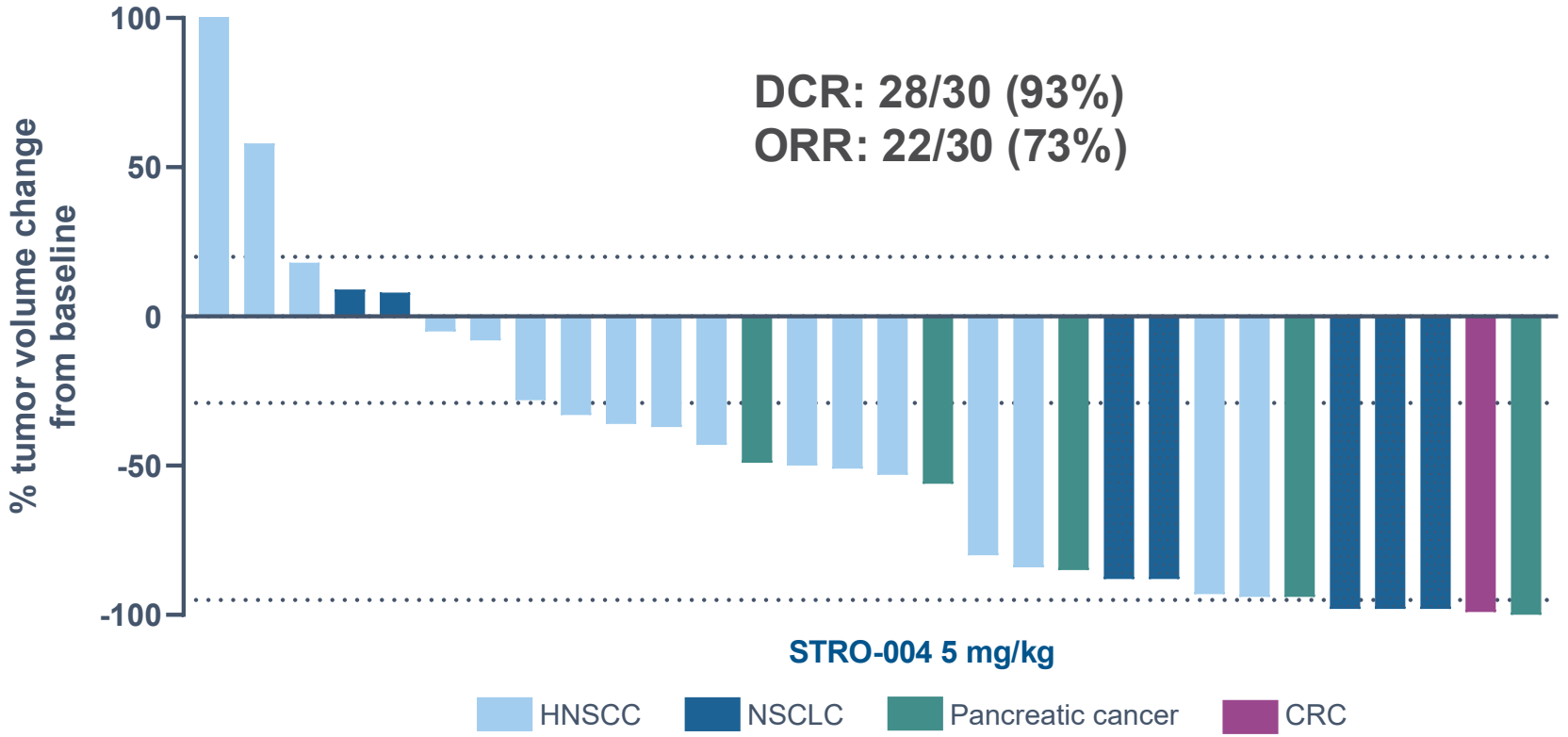
Detroit562 Growth Curves





DAR – Drug to antibody ratio; HNSCC – Head and neck squamous cell carcinoma; NSCLC – Non-small cell lung cancer; TF – Tissue Factor

STRO-004 Showed Promising Anti-tumor Activity in TF-Positive PDX Models of HNSCC, NSCLC, and Pancreatic Cancer



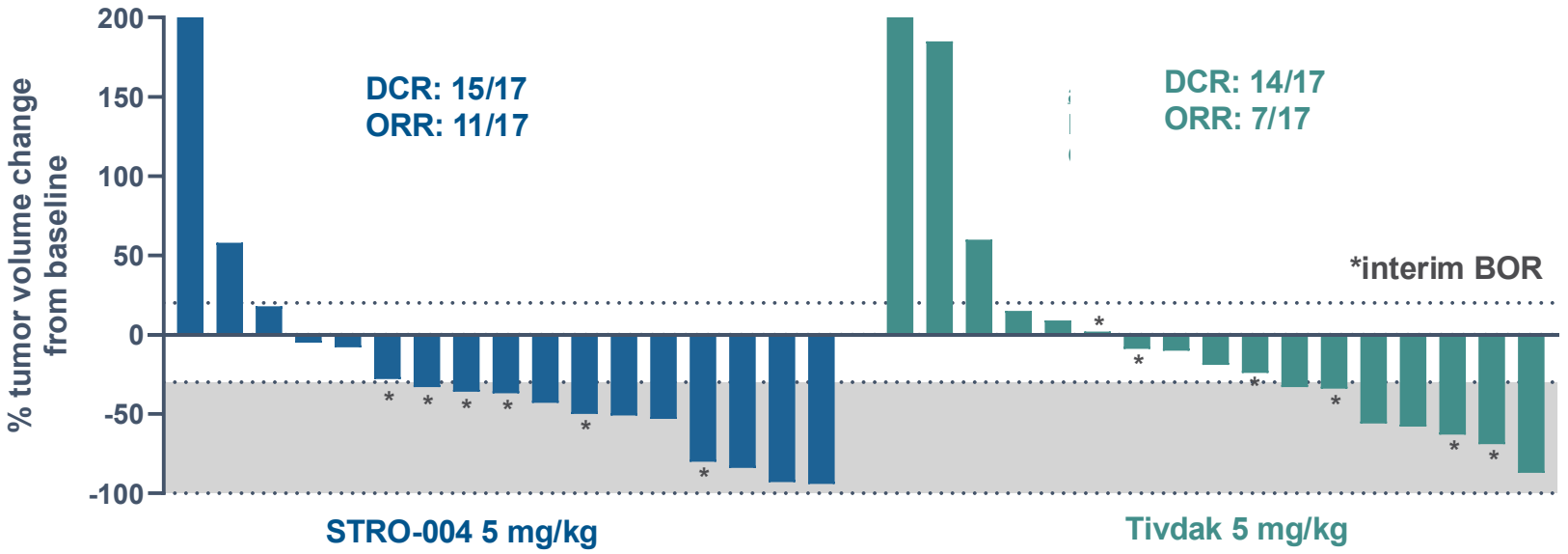
*Interim Best Overall Response (BOR), model ongoing

	STRO-004			
	ORR	CR	PR	SD
Cancer	N (%)			
HNSCC	17	11 (65)	0	11 (65)	4 (24)
NSCLC	7	5 (71)	3 (43)	2 (29)	2 (29)
PDAC	5	5 (100)	1 (20)	4 (25)	0
CRC	1	1 (100)	1 (100)	0	0

CR – Complete response; CRC – Colorectal cancer; DCR – Disease control rate; HNSCC – Head and neck squamous cell carcinoma; NSCLC – Non-small cell lung cancer; ORR – Overall response rate; PDAC – Pancreatic ductal adenocarcinoma; PDX – Patient-derived xenograft; PR – Partial response; SD – Stable disease; TF – Tissue Factor

Anti-Tumor Activity Following a Single Dose of STRO-004 is Greater Compared to Single Dose of Tivdak in HNSCC PDX Models

% Best Response in Head and Neck Squamous Cancer PDX Models



		STRO-004, 5 mg/kg single				Tivdak, 5 mg/kg single			
Cancer	N (%)	ORR	CR	PR	SD	ORR	CR	PR	SD
HNSCC	17	11 (65)	0	11 (65)	4 (24)	7 (41)	0	7 (41)	7 (41)

BOR – Best overall response; DCR – Disease control rate; HNSCC – Head and neck squamous cell carcinoma; ORR – Overall response rate; PDX – Patient-derived xenograft

Detailed Monotherapy Development Strategy: Phase 1 Trial Ongoing

Initial data expected in mid-2026

Tumor type eligibility
Selected for TF expression:

- NSCLC
- HNSCC
- Colorectal
- PDAC
- Bladder
- Cervical
- Endometrial

- Better for patients
- Early signs of activity
- Relevant to look at safety in potential-forward indications

Dose Escalation
Advanced Solid Tumors with Tissue Factor Expression

- Dose Level 5
- Dose Level 4
- Dose Level 3
- Dose Level 2
- Dose Level 1

HNSTD of 50 mg/kg permits high entry into dose escalation ladder
- Shortens time to observing activity
- Increases probability of wide therapeutic window – facilitates dose optimization

Move Forward with Recommended Dose(s)

- Early detection of activity
- Early characterisation of safety profile
- Early transition to registrational development path

- Recommended Dose 2
- Recommended Dose 1

HNSCC – Head and neck squamous cell carcinoma; HNSTD – Highest non-severely toxic dose; NSCLC – Non-small cell lung cancer; PDAC - Pancreatic ductal adenocarcinoma; TF – Tissue factor

Pipeline of Next-Generation Single- and Dual-Payload ADCs

	PROGRAM	MODALITY/TARGET	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/1B	PHASE 2	PHASE 3/ REGISTRATIONAL	MILESTONES
WHOLLY-OWNED PROGRAMS	**STRO-004**	Tissue Factor ADC	Solid Tumors						Initial Phase 1 data expected mid-2026
	STRO-006	Integrin αvβ6	Solid Tumors						IND submission expected 2026
	STRO-227	PTK7 Dual-Payload ADC	Solid Tumors						IND submission expected 2026
	STRO-00Y	Dual-Payload ADC	Solid Tumors						
PARTNERED PROGRAMS	**VAX-24** VAXCYTE	24-Valent Conjugate Vaccine	Invasive Pneumococcal Disease						
	VAX-31 VAXCYTE	31-Valent Conjugate Vaccine	Invasive Pneumococcal Disease						
	Undisclosed Programs Astellas	Immunostimulatory ADCs (iADCs)	Cancers						1st program expected to enter clinic in early 2026

Dual Payloads to Overcome Treatment Resistance

Challenge: Development of resistance to single payload ADCs in solid tumors

- Drivers of resistance are the payloads, not target downregulation[1]
- Increased focus on novel payloads/dual payload ADCs

Compelling clinical evidence for multi-MOAs improving pharmacology

- Chemotherapy combines different toxin classes[2]
- Drivers of success seen with CPI combos: MOA diversity and non-overlapping toxicity[3]

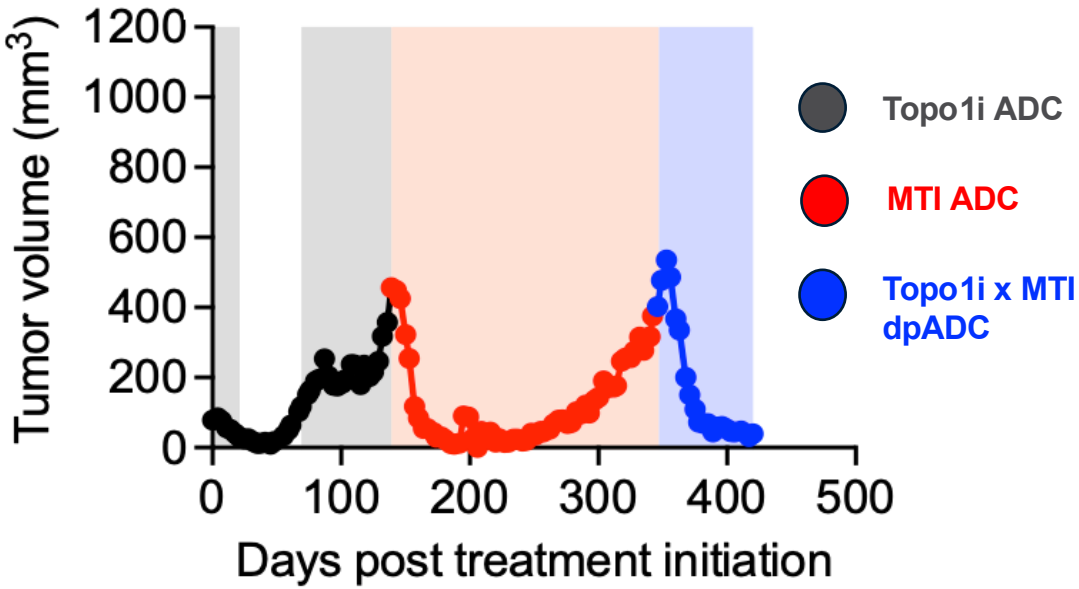
Sutro is positioned to become a leader in multi-payload ADCs

- Payload diversity (Topo1i, MMAE, DDRi, IO)
- Key design advantages enabled by our cell-free platform
- Preclinical efficacy without compromising tolerability

[1] Shitara & Yamaguchi, Nat Med, 2024 [2] Palmer & Sorger, Cell, 2017; Schmidt & Chen, AnRevCanBiol,2023; [3] Jin & Bernards, Nature, 2023; Schmidt & Uebele, JAMA, 2020

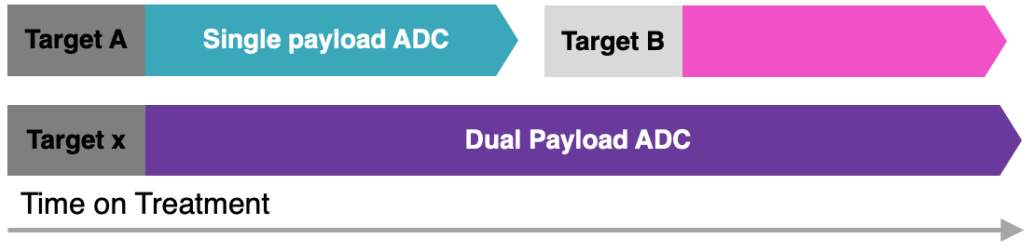
Dual-Payload ADCs Have Potential to Overcome Resistance and to Expand Clinical Opportunities

Tumors Resistant to both Topo1i and MTIs respond to dpADC

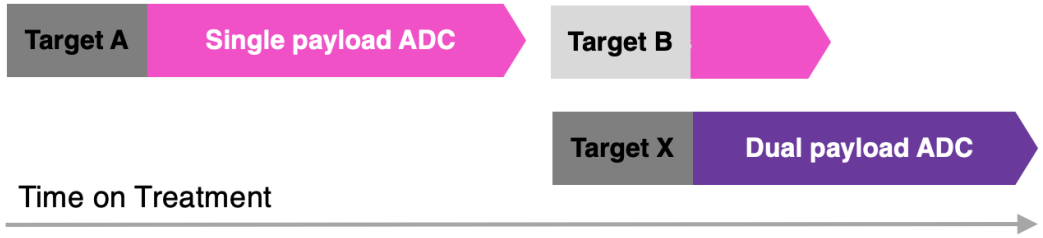


Clinical Development Opportunity: Relapse to Front-Line

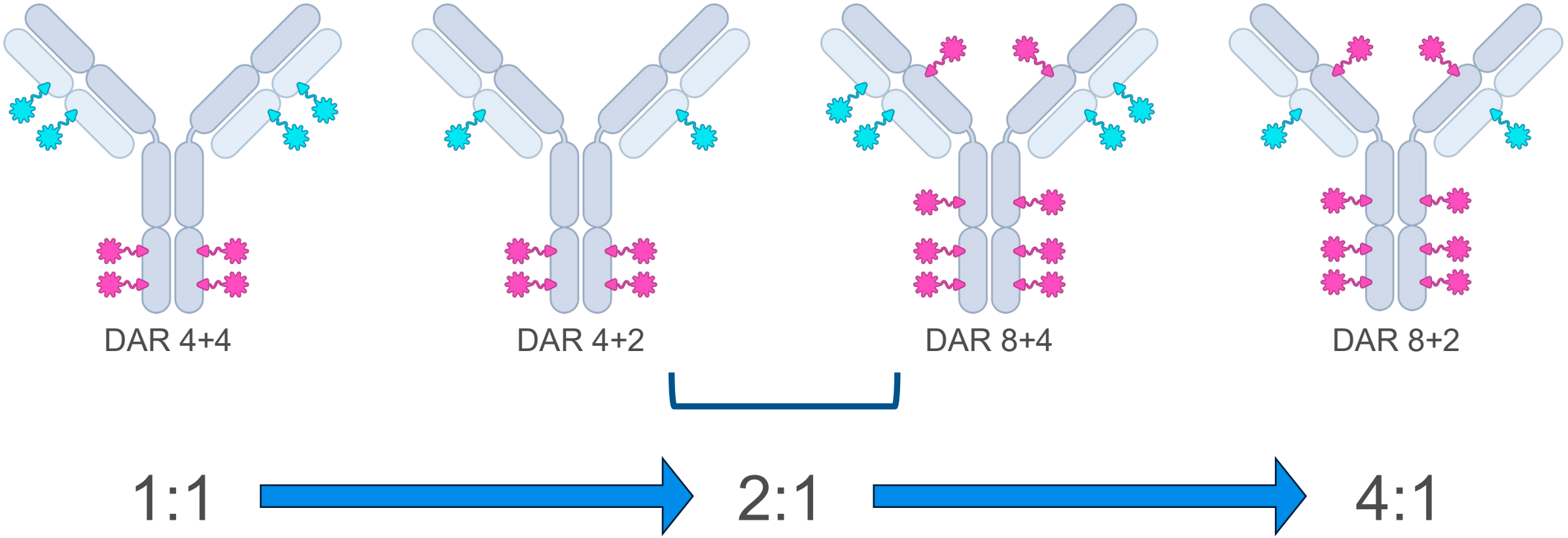
Early Line: Instead of two sequential spADCs



Late Lines: dpADC after relapse from spADC

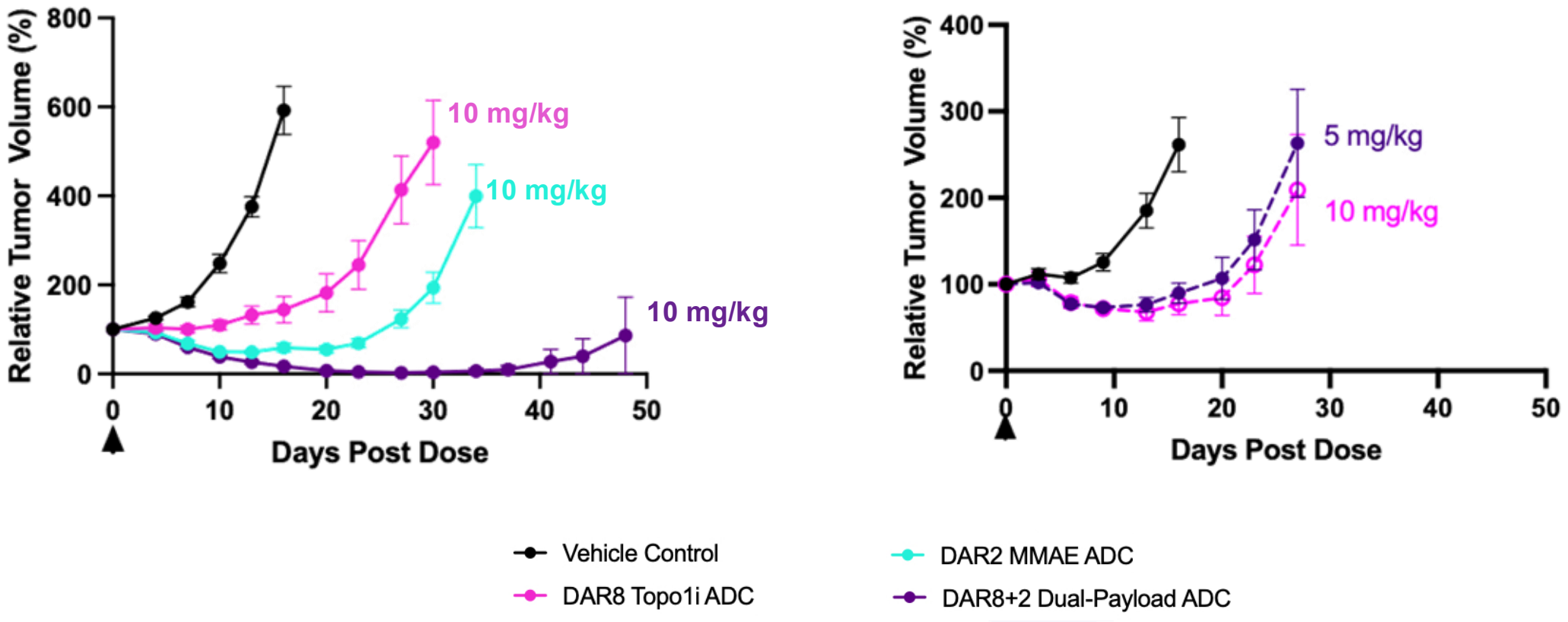


Cell-Free Platform Enables Site-Specific Tuning of Linker-Payload Ratios



Better Together: Dual-Payload ADC Outperforms Single-Payload ADCs

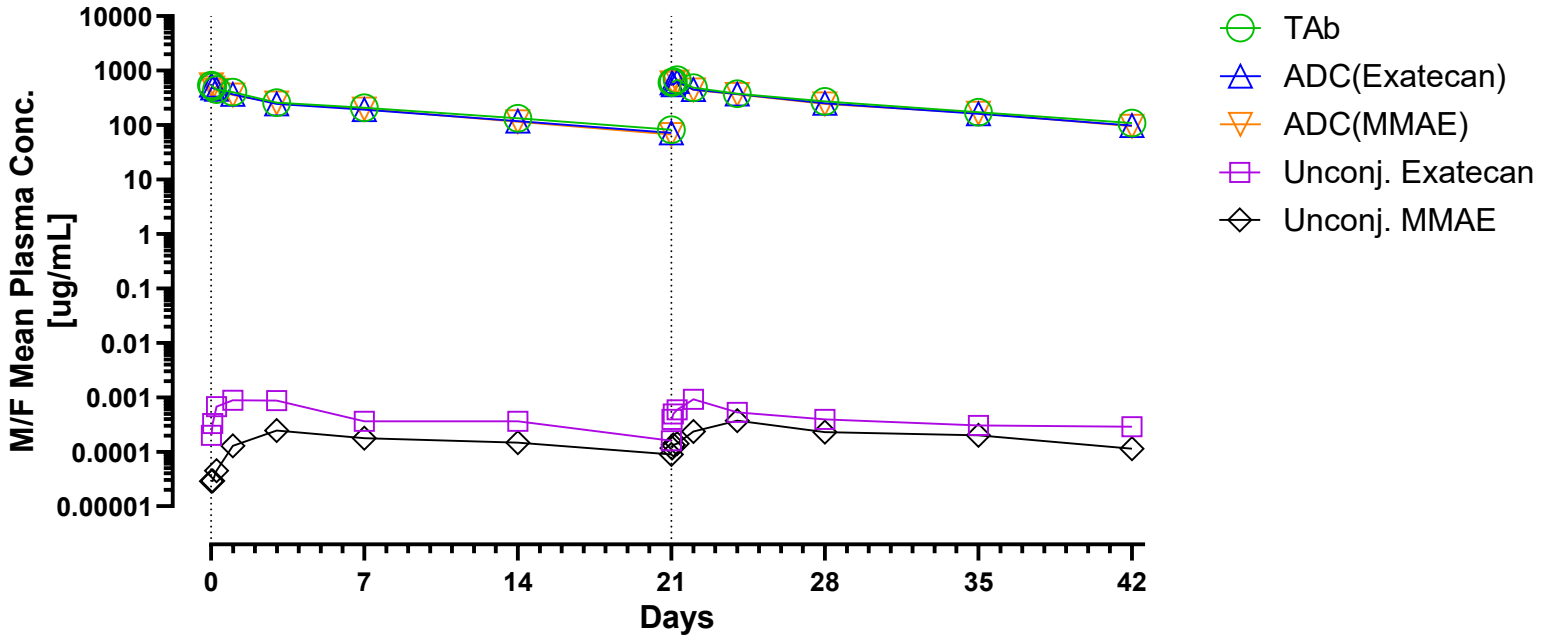
Breast Cancer Xenograft Models – Tumor Growth



MMAE – Monomethyl auristatin E; Topo1 – Topoisomerase I inhibitor

Encouraging PK and Safety Profile for STRO-227 (PTK7) in NHP

25 mg/kg 8+2 PTK7 dpADC (Q3Wx2)



Dose (mg/kg)	Analyte	C_{max} (ug/mL)		AUC_{last} (d·µg/mL)		CL (mL/d/kg)	V_{ss} (mL/kg)	$t_{1/2}$ (d)	
		C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2
25 (MF Mean)	TAb	541	684	3940	5220	4.89	70.5	10.3	10.8

Sutro Dual-Payload ADC: Preclinical Tolerability Meets Single-Payload Benchmarks [1 of 2]

ADC	Target	Linker	Payload	DAR	NHP HNSTD	Highest Clinical Phase
Padcev	Nectin-4	Val-cit	MMAE	4	3 mg/kg[a] (Q1Wx4)	Approved
Tivdak	TF	Val-cit	MMAE	4	3 mg/kg[a] (Q3Wx5)	Approved
SGN-B6A	ITGB6	Val-cit	MMAE	4	6 mg/kg[a] (Q3Wx2)	3
LCB84	Trop-2	β-Glu	MMAE	4	10 mg/kg[b] (Q3Wx2)	1/2
LNCB74	B7-H4	β-Glu	MMAE	4	10 mg/kg[c] (Q3Wx2)	1
STRO-227	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

[a]PMID: 38692647. [b]LCB84 doi:10.1158/1538-7445.AM2022-328. [c]LNCB74 doi:10.1158/1538-7445.AM2024-1898

Sutro Dual-Payload ADC: Preclinical Tolerability Meets Single-Payload Benchmarks [2 of 2]

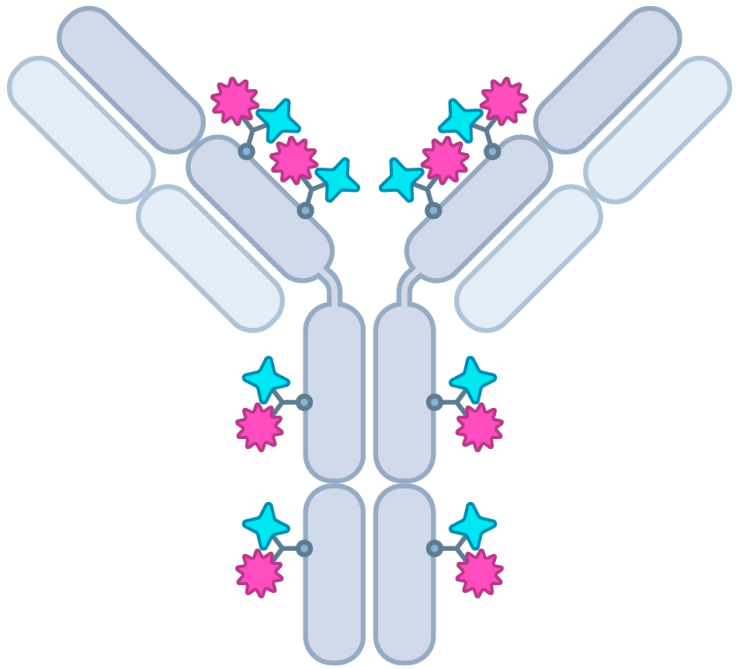
ADC	Target	Linker	Payload	DAR	NHP HNSTD	Highest Clinical Phase
Enhertu	HER-2	GGFG	Deruxtecan	8	30 mg/kg[a] (Q3Wx3)	Approved
Datroway	Trop-2	GGFG	Deruxtecan	4	10 mg/kg[b] (Q3Wx5)	Approved
HER3-DXd	HER-3	GGFG	Deruxtecan	8	30 mg/kg[c] (Q3Wx5)	3
I-DXd	B7-H3	GGFG	Deruxtecan	4	30 mg/kg[d] (Q2Wx3)	3
R-DXd	CDH6	GGFG	Deruxtecan	8	30 mg/kg[e] (Q3Wx3)	2/3
Rina-S	FOLR1	Val-Cit	Exatecan	8	30 mg/kg[f] (Q3Wx2)	3
STRO-227	**PTK7**	**β-Glu**	**Exatecan + MMAE**	**8 + 2**	**25 mg/kg (Q3Wx2)**	**Preclinical**

[a]PMID: 27026201 [b]PMID: 34413126 [c]PMID: 31471314

[d]PMID: 35149548 [e]PMID: 38205802 [f]DOI:10.1158/1538-7445.AM2023-CT244

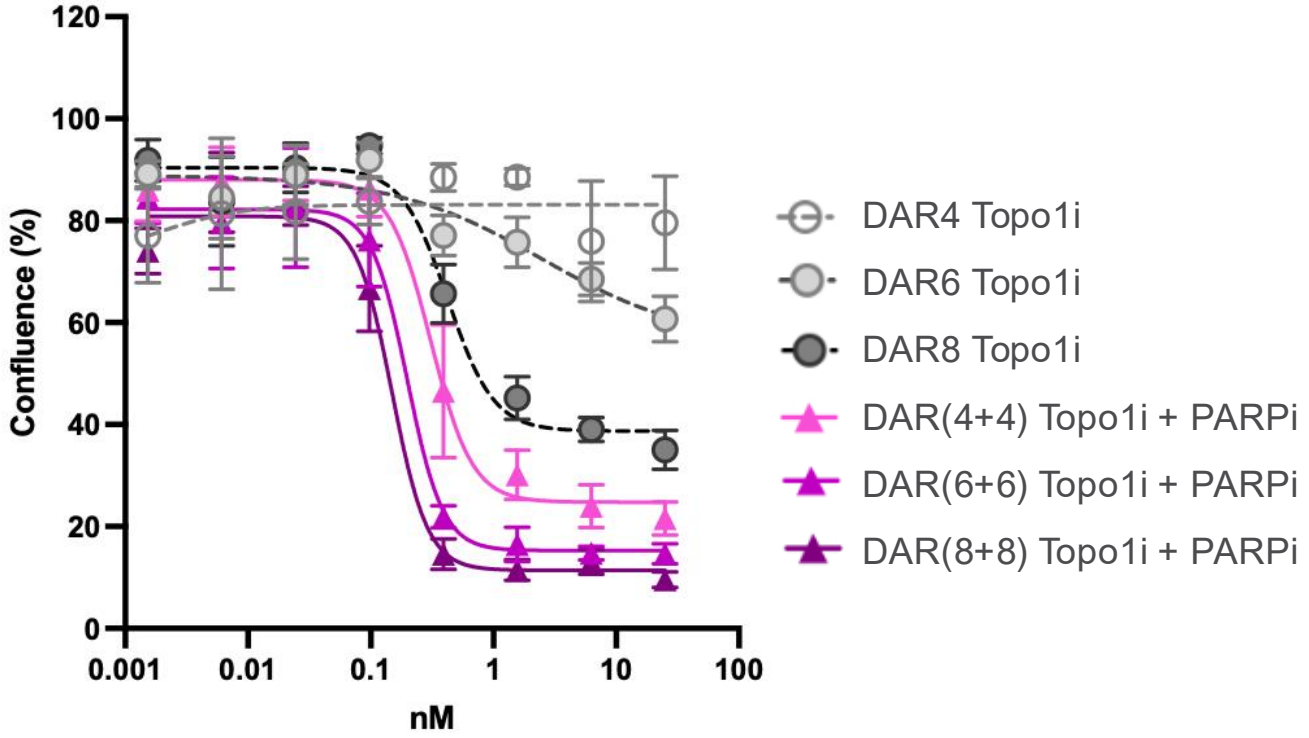
Cell-Free Platform Supports High DAR (8+8) Dual-Payload ADC with Superior *In Vitro* Activity Compared to Single-Payload ADC

Anticipated NHP POC in Q2/26



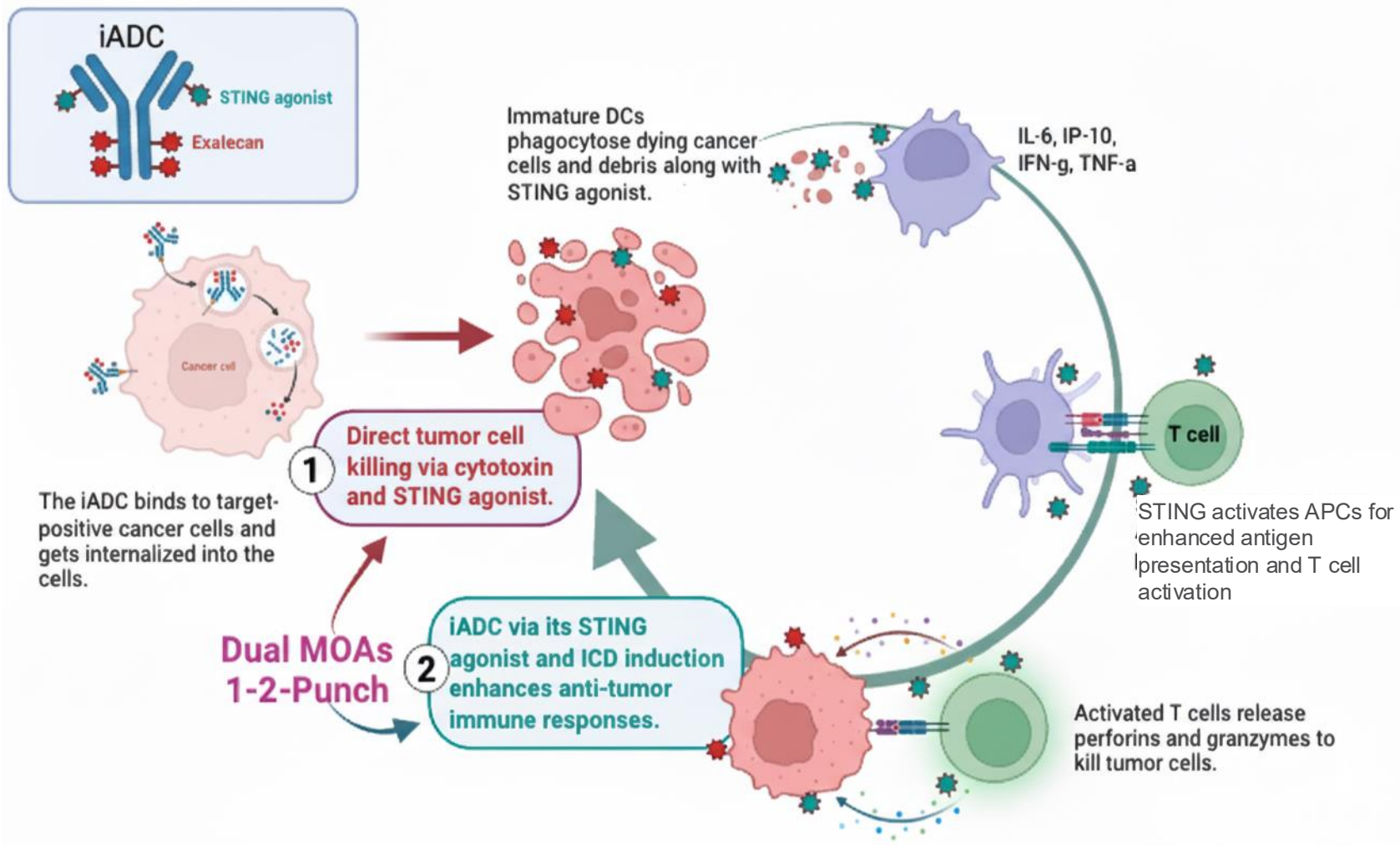
DAR(8+8)

Breast Cancer Cell Line
Cell viability assay



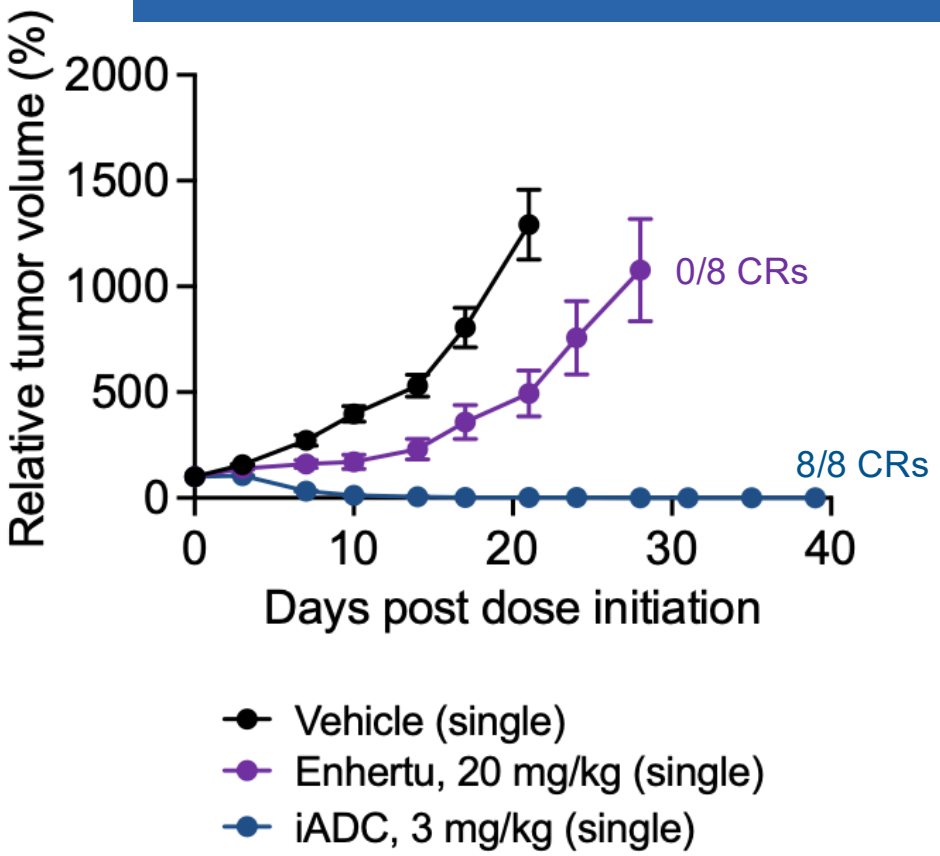
Dual Payload ADCs: Topo1 and STING: Immunostimulatory Antibody Drug Conjugate (iADC)

- **iADC enhanced immune activity**
  - Cytotoxic cell killing
  - STING-mediated activation of dendritic cells
  - Enhanced antigen presentation and T cell activation
- **iADC enhanced cytotoxic activity**
  - Enhanced topo1i sensitivity via Schlafen11 upregulation
  - Enhanced ADC processing via lysosomal biogenesis



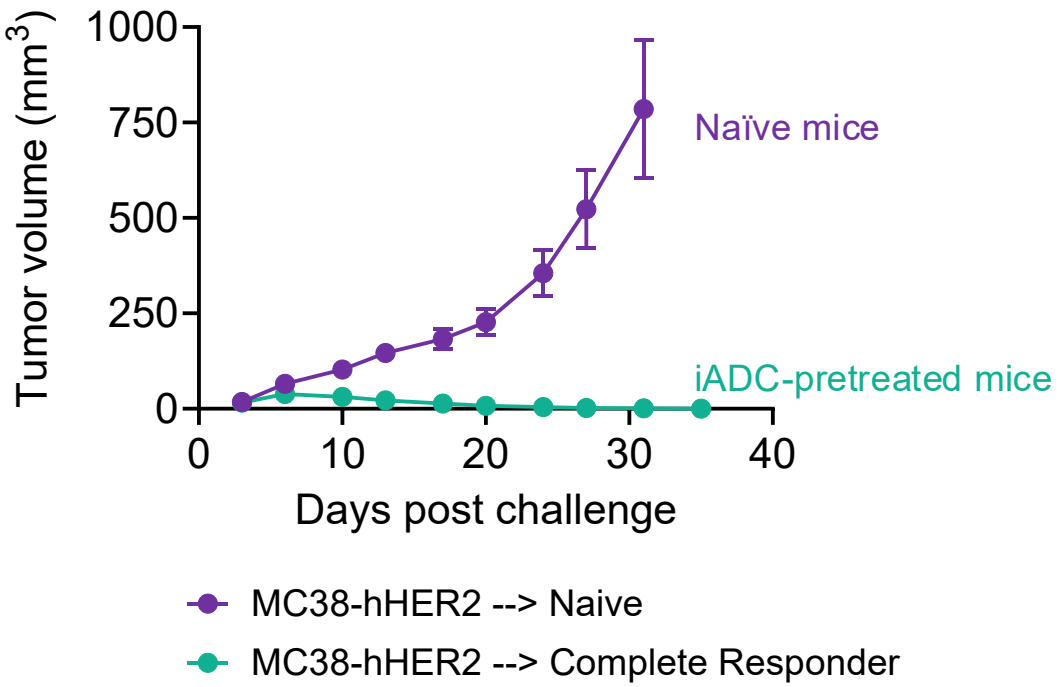
HER2-iADC Induces Complete Responses and anti-Tumor Immune Memory Against an hHER2-expressing Syngeneic Model

iADC elicits complete responses



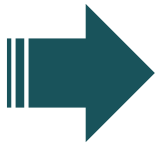
Tumor Rechallenge

iADC-pretreated mice are resistant to tumor rechallenge



iADC MOA: Novel Cross Talk Identified Between STING and Topo1 Payloads Sensitizes Tumors to Topo1 Payloads

- **STING mechanism**
  - Induction of apoptosis
  - Type 1 IFN signaling
  - upregulation of Schlafen11
  - Triggers lysosome biogenesis
  - Dendritic cell activation

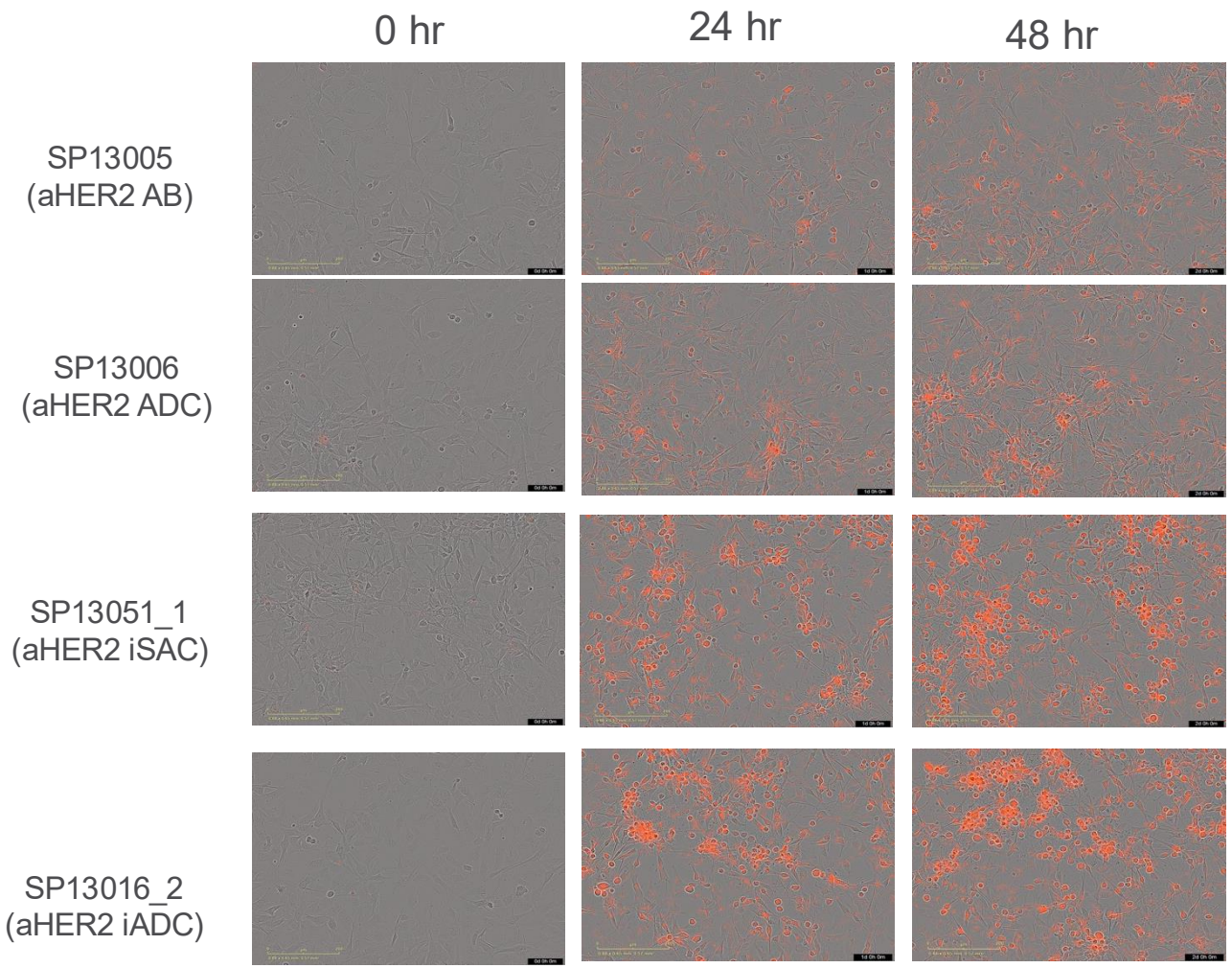


- **Exatecan mechanism**
  - Topo1 inhibitor leading to dsDNA breaks
  - Cytotoxic cell killing
  - Generation of tumor peptide antigens

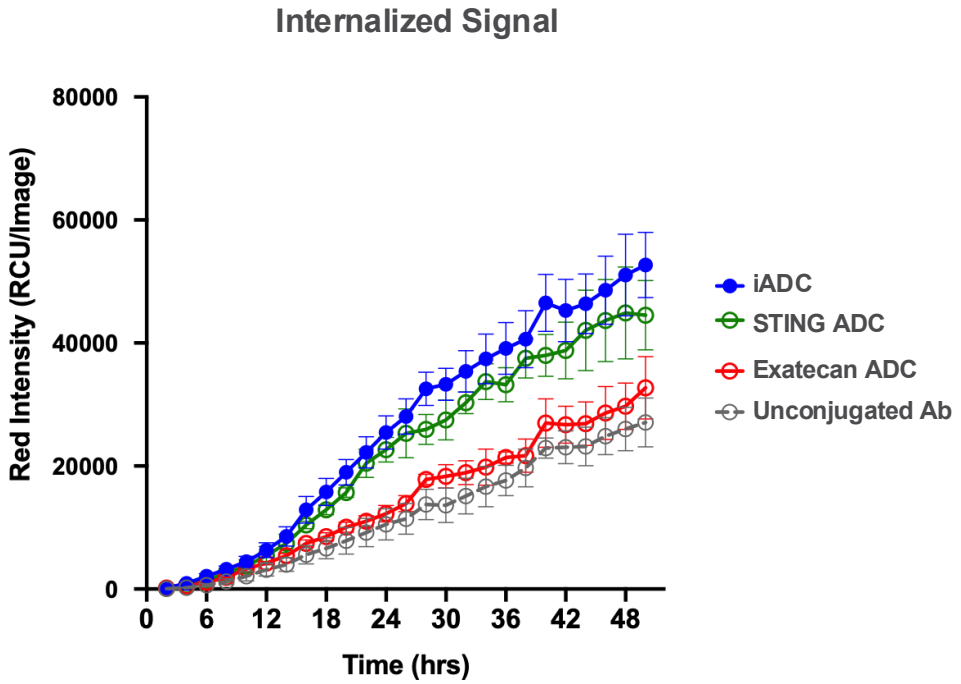
Synergistic potential of STING and exatecan:

Increased sensitivity to Topo1i
Increased ADC processing and payload release
Enhanced tumor antigen presentation and T cell activation

iADC and iSAC Show More Internalization Compared to Her2 ADC



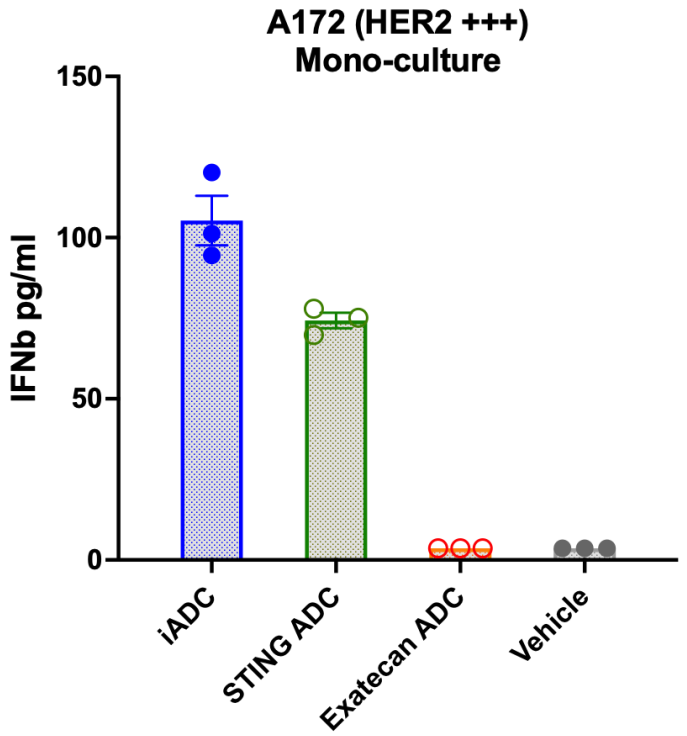
Red: Internalized pHrodo Signal



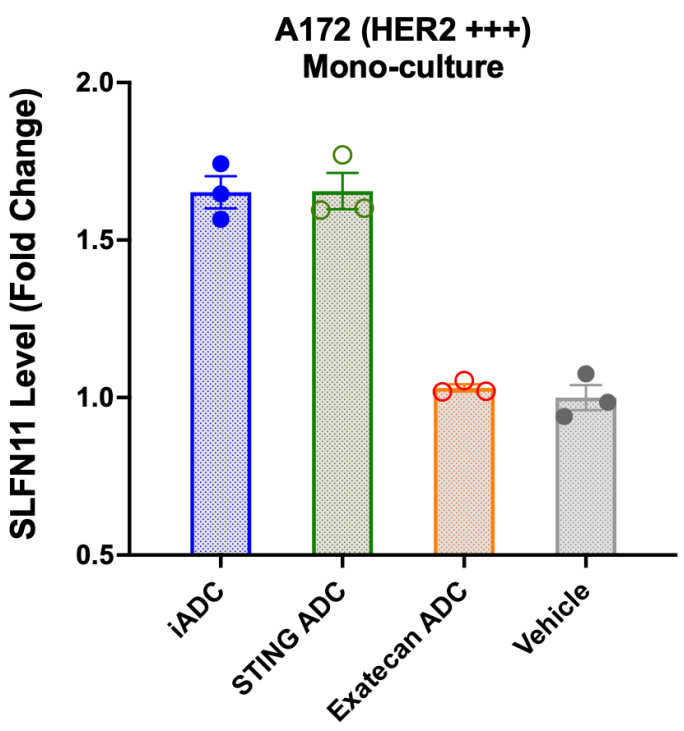
STING activation increased lysosome content, which leads to more iADC in lysosome.

Activation of STING Pathway by iADC and iSAC Increases SLFN11 Expression in Tumor Cells: Rendering Tumors Sensitive to Topo1

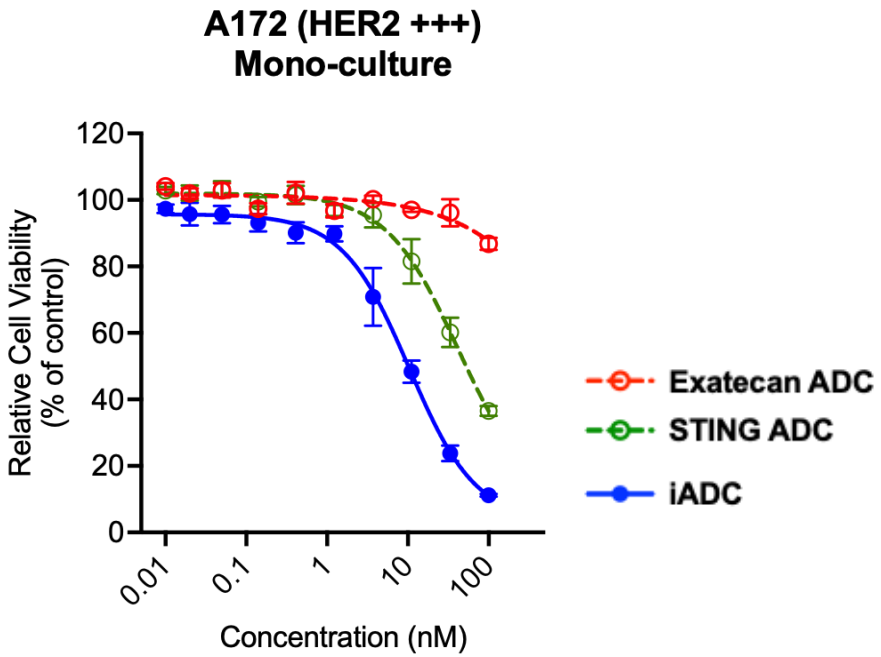
iADC and iSAC Induced Release of Type I Interferon



iADC and iSAC Induced SLFN11 Expression

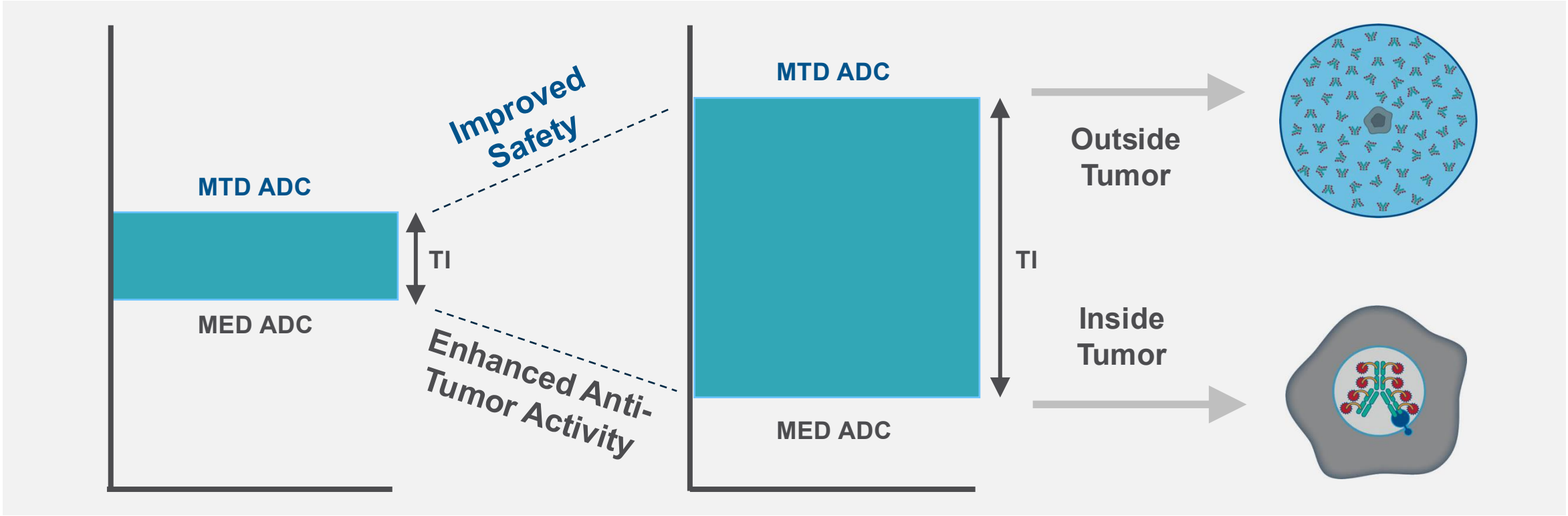


iADC and iSAC Induced More Potent Tumor Cell Killing



Sutro's Platform Enables Therapeutic Index (TI) Improvements of ADCs

Maximum Tolerated Dose (MTD) vs. Minimum Effective Dose (MED)



Adapted from Gerber et al, mAbs, 2023
HNSTD – highest non-severely toxic dose

Improving the TI to Increase ORR and PFS of ADCs

Leading single (Topo1)- and dual payload ADC platform

- Highest cyno exposure and best anti-tumor activity (PDX)
- Clinical validation imminent

Large selection of payload classes to match tumor biology

- Topo1i, MMAE, PARPi, ATRi, STING, + 1 non-disclosed
- Large span of payload ratios with IgG1 like PK and DAR $\geq$ 16

Competitive development timelines and COGs

- Fully externalized ADC manufacturing
- 12 -14 months from Clinical Candidate to IND filing

Contact Information for Dual-Payload ADC Collaborations:
Hans-Peter Gerber, R&D: hgerber@sutrobio.com
Vas Ramamurthy, BD: vramamurthy@sutrobio.com

SUTRO BIOPHARMA

Industry Leading Cell-Free Protein Synthesis Platform

Enables Rapid Make/Test Cycle for Empirical Selection of Optimal Leads

The extract is readily available, eliminating the need to establish a new cell line or strain for discovery or manufacturing.

Stockpiled Extract

A

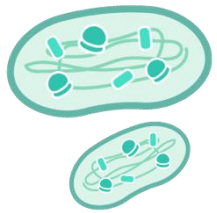
Biophysical Properties

Functional Activity

Potency

Pharmacology

Rapid make/test cycle To optimize protein design



1	2	3	4	5	6	7
Grow Cells from E. Coli	Cell Lysis	Cellular Extract	Cell-Free Protein Synthesis	IgG with Non-Natural Amino Acids	Linker-Warhead Click Chemistry	Homogenous ADC

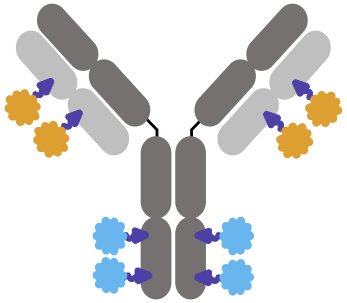
Proprietary Cell-Free Platform Positions Sutro at the Forefront of Dual-Payload Innovation

Multiple Modalities

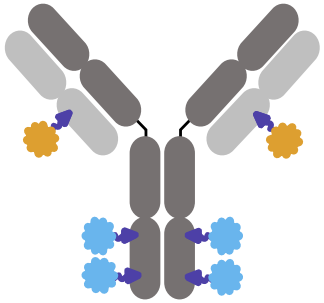
- Topo1 x Tubulin
- Topo1 x DDRi
- Topo1 x IO

Enables novel drug combinations and tuning of ratios with the broadest payload diversity to overcome tumor resistance and improve tolerability

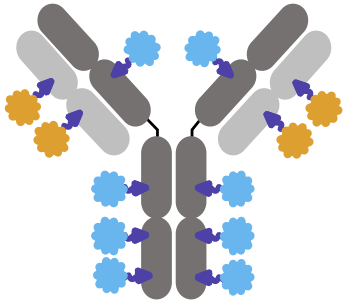
Tailored Ratios



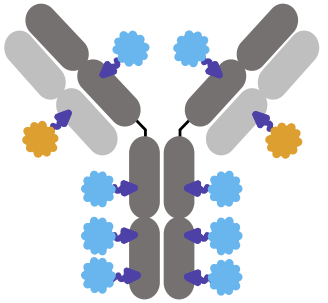
DAR 4+4



DAR 4+2



DAR 8+4



DAR 8+2

Safety

Well-tolerated in non-human primates at 25 mg/kg (2XQ3W) with dual cytotoxin ADC

DAR – Drug to antibody ratio; DDRi – DNA damage response inhibitors; IO – Immuno-oncology

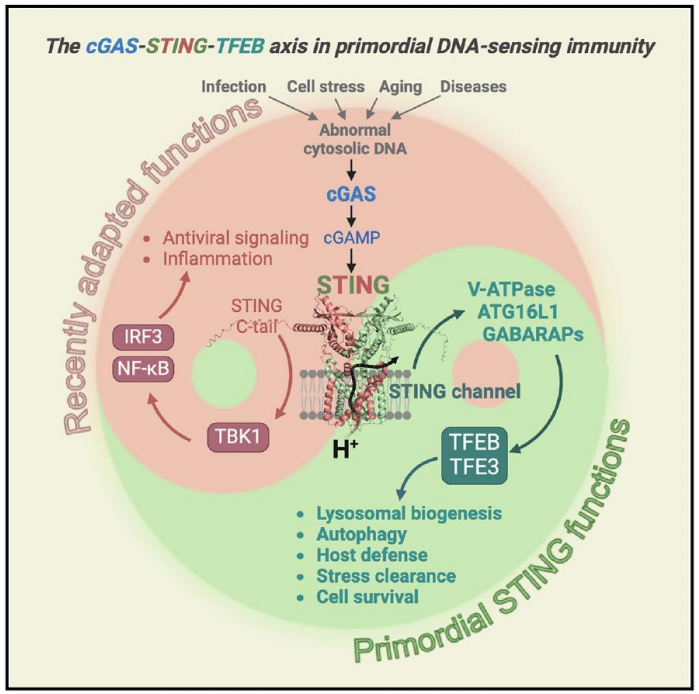
Activation of STING leads to lysosomal biogenesis

Article

Molecular Cell

A TBK1-independent primordial function of STING in lysosomal biogenesis

Graphical abstract



Authors

Bo Lv, William A. Dion, Haoxiang Yang, Jinrui Xun, Do-Hyung Kim, Bokai Zhu, Jay Xiaojun Tan

Correspondence

jay.tan@pitt.edu

In brief

Lv et al. discover TFEB/TFE3 as evolutionarily ancient effectors of the cGAS-STING DNA-sensing innate immune pathway. TFEB/TFE3 activation via the channel of STING integrates cytosolic DNA sensing, a general cellular stress-sensing mechanism, with lysosomal biogenesis and autophagy upregulation, conserved and general strategies for host defense and stress clearance.

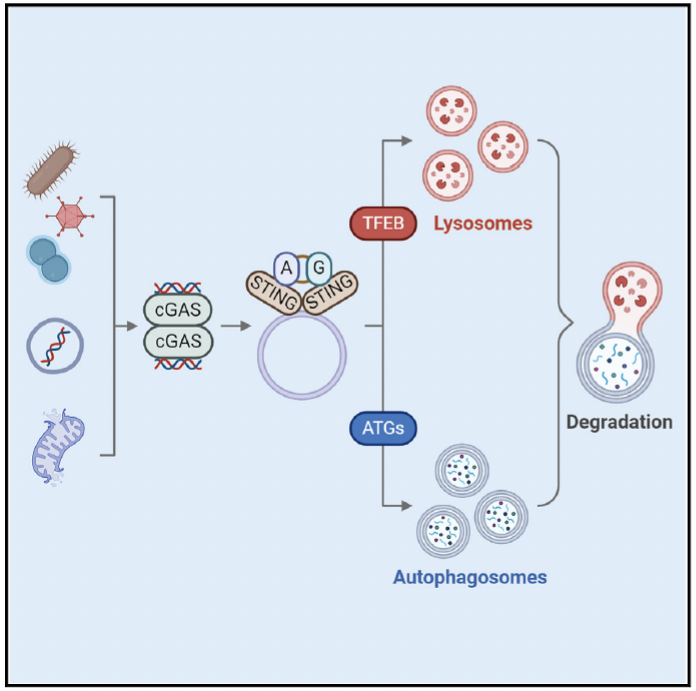
Molecular Cell 84, 3979–3996, 2024

Article

Immunity

The cGAS-STING pathway activates transcription factor TFEB to stimulate lysosome biogenesis and pathogen clearance

Graphical abstract



Authors

Yinfeng Xu, Qian Wang, Jun Wang, ..., Zhengfu He, Wei Liu, Wei Wan

Correspondence

yinfengxu@hnfnu.edu.cn (Y.X.), liuwei666@zju.edu.cn (W.L.), wanwei@zju.edu.cn (W.W.)

In brief

The cGAS-STING pathway induces autophagy to deliver cytoplasmic DNA and invading pathogens to lysosomes for elimination. However, whether lysosome function is regulated by the cGAS-STING pathway remains unknown. Xu et al. discover that the cGAS-STING pathway activates transcription factor TFEB to stimulate lysosome biogenesis independently of the protein kinase TBK1.

Xu et al., 2025, Immunity 58, 309–325