SUTRO BIOPHARMA

Optimizing High DAR & Dual Payload ADCs: Discovery of Hydrophilic β-glu Cleavable Linker Payloads for Superior Efficacy and Safety

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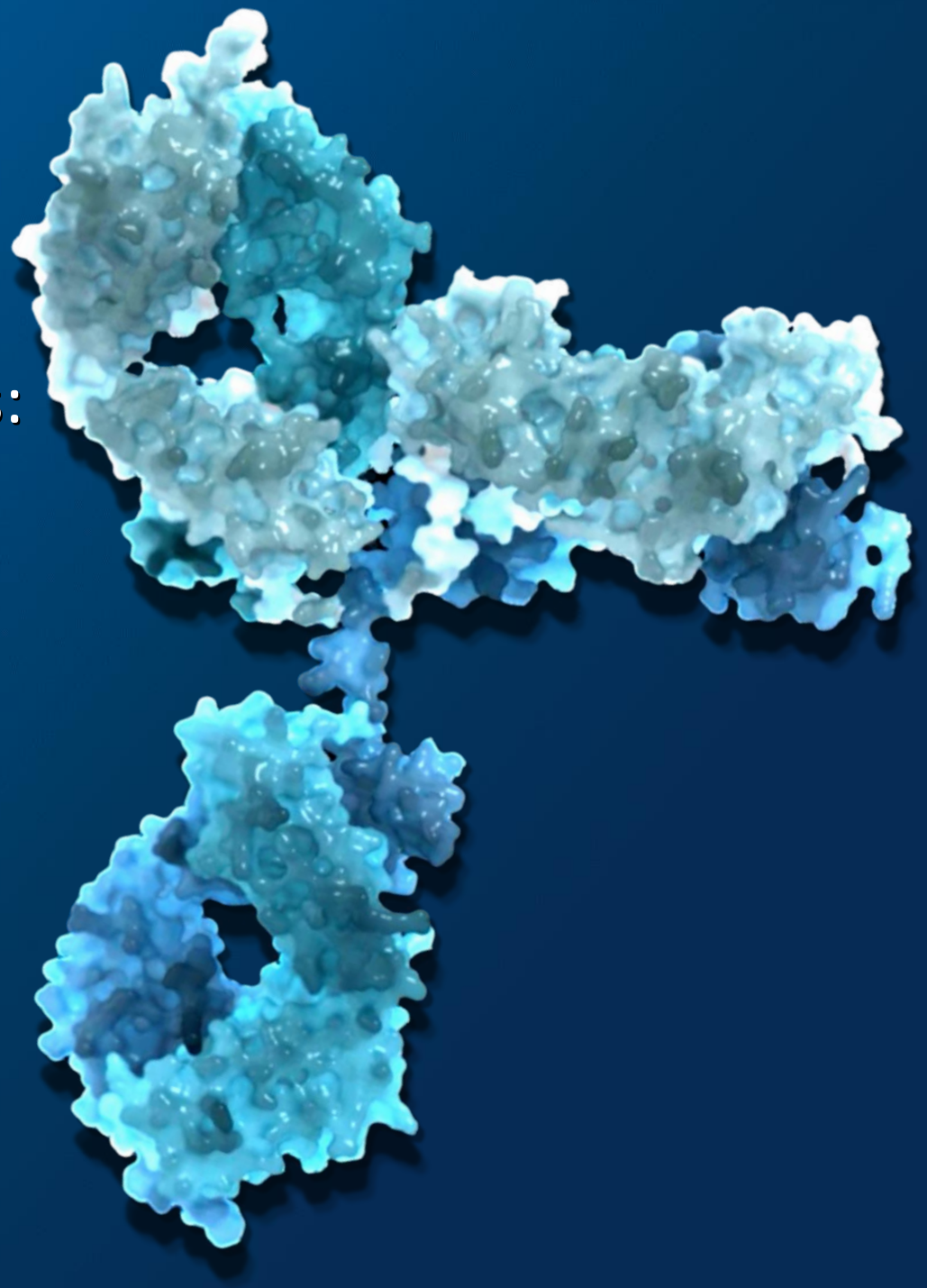


Presentation Outline

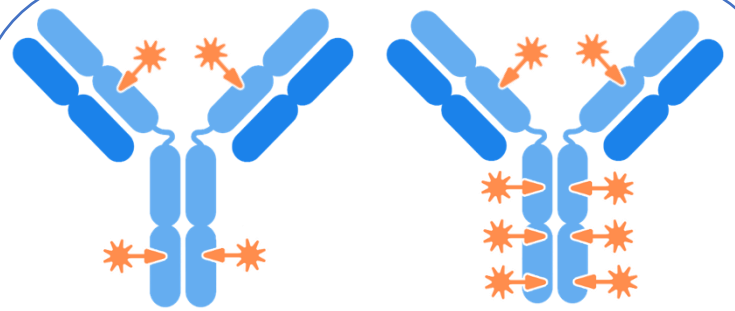
- **Increasing ADC potency and safety**
  - Exploration of novel tumor-selective β-glu cleavable linker payloads to enhance the efficacy and therapeutic index of site-specific high DAR ADCs
- **Dual Payload ADC^2/iADC to overcome resistance & next generation IO**
  - Novel MoA LPs for combining with TOP1i as ADC^2/iADC to induce ICD & overcome resistance

Industry Leading Cell-Free Protein Synthesis Technology Empowers Diverse Next-Generation ADCs

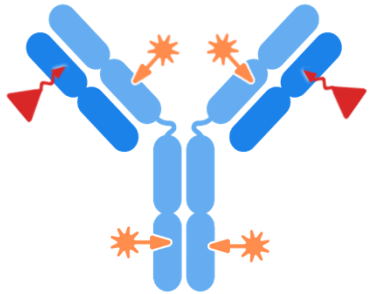
Rapid Make/Test Cycle to Optimize Next-Gen ADC Design

Antibody Discovery Platform
- XpressCF+® synthesis derived IgGs with non-natural amino acid(s)
- Robust process, 4000L GMP run demonstrated

Site-Specific Conjugation Chemistry
- Stable homogenous high DAR (8, 12 & 16) ADCs
- Dual non-natural amino acids enabled for iADCs and ADC^2



Homogenous ADCs (STRO-002, STRO-004)

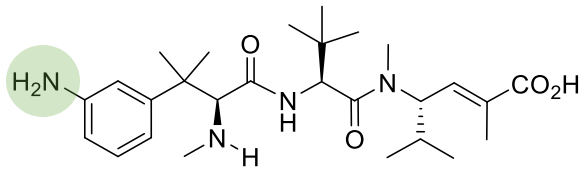


Dual Payload ADCs (ADC^2, iADC) for Enhanced Potency, Overcoming Resistance

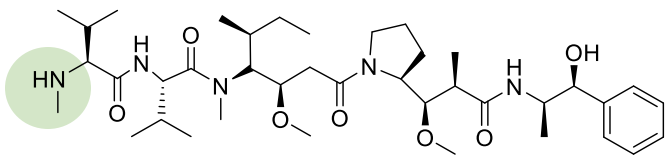
Diverse MoA Class of Payloads
- MT inhibitors (Hemiasterlin, MMAE)
- Top1 inhibitors (Exatecan, Belotecan)
- DNA damaging (PBD, Anthracyclines)
- DNA repair Inhibitors (DDRi)
- Immune stimulants (STING, TLR7 & TLR7/8)

Proprietary Tumor Selective Linkers
- Hydrophilic β-glucuronidase & protease cleavable linkers
- Branched linkers
- Non-cleavable linkers

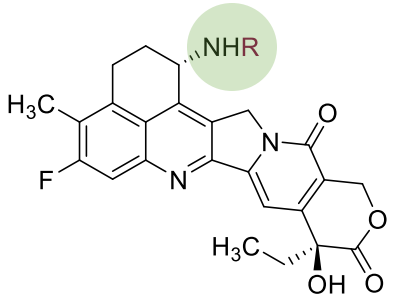
Expanding Diverse Classes of Payloads for Site-Specific ADC/ADC²/iADC



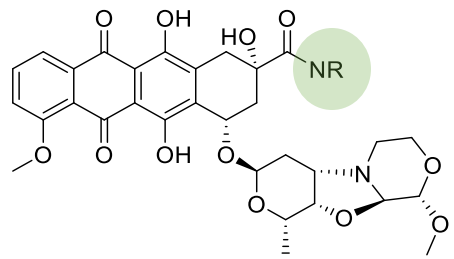
3-Aminophenyl hemiasterlin



Monomethyl auristatin



R = H (Exatecan)
R = Gly (Gly-Exatecan)



PNU ADC payload

Hemiasterlin Analog

- Proprietary payload used in two clinical programs
- Tubulin inhibitor
- Reduced P-gp efflux liability - best in class within tubulin binders
- Induces strong ICD
- IC_{50}: 0.3 - 4.2 nM

MMAE

- Clinically validated payload
- Tubulin inhibitor
- P-gp substrate
- Vedotin ADCs combo with CPI showed improved ORR in hot and cold tumors
- IC_{50}: 0.5 - 2 nM

Exatecan/Gly-Exatecan

- Top1 Inhibitor
- More potent Topo1 inhibition and cell killing
- Multiple novel linker payloads for high DAR ADCs
- Not a P-gp substrate
- IC_{50}: 0.32 - 12nM/3.8-4 nM

PNU Anthracycline

- Multiple effects on DNA including intercalation and alkylation
- Various potency ranges
- Multiple stable linkers in evaluation
- Not a P-gp substrate
- strong ICD inducers, best in class activators of DCs
- IC_{50}: 0.01 - 8 nM

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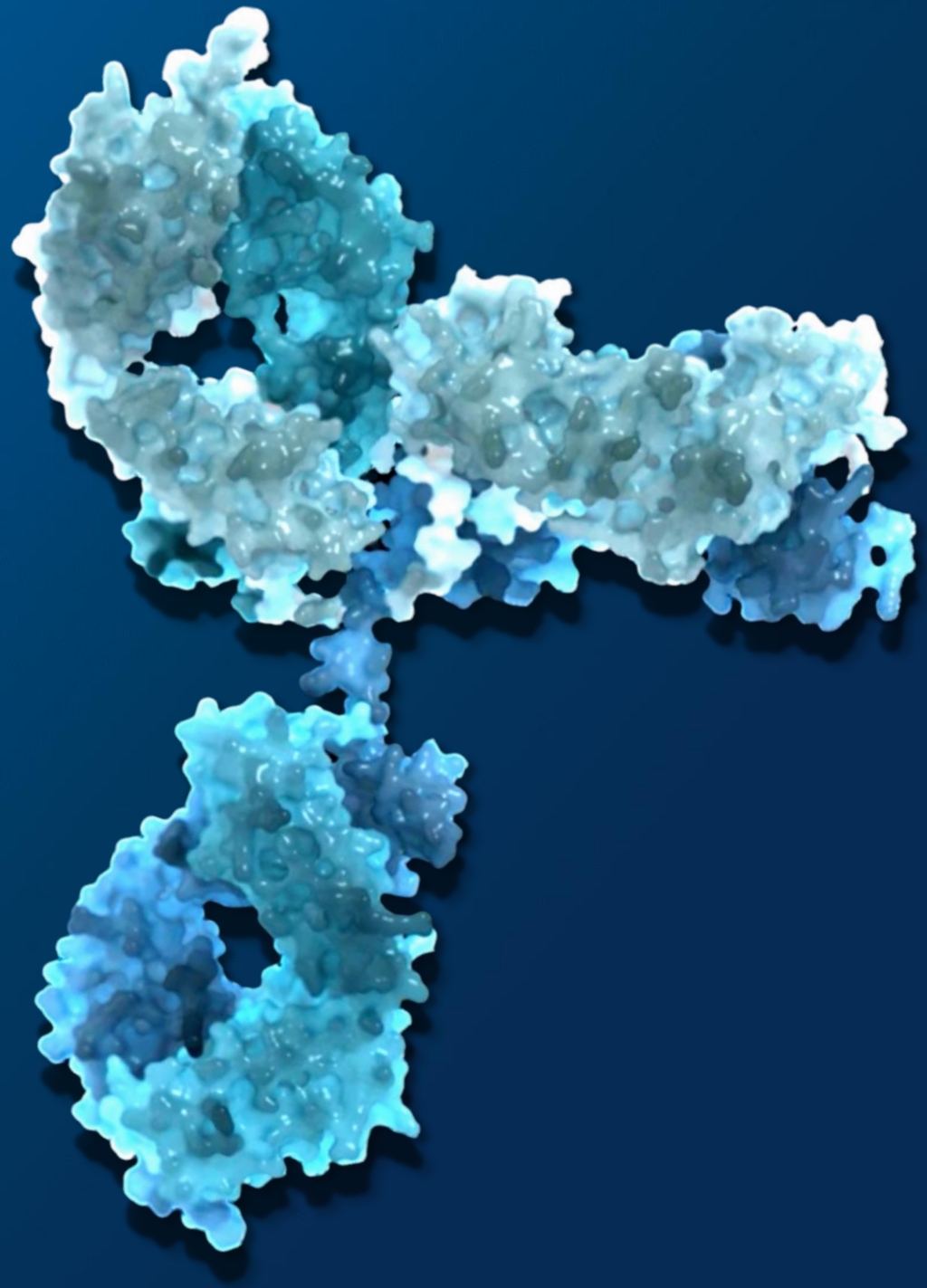
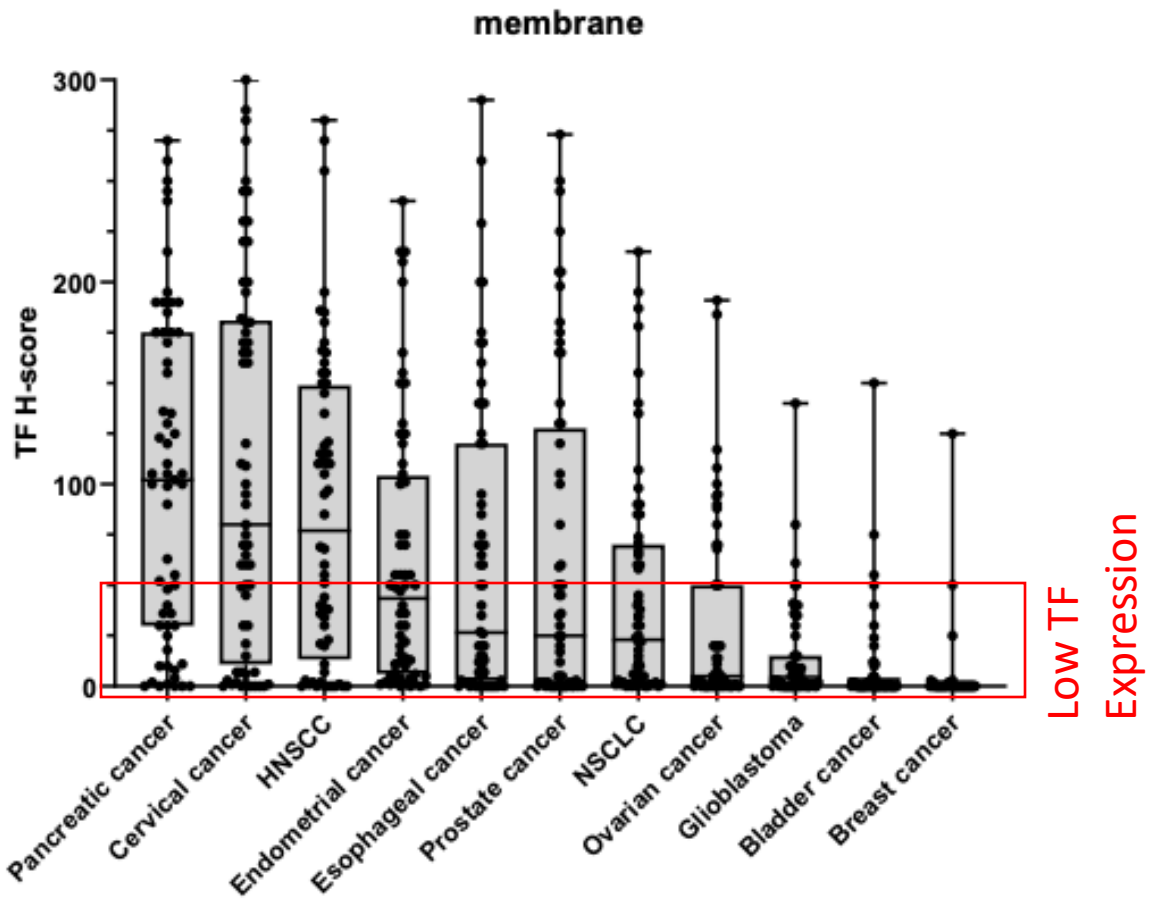
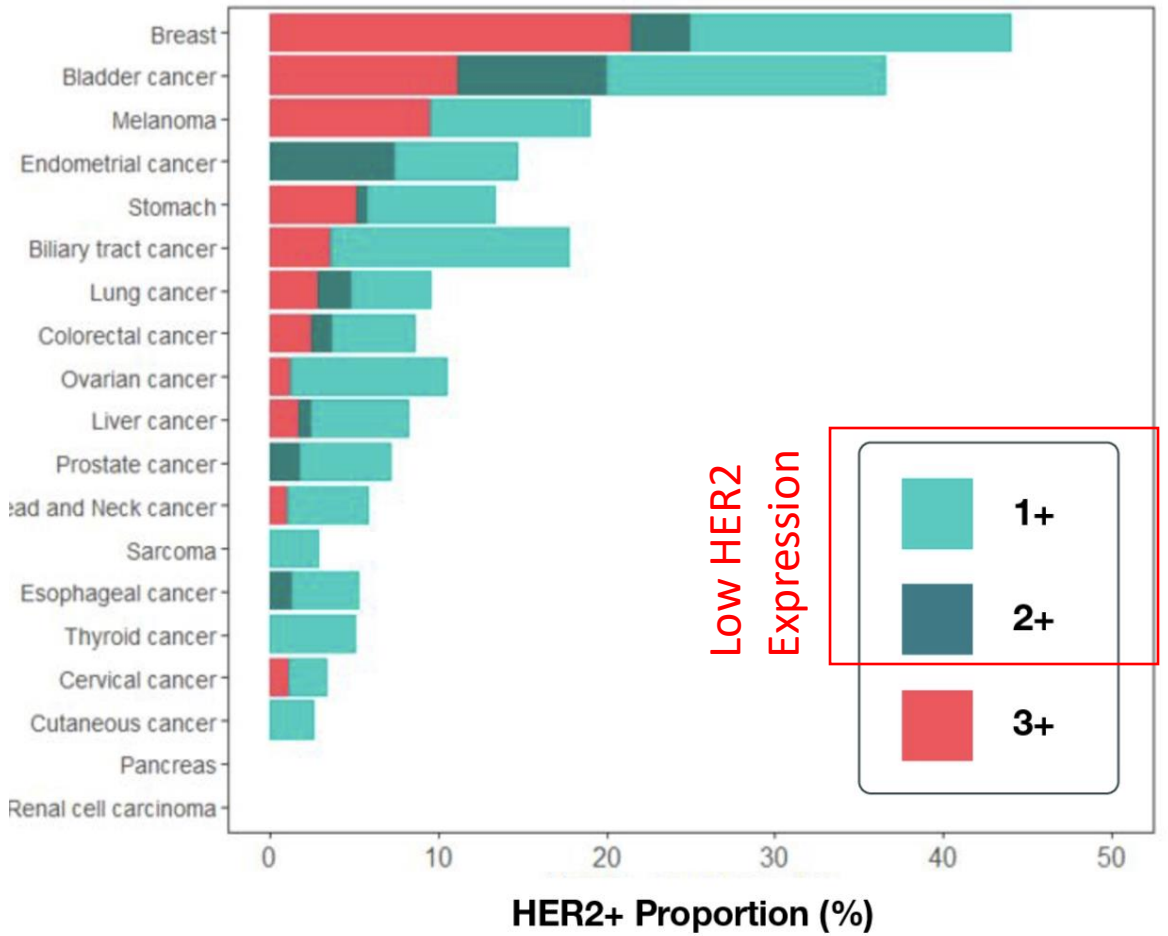
Next-Generation High DAR ADCs for Increasing ADC Potency and Safety



Higher DAR TOP1i is Required for Targeting Low Antigen Expressing Tumors



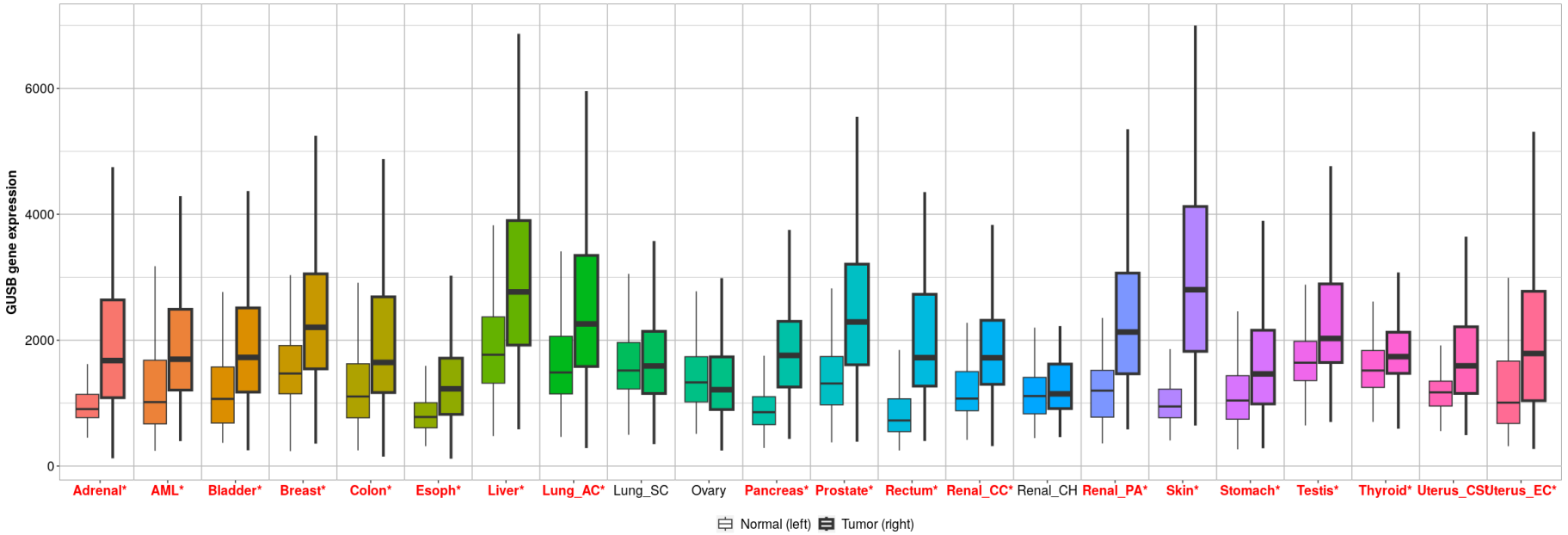


de Bono, et al (2022) Cancer Report

- High DAR ADCs could be advantageous to deliver more payload for targeting low Ag tumors and a wider pt population

β-glucuronidase (GUSB) is Broadly Expressed Across Multiple Tumor Indications

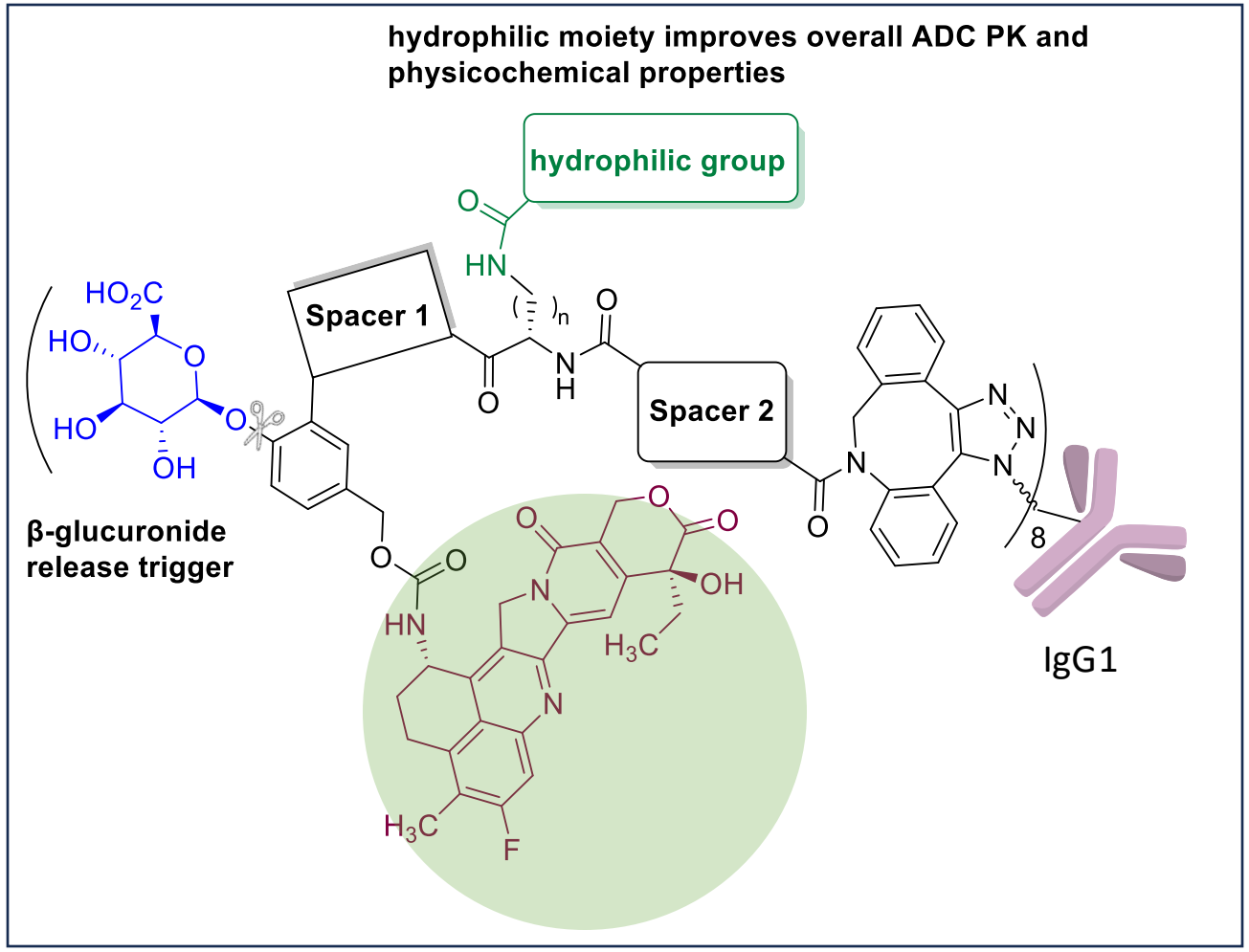
GUSB gene expression using RNA seq data (*https://tnmplot.com/analysis/*)



- β-glucuronidase is overexpressed in the majority of known solid and blood cancers
- Intrinsic hydrophilicity due to the sugar linker, improved physicochemical properties as high ADCs

Optimized Proprietary PEGylated β-glucuronidase Cleavable Exatecan LP for High DAR ADCs With Improved Efficacy and Safety

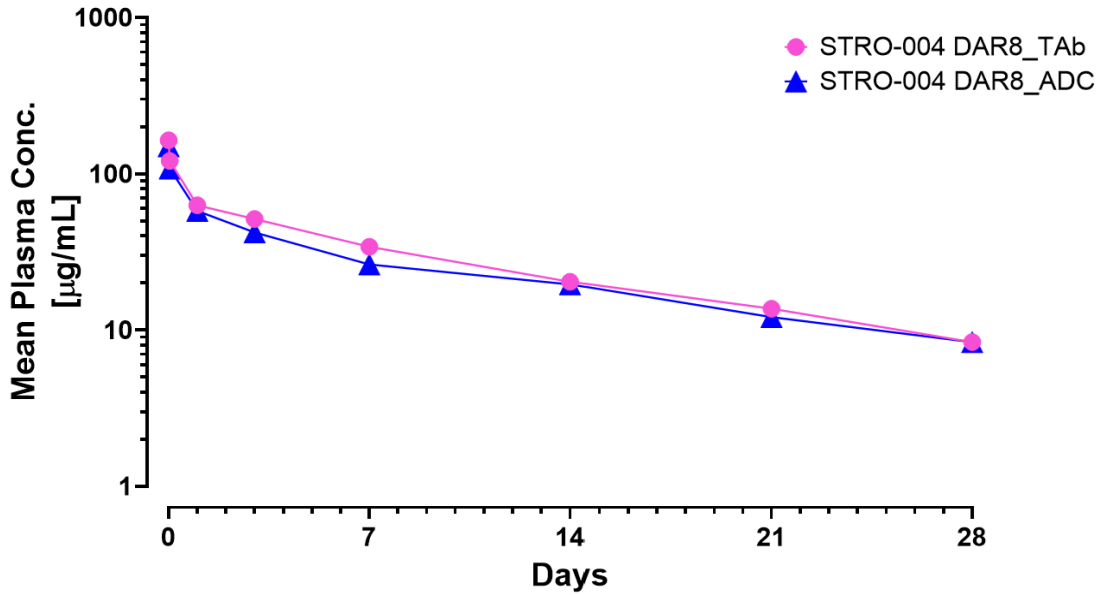
Homogeneous β-glu cleavable exatecan high DAR ADC structure



- ✓ Enhanced stability in circulation
- ✓ Increased hydrophilicity facilitating the development of high DAR ADCs with improved TI

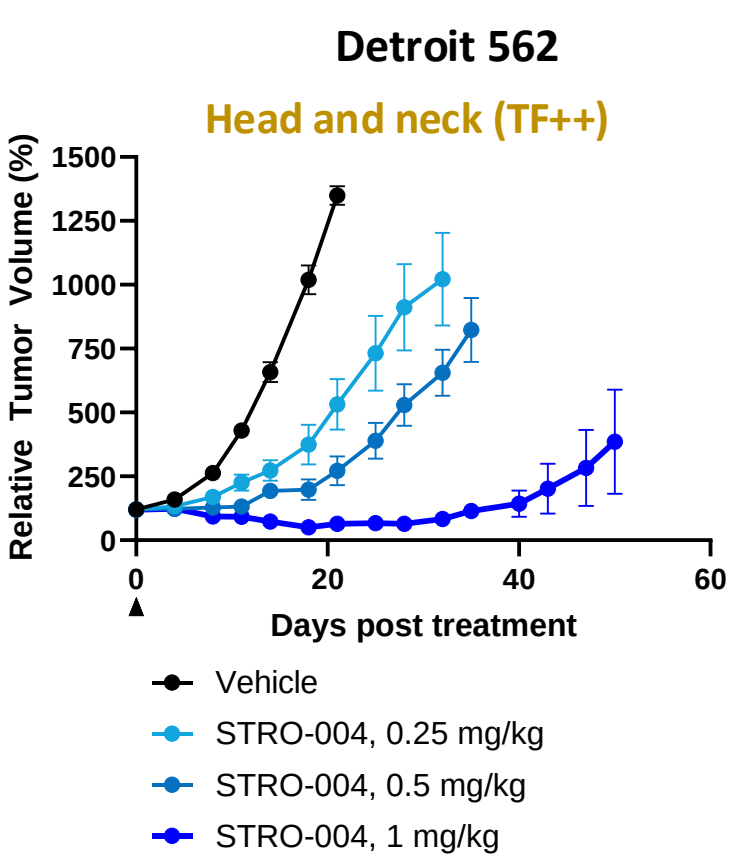
STRO-004 αTF DAR8 ADC Displays Excellent Mouse (Tg32) PK and *In-Vivo* DAR Stability

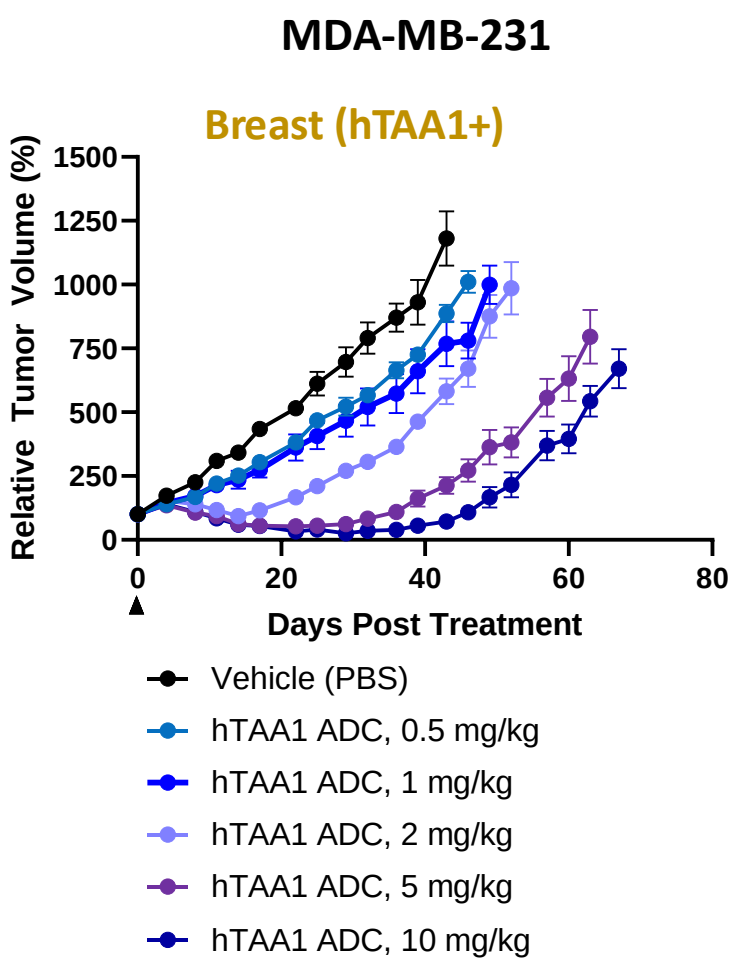
Single IV PK Profiles of TF ADCs in Tg32 Mice @5mpk

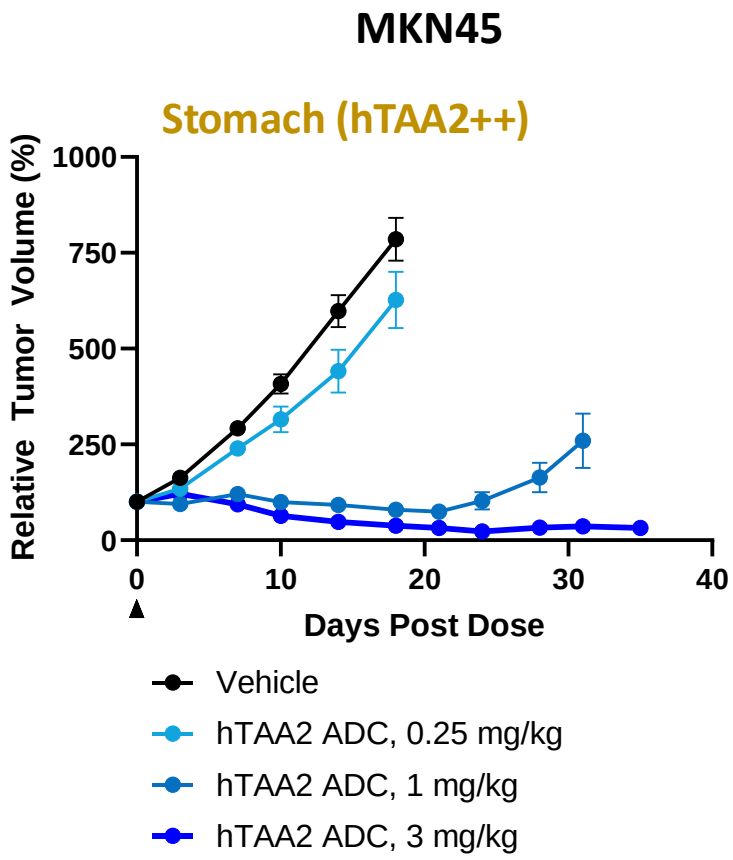


Test Article	$t_{1/2}$ (days)	CL_{obs} (mL·d^{-1}/kg)	V_{ss_obs} (mL/kg)
STRO-004	12.4	6.21	100

Sutro's Site-Specific High DAR ADCs Utilizing the Hydrophilic β-glu Cleavable Exatecan LP Displayed Potent Efficacy and Improved Safety



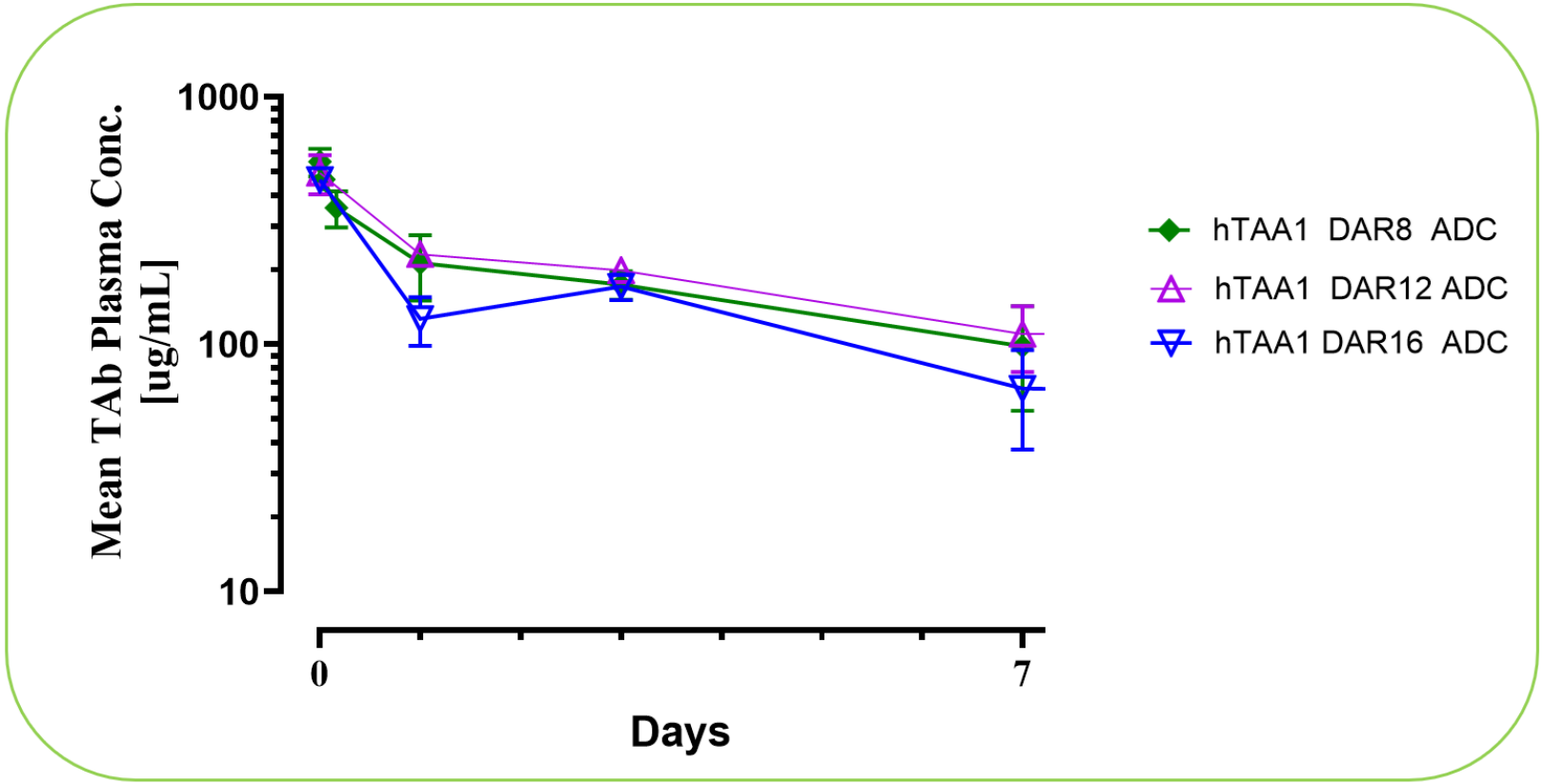




- **STRO-004 is well tolerated in NHP**
- **HNSTD in NHPs (q3w x 2) 50mg/kg**

Sutro's Site-Specific High DAR(12, 16) ADC Technology Displayed Desirable Mouse PK Properties, Comparable to DAR8 ADCs

Single IV PK profile of DAR12/16 ADCs in C57BL/6 mice



- DAR12/16 ADCs with optimized conjugation sites and linker technology demonstrated robust conjugation, excellent recovery, desirable PK properties

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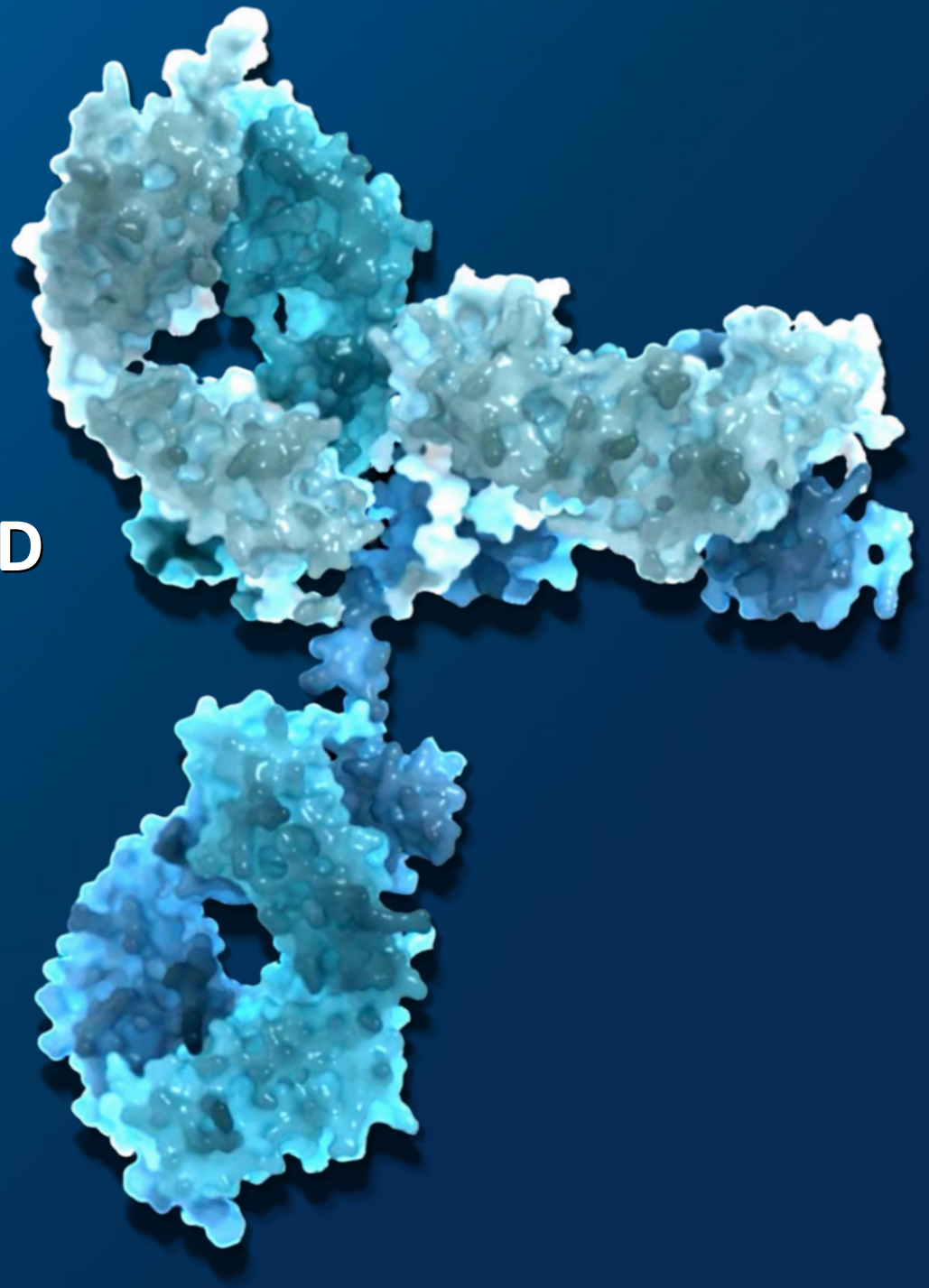
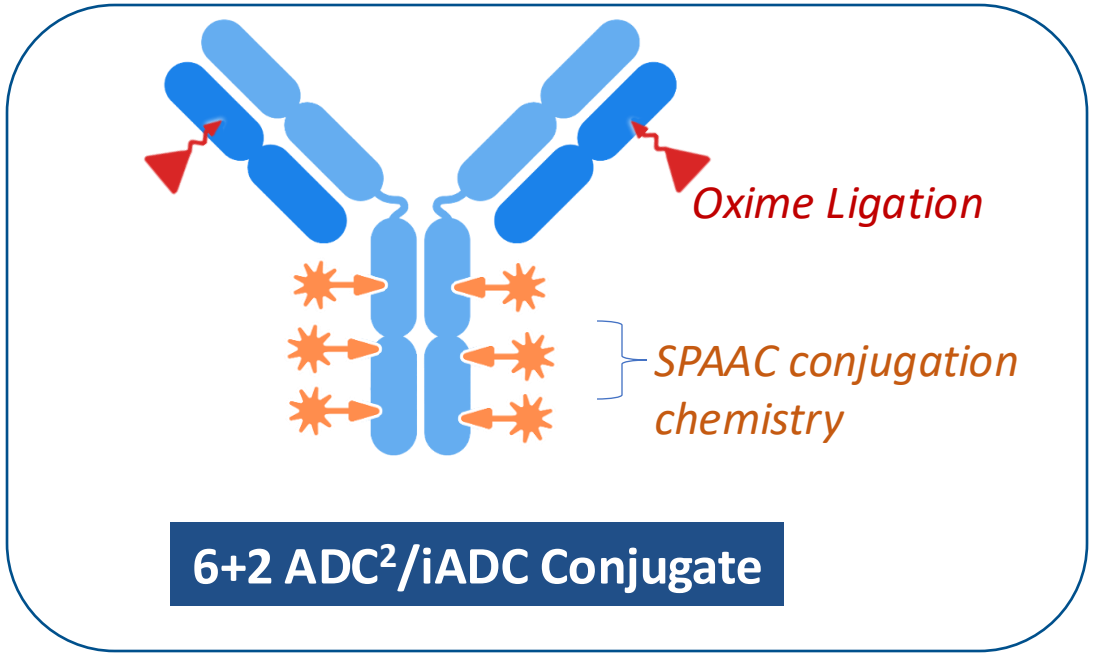
Next-Generation Dual Payload iADC/ADC^2 Conjugates for Enhanced ICD and Overcoming Resistance



Leveraging the CF Platform to Enable Next-Generation Dual Payload iADC/ADC^2 Conjugates

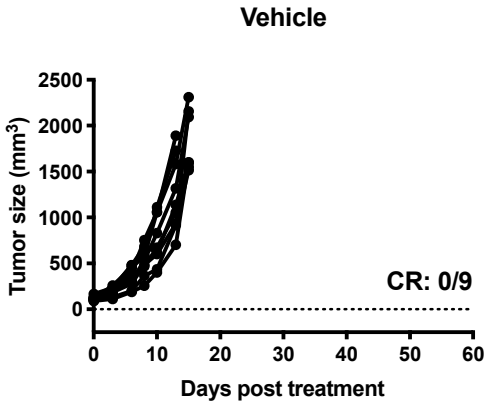


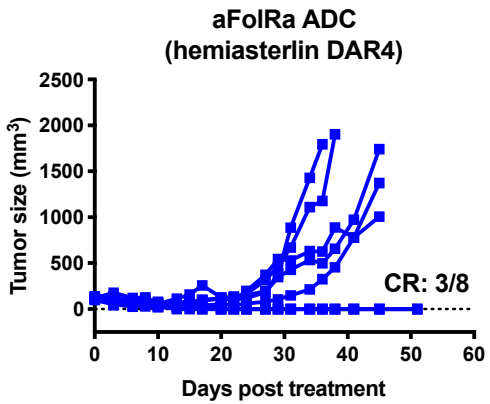
Best-in-class dual conjugation technology for targeting diverse cancer patient population

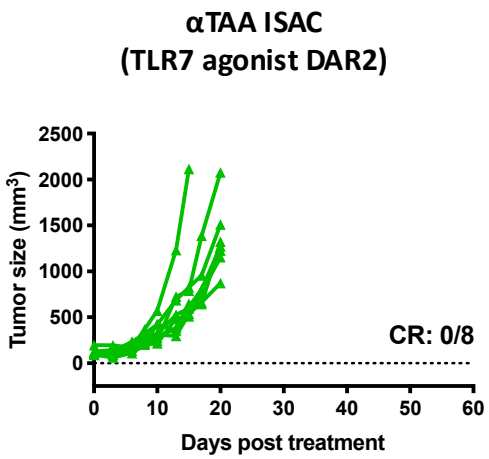
- Optimal delivery of orthogonal payloads with controlled stoichiometries
- Overcome primary resistance
- Increase efficacy in target-low or heterogeneous tumors
- Delay acquired resistance
- Improved safety, TI

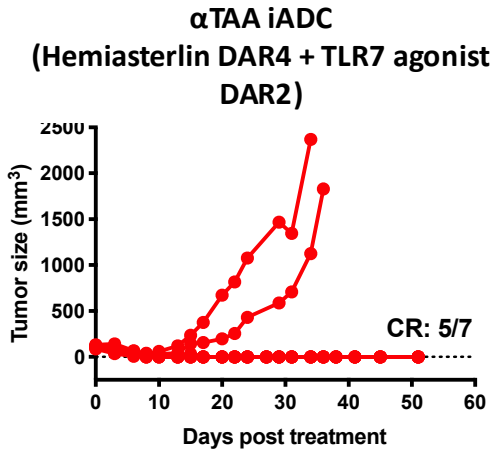
Single Dose of iADC Molecule Elicits Superior Anti-Tumor Response and Long-Term Protection

iADC platform





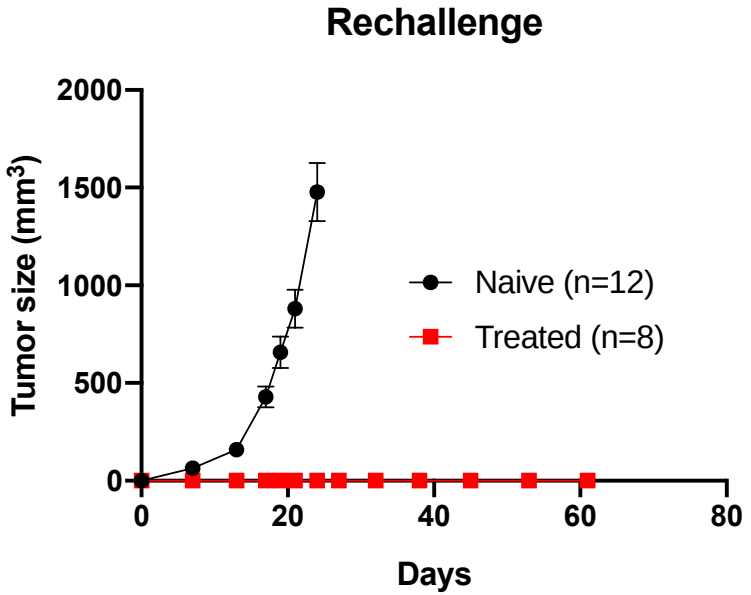




iADC consists of a TAA-directed mAb conjugated to

- DAR 4 CatB Cleavable Hemiasterlin (MTI) linker payload
- DAR2 CatB Cleavable TLR7 agonist linker payload

All treated animals that achieved CR were re-challenged with MC38-hTAA cells

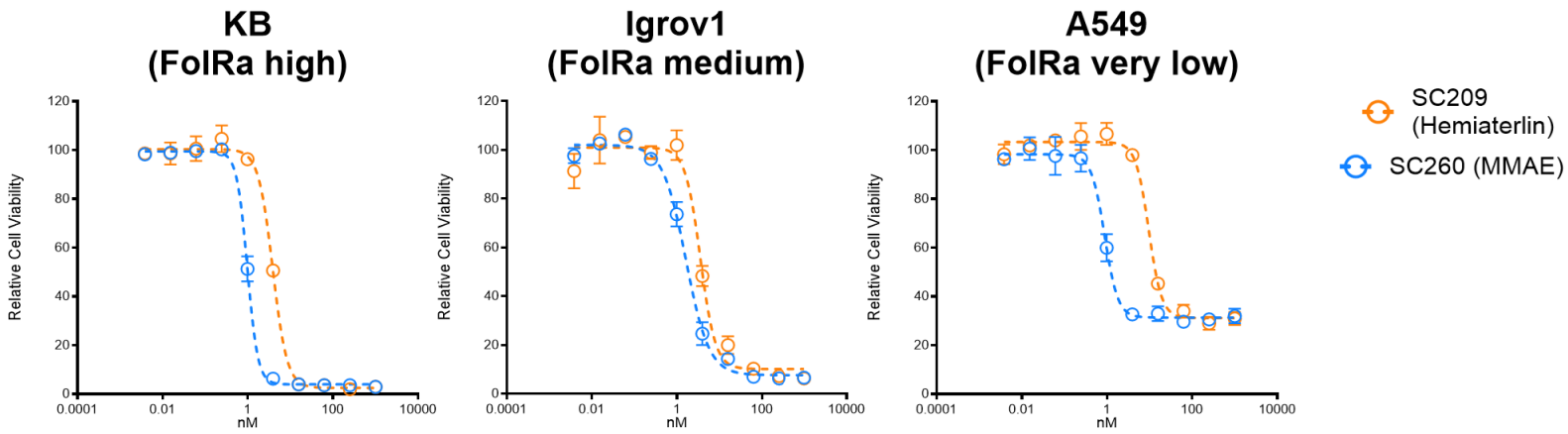


- iADC showed enhanced activity vs. ADC alone based on higher number of animals with complete responses and durable anti-tumor immunity
- We are currently developing new iADCs in a collaboration with Astellas

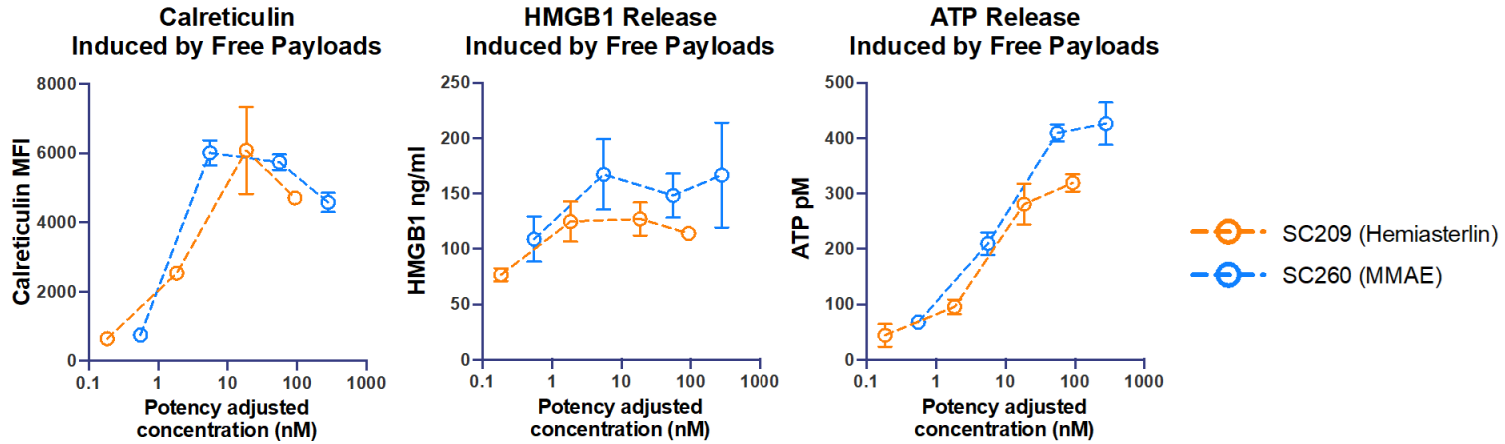
MMAE and Hemiasterlin Showed Similar Potency and Induces Comparable ICD Activity

In-Vitro

MMAE vs SC209 cell killing potency

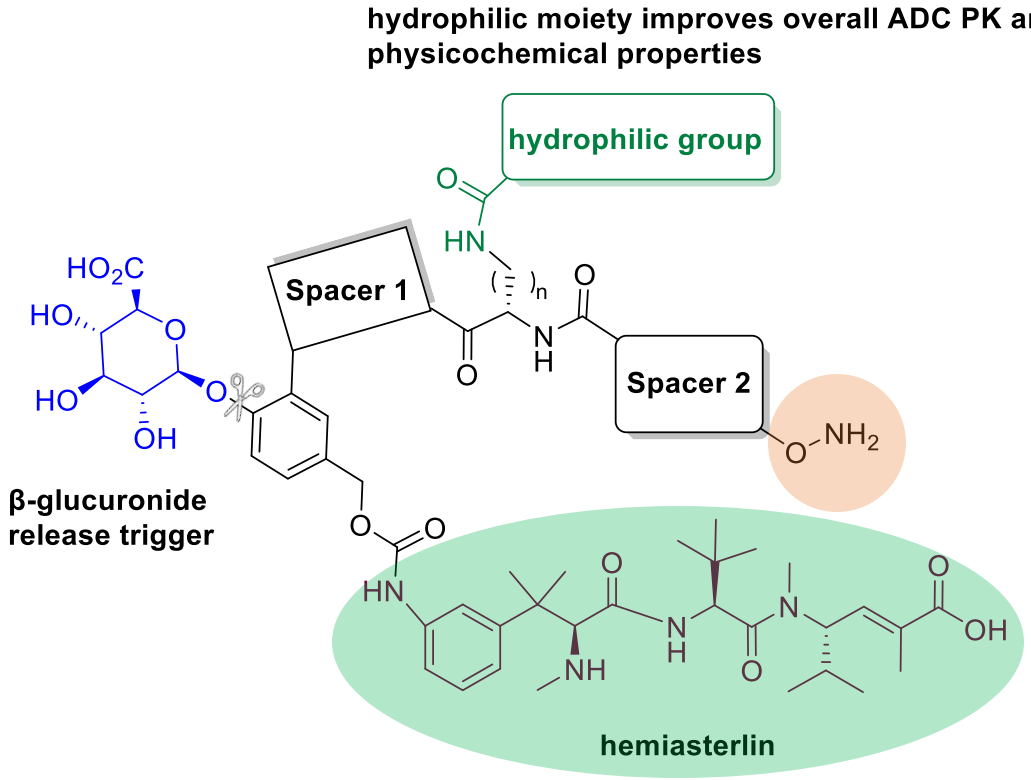


MMAE and SC209 Induces comparable ICD



Optimization of Tumor-Selective Hydrophilic β-glu Cleavable Tubulin LP for ADC²

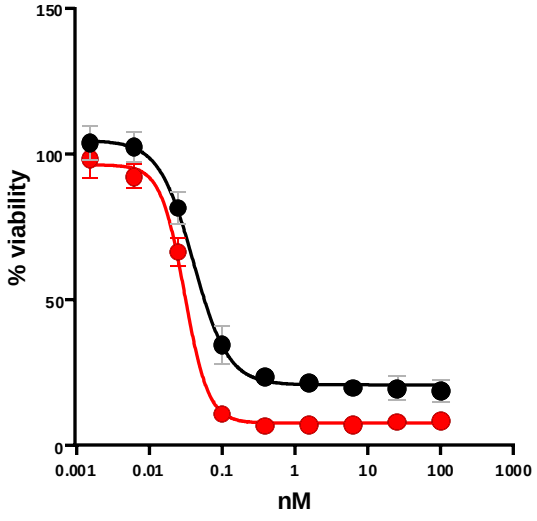
PEGylated β-glu Cleavable Hemiasterlin LP (SC4297)



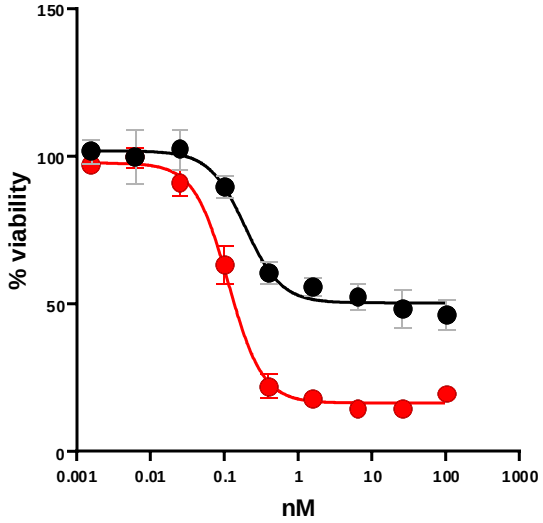
- Optimized tumor selective MTI aminooxy LPs for ADC²
- αHer2 ADC² in various DAR (8+2 & 8+4) formats showed excellent PK properties and *in-vivo* DAR stability

Improved *In Vitro* Activity of Dual Payload Top1i+ Hemiasterlin αHER2 8+2 ADC

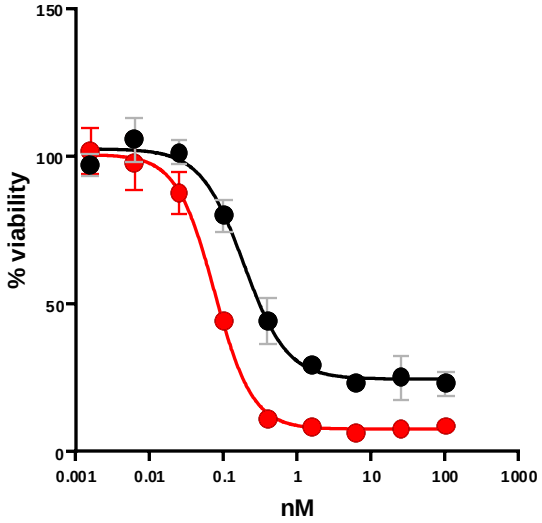
SKBR3



HCC1954



KPL-4



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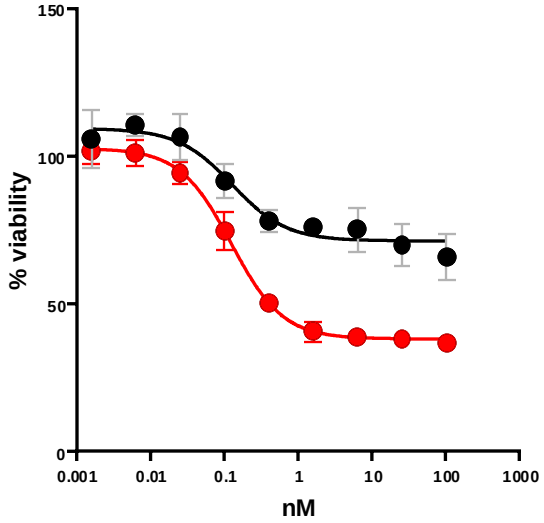

Enhertu (Tras-Dxd) Trastuzumab DAR8 Topo1i + DAR2 Hemiasterlin

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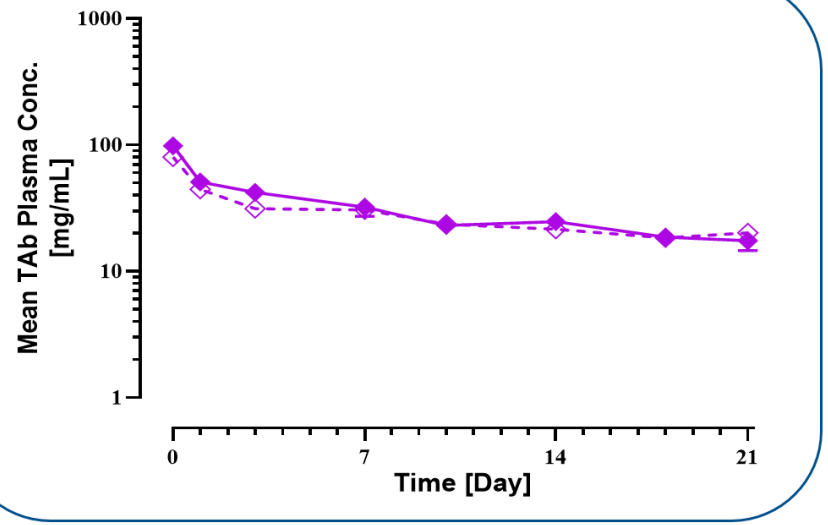
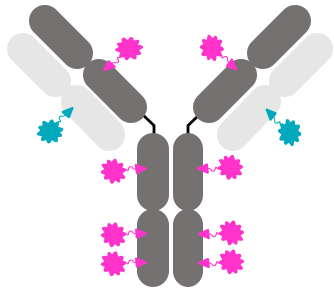
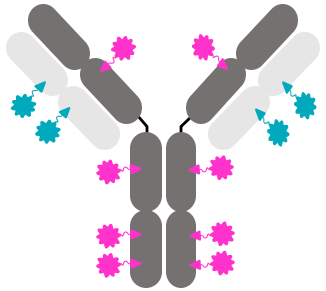
SUTRO's High DAR αHER2 (8+2/8+4) ADC^2 Displays Excellent Mouse PK & *In-Vivo* DAR Stability

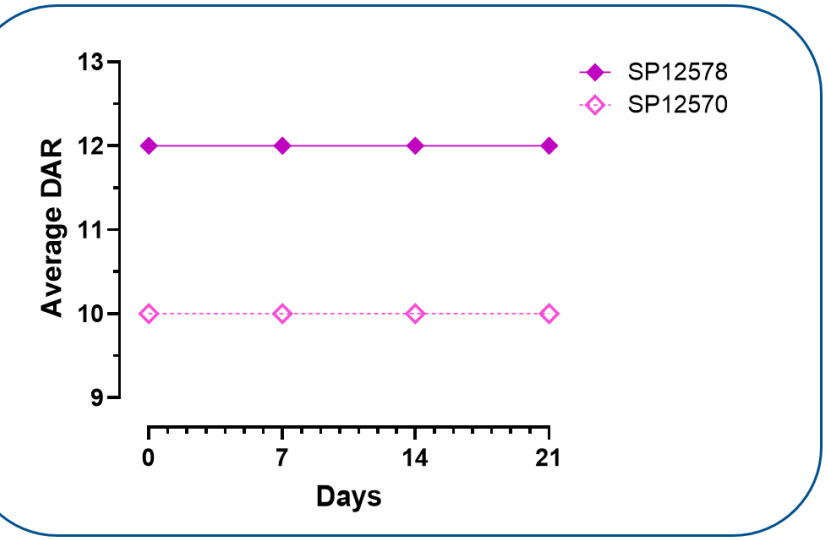
αHER2 ADC^2 Mouse PK





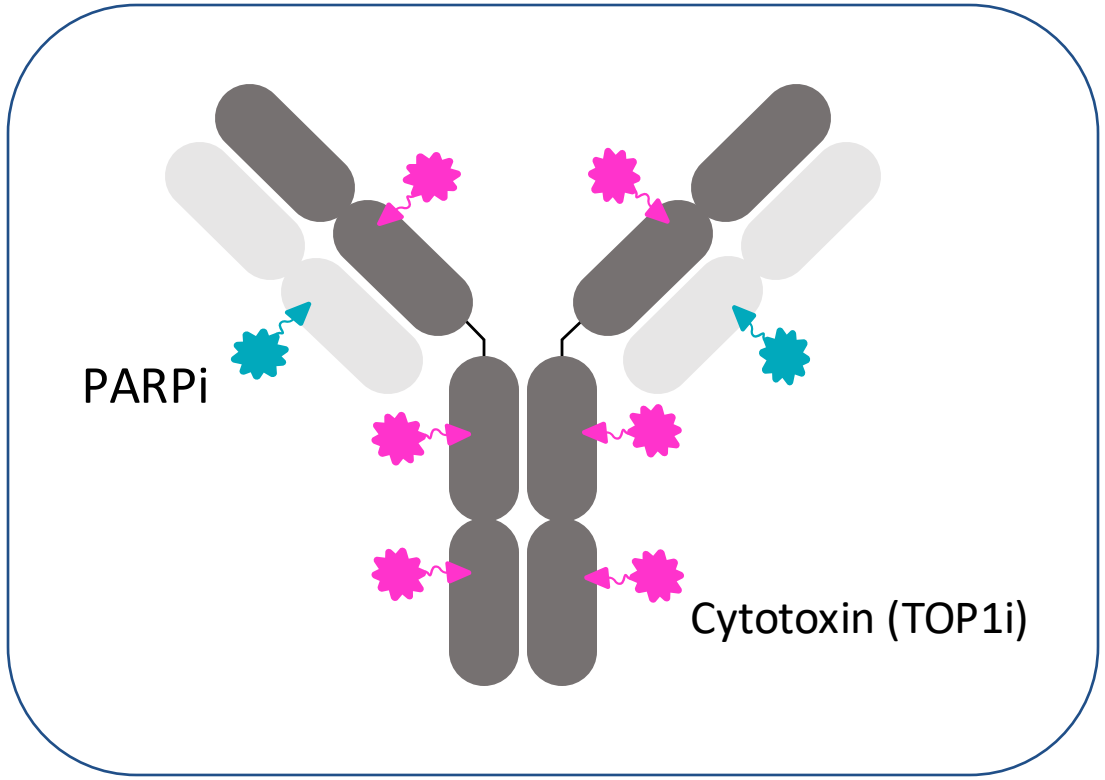


Parameter	SP12570	SP12578
DAR	Top1i/hemiasterlin (8+2)	Top1i/hemiasterlin (8+4)
CL [mL/d/kg]	2.42	2.79
V_{ss} [mL/kg]	80.7	71.8
$t_{½}$ [d]	23	17.5



- αHer2 (8+2/8+4) Top1i/hemiasterlin ADC^2 showed good PK properties and stability

Top1i and PARPi ADC^2 to Enhance Synthetic Lethality

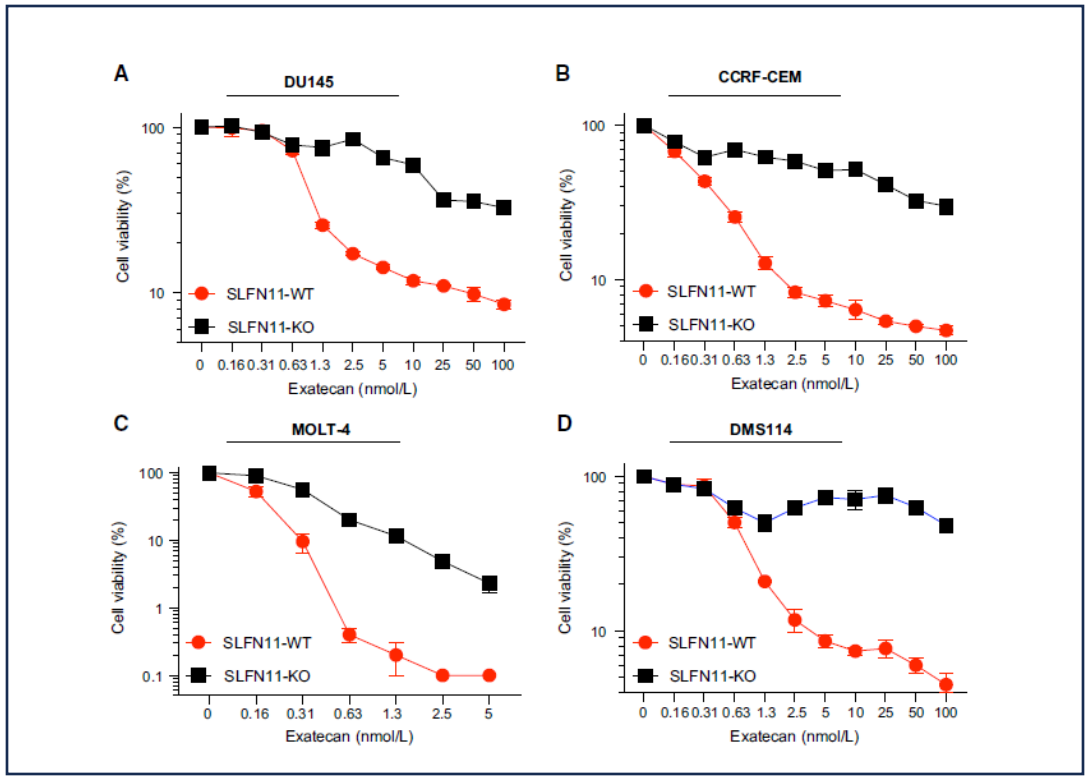


Synergy between PARP and Top1 inhibitors

- Established preclinically, but clinical application has been hindered by dose-limiting myelosuppression?
- Trodelvy dosed with PARPi concurrently is not tolerated clinically due to a narrow therapeutic window
- Best in class dual payload ADC technology to enhance synthetic lethality with less side effects

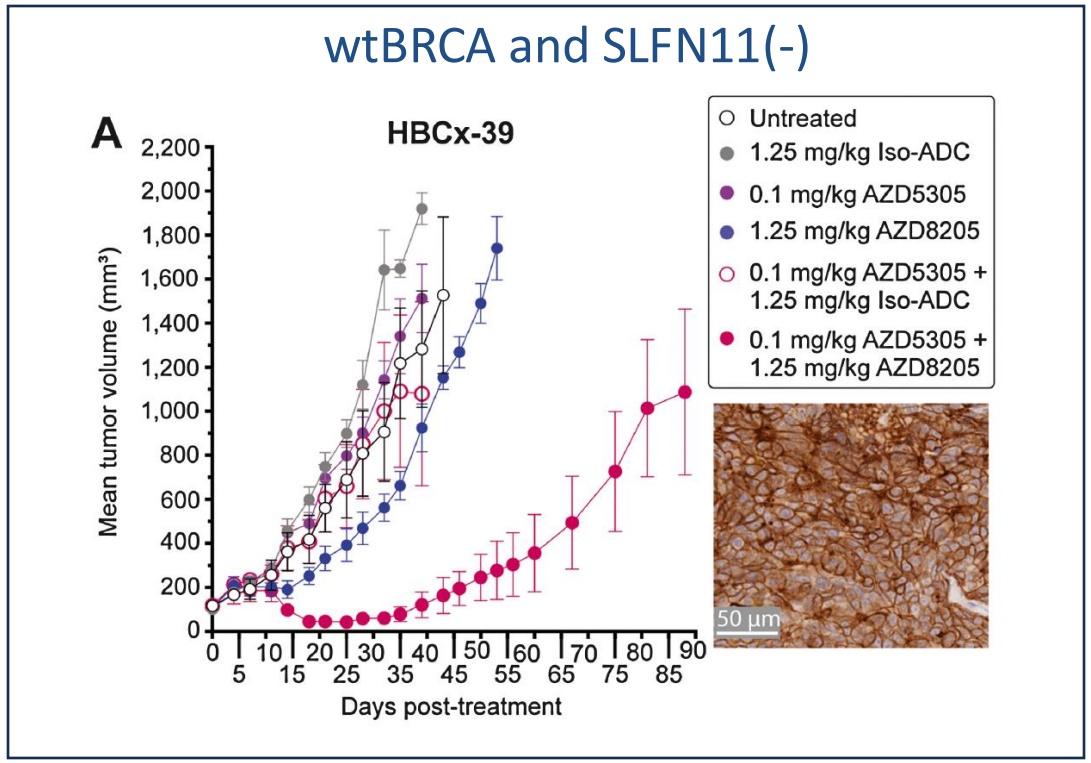
Preclinical Evidence of Synergistic Inhibition of PARP and Top1

- SLFN11-proficient and HR-deficient cells are preferentially susceptible to exatecan
- PARP prevents exatecan-based DNA damage directly through replication fork reversal
- PARP inhibition can sensitize HRP tumors to Top1 inhibition



Adapted from: Mol Cancer Ther (2022) 21 (7):1090–1102

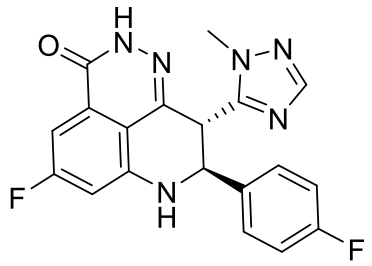
wtBRCA and SLFN11(-)



Clin Cancer Res. 2023 1086-1101

Clinically Validated Pan-PARPi Chosen for ADC^2 PoC to Boost Synthetic Lethality

Talazoparib (Pan-PARPi)

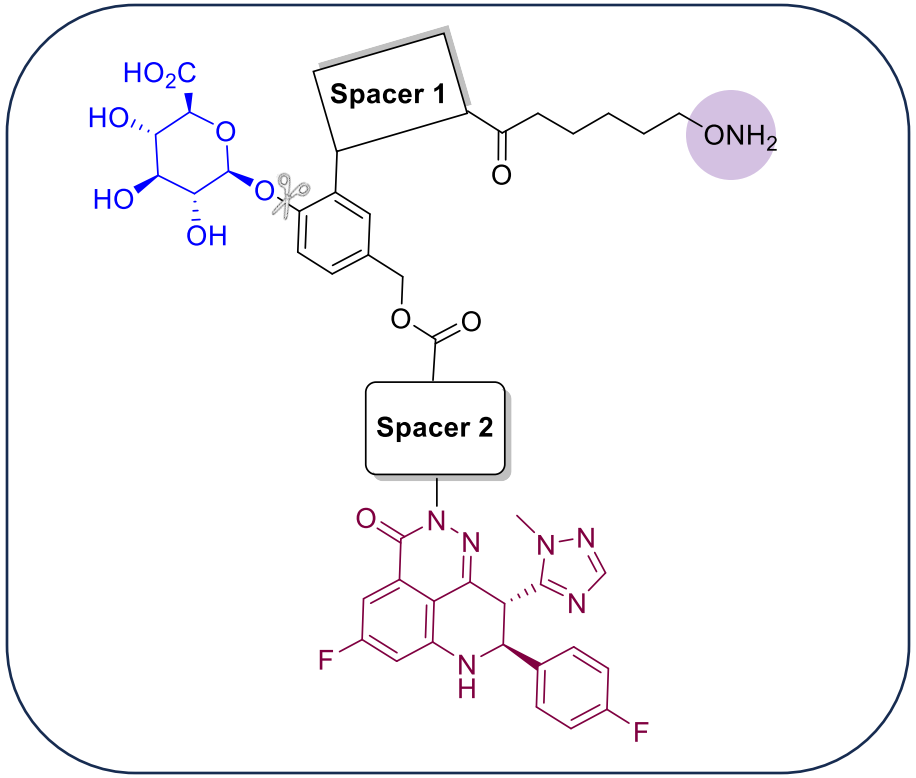


PARP1 Ki = 1.2 nM
PARP2 Ki = 0.87nM
PARP3/4 & TNKS1/2 Ki = 60 nM-322 nM
PARP16 Ki = 160-289 nM

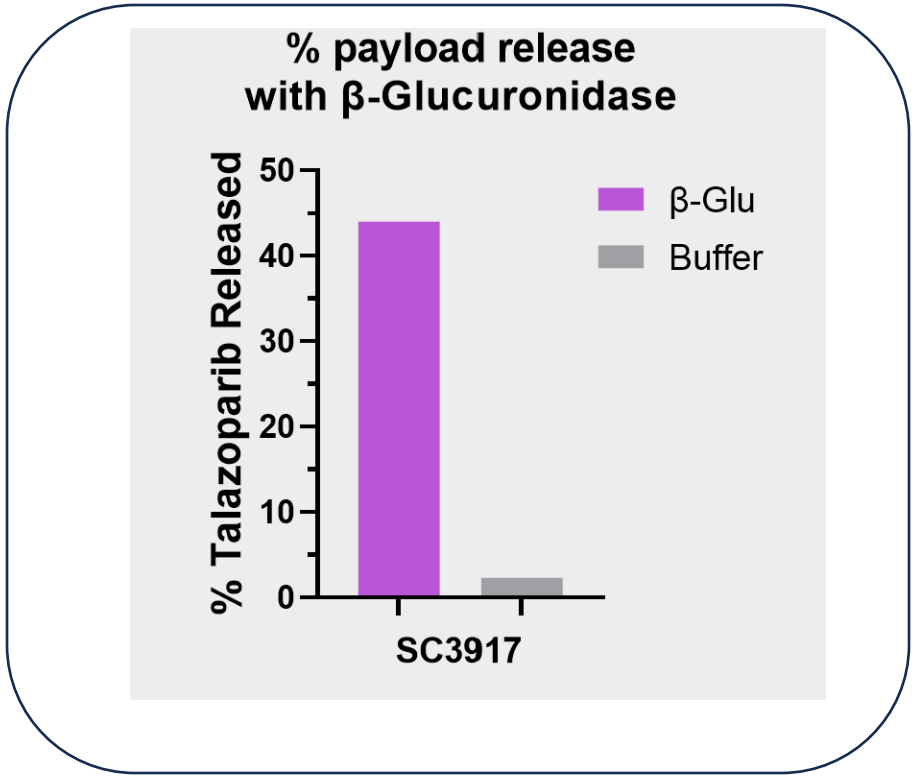
- Approved for gBRCAm HER2-negative locally advanced or metastatic breast cancer
- Combo with enzalutamide is approved for mCRPC
- Adverse reactions of any grade in the clinic, neutropenia, thrombocytopenia, alopecia, fatigue, anemia, etc

Novel β-glucuronidase Cleavable Talazoparib LP Enabled for Top1i + PARPi ADC[2]

β-glucuronidase Cleavable PARPi LP



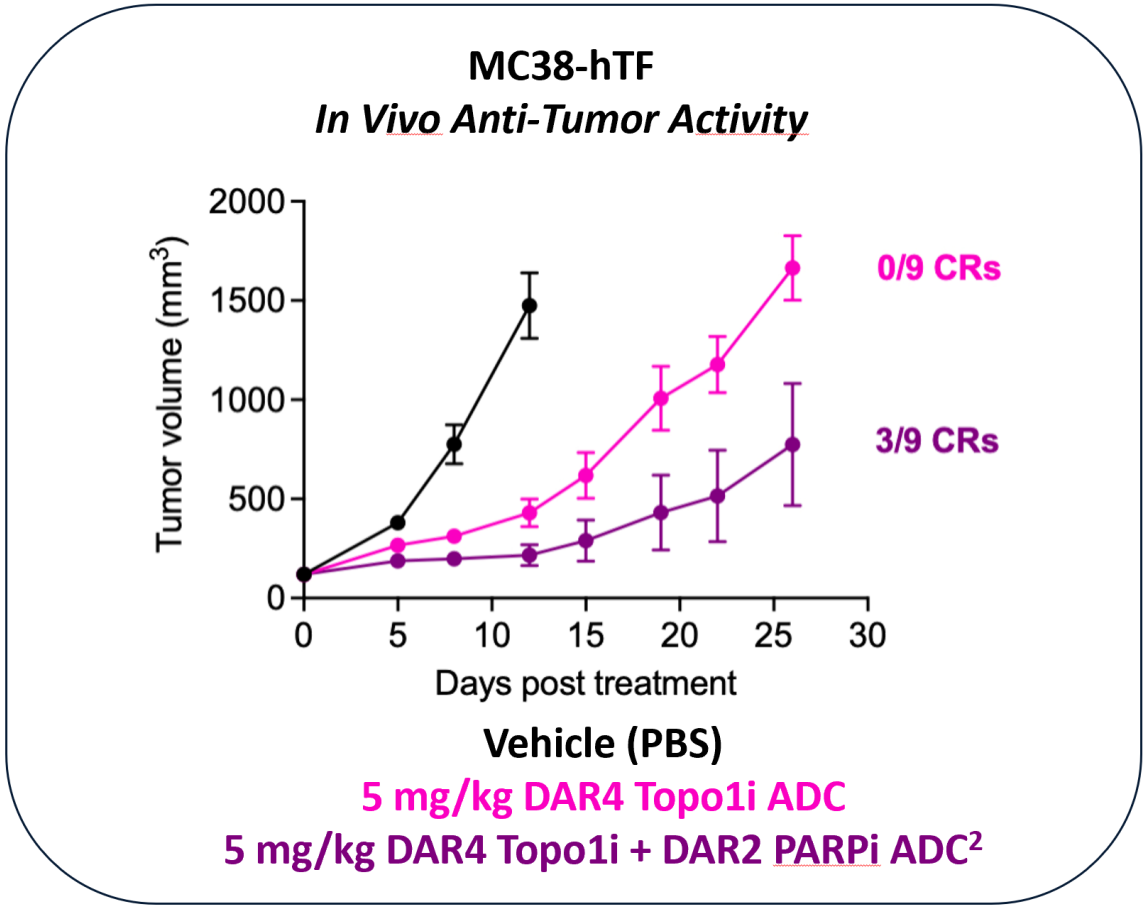
Payload Release Enzyme Incubation



- An optimized PARPi LP showed efficient payload release from enzyme/lysosomal incubation

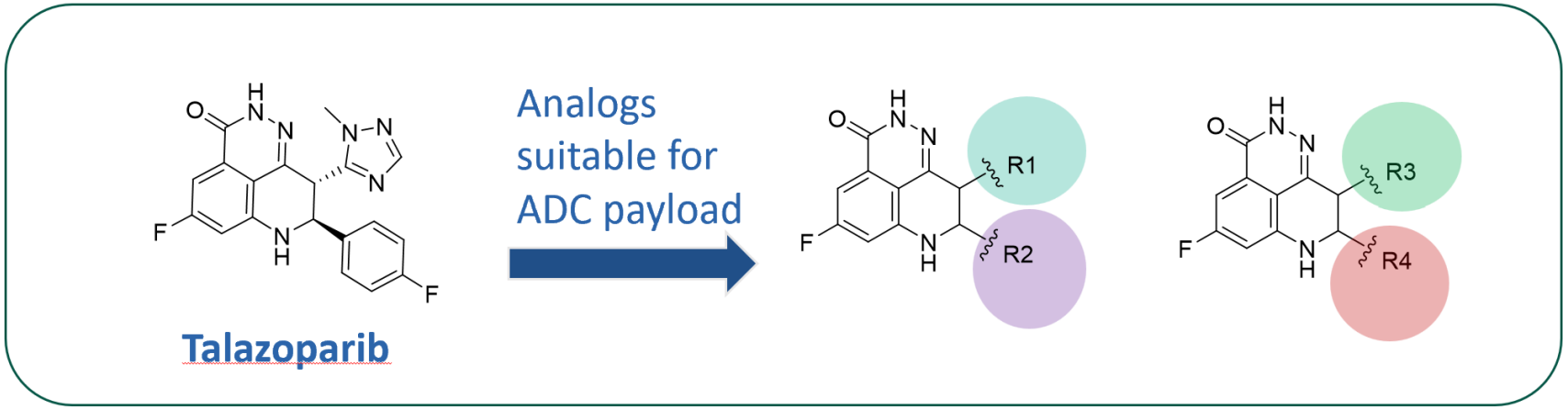
Exatecan + PARPi as 4+2 ADC^2 Shows Increased Activity Compared to ADC in a Mouse Syngeneic Model

Top1i+PARP ADC^2 PoC



- αTF ADC^2 (Exatecan + PARPi) conjugate group had an improved TGI and CRs when compared to ADC conjugate
- aTF ADC^2 and ADC molecules were well-tolerated

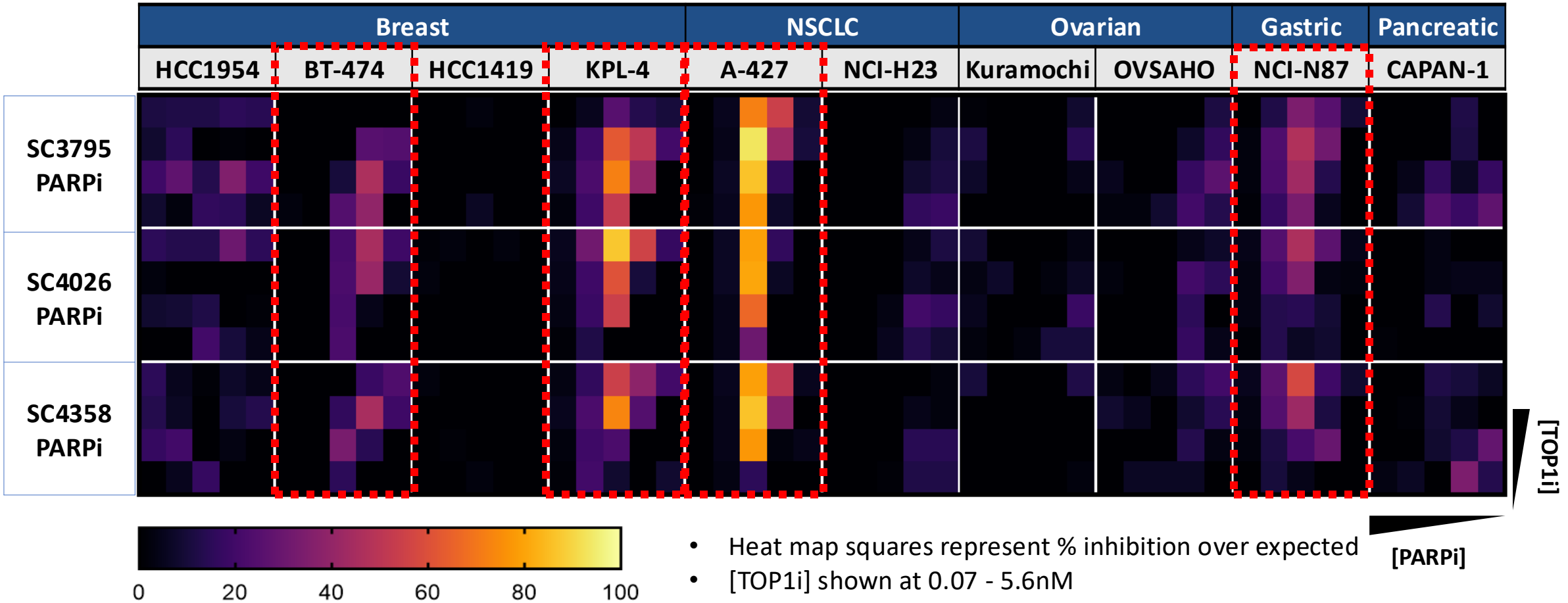
Proprietary Conjugatable Pan-PARPi Analogs Displayed Excellent Binding, Trapping and Not Substrate of the P-gp/BCRP Efflux Transporters



PARPi	*In-vitro* cell killing CAPAN-1 EC50 (nM)	PARP1 binding EC50 (nM)	PARP1 Trapping EC50 (nM)	PARP2 Trapping EC50 (nM)	Efflux Ratio $P_{app\ (BA)/(AB)}$	Efflux Ratio $P_{app\ (BA)/(AB)}$ + Vpm.)
Talazoparib	30	0.66	3.9	11	18.85	1.44
SC4026	73	1.1	4.8	5.1	0.75	0.67
SC4358	198	0.98	4.1	7.4	3.0	2.0

- Potential Pan-PARPi payloads with less/no P-gp/BCRP substrates compared to Talazoparib for ADC[2]

Next Generation PARPi Showed Synergy With Top1i Across Different Cancer Cells



- Heat map squares represent % inhibition over expected
- [TOP1i] shown at 0.07 - 5.6nM
- [PARPi] shown at 8 - 1000nM

- **We are in the process of optimizing the DDRi LPs, DAR ratios for ADC[2] development**

Acknowledgments

If anyone is interested in speaking with our BD team

- Barbara Leyman, Chief Business officer
- Vas Ramamurthy, Senior Director, BD