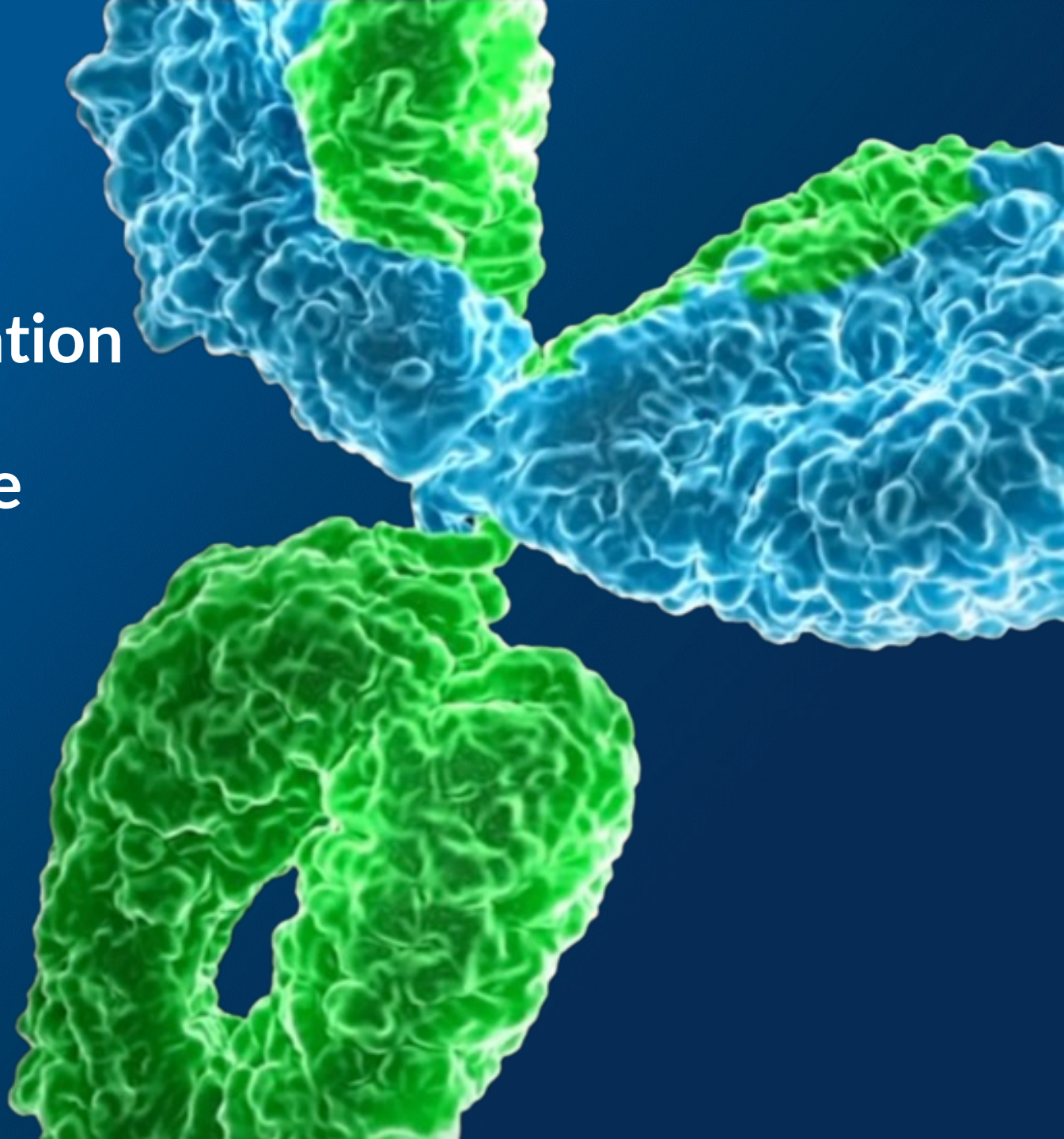




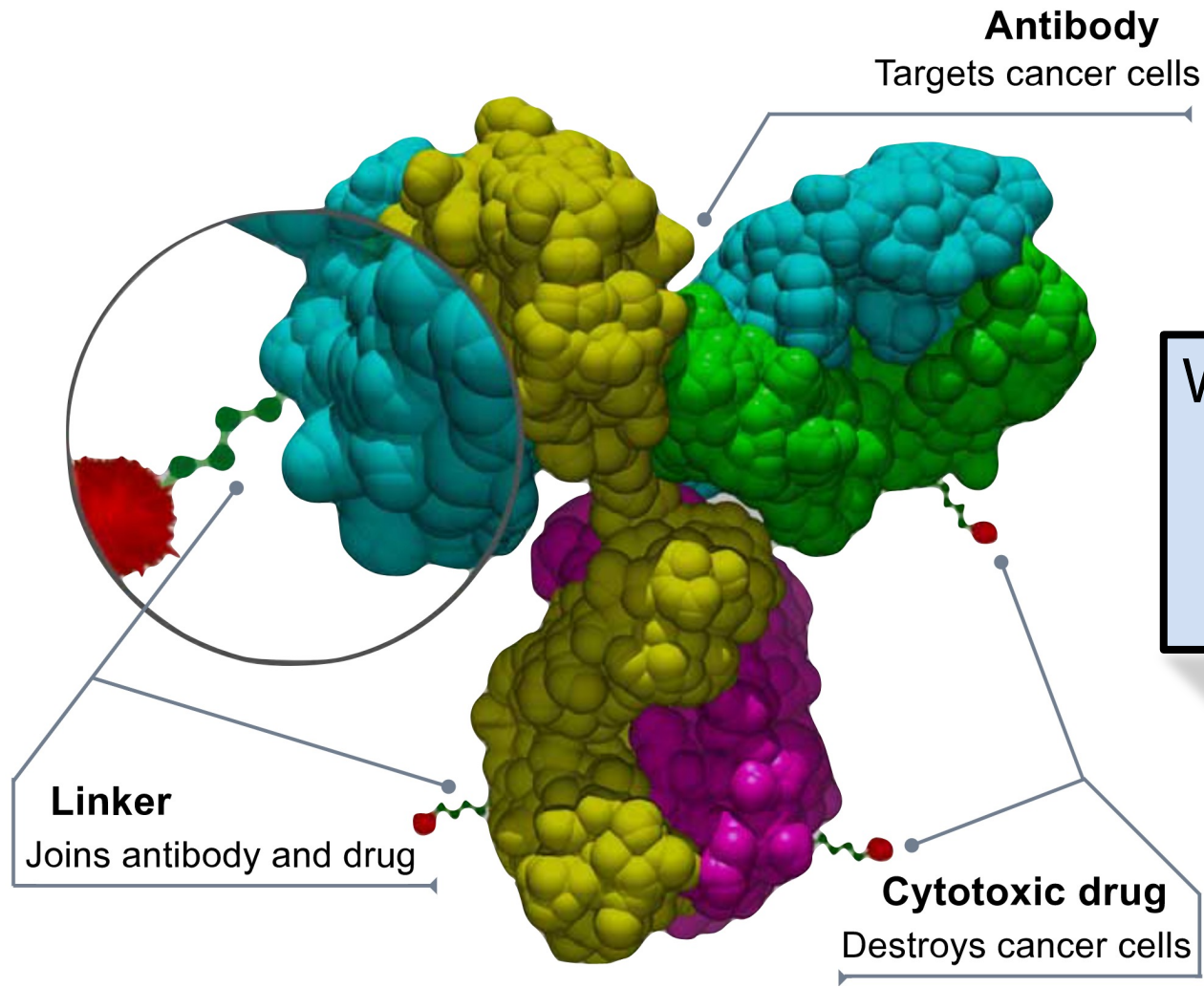
Development of Next Generation ADCs Using Novel Expression Platform & Precise Conjugation

Gang Yin, PhD

VP, Platform Engineering & Process Research



Three Five Major Considerations for ADC



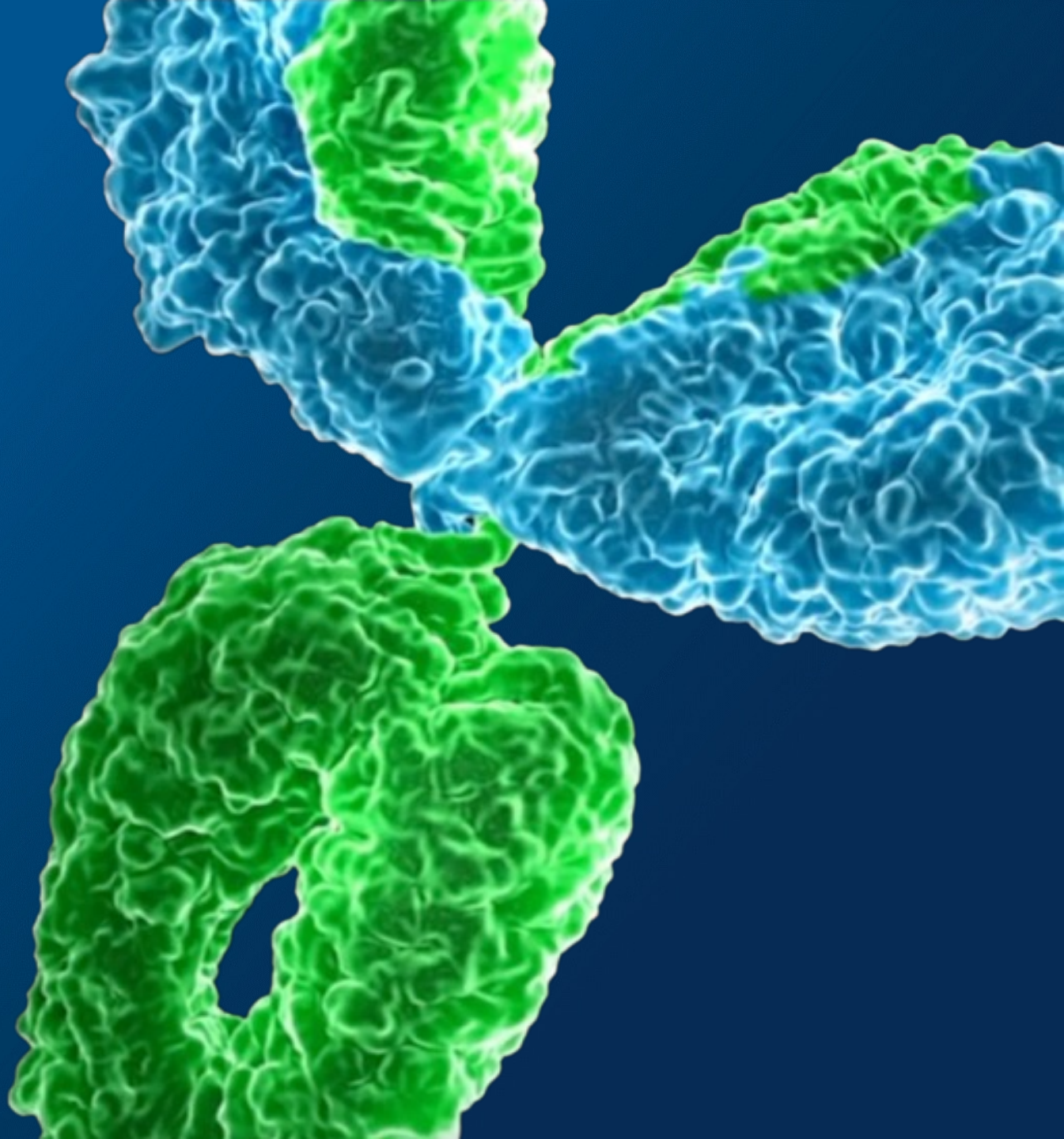
What is missing here:
Position(s)
Drug to Ab Ratio (DAR)

https://en.wikipedia.org/wiki/Antibody-drug_conjugate



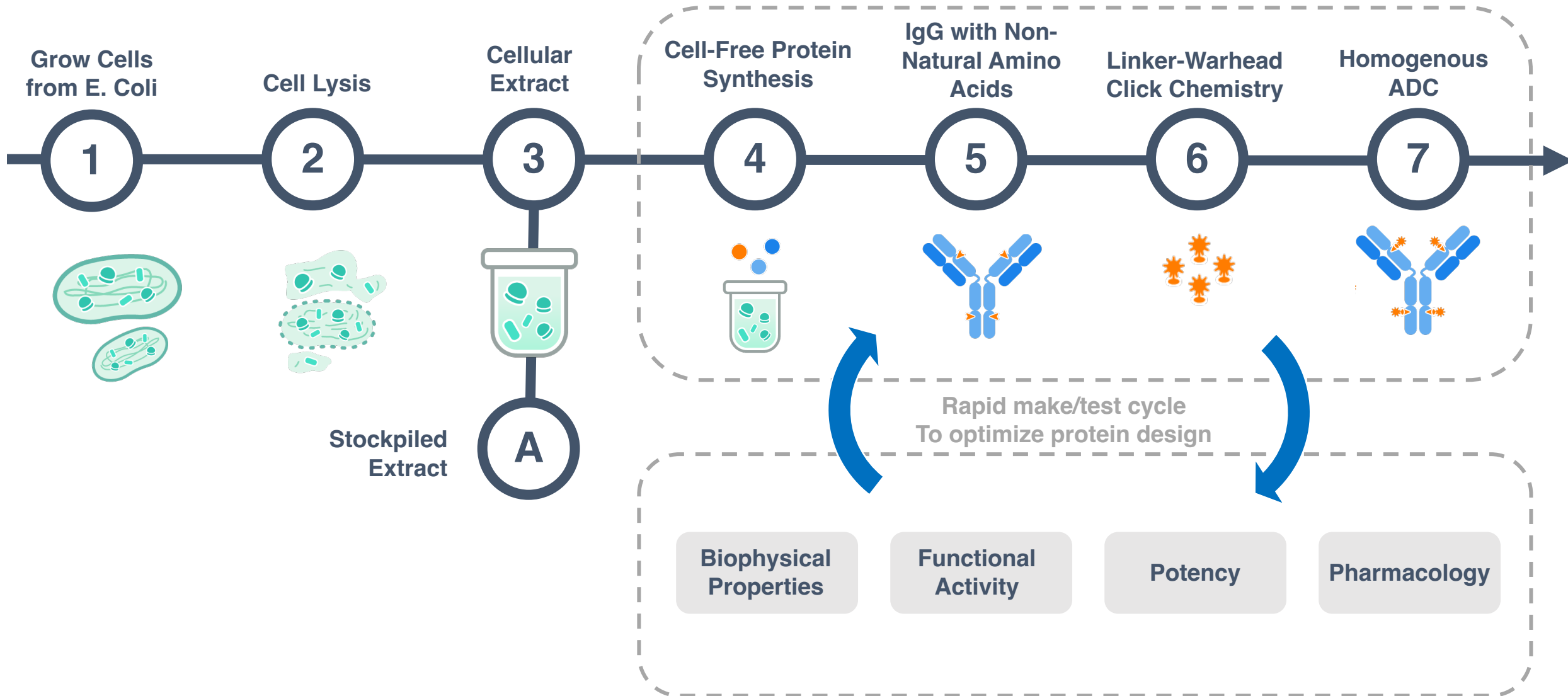
Cell-Free Expression Platform

Rapid, Precise and Flexible

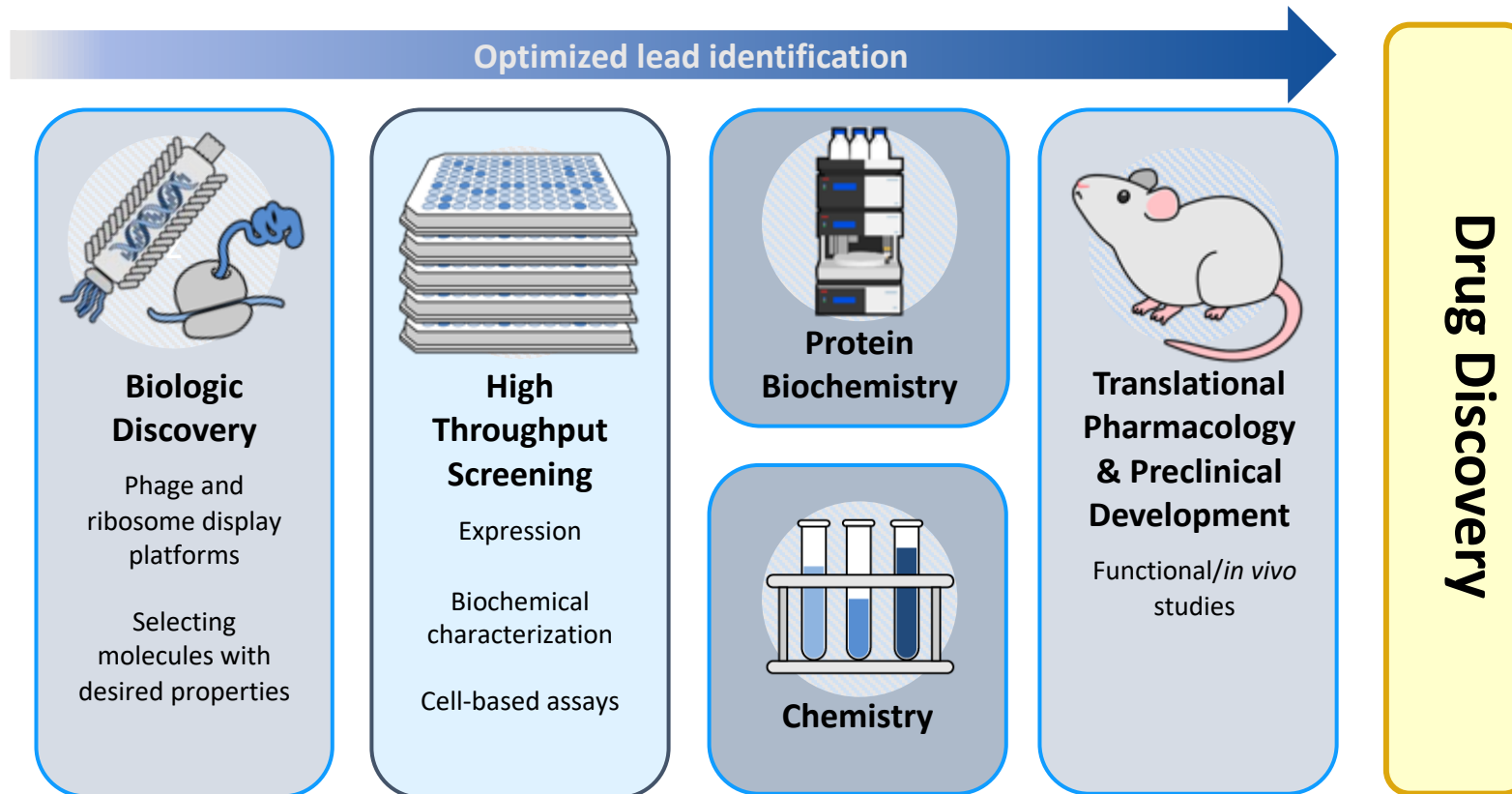


Industry Leading Cell-Free Protein Synthesis Platform

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

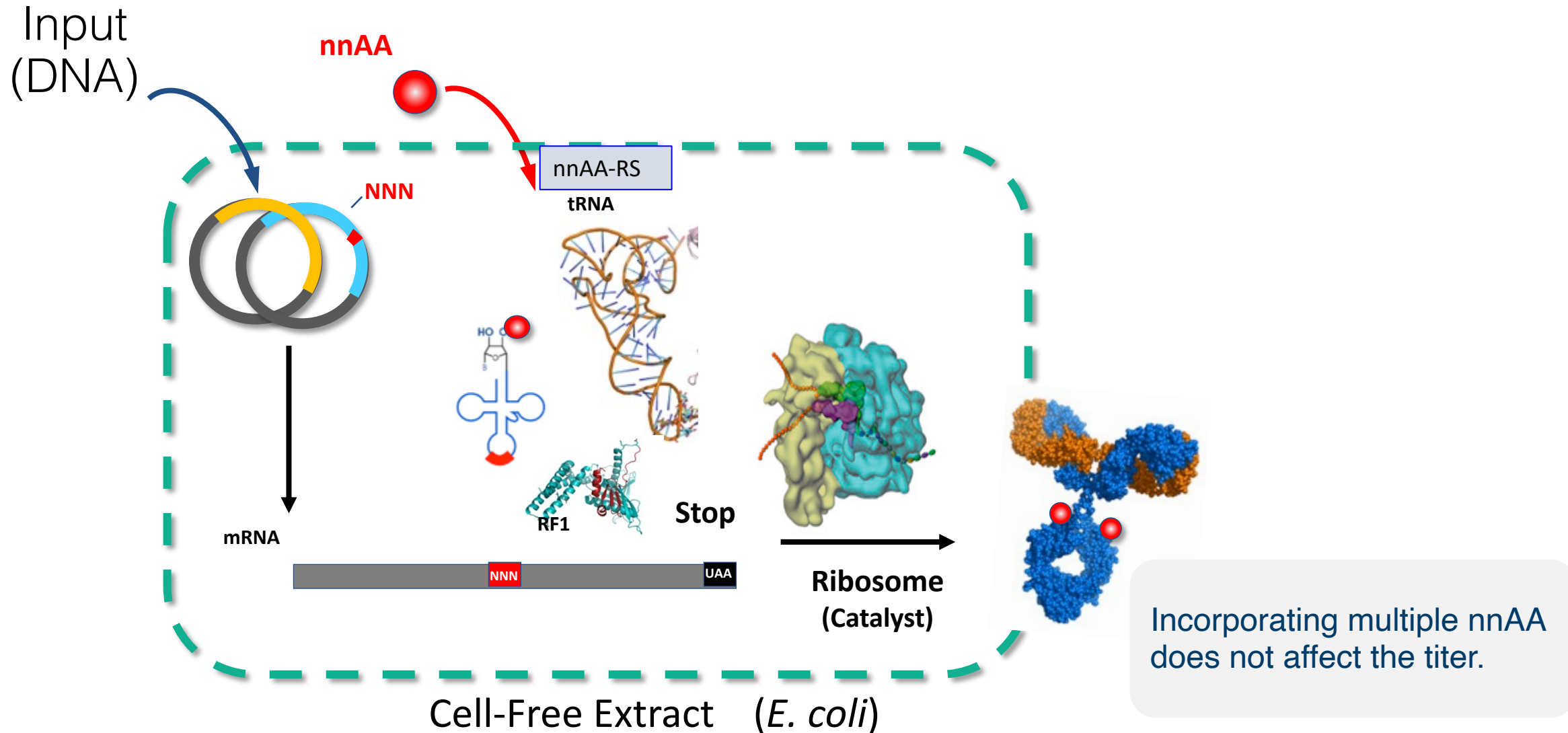


Rapid Biologic Discovery Enabled by Rapid Make / Test Cycle

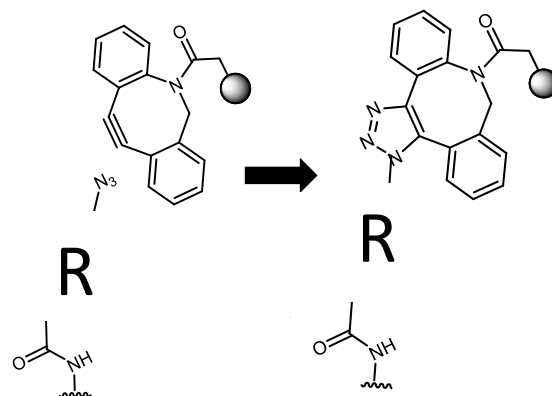
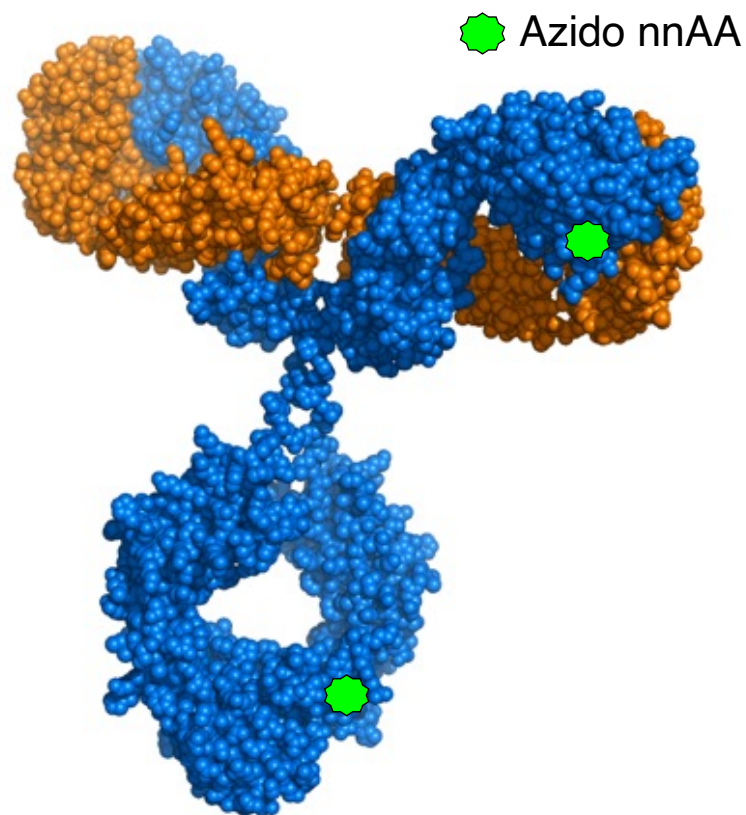


- Cell-free protein synthesis is rapid, allowing the production and characterization of thousands of variants in weeks.
- Capable to produce sufficient materials for *in vivo* studies even in early stage, including NHP toxicity studies.

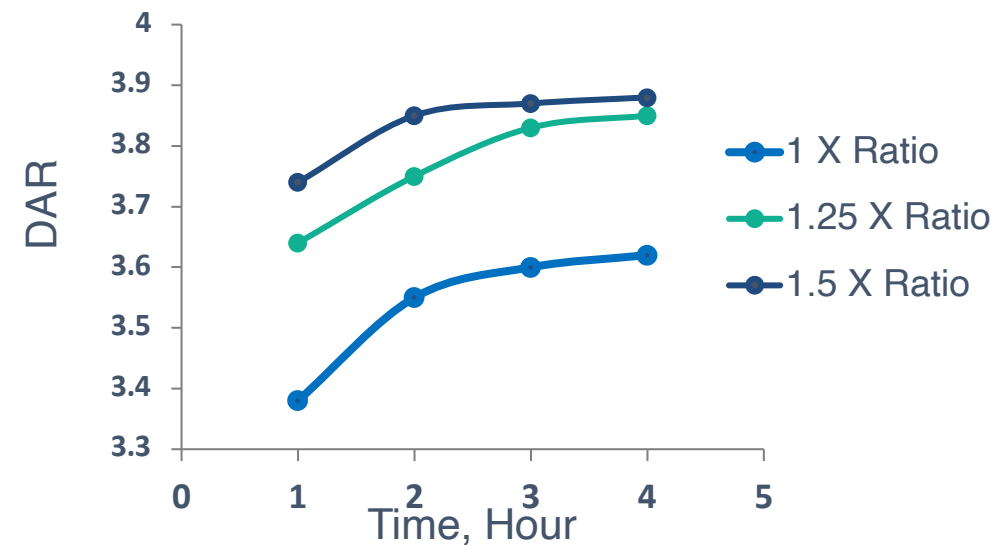
Translation of nnAA-Containing Proteins Enables Site-Specific Conjugation



Azide Containing nnAA Enables Highly Efficient Cu free Click Conjugation Chemistry



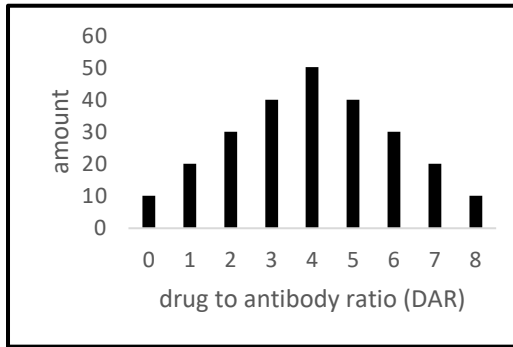
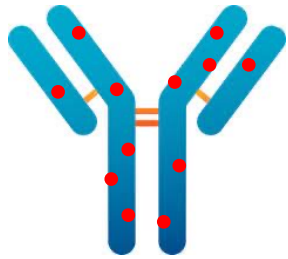
1.25 X Molar Ratio results in conjugation (DAR=4) completion by 4 hr



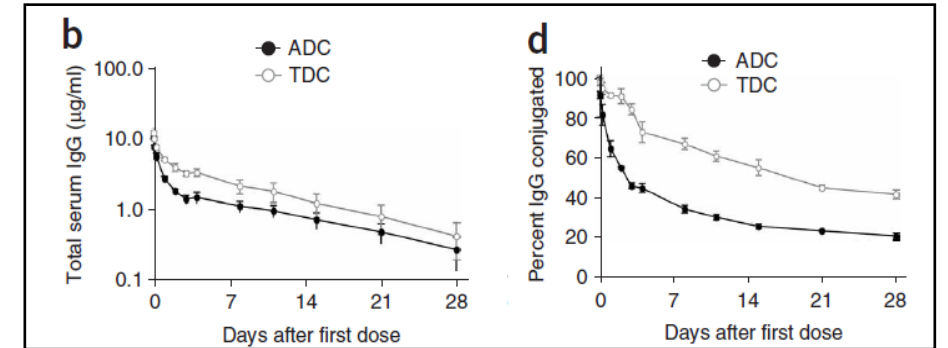
Conjugation technology is specific, irreversible, highly reactive and efficient in manufacturing

Random conjugation vs. site-specific conjugation

Stochastic conjugation

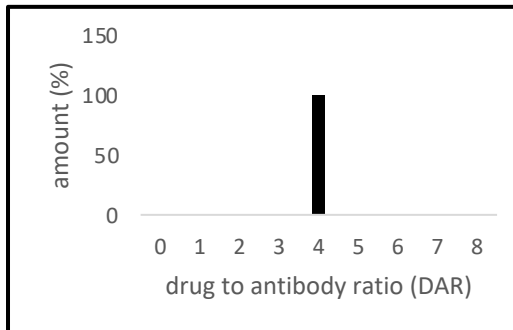
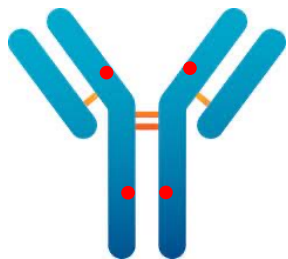


Wide DAR distribution

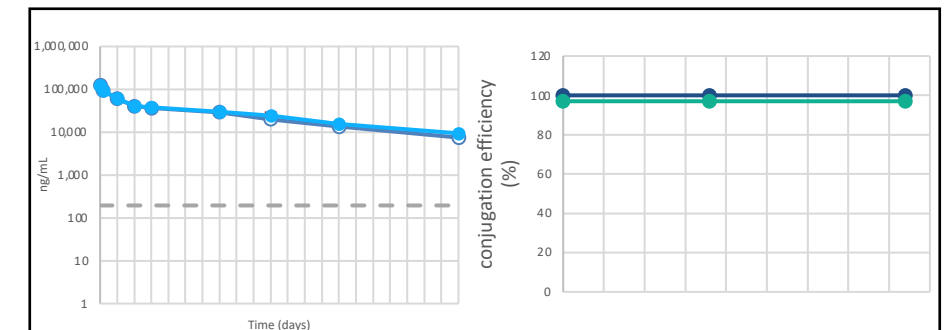


poor PK profile and LP stability

Site-specific conjugation



Well defined DAR



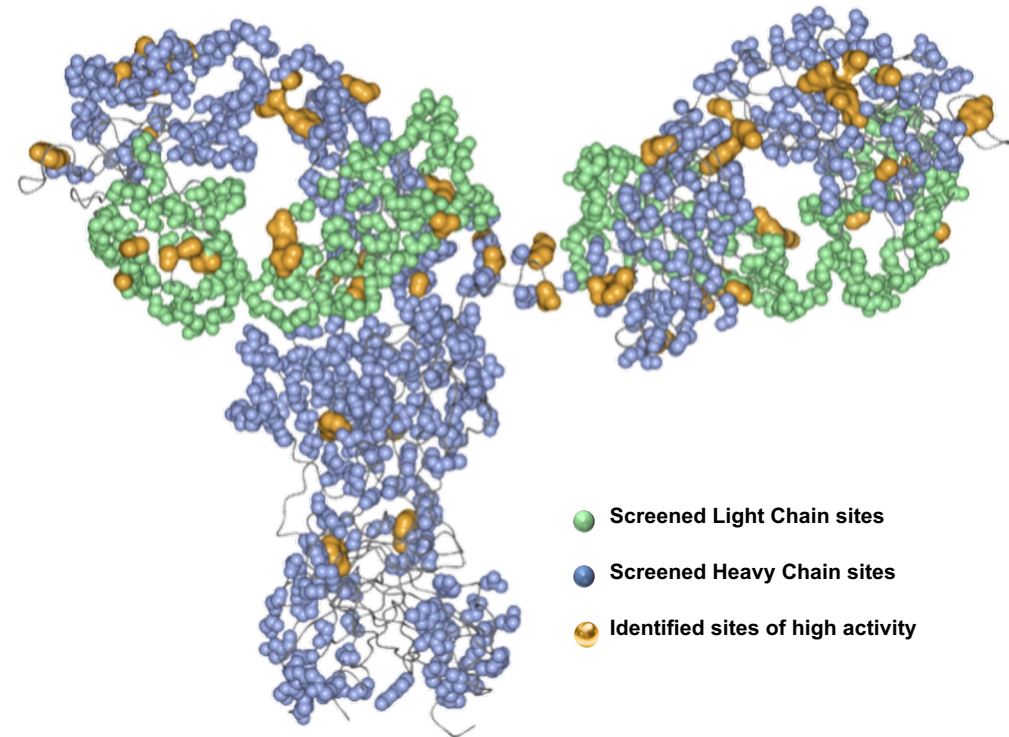
PK profile and stable LP independent of DAR

selection of the best single species

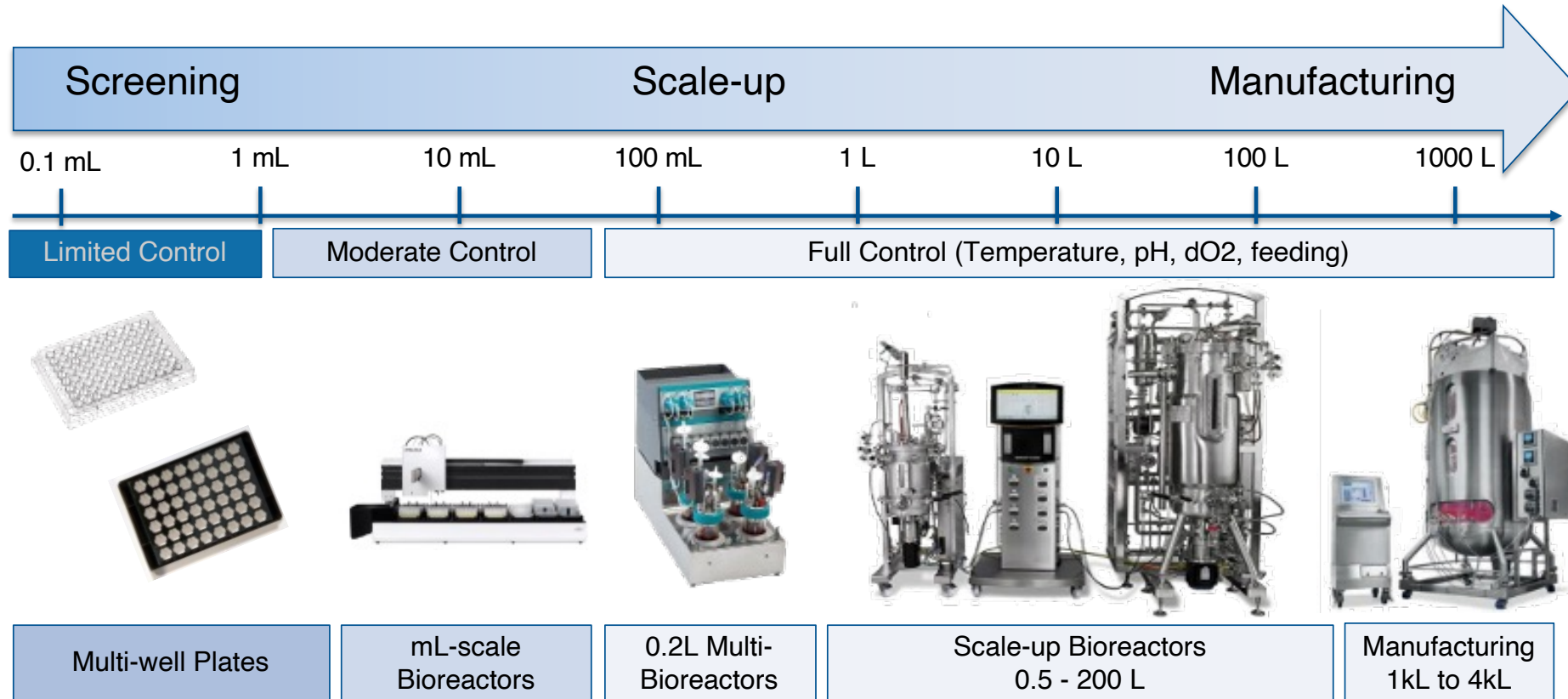
XpressCF+™ Screening Platform Allows for Rapid Empirical Evaluation and SAR Analysis to Identify the Best Conjugation Sites

- Extensive screening of ~300 sites and site combinations conducted to identify sites that exhibit favorable characteristics such as high conjugation efficiency, linker stability, potent cell-killing properties, optimal PK and efficacy.
- These proprietary sites are utilized across various ADC programs at Sutro and may not be accessible through other conjugation technologies.
- Developing best-in-class ADCs

Surface Sites Screened on an IgG during an ADC Campaign:

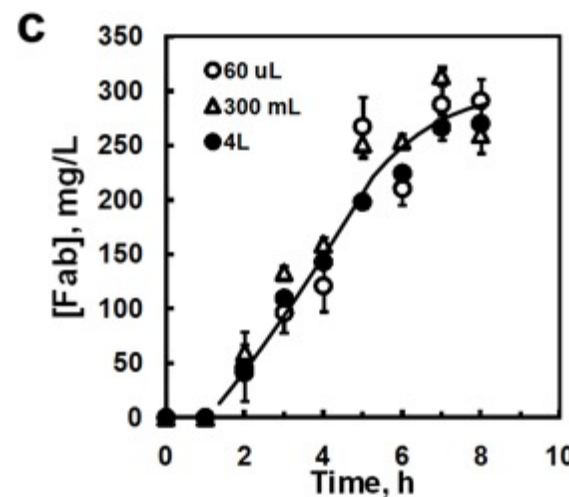
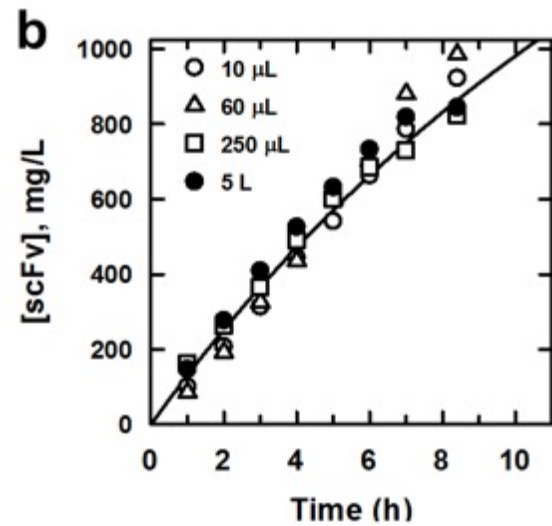
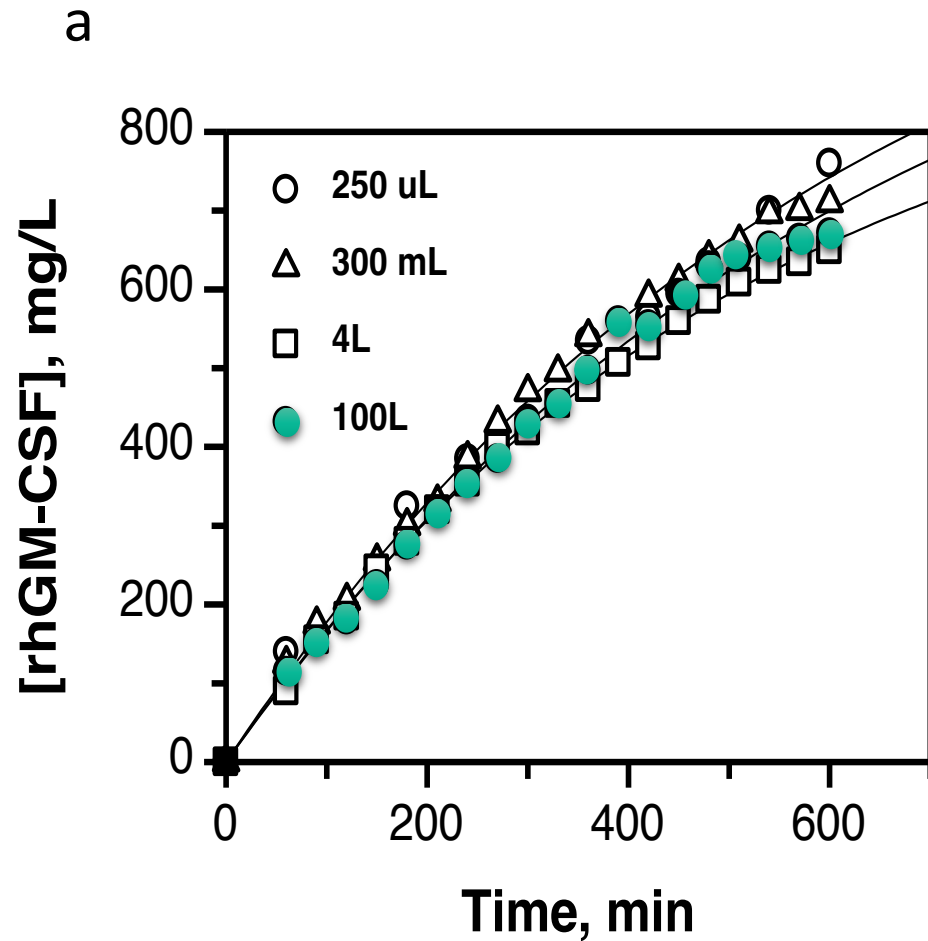


XpressCF+® Platform Enable Same Process from Discovery to Large Scale Manufacturing



- **Direct linear scale-up from HTS to production scale**
- **Minimal, rapid process development**
- **Uses standard bioreactors & downstream equipment**
- **Gene sequence to drug substance in days**

XpressCF Enables Rapidly Scalable Expression: 250uL → 100L → 1,000L



- 1kL GMP Manufacturing Successfully Demonstrated with Clinical Assets;
- Enabling Commercial Manufacturing at CMO

Advantages of Precision Protein Therapeutics

Homogenous, precisely designed complex biologics with optimized performance

Challenges in Traditional Cell-Based Complex Biologics Discovery and Manufacturing

Low throughput lead evaluation with **transient stable cell lines**



Incomplete and unstable conjugations yielding poorly optimized products



Heterogeneous mixtures have less favorable therapeutic window due to varying performance of each species



Cell-based production requires **different process with scale, causing complexity and unreliability** with CMC and manufacturing



Advantages of Sutro's Cell-Free Synthesis Platform for Best-in-Class Biologics



High throughput lead evaluation and **empirical selection of best lead**



Click chemistry and non-natural amino acids **completely conjugate at precise positions**



Precisely designed proteins in a **homogeneous product widens therapeutic window** due to the selection of the best single species

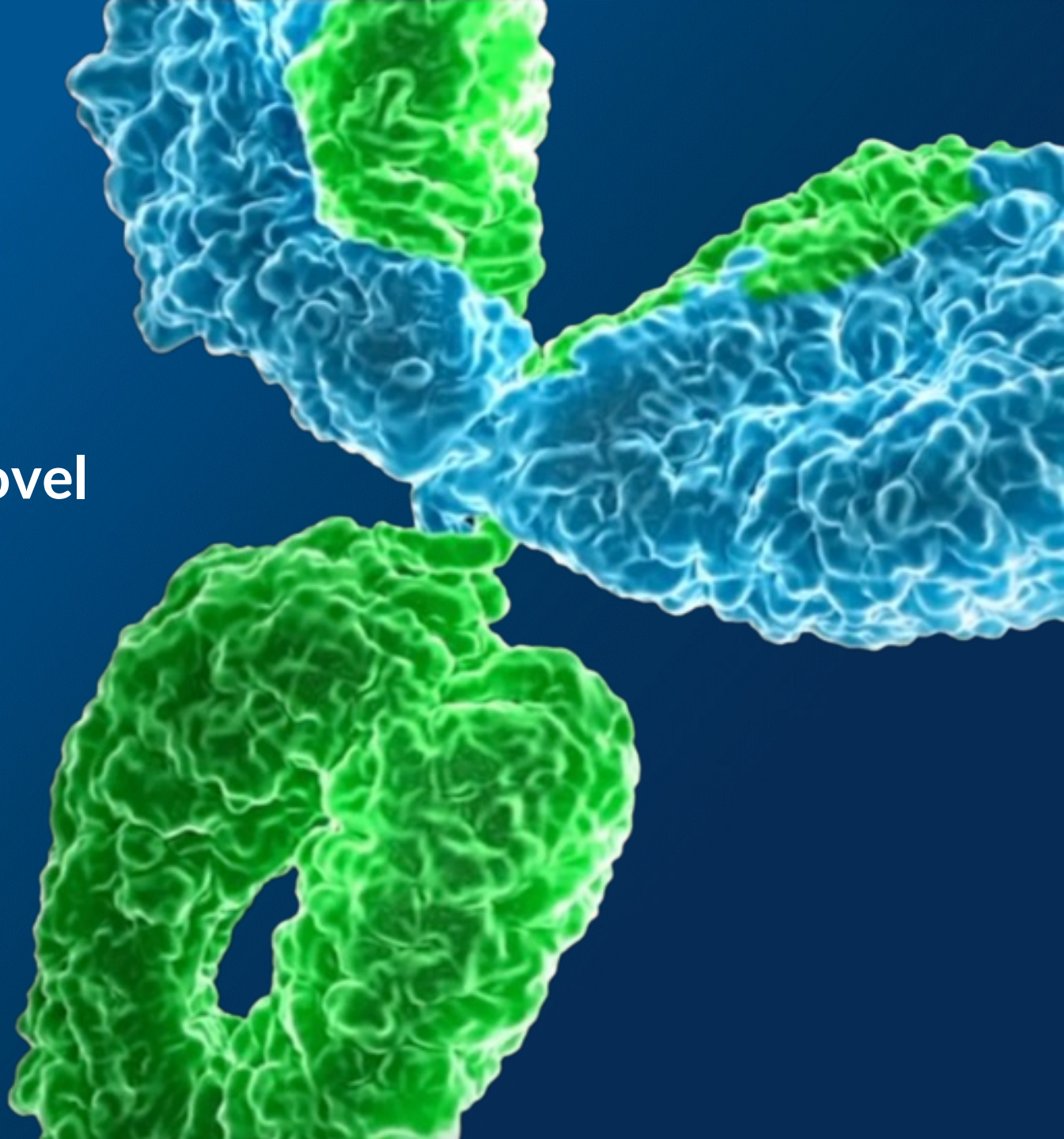


Cell-free production is scalable – the same process in **lead discovery** as at **commercial scale**

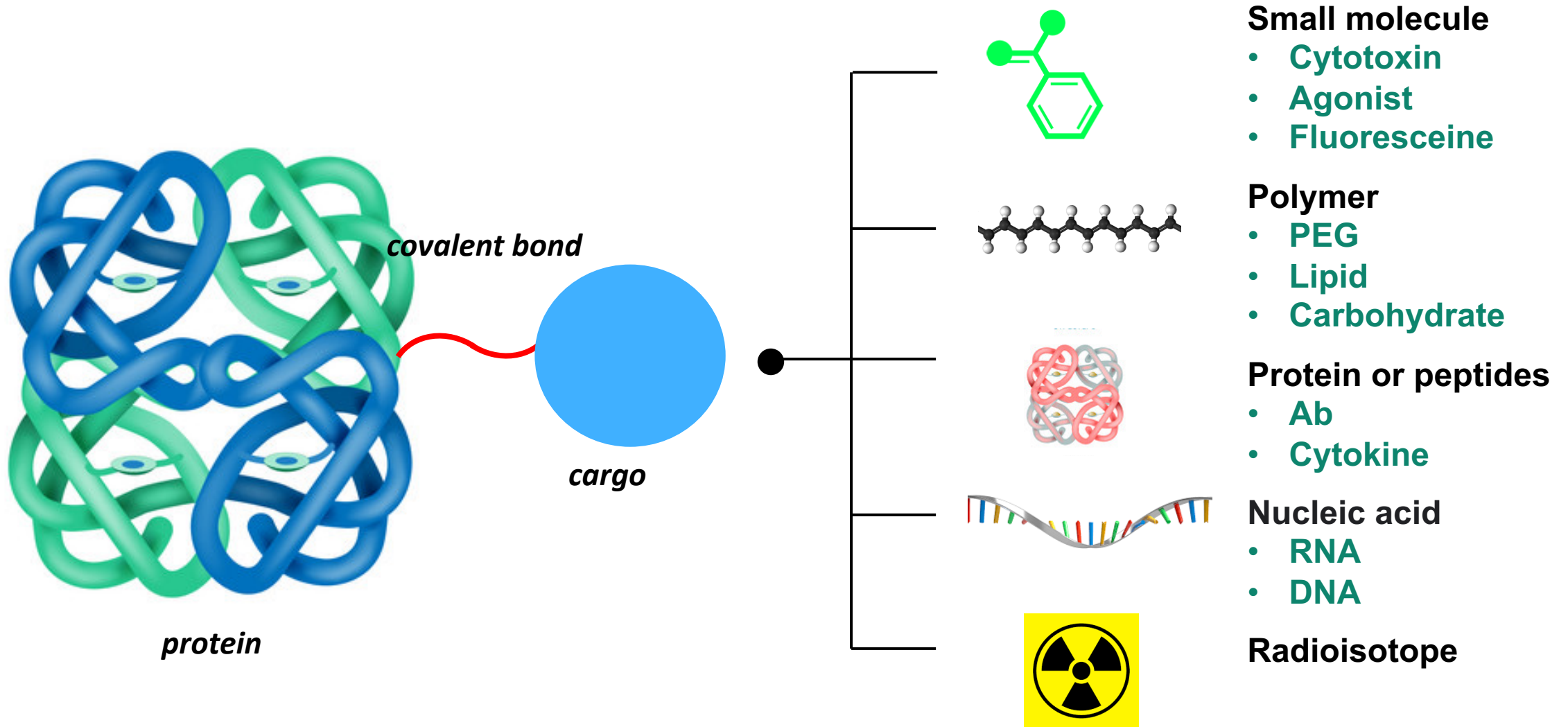




Precise Conjugation to Enable Novel Product Concepts



The Site-specific Conjugation to A large Variety of Molecules Enabled Through nnAA Incorporation



Product Concepts Enabled by Site-specific Conjugation

antibody drug conjugate

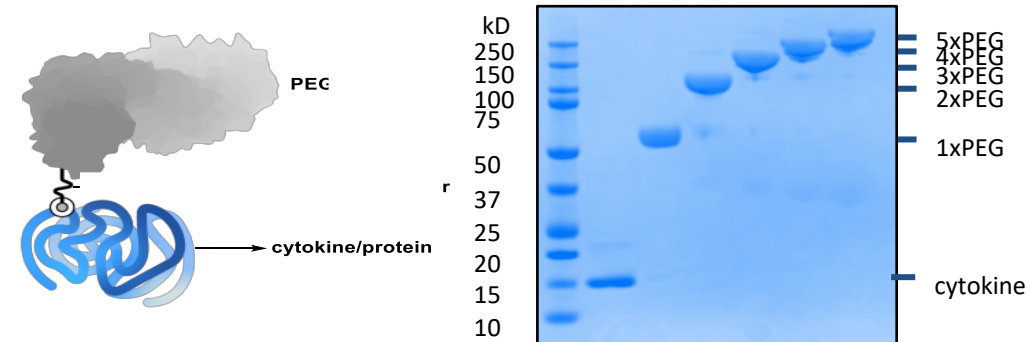


STRO-001

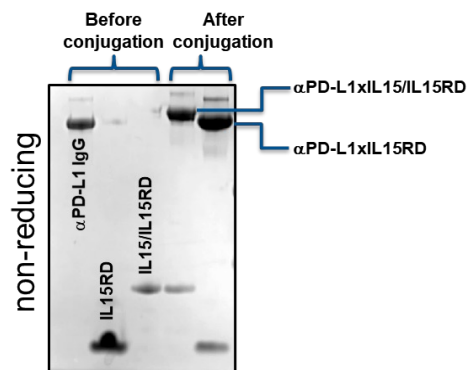
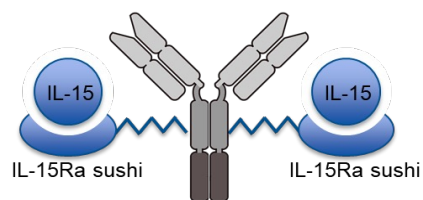
STRO-002

STRO-003

PEGylated cytokine

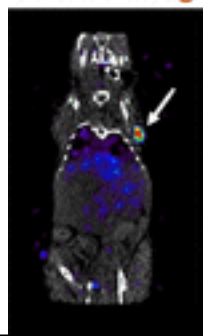


protein-protein conjugate (αPD-L1-IL15RD)

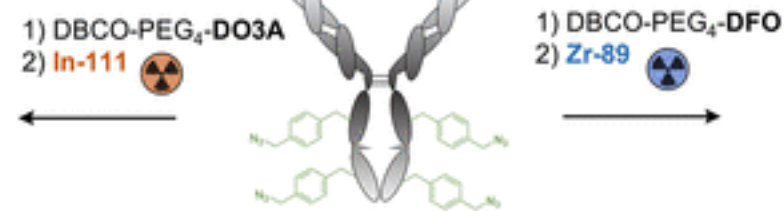


antibody radioisotope conjugate

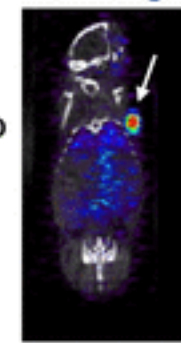
SPECT imaging



Cell-free mAb synthesis, site-specific incorporation of pAMF



PET imaging



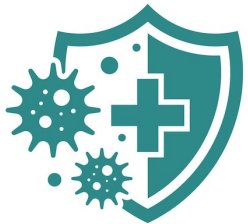
Bioconjug Chem, 2020 Apr 15;31(4):1177-1187

Combining Multiple Mechanism of Action to Maximize ADC Efficacy

Dual Precision Conjugates Can Reduce Drug Resistance, Promote Anti-Tumor Immunity and More...

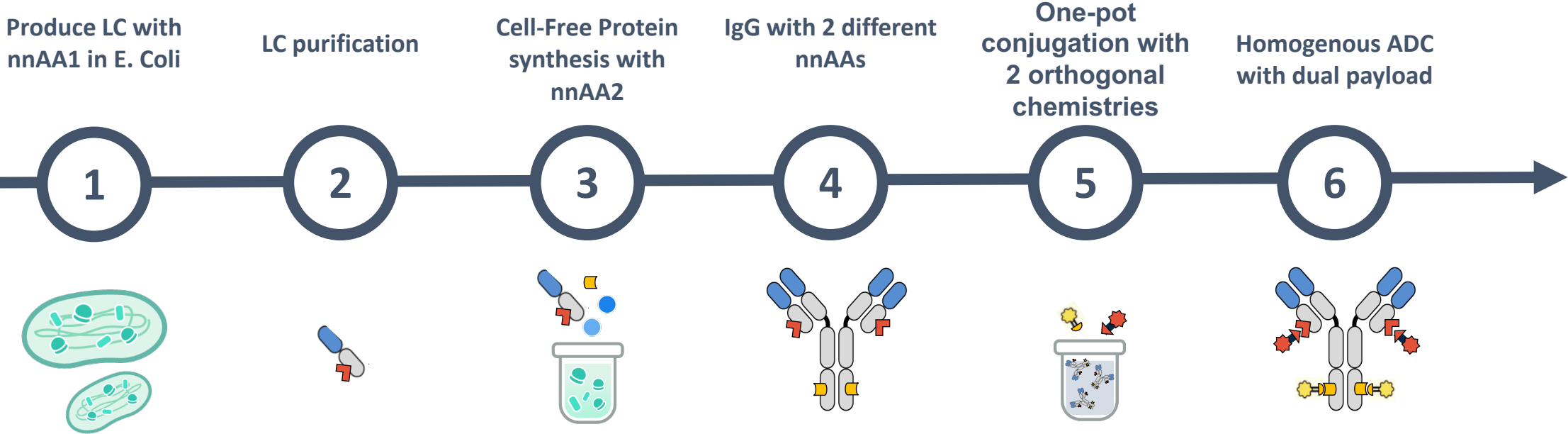


- Combat drug resistance: disrupt DNA while simultaneously impairing resistance;

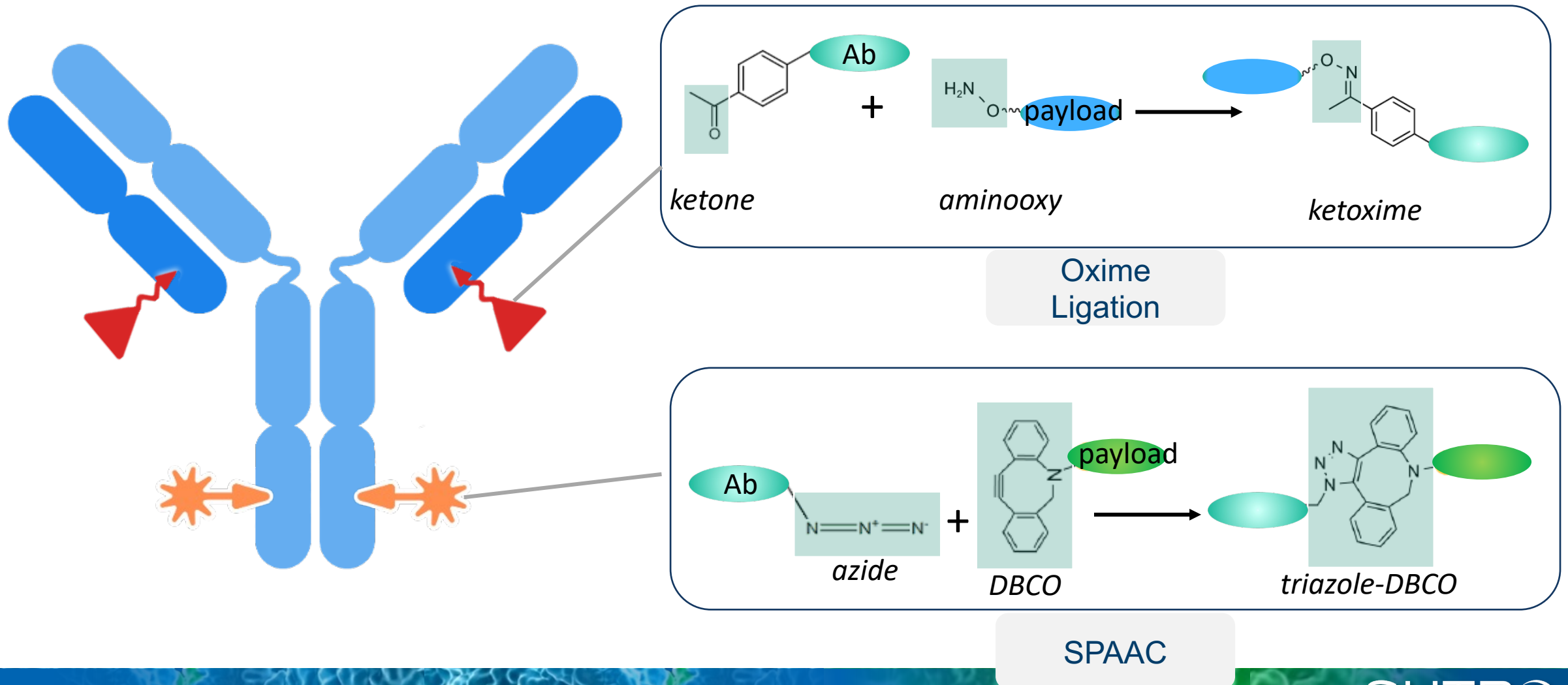


- Promote anti-tumor immunity: cause tumor cell disruption together with innate immune cell stimulation and result in anti-tumor immunity.

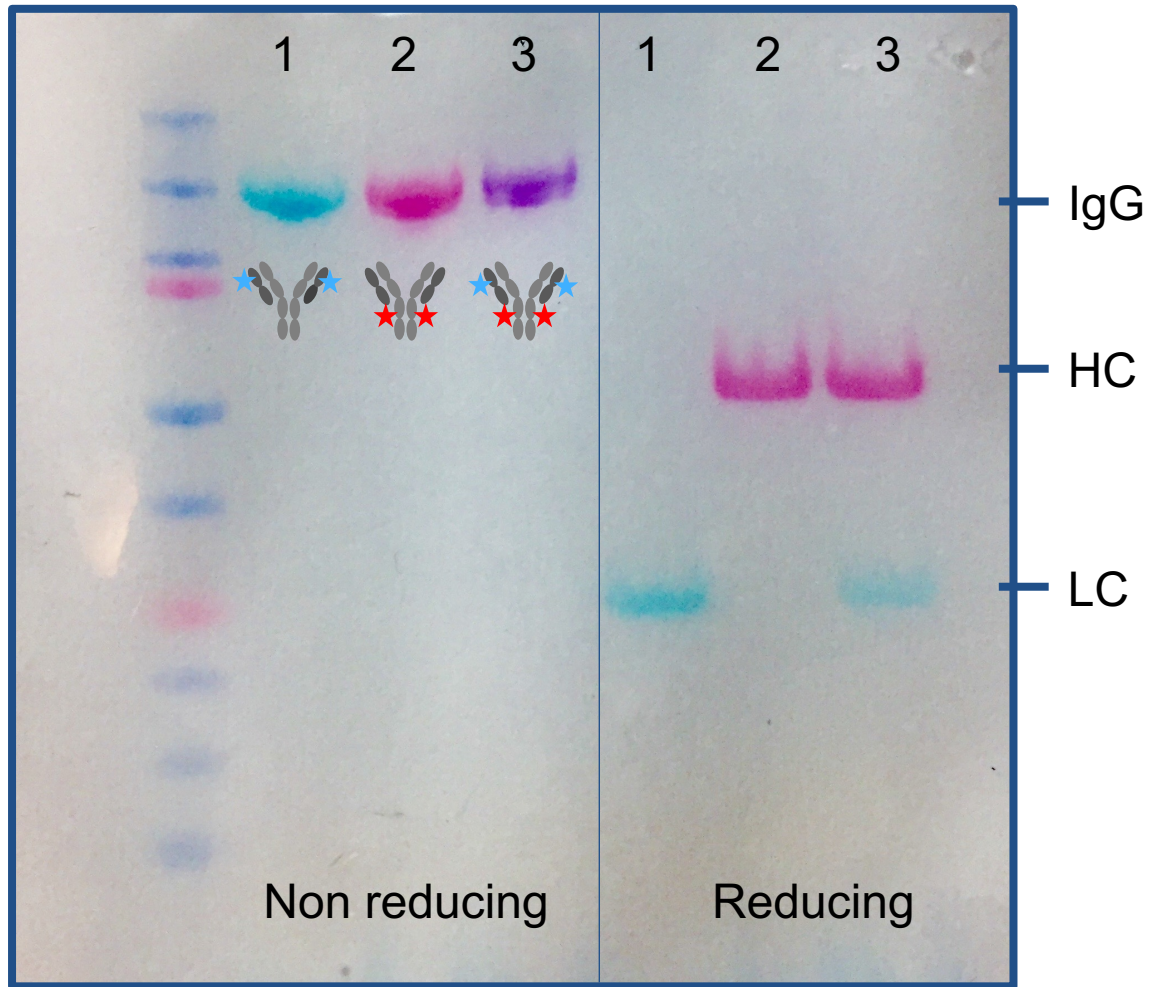
Sutro's State of the Art Technology to Achieve Precise Dual Conjugation



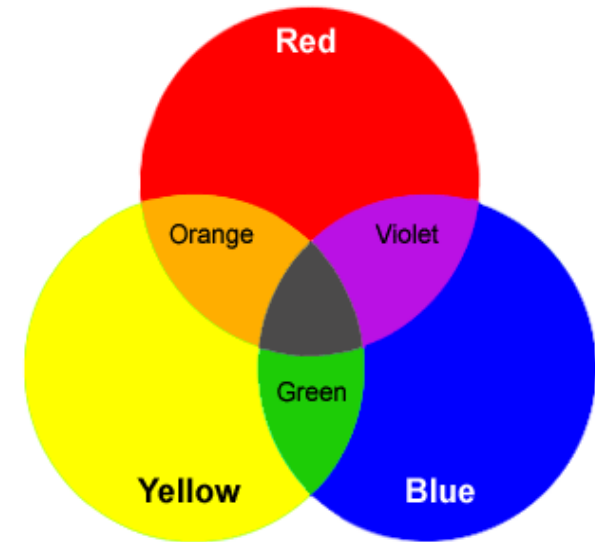
Orthogonal Conjugations Enabled in a Single-Pot Reaction



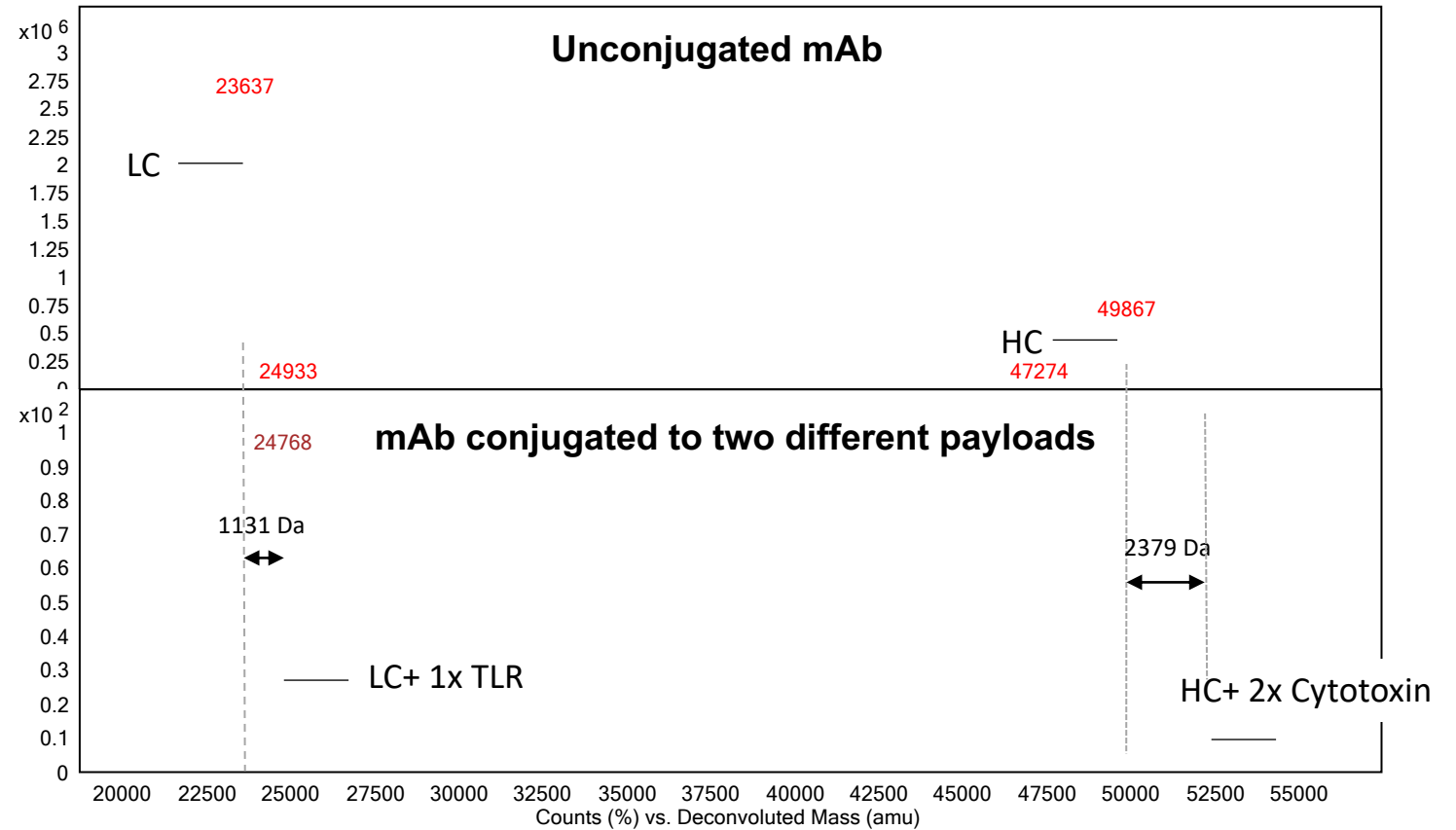
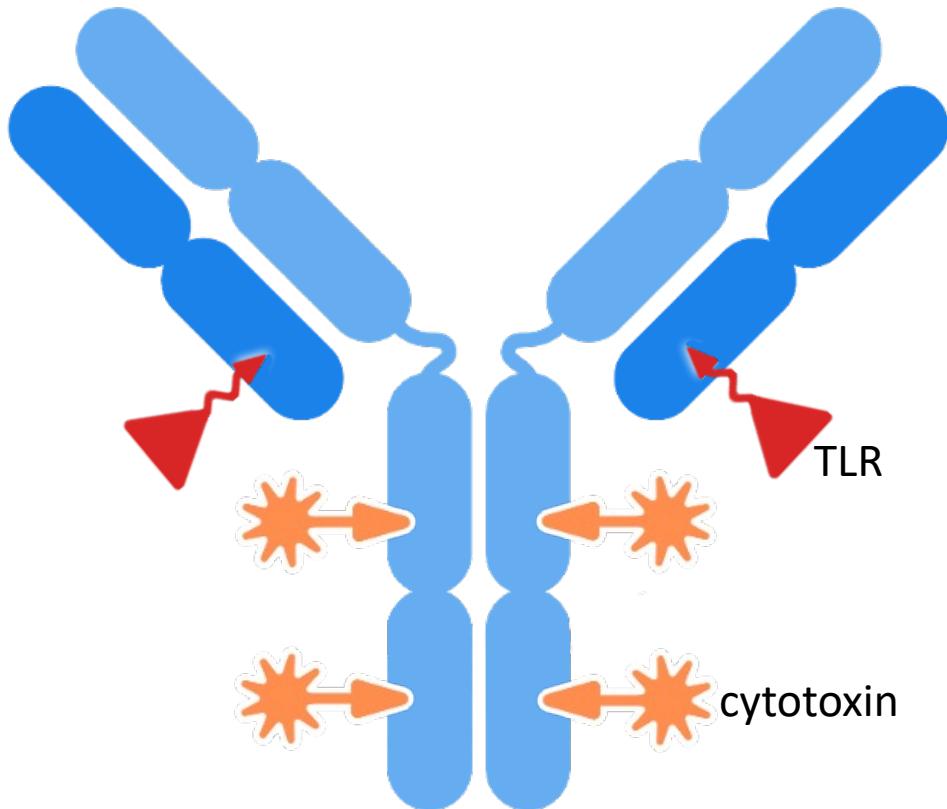
Visualization of Targeted Dual-Conjugation on SDS-PAGE



- 1 label blue dye on LC
- 2 label red dye on HC
- 3 label blue dye on LC and red dye on HC



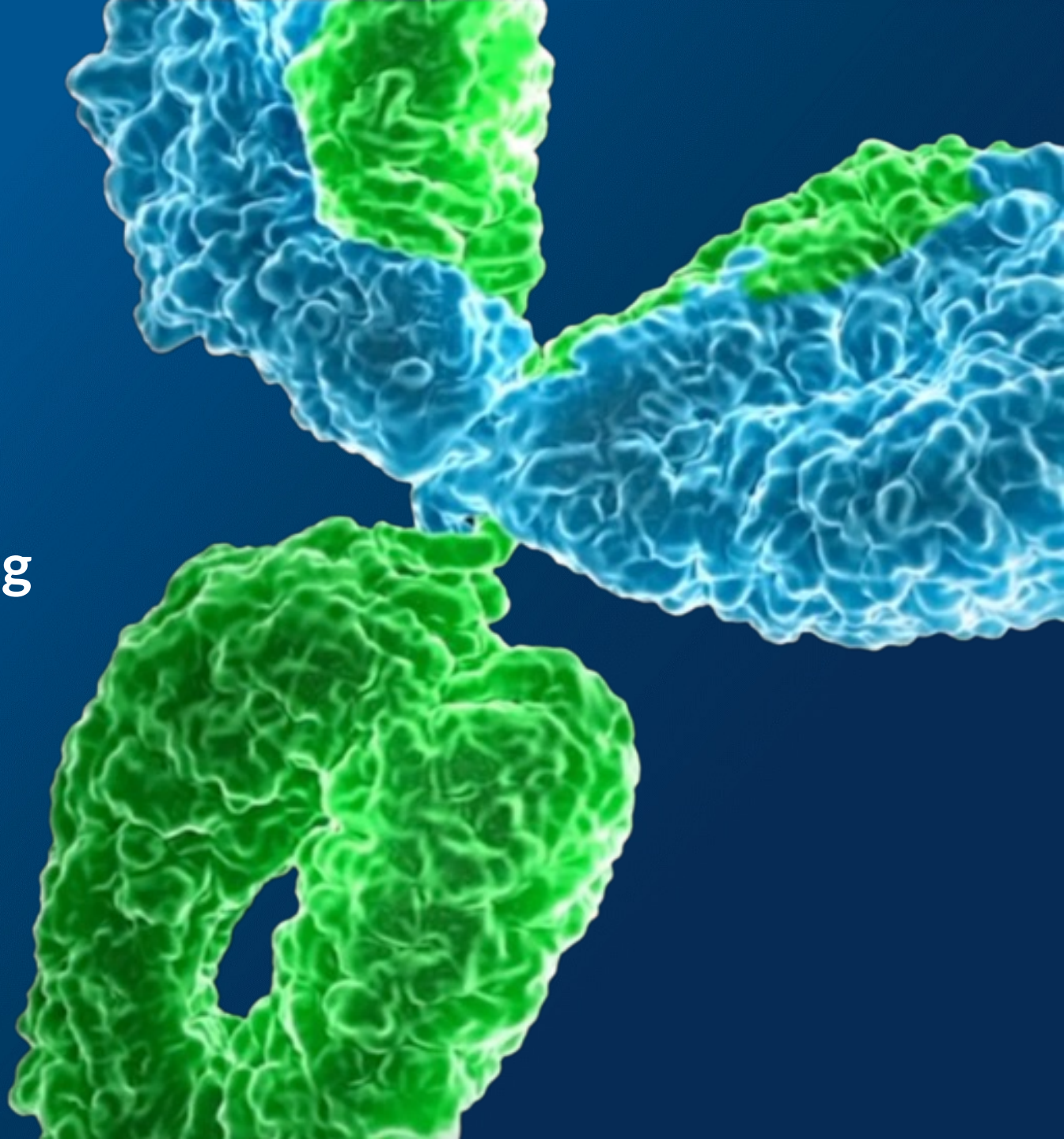
Precise Dual-Conjugation Confirmed by LC-MS



Dual conjugation complete, no post conjugation purification required



Next-Generation Tumor Targeting Immunostimulatory ADC (iADC)



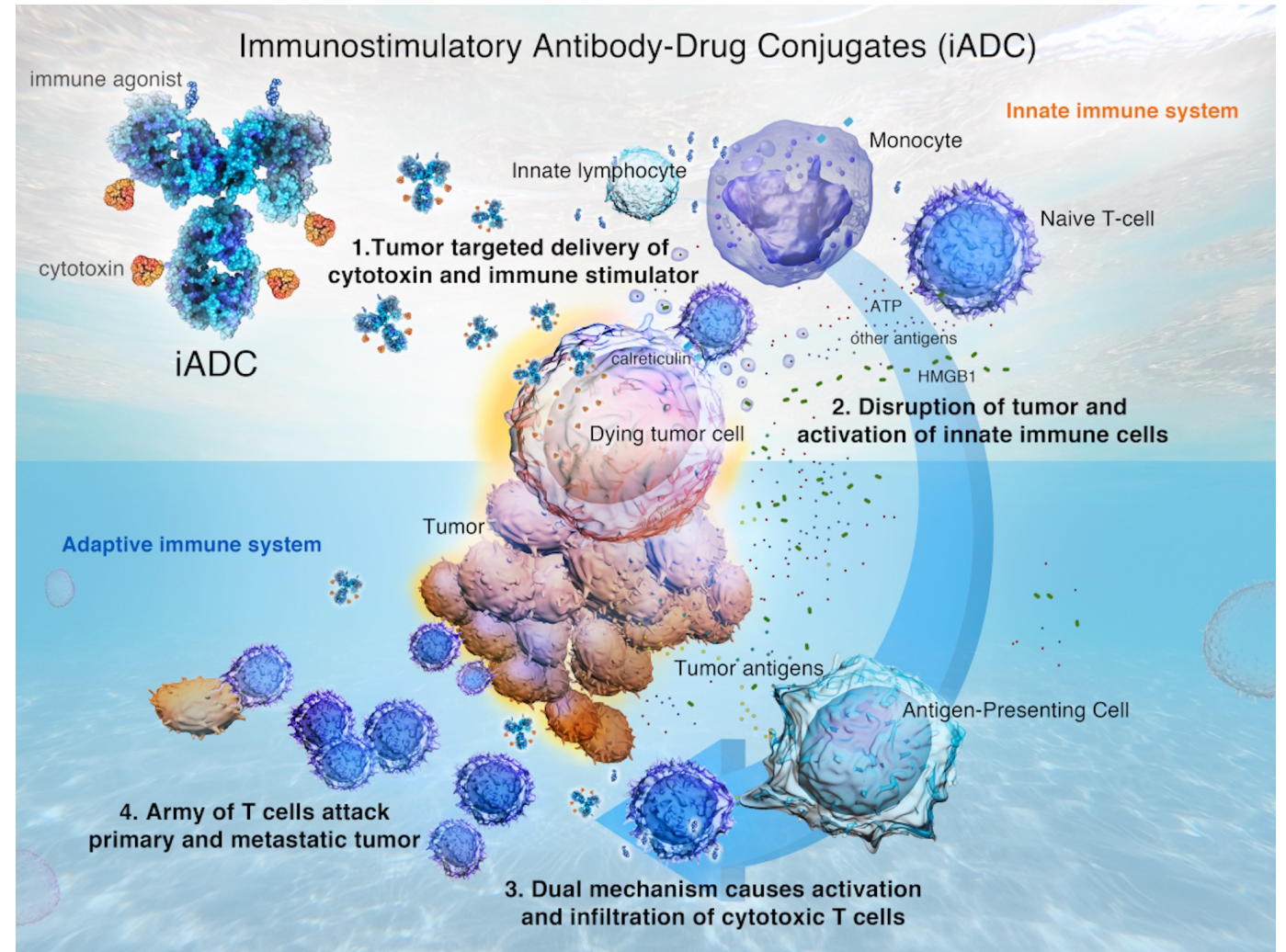
New Modality for Cold Tumors: Immunostimulatory Antibody Drug Conjugate (iADC)

Strategic iADC Collaboration

June 27, 2022



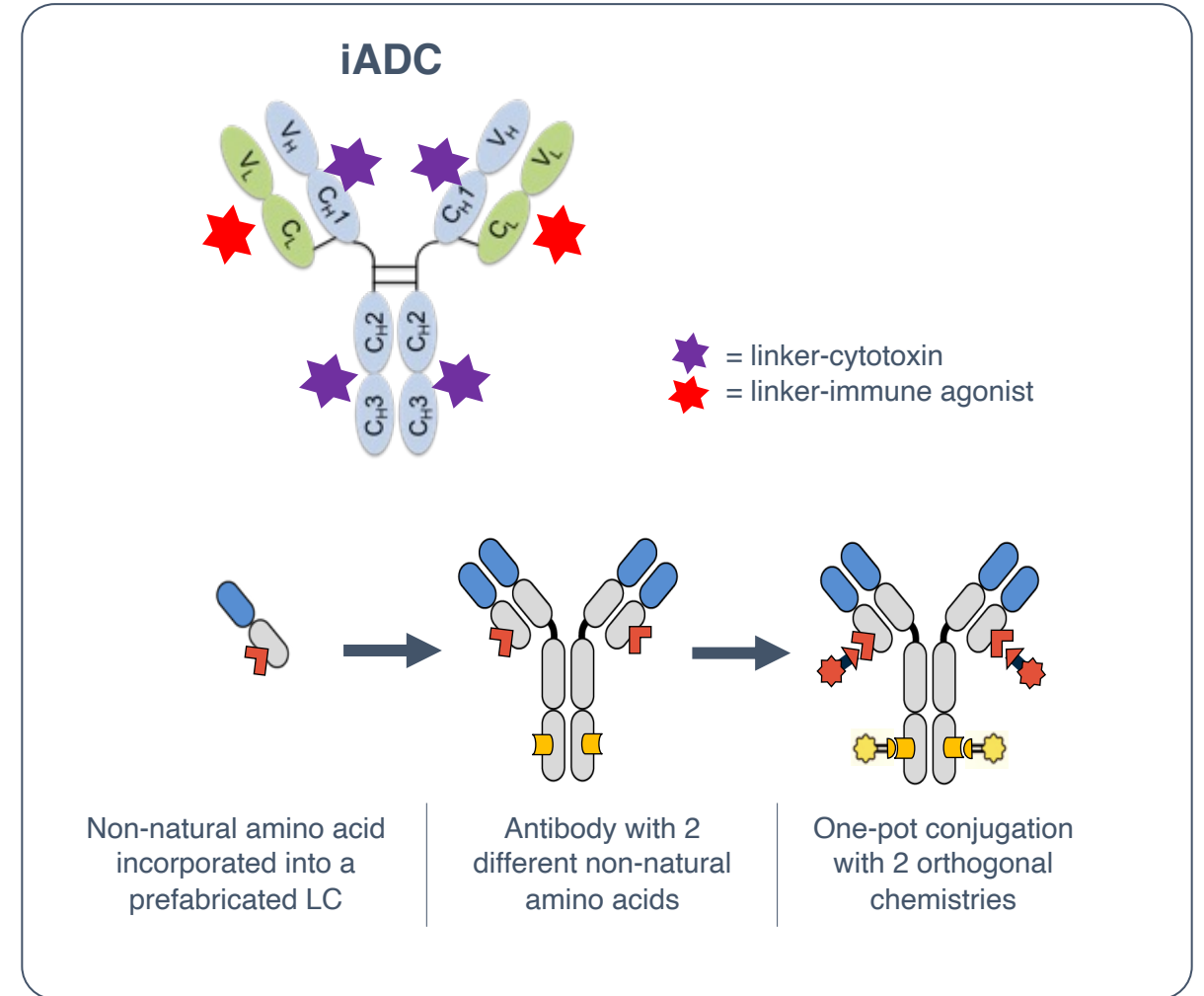
- Develop iADCs for up to **three targets**
- Builds on success of Sutro's **ADC platform and engineering expertise**
- Leverages Astellas' primary focus on **immuno-oncology**



Sutro's Next-Generation Tumor Targeting Immunostimulatory ADC

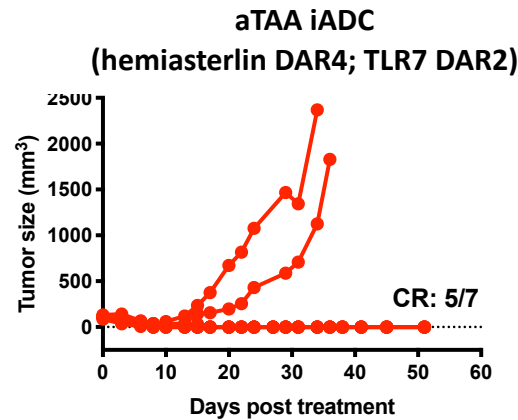
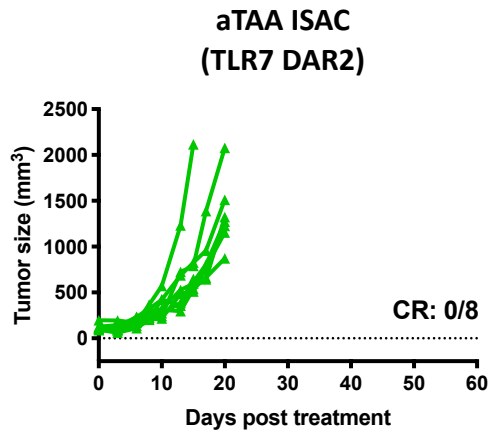
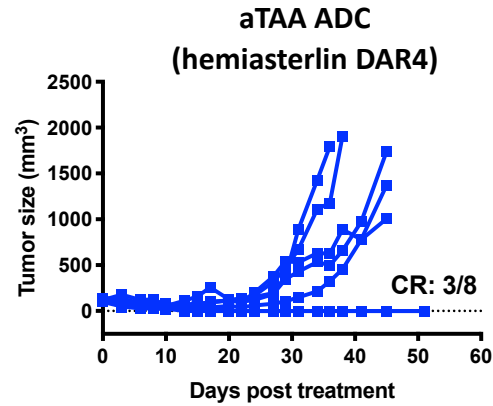
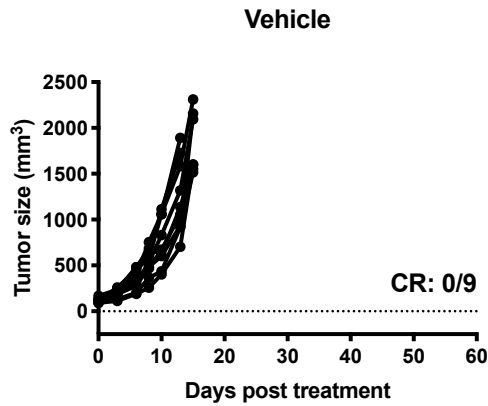
A systemically administered monotherapy that drives anti-tumor immunity

- Precision technology for **dual conjugated immunostimulatory antibody drug conjugate**
- POC molecule enables simultaneous and precise tumor targeting of a cytotoxin and a novel toll-like receptor (e.g. TLR) agonist with **systemic delivery**
- Novel design intended to prime an **adaptive anti-tumor response** in a systemic monotherapy
- Potential to reprogram the patient's tumor microenvironment and generate **protective anti-tumor immunity**



Data Presented at the World ADC Meeting in London, 3/2020

Superior Anti-Tumor Response with Single Dose of iADC



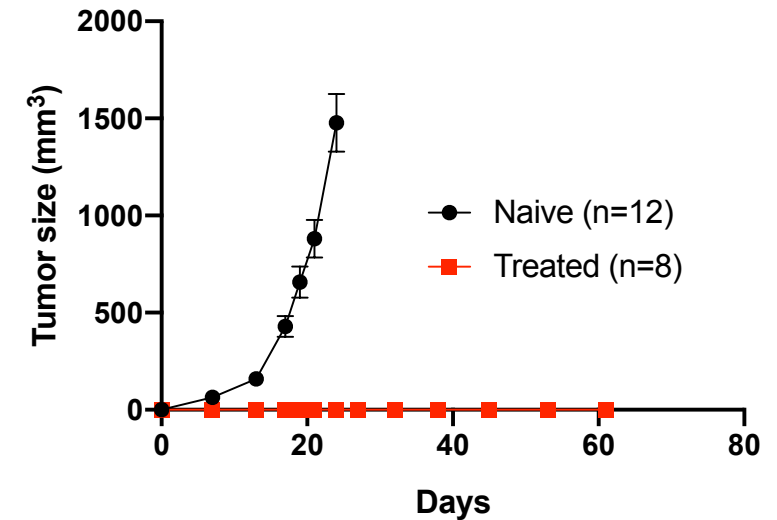
iADC consists of a **TAA-directed mAb** conjugated to:

- 4 **CatB-Hemiasterlin** linker-cytotoxic payloads
- 2 **CatB-TLR7 agonist** linker payloads

ADC: 4 CatB-Hemiasterlin

iSAC: 2 CatB-TLR7 agonist

Rechallenge

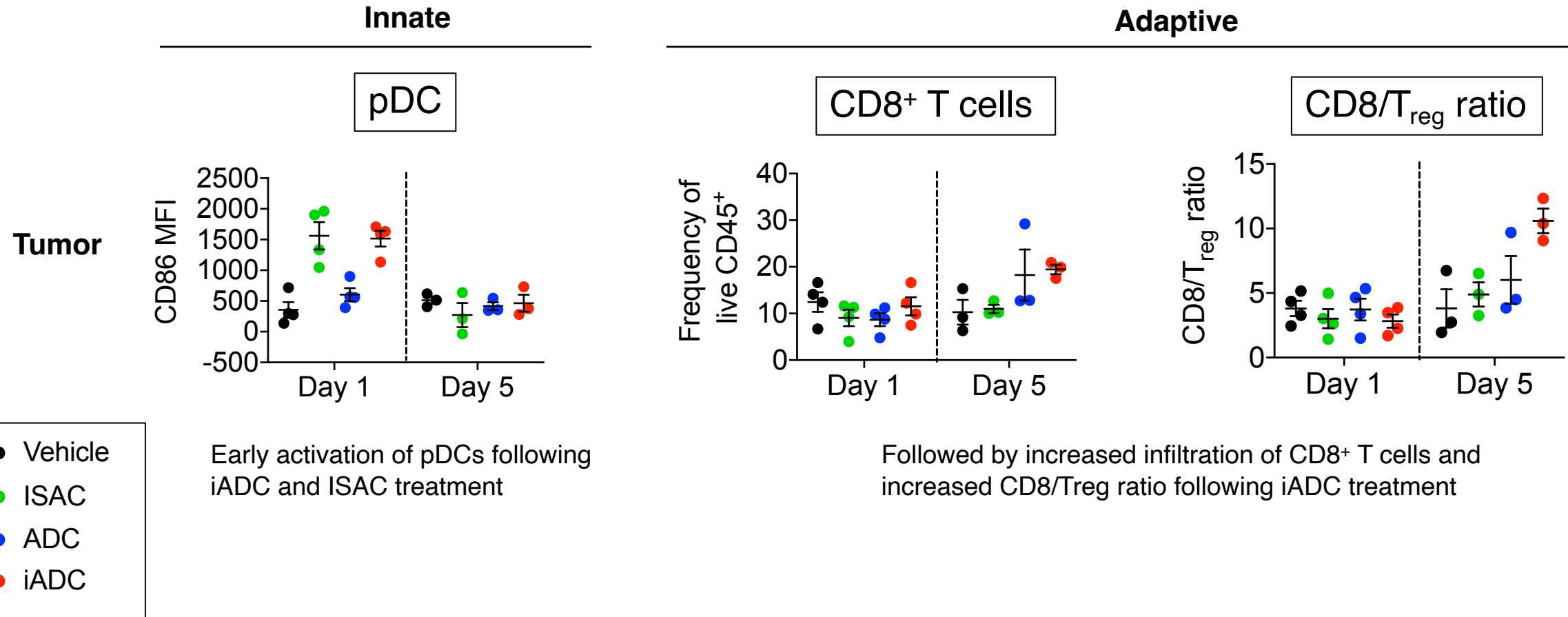


→
All treated animals that achieved CR were re-challenged with MC38-hTAA cells

iADC showed enhanced activity vs. ADC alone based on higher number of animals with complete responses and durable anti-tumor immunity

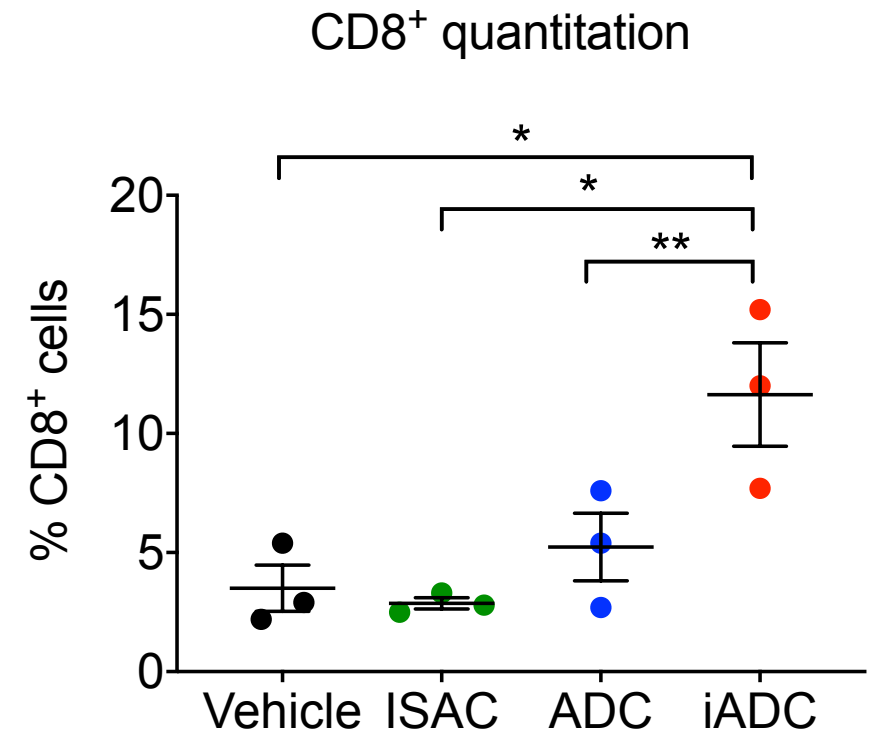
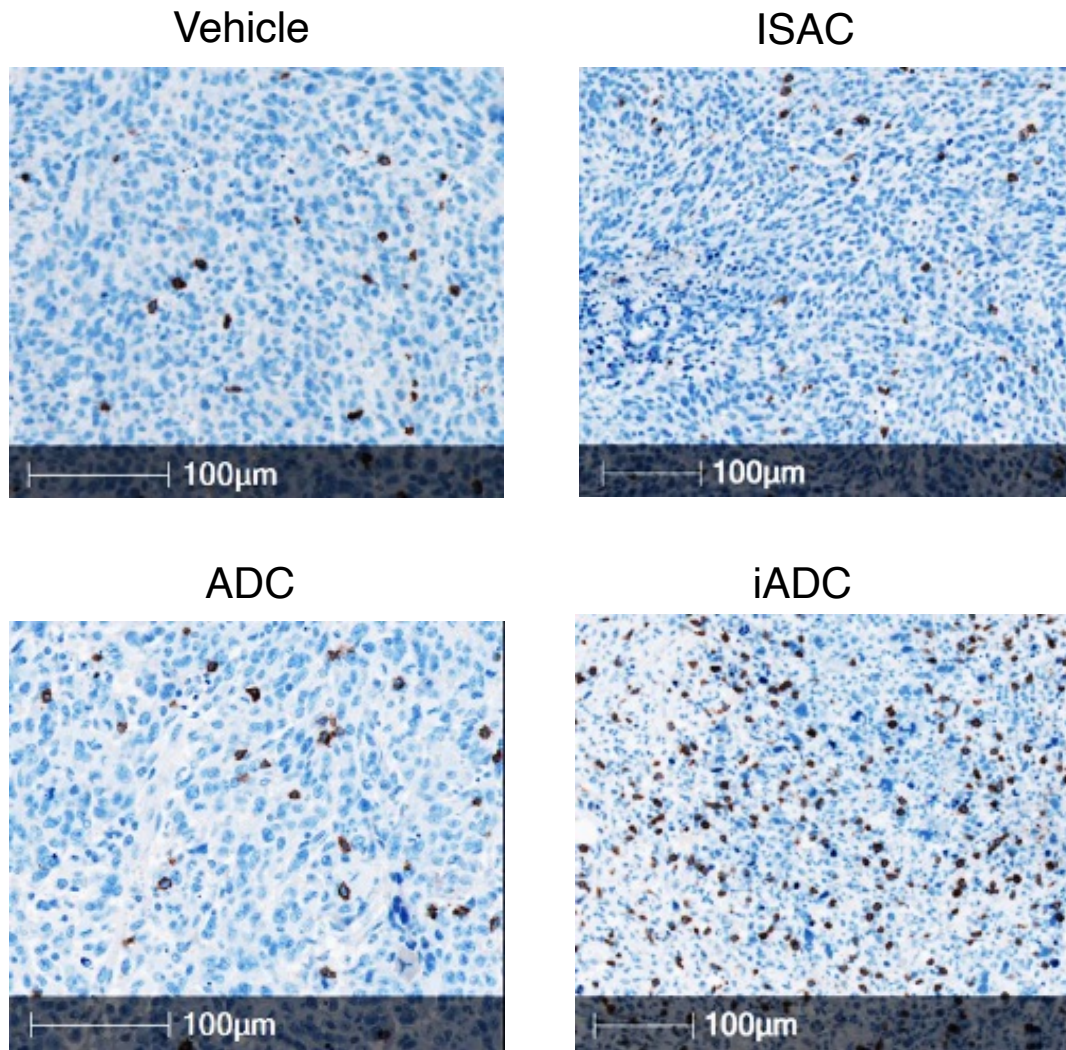
Data Presented at FOCIS Meeting June 2022

iADC Engaged Both Innate and Adaptive Immune Compartments in hTAA-MC38 Tumor Bearing Mice




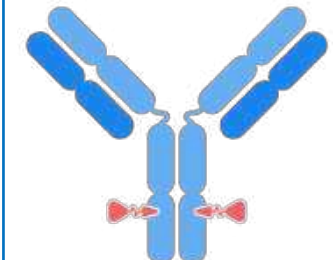
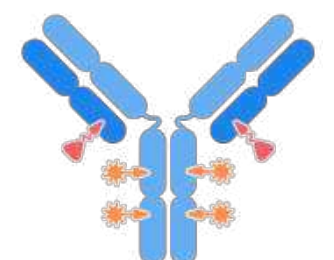
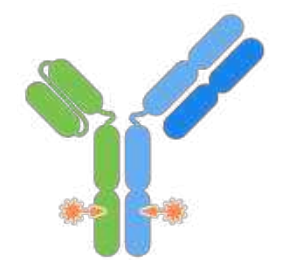
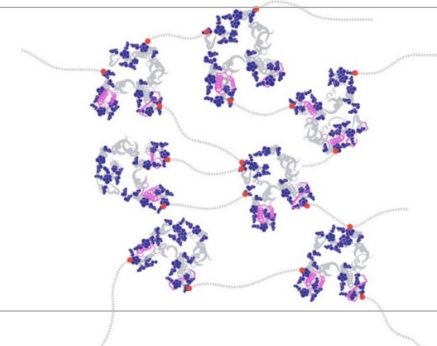
Single 10 mg/kg dose
Data Presented at FOCIS Meeting June 2022

iADC Increased CD8+ T cells in Tumor Microenvironment



Data Presented at FOCIS Meeting June 2022






Drug Discovery Platform Can Enable Multiple Modalities

	Cytokine Derivative	Conjugated Antibody			Conjugate Vaccines
Modality	<i>Prodrug Cytokine Derivative</i>	<i>ADC or ISAC</i>	<i>iADC</i>	<i>Bispecific ADC</i>	<i>Multi-valent Conjugate Vaccine</i>
Target	Tumor Selective Mask	Tumor Antigen	Tumor Antigen	Dual Tumor Antigens	T-cell / B-cell Antigens
Structure	 <p>cytokine Releasable mask</p>				
Drug Properties	Prodrug cytokine targeting functional cytokine to tumor	ISAC: Immune-stimulating ADC: targeting novel payloads	Site-specific dual drug conjugate with complementary modalities (TME modulator +/- immune modulator)	Enhanced tumor targeting of cytotoxic payloads	Precise, site-specific conjugation sites on protein carrier, conjugated to polysaccharide antigens

iADC = immunostimulatory ADC, ISAC = immune-stimulating antibody conjugate

Multiple Product Candidates in Development Enabled by Sutro's Platform

Modalities in Clinic: Antibody-Drug Conjugate, Cytokine derivative, Vaccine

PROGRAM	MODALITY/TARGET	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/1B	PHASE 2/3	WORLDWIDE OR GEOGRAPHIC PARTNER	
SUTRO-LED PROGRAMS								
Luveltamab tazevibulin (STRO-002)	FolRα Antibody-Drug Conjugate (ADC)	Ovarian Cancer	<i>Fast Track Designation</i>					 天士力生物 TASUI BIOPHARMA (Greater China Rights)
		Ovarian Cancer (bevacizumab combo)						
		Endometrial Cancer						
		CBF/GLIS2 Pediatric AML	<i>Orphan Drug & Rare Pediatric Disease Designation</i>					
		Adenocarcinoma, NSCLC						
STRO-001	CD74 ADC	B-cell Malignancies	<i>Orphan Drug Designation</i>				 Eli Lilly (Greater China Rights)	
STRO-003	ROR1 ADC	Solid Tumors Cancers						
STRO-004	Tissue Factor ADC	Solid Tumors						
PARTNER PROGRAMS								
VAX-24	24-Valent Conjugate Vaccine	Invasive Pneumococcal Disease					 VAXCYTE protect humankind	
MK-1484	Selective IL-2 Agonist	Advanced or Metastatic Solid Tumors					 MERCK	
Undisclosed	Immunostimulatory ADCs (iADCs)	Cancers					 astellas	

You May Also Have Interest in

Day 1 2:00pm
Discovery Chemistry

Day 1 5:30pm
Plenary

Day 1 6:00pm
Poster Session

Day 2 2:00pm
Translational

Day 2 12:00pm
Manufacturing &
Supply Chain

Discovery of Novel
Linker
Payloads for Site-
Specific ADCs with
Improved Efficacy
& Therapeutic Index

Krishna Bajjuri

Precision
Engineering for
Enhanced TI:
Designing STRO-
004, a Tissue Factor
Targeted ADC for
Broadened Efficacy
& Safety

Alice Yam

Site-specific Dual
Conjugation
Enabled by an
Integrated in vivo / in
vitro Antibody
Production Platform

Miao Wen

Preclinical
Development of
STRO-003, α ROR1
Targeting ADC For
Treatment of
Hematologic & Solid
Cancers

Helena Kiefel

Stress Free ADC
Production with Cell-
Free Technology

Ganesh
Vissvesvaran

Acknowledgment



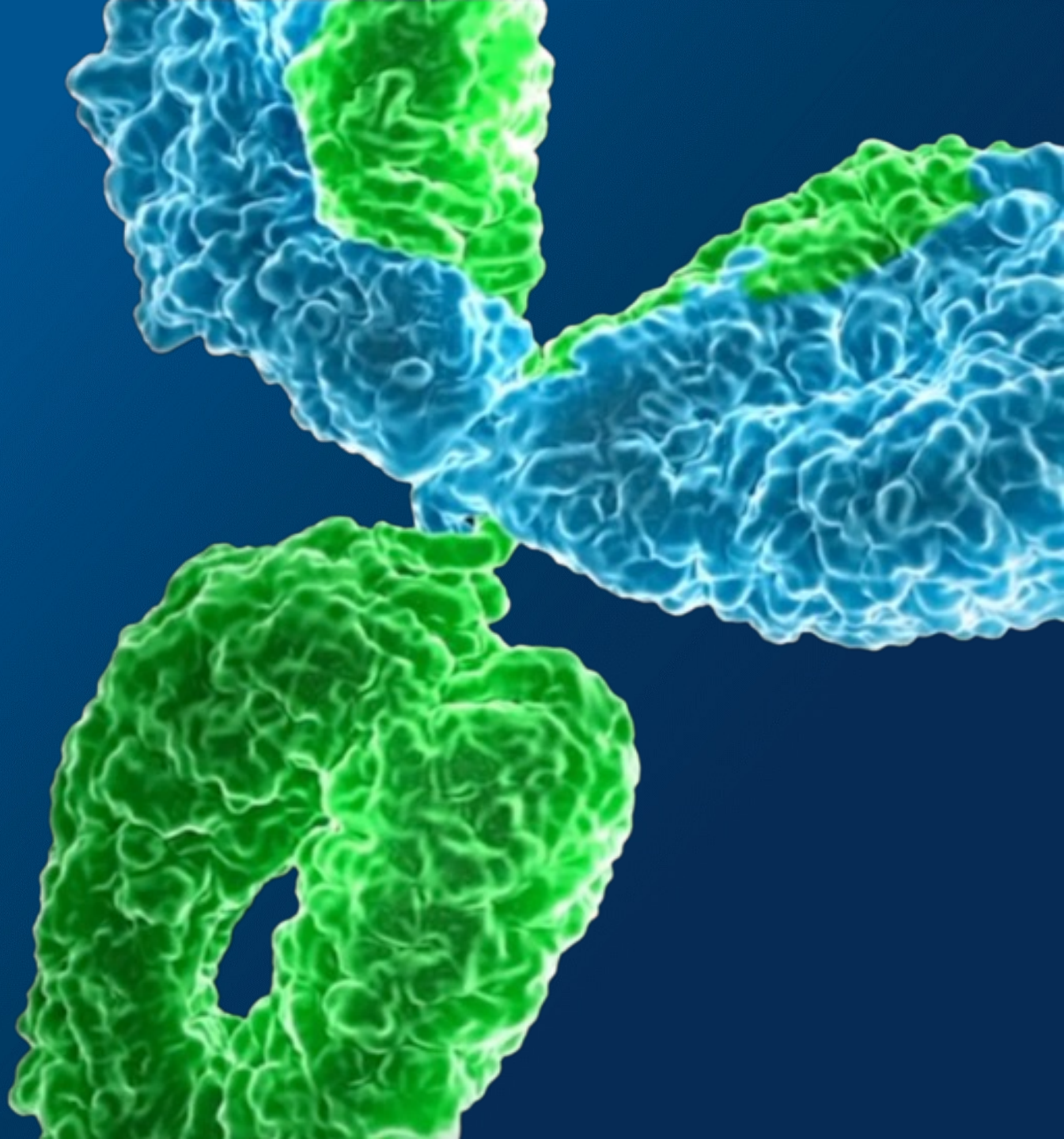
**Exceptional
TEAM**

**Robust
PLATFORM**

**Compelling
PIPELINE**

**Delivering
FOR PATIENTS**





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