

Process Development and Biological Evaluation of Antibody Drug Conjugate Based on a Novel Site-Specific Chemical Conjugation Platform



BIO-PHARMA SERVICES



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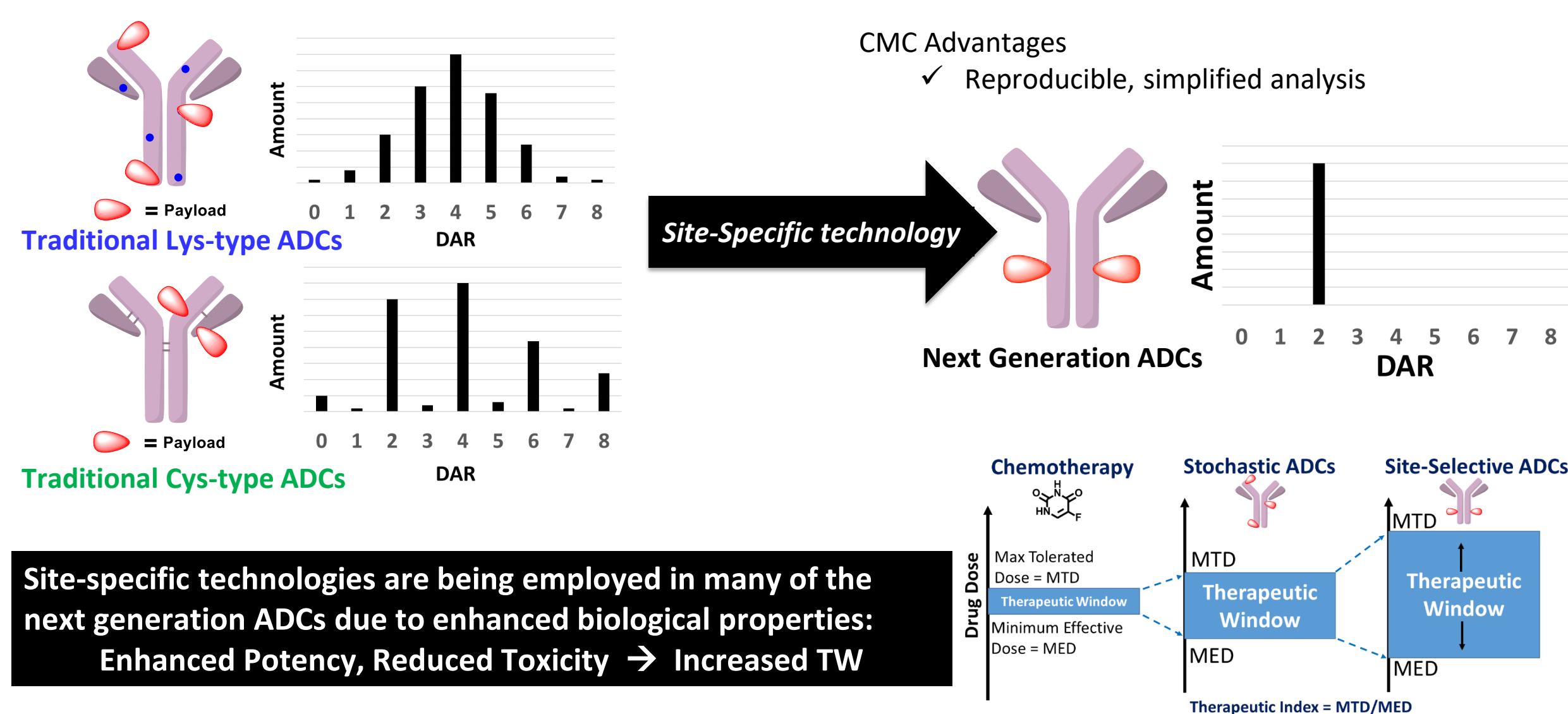
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Ajinomoto Bio-Pharma Services



Ajinomoto OmniChem and Ajinomoto Althea were integrated to "Ajinomoto Bio-Pharma Services"

Introduction



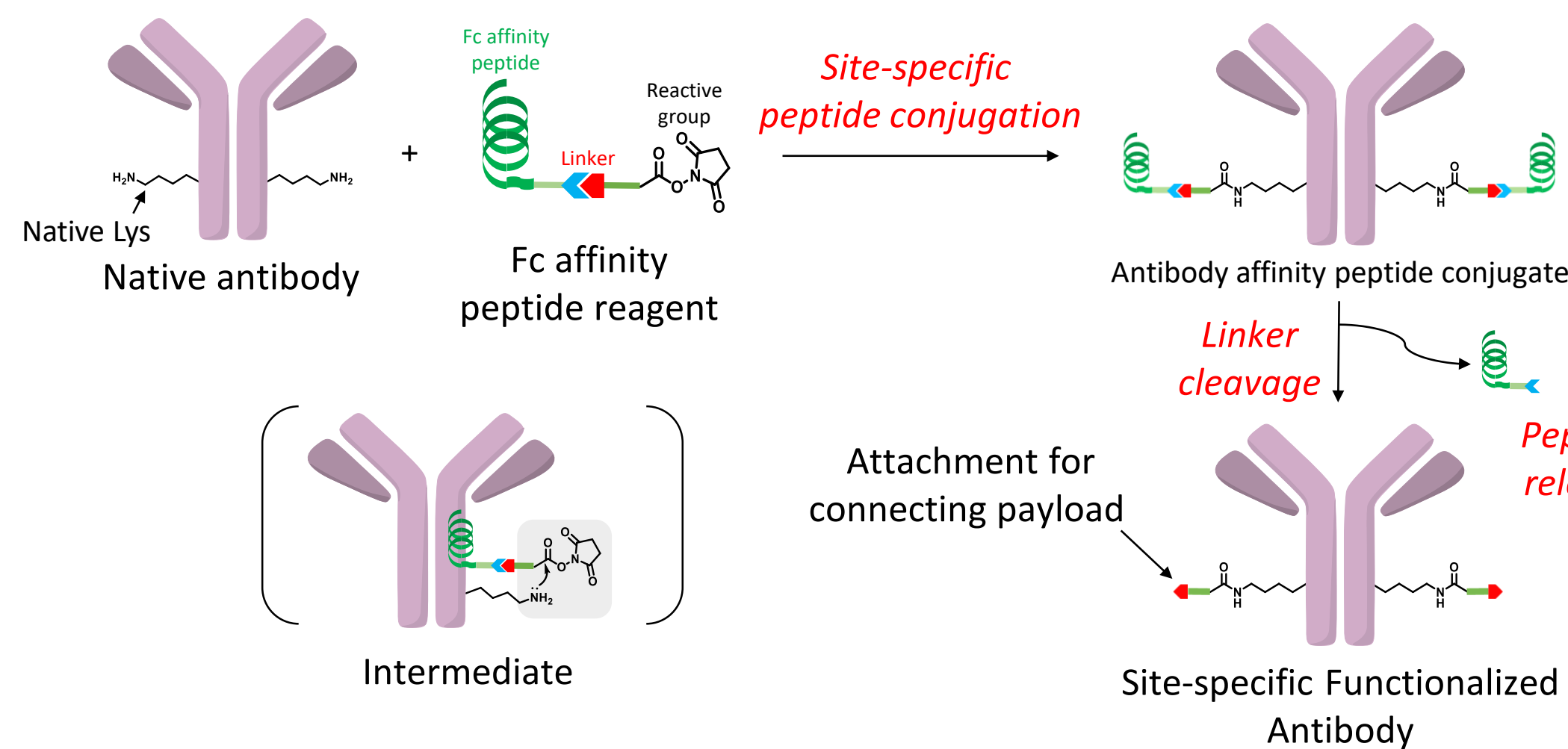
ADCs employ a monoclonal antibody (mAb) to deliver a potent cytotoxic payload selectively to cancer cell which can increase efficacy and decrease toxicity in comparison to traditional chemotherapeutic cancer treatments.

With first generation stochastic conjugation technologies, random conjugation of payload, DAR (Drug Antibody Ratio) and varying binding position occurs.

Next Generation ADC needs: homogeneous DAR and conjugation position

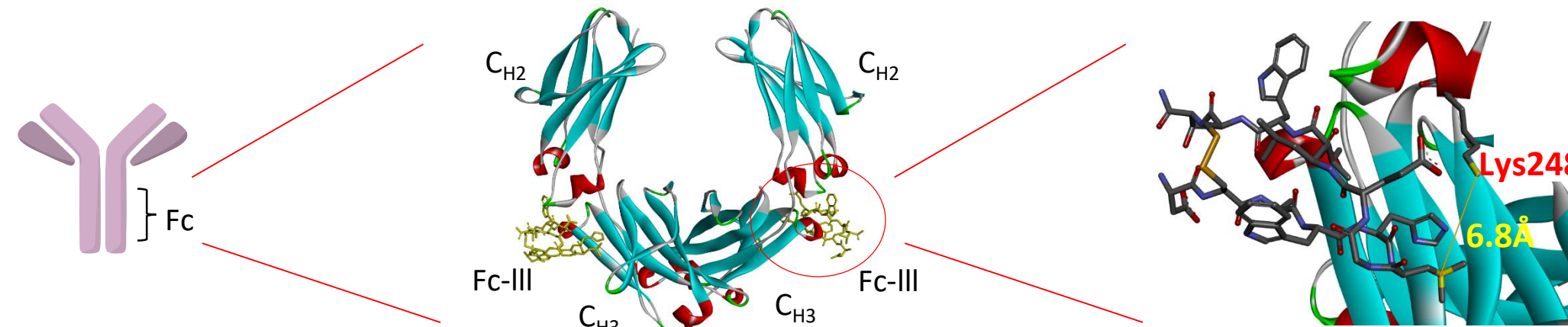
Methods

1. Concept of AJICAP™ Technology¹⁾²⁾



2. Determine Target Lysine Residue

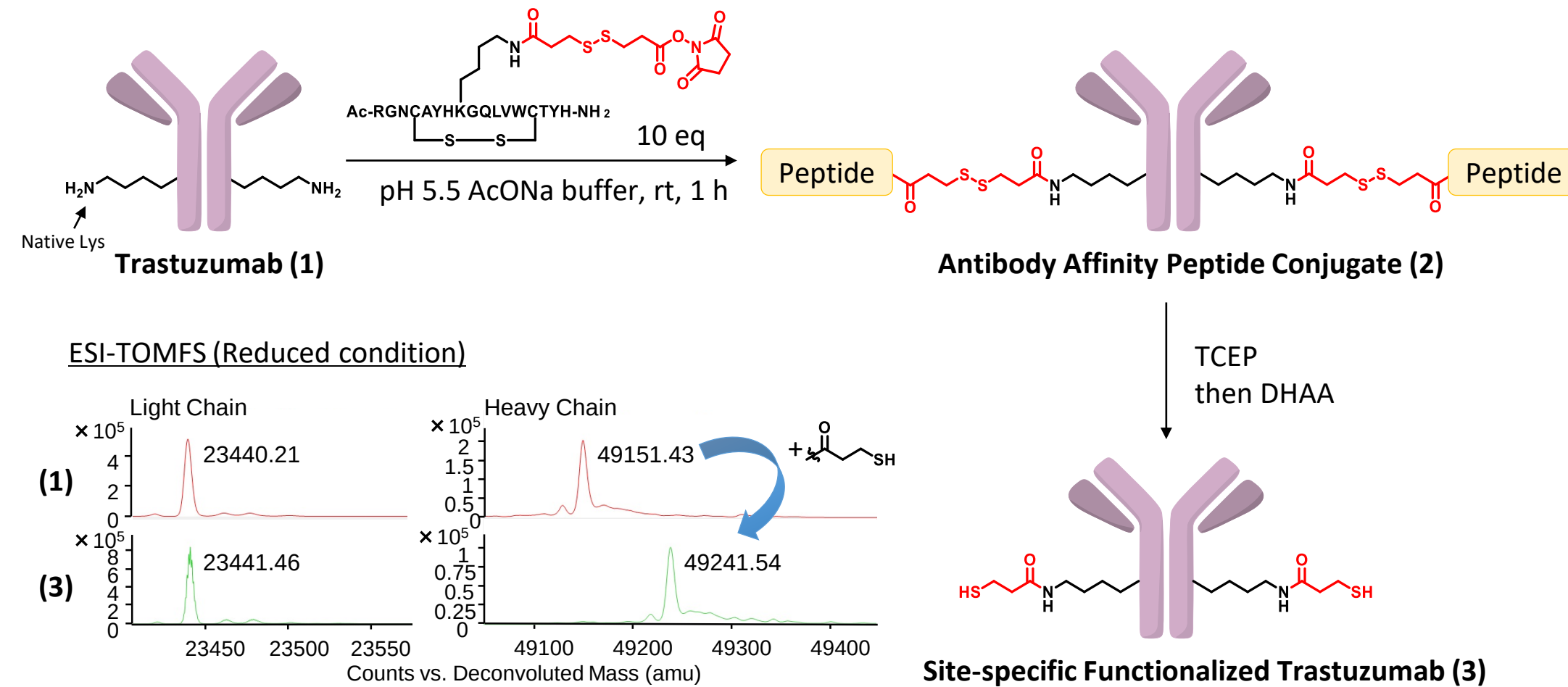
Human IgG Fc and Fc-III peptide co-crystal structure



Fc-III³⁾
✓ K_D 20 nM
✓ 13 amino acids

An example of peptides for AJICAP⁴⁾
✓ K_D 4 nM
✓ 17 amino acids
✓ Selected by phage display

3. Synthesis of Site-Specific ADC by AJICAP™

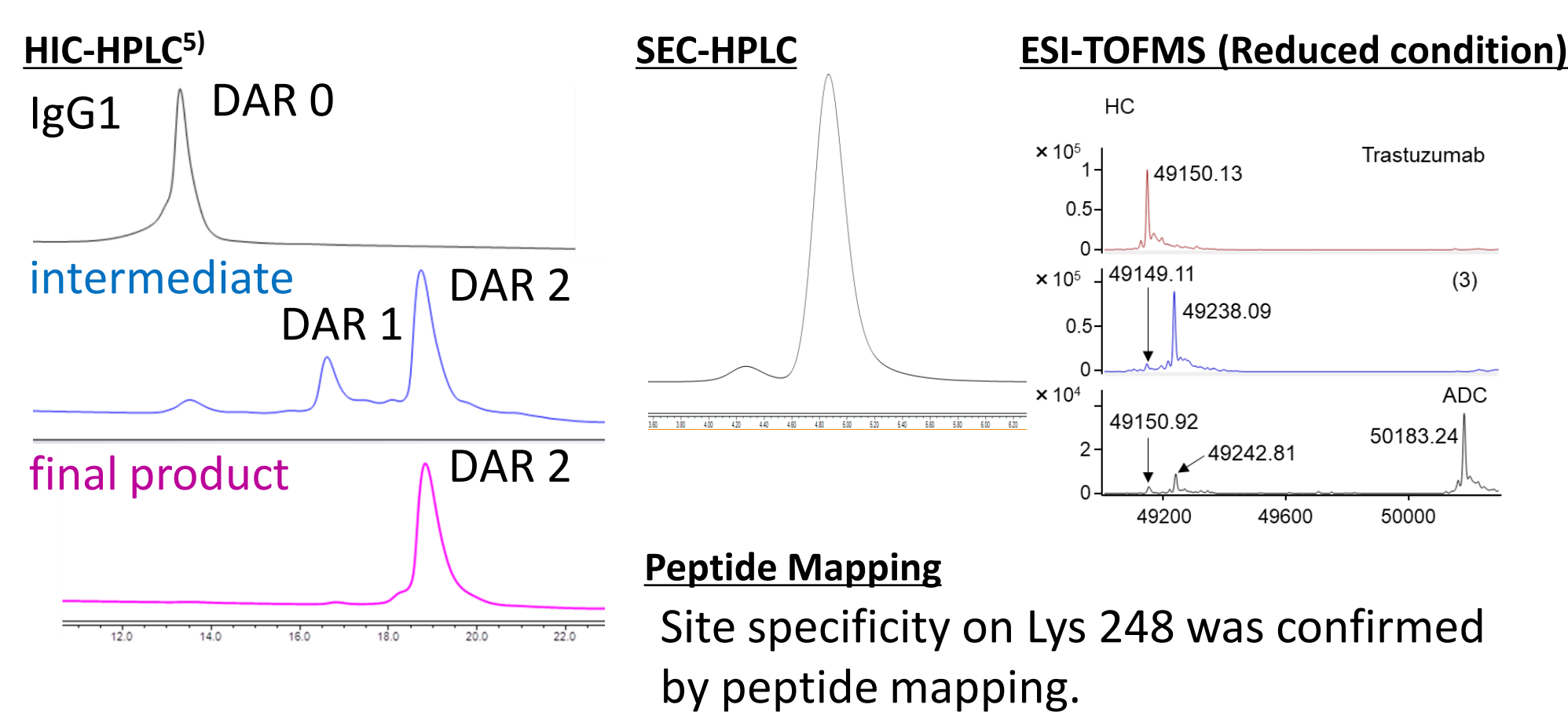


Significant Advantages of AJICAP™ Technology

- Straightforward CMC**
 - Direct modification of intact antibody
 - No genetic modification required
- Enhancement of Therapeutic Window compared to random ADCs**
 - Site specific, controlled DAR 2
- Wide drug-linker compatibility: reactive group compatibility (thiol, alkyne, azide, etc)**
- High productivity, short conjugation reaction times, ease to manufacture**

Results and Discussion

1. Analytical Results of AJICAP-ADC



2. Materials

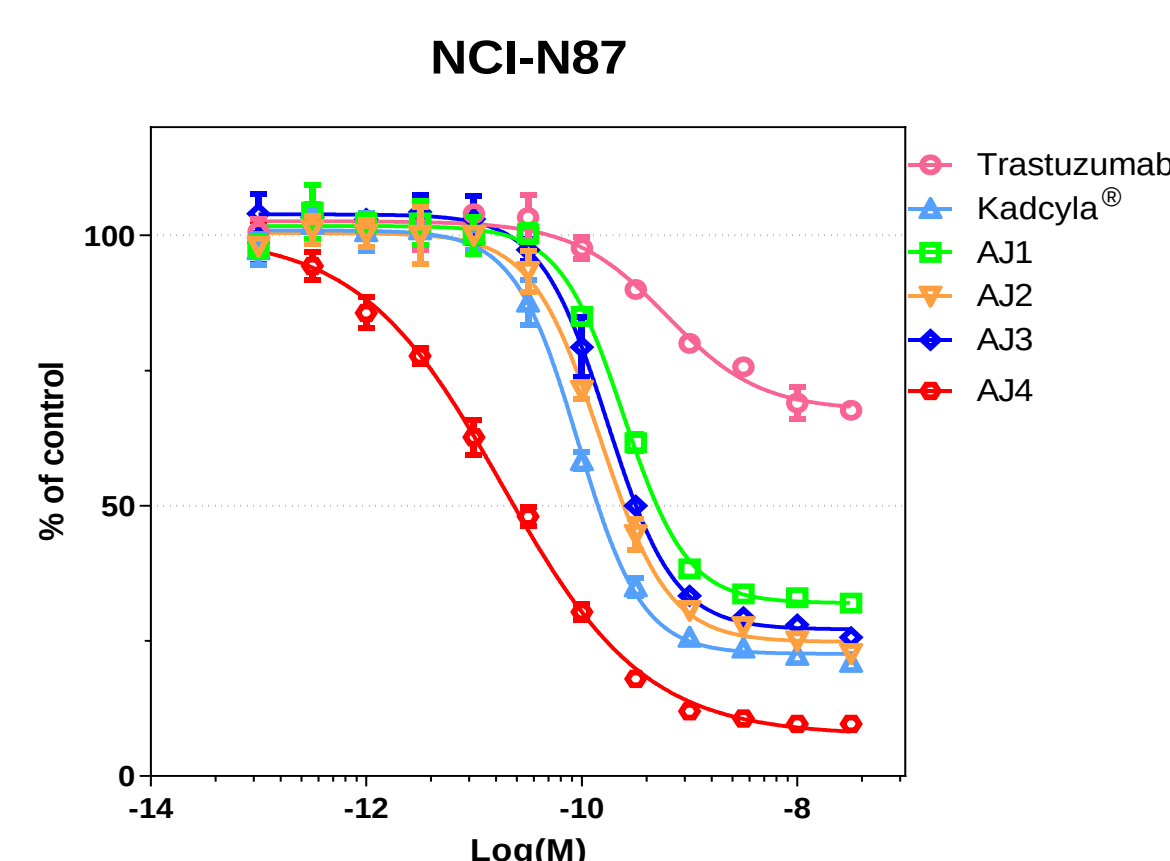
Definition of ADCs	mAb	Conjugation	Attachment	Payload
AJ1	Trastuzumab	AJICAP	Thiol-Maleimide	DM1
AJ2				MMAE
AJ3				MMAF
AJ4				PBD
Kadcyla®		Stochastic		DM1

3. Capability of AJICAP™

Isotype	mAb	Attachment	Structure	Linker	Payload
IgG1	Trastuzumab	Thiol (-maleimide)		Cleavable	DM-1
	Rituximab				MMAE
	Adalimumab	Azide (-cycloalkyne)		Non-cleavable	MMAF
	X company-mAb A (client project)				PBD
IgG2	X company-mAb B (client project)	Aldehyde & (-hydroxylamine)			α-amanitin
	Y company-mAb (client project)				Confidential payload (Client project)
IgG4	Denosumab				
	Dupilumab				

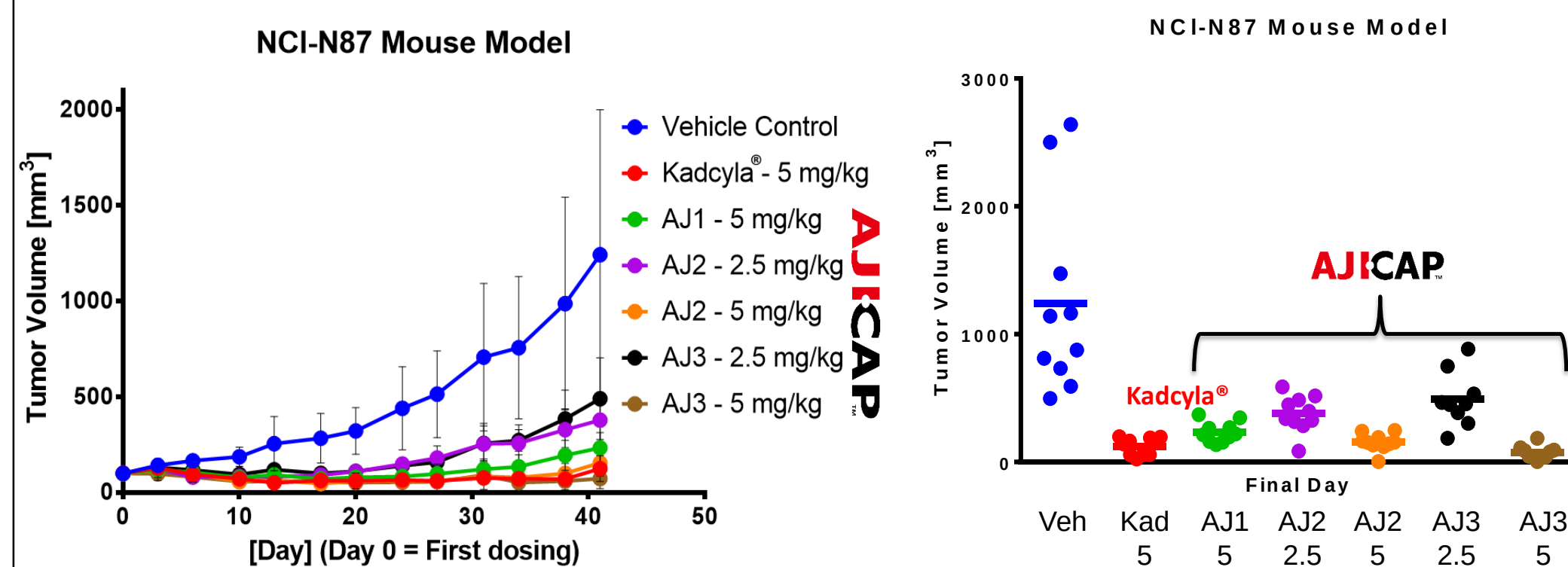
AJICAP technology is compatible with a wide variety of mAbs, attachments, linkers, and payloads.

4. In Vitro Cytotoxicity



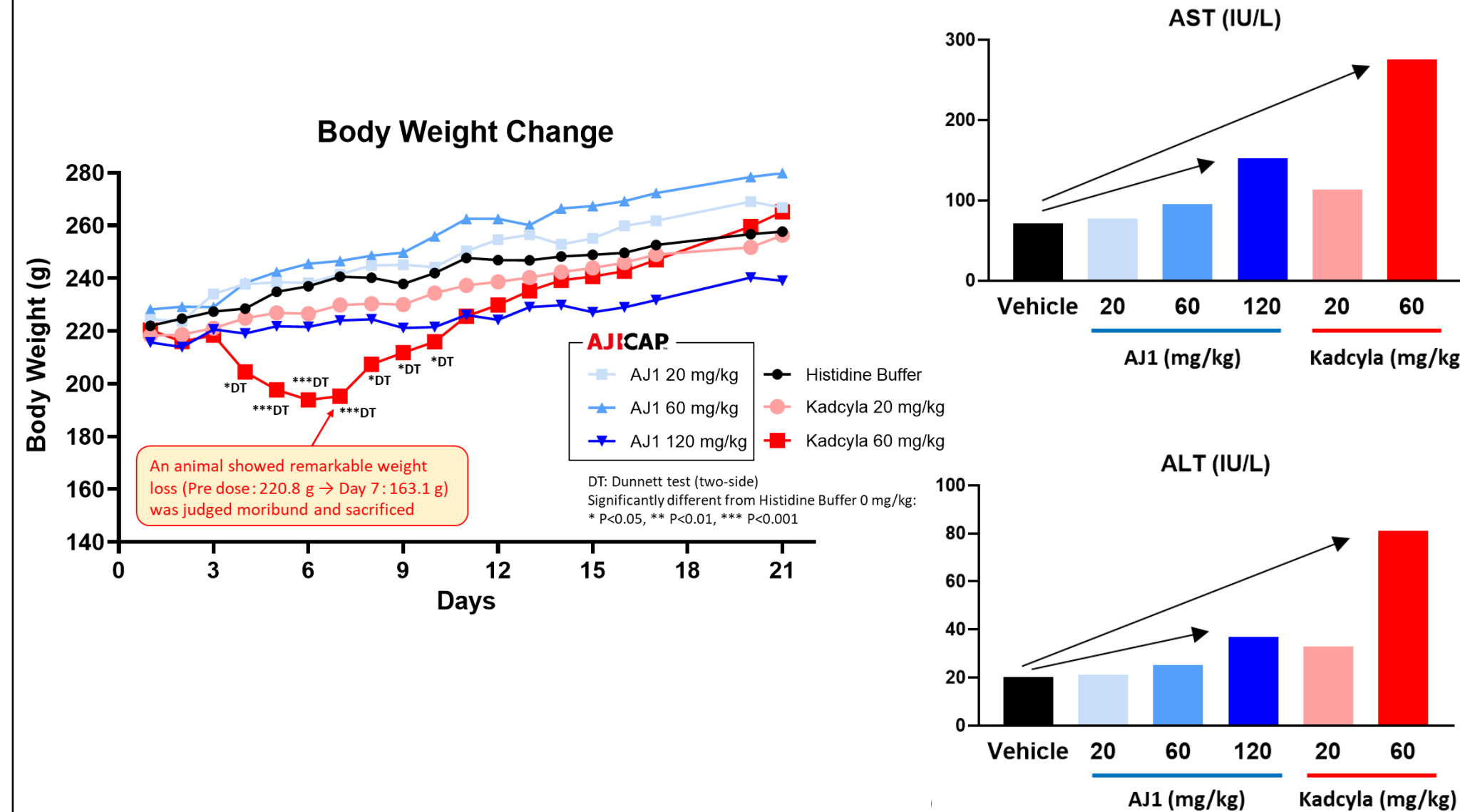
AJICAP ADCs have in vitro cytotoxic activity reflecting payload cytotoxicity.

5. Mouse Xenograft Model

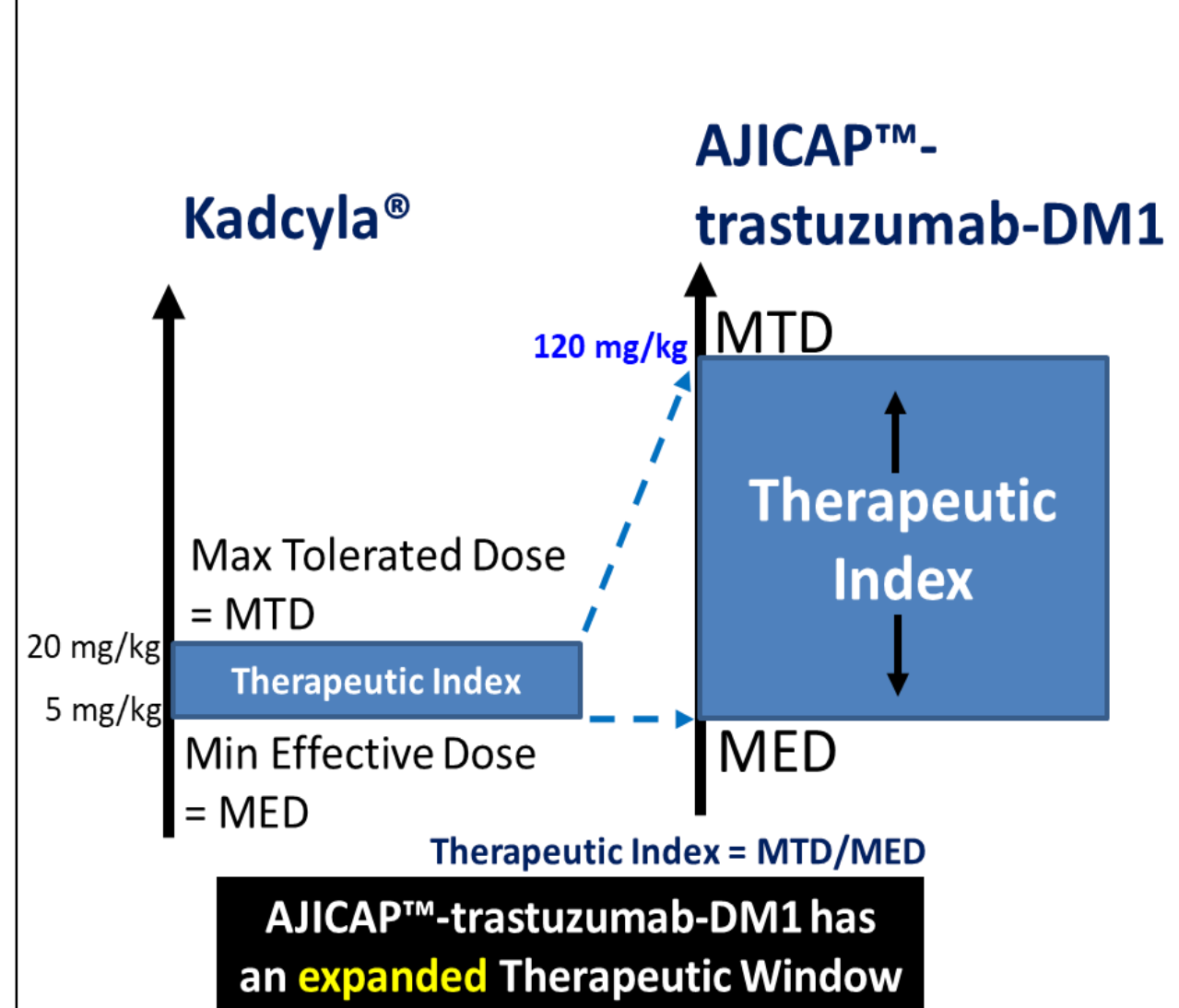


5 mg/kg AJICAP™ ADC shows tumor inhibition comparable to Kadcyla®

7. Safety Study in Rats

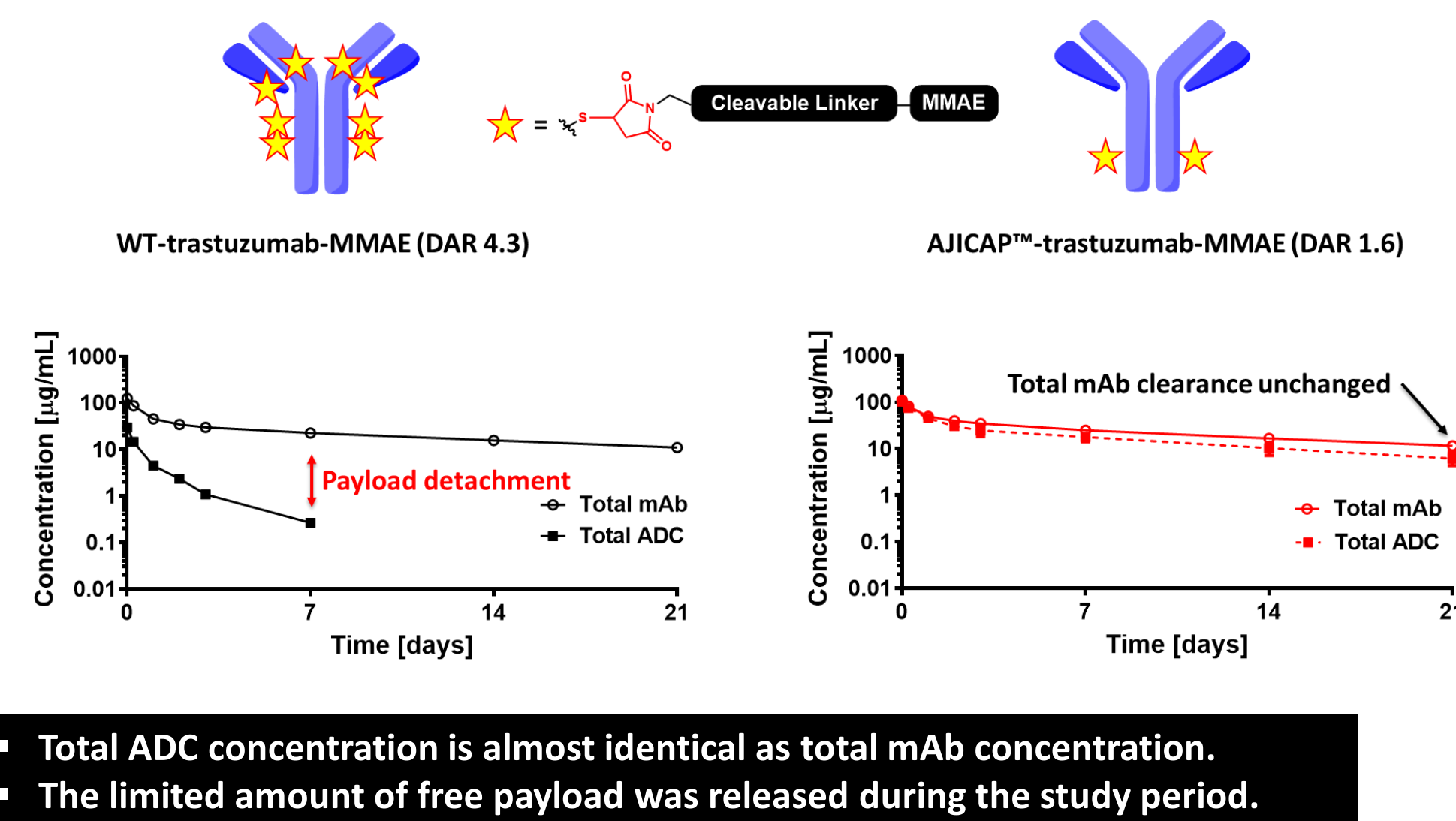


8. Therapeutic Index of AJICAP™-ADC



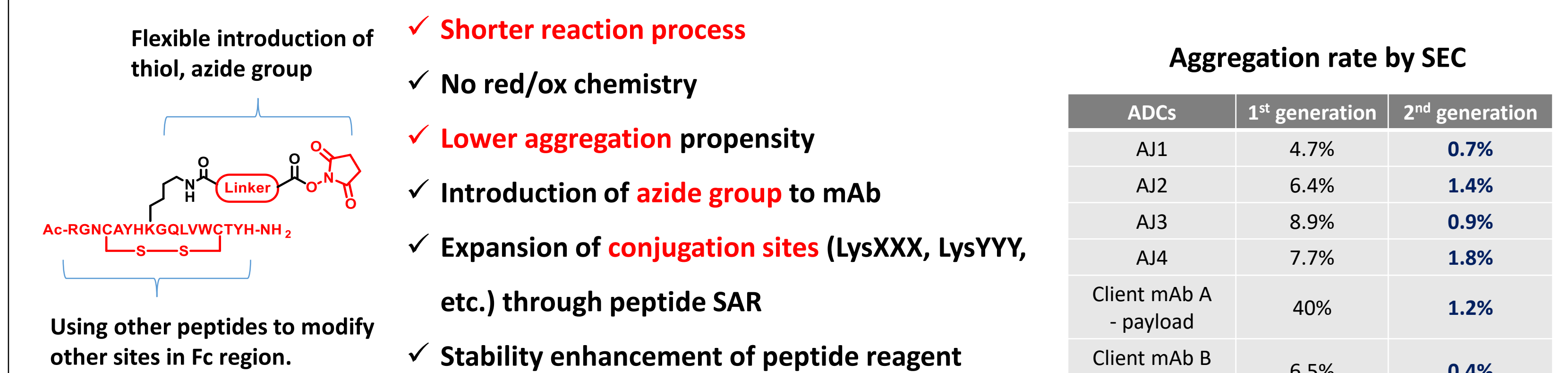
AJICAP™-trastuzumab-DM1 has an expanded Therapeutic Window

9. Pharmacokinetics in Rats



Total ADC concentration is almost identical as total mAb concentration. The limited amount of free payload was released during the study period.

10. A Glance at Second Generation AJICAP™ Technology



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