Dolasynthen:

A Novel, Homogeneous Auristatin F Hydroxypropyl Amide Antibody-Drug Conjugate Platform

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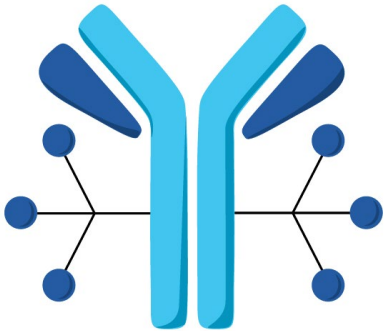
Dolasynthen ADC Platform

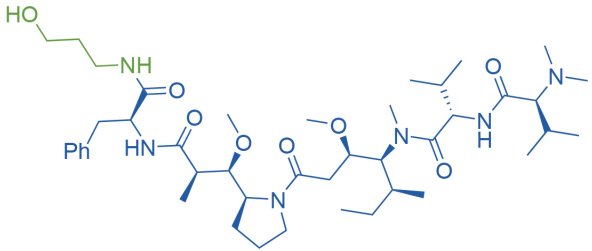
Overview of the talk



- Dolasynthen is a novel, fully synthetic ADC platform based on the AF-HPA payload
- Optimization in 3 Phases:
  - Phase 1 – Scaffold optimization
  - Phase 2 – Impact of Bioconjugation Technologies
  - Phase 3 – Applicability across antibodies and targets
- Herein we demonstrate that Dolasynthen platform enables
  - Precise modulation of the drug-to-antibody ratio (DAR)
  - Flexibility with bioconjugation technology
  - Selection of optimal ADCs for clinical development

Proprietary Auristatin DolaLock Payload with Unique Pharmacology

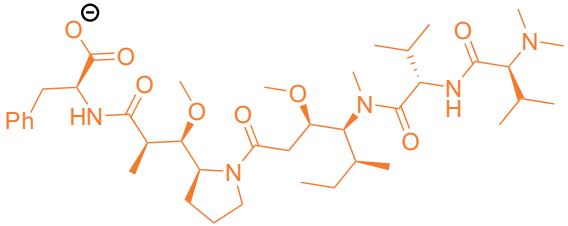
Auristatin F-HPA (AF-HPA)



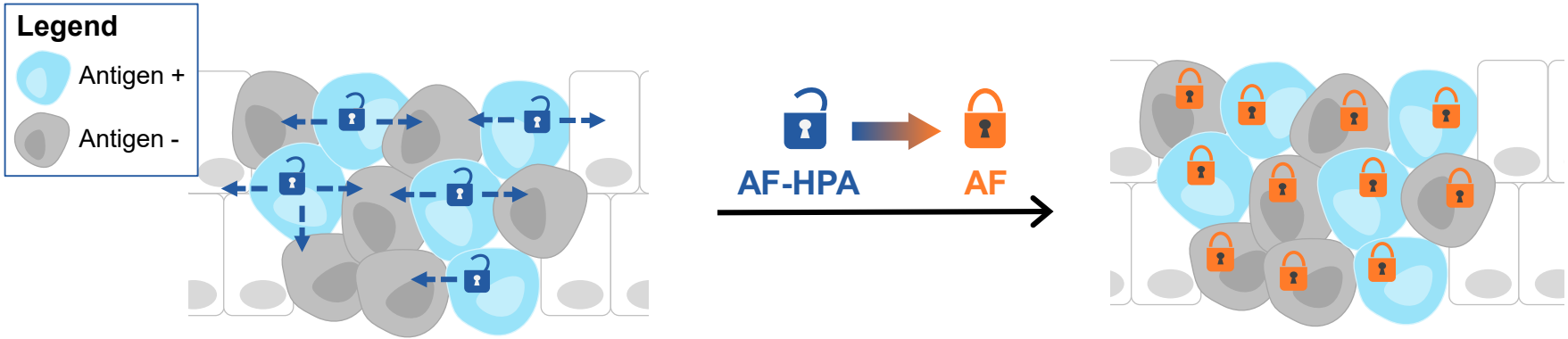
Bystander Killing

Metabolic Conversion in Tumor Cell

Auristatin F (AF)



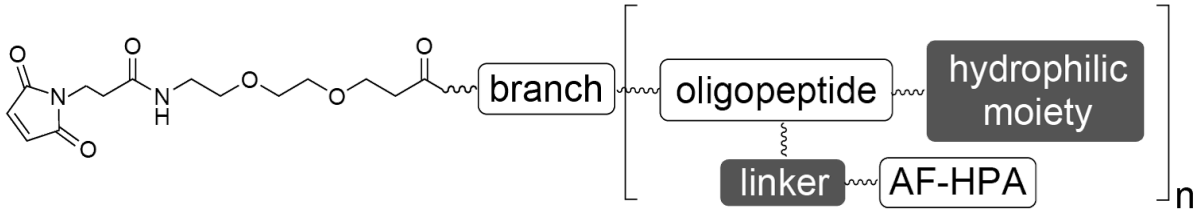
No Bystander Killing
Not a Pgp substrate



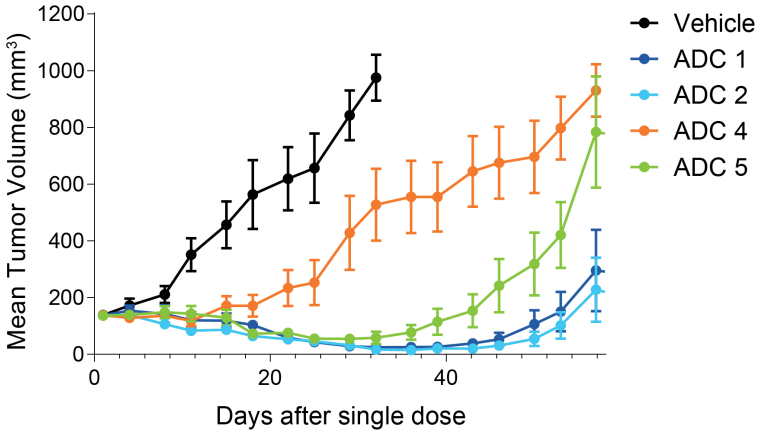
Presented at the AACR, Chicago, 2018, Abstract No.754

Phase 1: Modular Scaffold Optimization

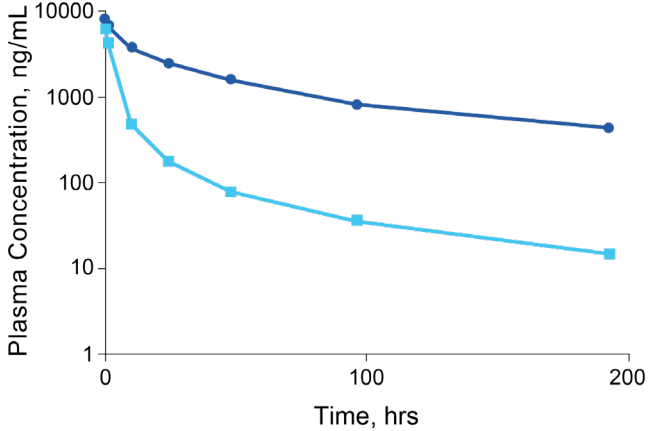
- Vary linker and hydrophilic moiety
- Determine optimal scaffold *in vivo*



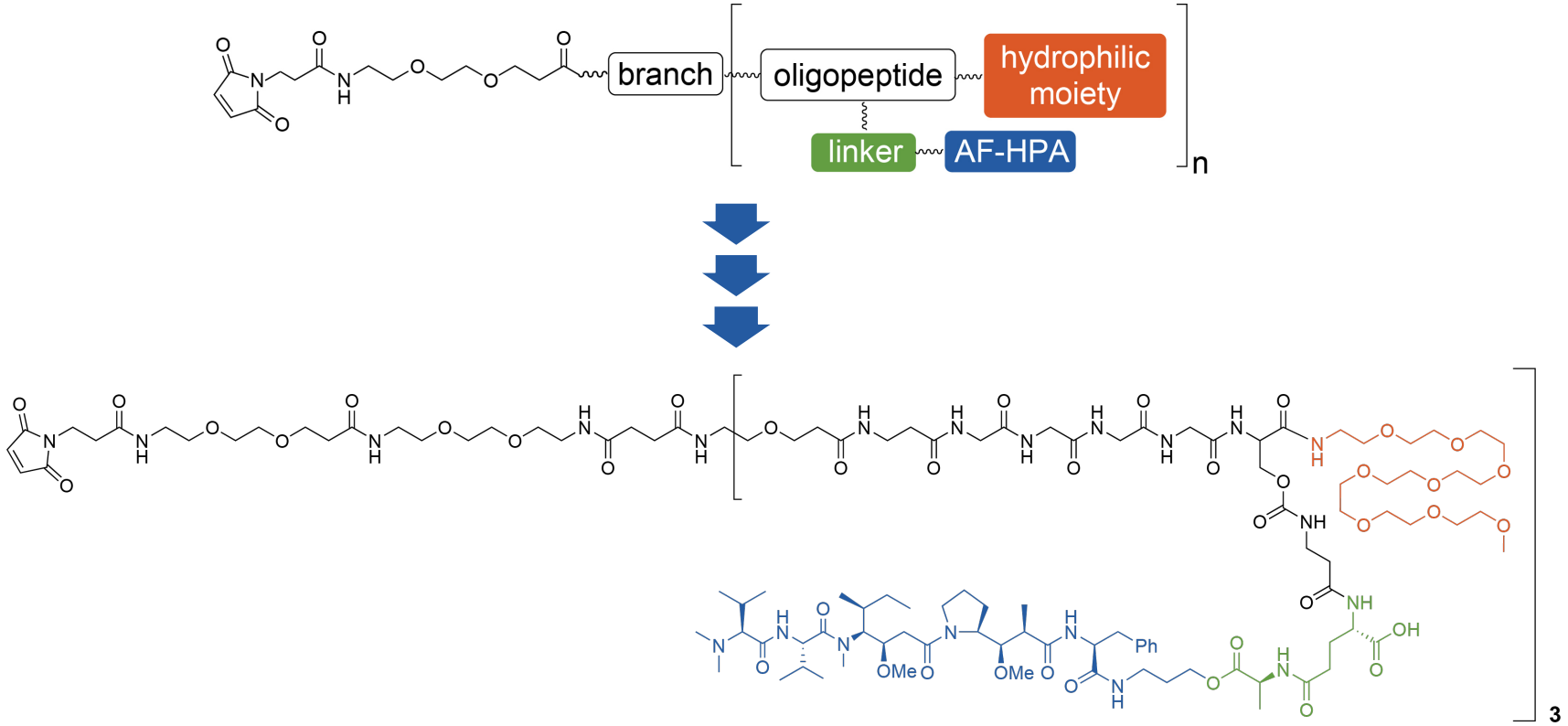
Anti-Tumor Efficacy in Xenografts



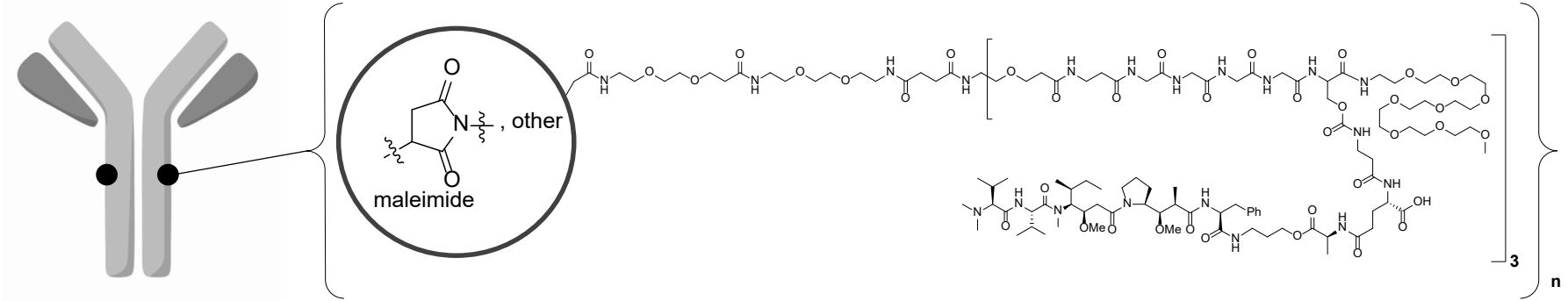
Pharmacokinetics in NHP



Optimized Dolasynthen Trimeric Scaffold



Phase 2: Screening Bioconjugation Technologies and Sites

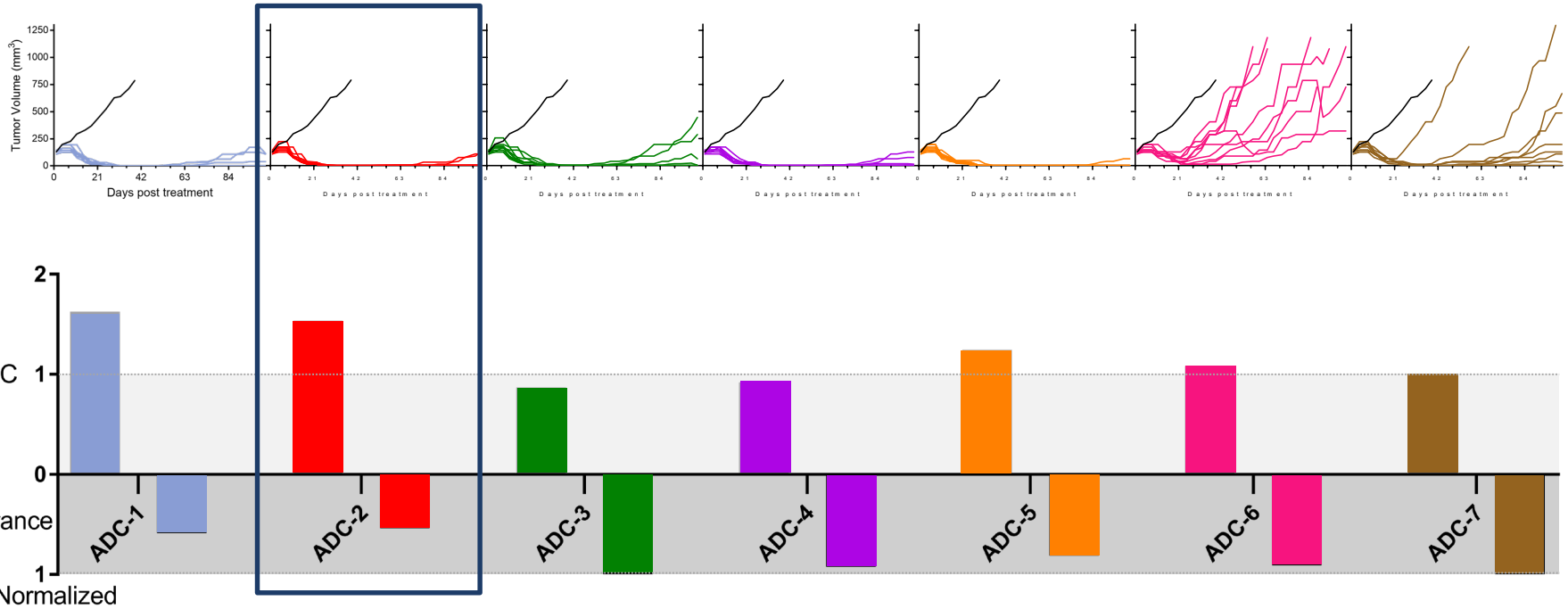


- Trastuzumab was used as a model to synthesize
  - ADCs with DAR6 (n=2 site specific, n=2-4 stochastic) and DAR12 (n=4 site specific, n=2-8 stochastic)
  - Stochastic maleimide ADCs
  - Site specific ADCs with a variety of technologies and sites of conjugation

	ADC 1	ADC 2	ADC 3	ADC 4	ADC 5	ADC 6	ADC 7
Bioconjugation	A	B	A	C	C	D	A
DAR	6	6	6	6	6	12	12
Site specific	●	●		● (site 1)	● (site 2)	●	

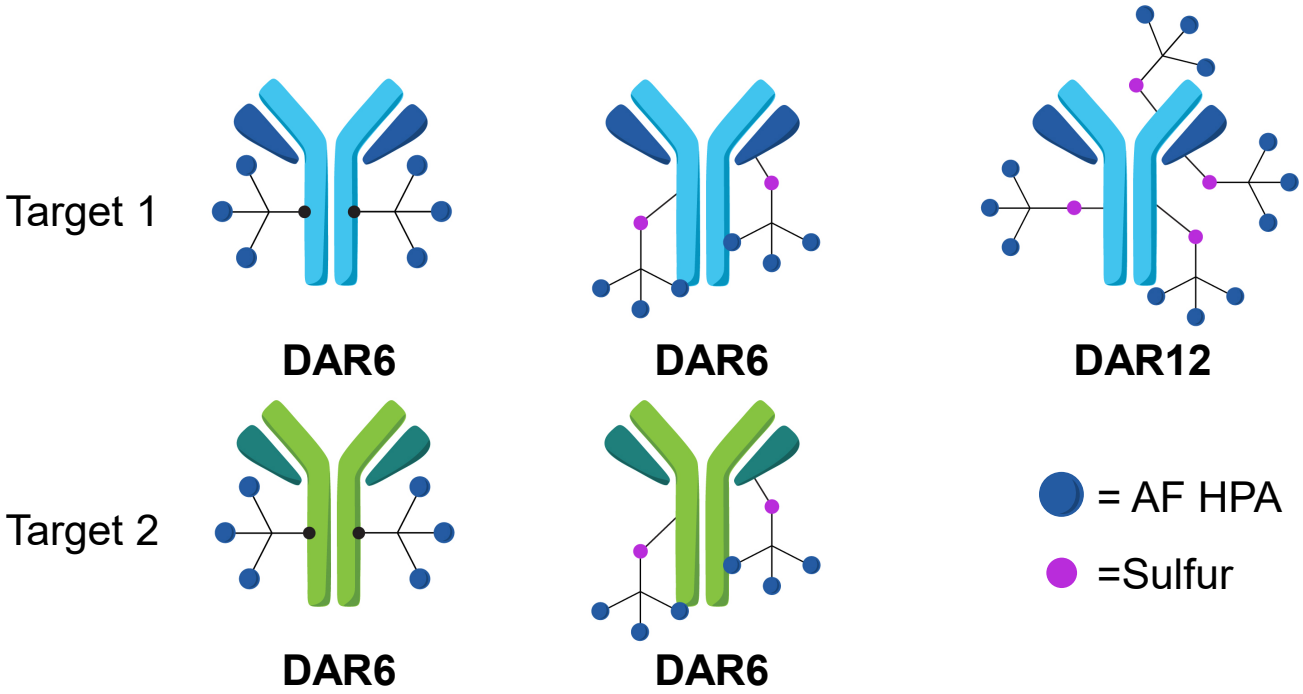
Differentiated Pharmacokinetics Enabled Selection of Lead Technologies

Efficacy JIMT1 Breast Xenograft Model (0.067 mg/kg payload single dose)



PK in tumor bearing mice (0.133 mg/kg payload single dose)

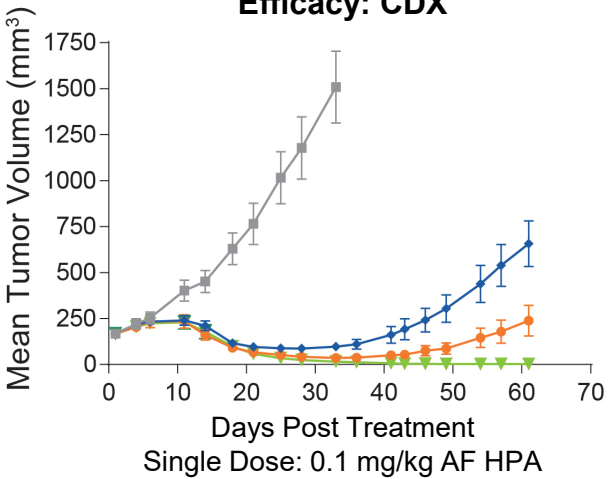
Phase 3 Explore Applicability Across mAbs and Targets



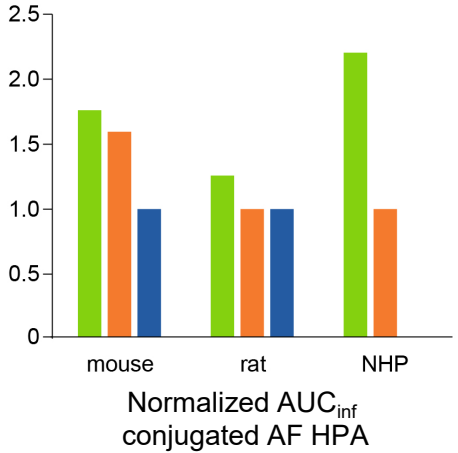
Efficacy, tolerability and PK were key parameters that were used to understand the clinical potential of the Dolasynthen platform

Site Specific Dolasynthen ADC was Superior to Stochastic ADCs for Target 1

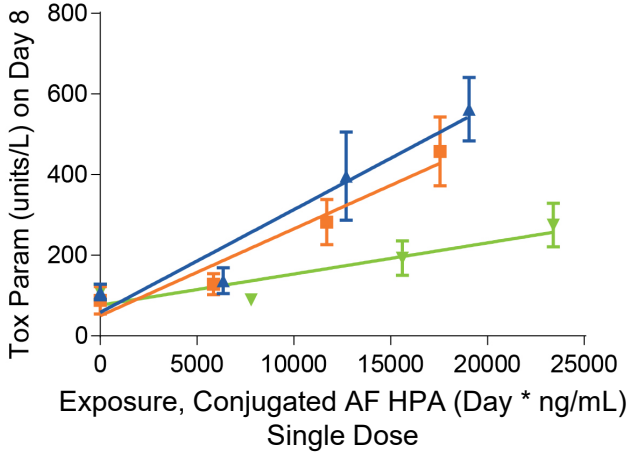
Efficacy: CDX

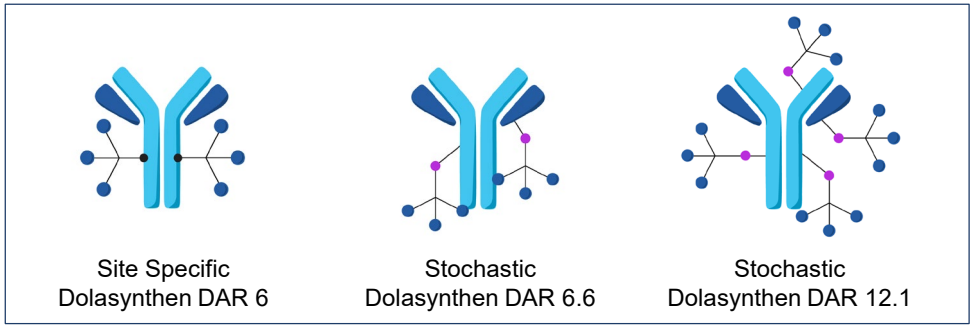


Exposure (day*ng/mL)



Toxicology parameter in Rats

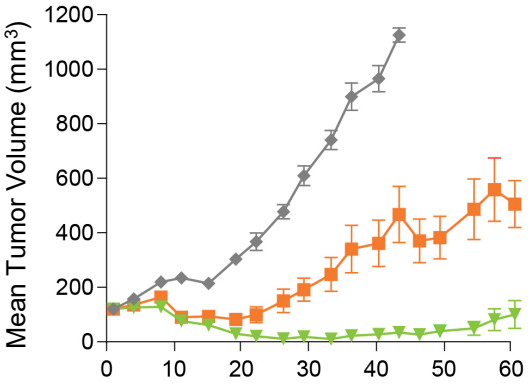




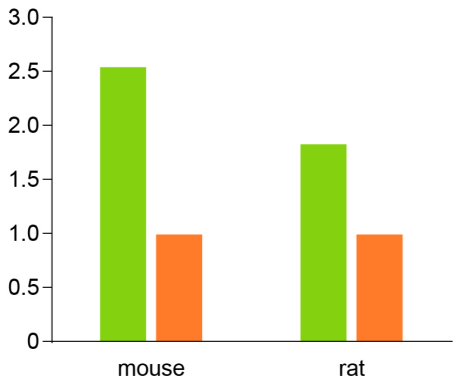
- Site Specific Dolasynthen DAR 6
- Stochastic Dolasynthen DAR 6.6
- Stochastic Dolasynthen DAR 12.1

Site Specific Dolasynthen ADCs Showed Consistently Improved *In Vivo* Performance Against Target 2

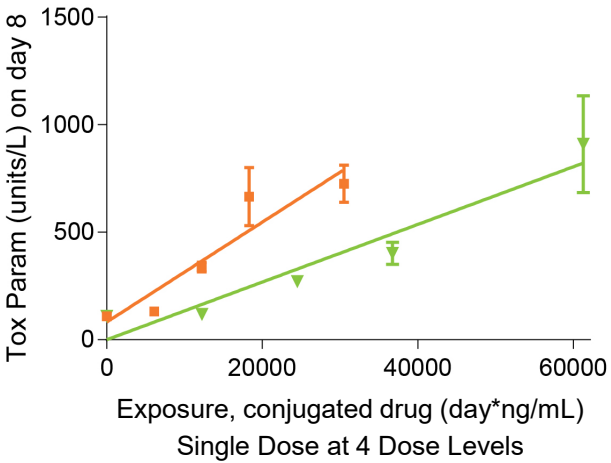
Efficacy: CDX

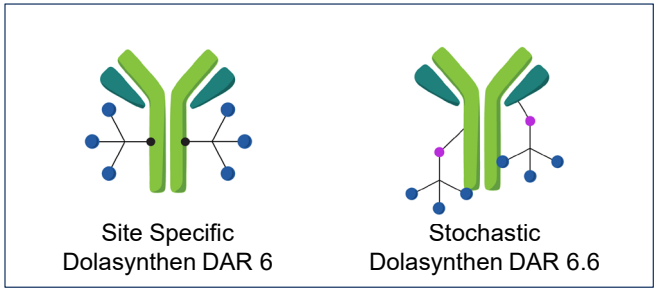


Exposure (day*ng/mL)



Toxicology parameter in Rats

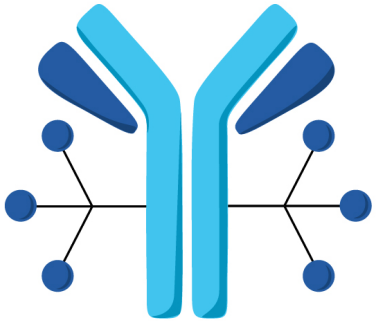




Site Specific Dolasynthen DAR 6

Stochastic Dolasynthen DAR 6.6

Conclusions



Dolasynthen

- Novel ADC platform based on the DolaLock payload
- Flexibility and precision enables ADC optimization for each target
- Significant potential for clinical application