



Antibody–Oligonucleotide Conjugates Landscape and WuXi XDC’s Capabilities in AOCs

WuXi XDC

Jul, 2024

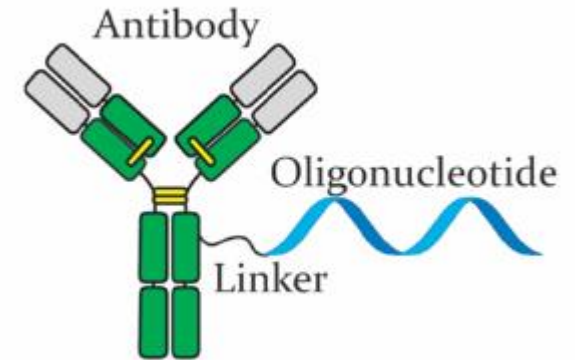


Antibody–Oligonucleotide Conjugates (AOC) Landscape



What are Antibody–Oligonucleotide Conjugates?

- ❑ Antibody–oligonucleotide conjugates (AOCs) combine the high precision of small interfering RNA (siRNA) and anti-sense oligonucleotides (ASO) with the deliverability of antibodies, thus synergizing the advantages of both technologies.
- ❑ Although siRNA and ASO offer selectivity, both of them suffer from challenges such as short serum stability, low membrane permeability, and lack of tissue selectivity.
- ❑ Currently, the main delivery systems of the approved oligonucleotide drug are the **LNP** delivery system and the **GalNAc** delivery system, but neither is capable of drug-targeted delivery outside the liver.
- ❑ Antibodies, with their longer half-life, ability to selectively deliver therapeutics inside the cells, and targeting properties, make them ideal partners for the targeted delivery of oligonucleotides.





As compared to oligonucleotides

- Better selectivity
- Better stability
- Better transmembrane properties



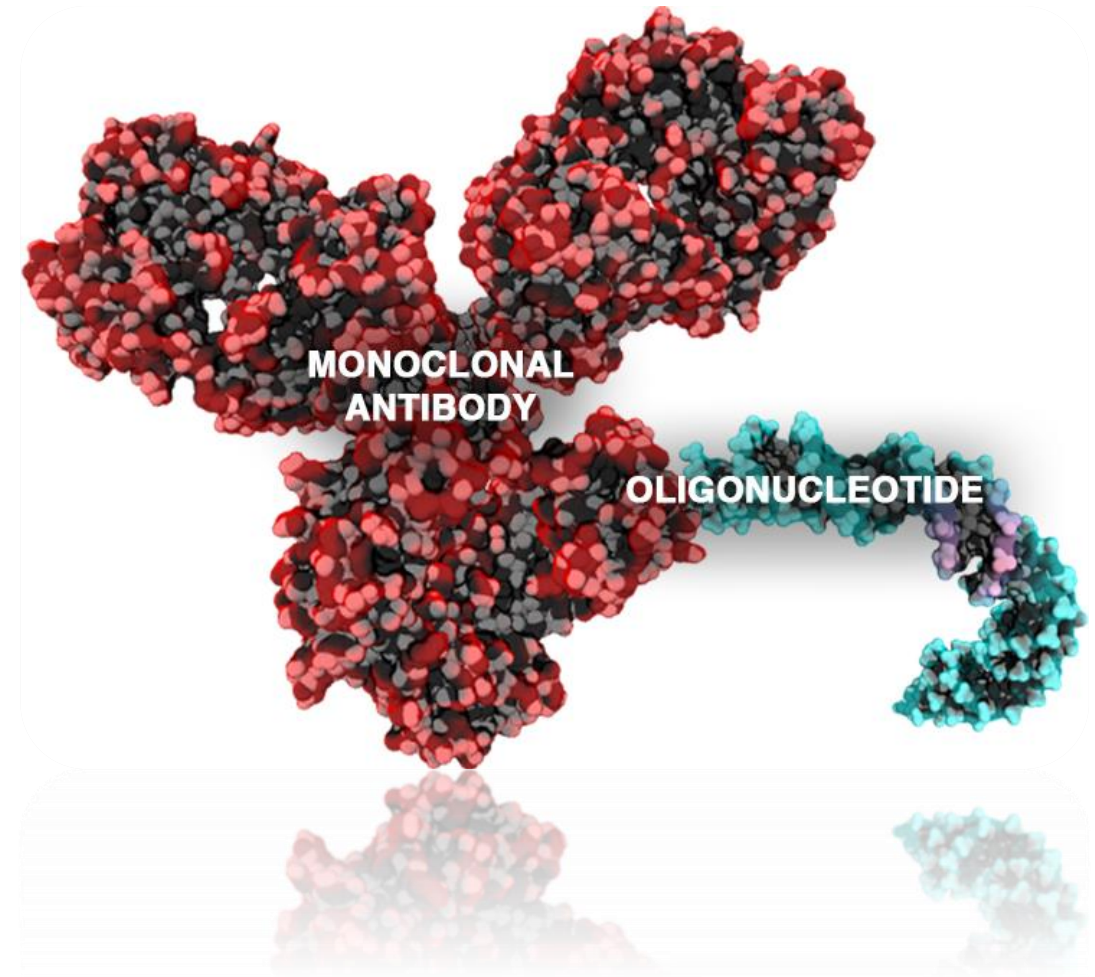
As compared to **LNP**

- Simpler components
- Better targeting



As compared to **GaINAc**

- More diverse targets to select



Competitive landscape of AOC field



Indications:	DMD; FSHD; Cancer; Cardiovascular Diseases; Metabolic Disorders; Atrophy; Pompe Disease; Spinal muscular atrophy; Pruritus; Undisclosed	Myotonic dystrophy type 1 (DM1); Duchenne Muscular Dystrophy (DMD); Facioscapulohumeral muscular dystrophy (FSHD); Cancer
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Selected AOCs in Clinical Trials

Drug	Sponsor	Antibody properties	Therapeutic payload	Tissue target	Indication	Status
AOC 1001	Avidity	TfR1-targeted mAb	<i>DMPK</i> siRNA	Muscle	DM1	Phase 3
AOC 1044	Avidity	TfR1-targeted mAb	Exon-44-skipping PMO	Muscle	DMD	Phase 2
AOC 1020	Avidity	TfR1-targeted mAb	<i>DUX4</i> siRNA	Muscle	FSHD	Phase 1/2
DYNE-251	Dyne	TfR1-targeted Fab	Exon-51-skipping PMO	Muscle	DMD	Phase 1/2
DYNE-101	Dyne	TfR1-targeted Fab	<i>DMPK</i> ASO	Muscle	DM1	Phase 1/2
TAC-001	Tallac	CD22-targeted mAb	CpG(TLR9 agonist)	Solid Tumors	Cancer	Phase 1/2

Avidity Biosciences: a Pioneer Company in AOCs

- Avidity's successful pivotal clinical trial proved finally the concept of AOCs
- Initiated in May 2024 global Phase 3 HARBOR™ trial of AOC 1001
- Avidity and BMS signed in November 2023 a \$2.3bn deal for cardiovascular targets.

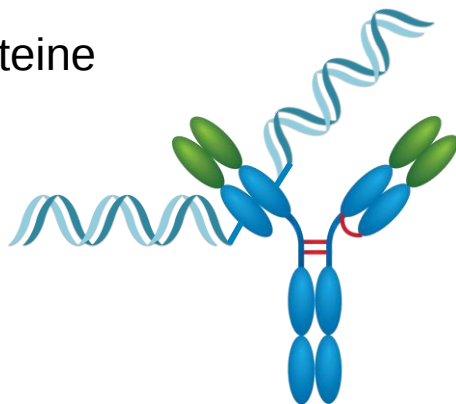
PROGRAM/INDICATION	TARGET	LEAD OPTIMIZATION	IND ENABLING	PHASE 1/2	PHASE 3
Del-desiran (AOC 1001) Myotonic Dystrophy Type 1 (DM1)	DMPK				
AOC 1044 Duchenne Muscular Dystrophy (DMD)	Exon 44				
AOC 1020 Facioscapulohumeral Muscular Dystrophy (FSHD)	DUX4				
Additional DMD Programs	Exon 45 & Undisclosed				
Rare Skeletal Muscle Program	Undisclosed				
Rare Cardiac Program	Undisclosed				

*Phase 3 HARBOR Trial Initiation planned for Q224

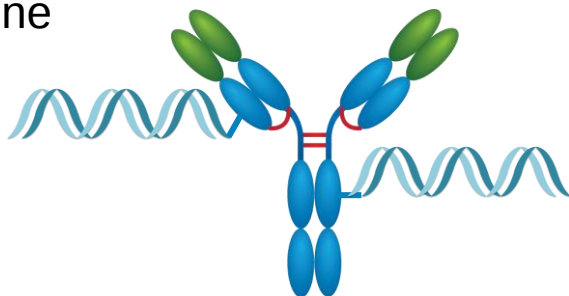
General Methods to Conjugate Oligonucleotides

Random Conjugations

Cysteine

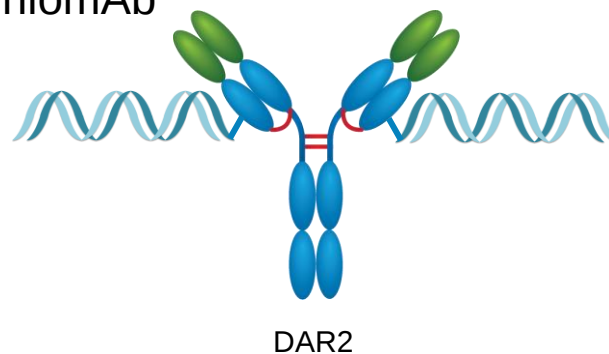


Lysine

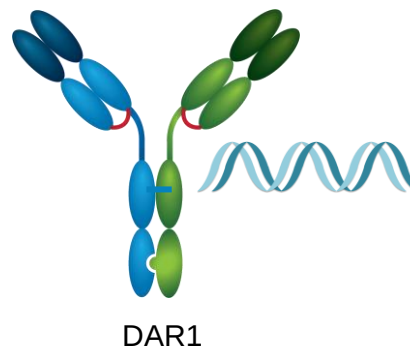


Site Specific Conjugations

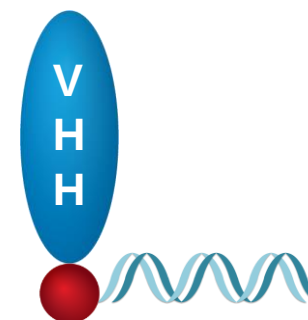
ThiomAb



BsAb



Nanobody

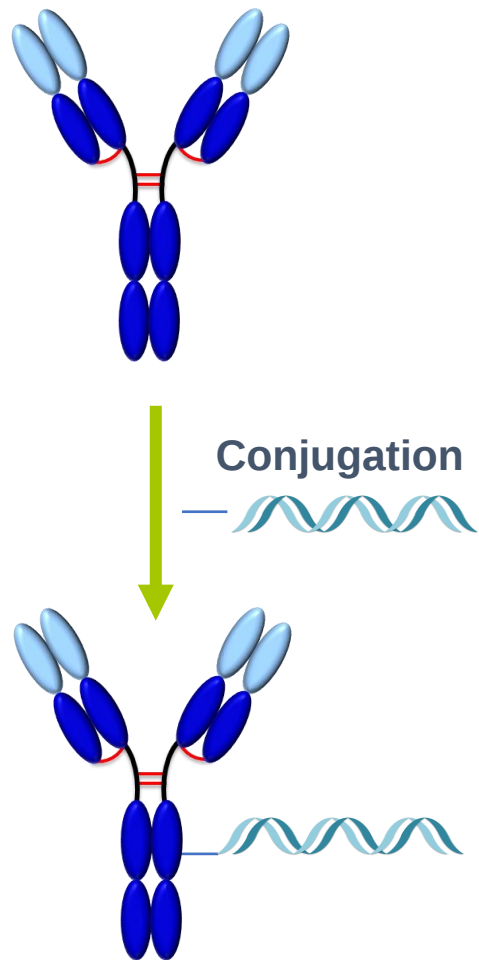




WuXi XDC's Capabilities in AOCs and Beyond



WuXi XDC Has Extensive Experience On Diverse AOCs



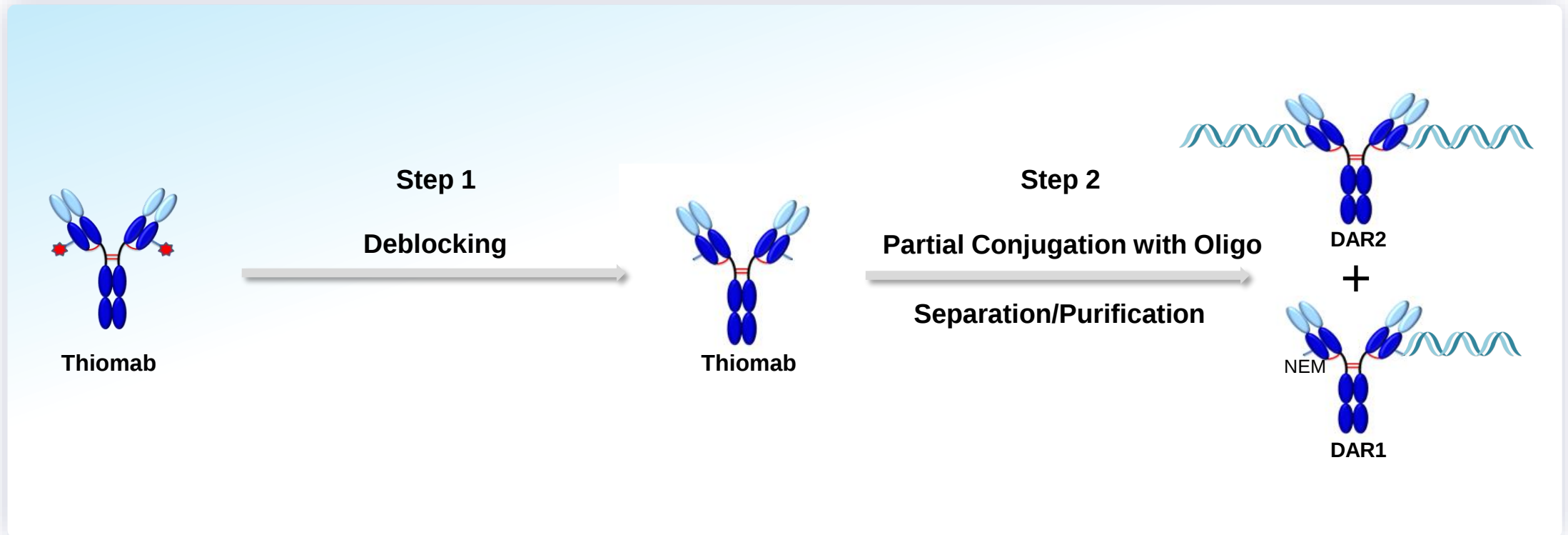
Delivered **400+** AOC Products

Scale: **1mg~100g**

Multiple **Conjugation** methods

Comprehensive **Purification / Characterization** methods

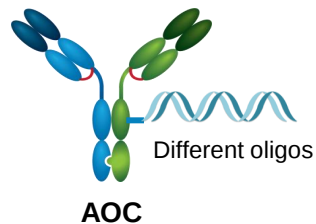
Case 1: One Conjugation to Get Two AOCs With Two Different DAR values Simultaneously for Further Evaluation



- ❑ This project was at discovery stage, and the client had to assess which DAR value was optimal (DAR1 VS. DAR2). Thus, we used incomplete conjugation to generate a mixture of DAR1 and DAR2, and then separated them with column purification and obtained both DAR1 and DAR2 products simultaneously.

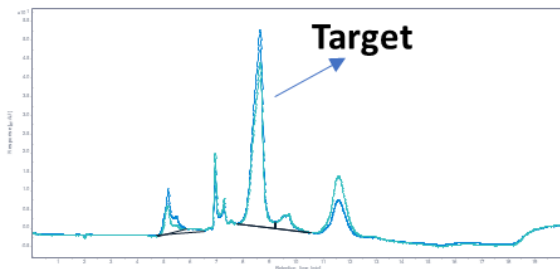
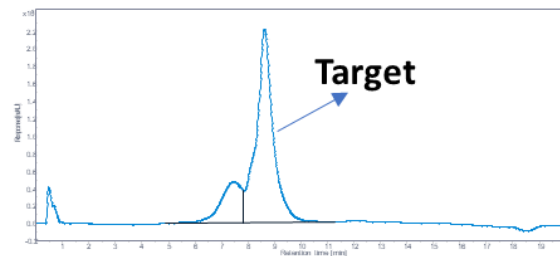
Case 2:

Comprehensive Purification Toolbox to Remove Different AOC Impurities



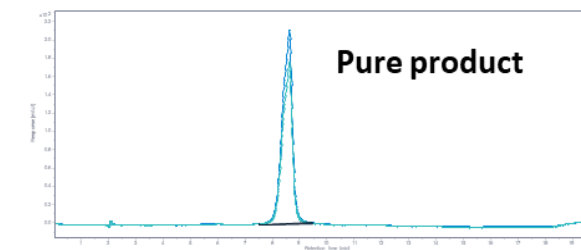
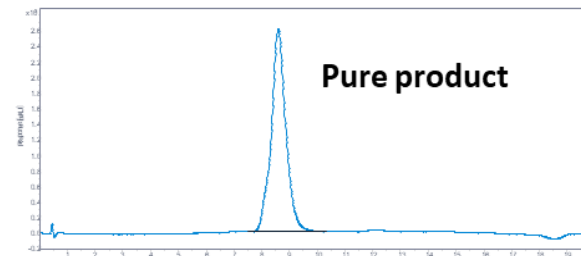
AOC with different oligos have different impurity profiles.

HPLC Profile of crude

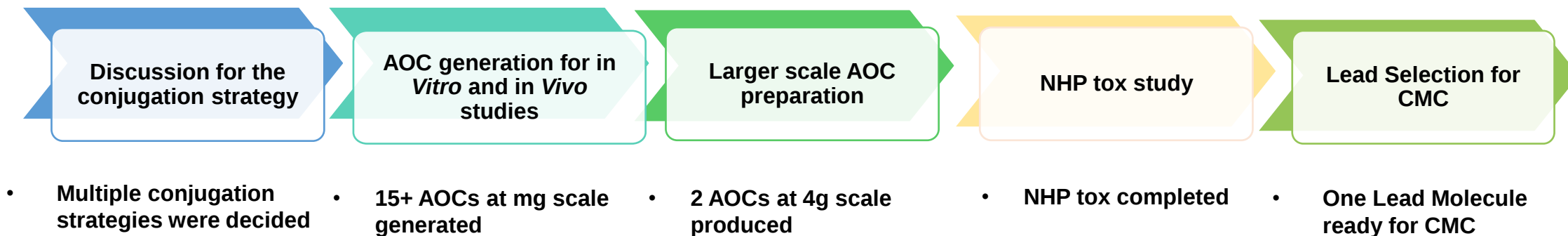


Comprehensive
AOC Purification
Toolbox

High purity products



Case 3: A Finished Integrated AOC Discovery Project



Quick turnaround time for AOC generation

- Quick AOCs generation within 8 weeks
- Large scale AOC prep for NHP tox study



WuXi XDC has toolbox for various challenging AOC conjugations

- Experienced SMEs in AOCs



Successful discovery AOC collaboration will translate to a first AOC CMC program soon

>>>



WuXi XDC's Capabilities in broader Bioconjugates



WuXi XDC Integrated One-Stop CRDMO Service



Antibody Discovery

Conjugation Research

CMC Development

IND Filing

Commercial
Manufacturing

Discovery

An integrated ADC Discovery Service from Target to PCC

- Target Nomination
- Antibody Discovery
- Payload-Linker Synthesis
- Bioconjugation
- In Vitro Biological Characterization
- In Vivo Pharmacological characterization
- Physicochemical & Chemogenic Research

Process Development

Industry-leading Process Development Platform Dramtically Reduces CMC Timelines

- Conjugation Process Development
- Formulation & DP Process Development
- Analytical Support & Development
- Non-GMP Manufacturing

Payload & Linker

Payload-Linker Integrated Service from Discovery to Manufacturing

- Integrated services from milligram to kilograms scale, at both clinical and commercial stages
- Customized Payload-Linker Synthesis
- Process Development & Analytical Support
- Non-GMP/GMP Manufacturing Service
- Inventory Payload-Linker

Manufacturing

- **Bio-conjugate Manufacturing**
 - XBCM1 up to 500L (5kg) per batch ,100 batches per year
 - XBCM2 has two dual function production lines for mAb intermediate and bioconjugate drug substance production, the scale per batch for conjugation production is up to 2000L
 - 290 batches of bioconjugate DS Completed Annually
- **Drug Product**
 - Complete production capacity for highly potent and aseptic products
 - Vials in sizes from 2R to 50R (liquid & Lyo)
 - XDP1 and XDP2 with 5 & 20 sqm lyo, 8M vials annual capacity
 - Fully automatic visual inspection and packaging-labeling line

570+

CMC&Discovery Projects⁽¹⁾

55+

Client IND Submissions Enabled⁽¹⁾

10+

Conjugate technologies⁽¹⁾

10,000+

Bioconjugate molecules⁽¹⁾

1,200+

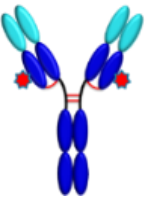
Payload-linkers⁽¹⁾⁽²⁾

Note:

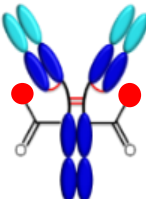
1. As of Dec 31, 2023

2. Payload, linker and/or payload-linker, which combines both the payload and the linker

WuXi XDC's Expertise is Much More Than in AOCs



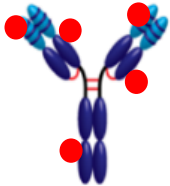
THIOMAB™



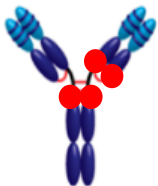
NNAA



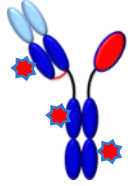
Enzyme-assisted



Lys-based



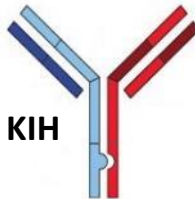
Cys-based



Bispecific ADC



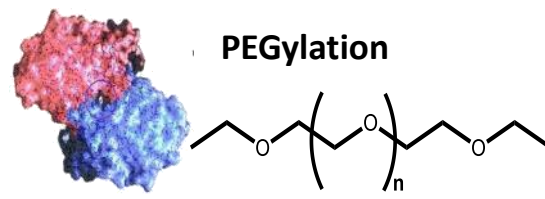
Dual-payload ADC



KIH



Micelle



PEGylation

Bioconjugate		Modules
ADC	Antibody	Native mAb: IgG1, IgG2, IgG4
		Engineered mAb: ThiomAb, NNAA
	LP	Bi-specific mAb, Nanobody etc.
		Small molecule linker-payloads (Highly potent & non-potent), Dual payloads
Novel Format Conjugate	Protein Based	Radioisotope chelators
		Oligonucleotide
		Peptide
	Non-protein Based	PEGylation, Biotinylation, etc.
		Polymer-drug conjugation
	Non-protein Based	Nanoparticle-peptide conjugation

200+ scientists for conjugation discovery and process development

Integrated ADC/Bioconjugate Discovery Service from Concept to PCC

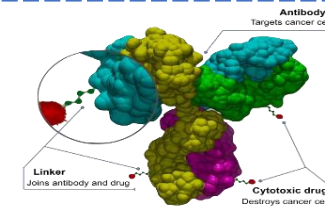
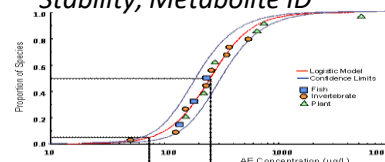
Antibody lead identification, optimization and production using our state-of-art technologies



• **Payload-linker library:** vcMMAE, MC-MMAF, SMCC-DM1, SPBD-DM4, GGFG-DXd, CL2A-SN38, Tesirine, etc.

• **Customized payload-linker synthesis**

Binding, Internalization, In vitro killing, Plasma/Serum Stability, Metabolite ID



Wikipedia

**Antibody
Discovery/Generation**

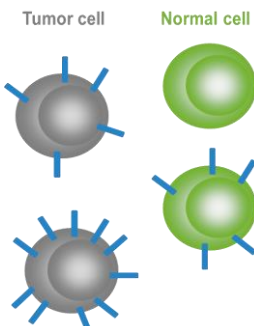
**Payload-linker
Synthesis**

**In vitro Biological
Characterization**

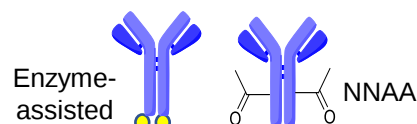
**Physicochemical &
Developability Characterization**

Target Evaluation

TAA evaluation and selection from multiple angle analysis



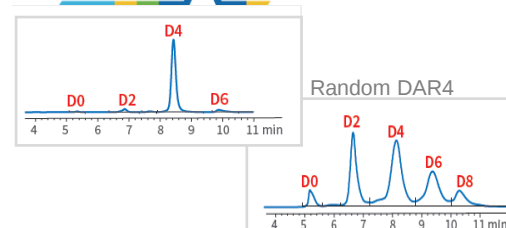
Bioconjugation



Multiple bioconjugation methods

Proprietary conjugation technology to improve homogeneity

WuXiDR4



**In vivo Pharmacological
Characterization**

Efficacy models
PK/PD and
exploratory tox

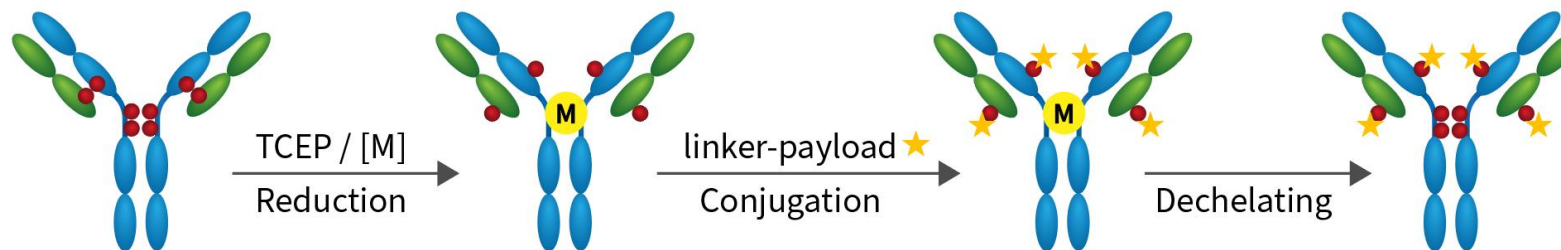
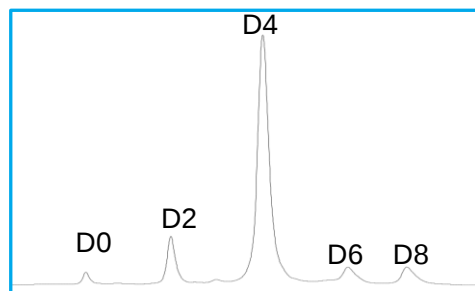


PCC

PCC: Preclinical Candidate

WuXi XDC's Proprietary Technology- WuXiDAR4™

WuXiDAR4™



Highly homogenous ADC

- **≥ 65% of a single conjugated species without column purification**
- **≥ 95% with column purification**

Compatible with native mAb

- **No antibody engineering modification is needed**

Meet clients' diversified needs

- **Compatible with common linker-payloads: MMAE, MMAF, DXD, PBD**
- **No connector modification needed**

Simple CMC and Cost Saving

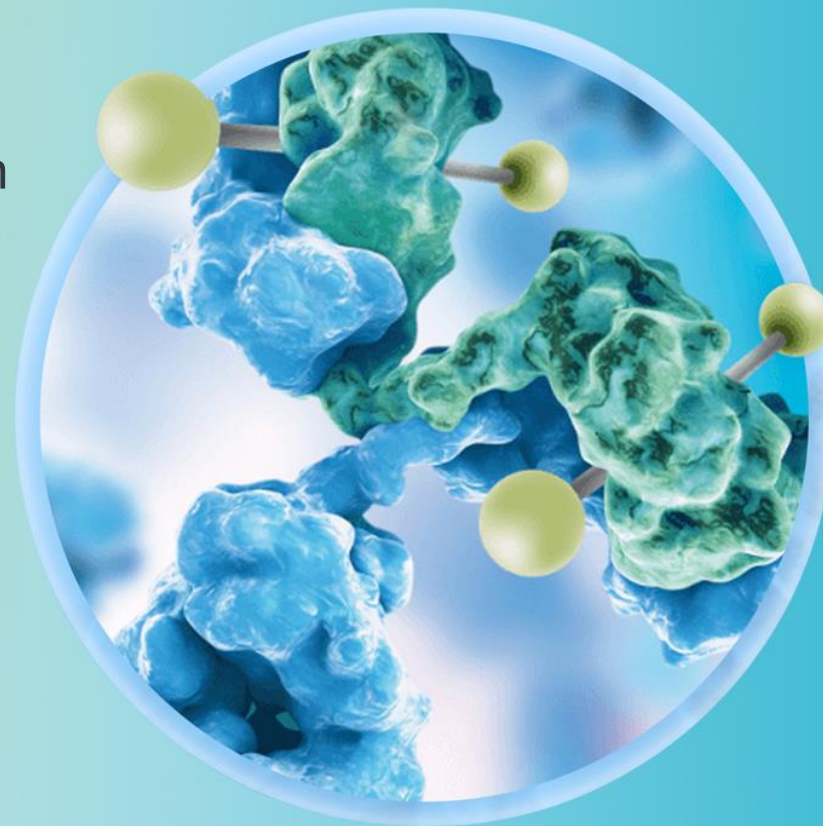
- **Simple conjugation process.**
- **Comparable COG with conventional Cys random conjugation.**

Contact Information

You are welcome to contact us via the following email or link if you are interested in our company's service in discovery, development and manufacturing of AOCs and other conjugates.

Email : wuxixdc_info@wuxibiologics.com

<https://wuxixdc.com/contact-us/>



Our Mission

To accelerate and transform the **discovery, development and manufacturing of bioconjugates** through a **comprehensive open-access platform**, enabling our global healthcare partners and benefiting patients worldwide.

STRONGER AS ONE

WuXi XDC - Your One-Stop Antibody Drug Conjugate (ADC) Development Solution

One Source:

- Payload-linker
- Antibody
- Conjugate
- Drug Product

One Platform:

- ADC Discovery
- ADC Technology
- CMC Development
- GMP Manufacturing

One Team:

- Service & Support
- Product Management
- Project Accountability



One Source
One Platform
One Team



Thanks !

