

# Novel Conjugation and Payload-Linker Technologies for Next Generation ADCs

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## Introduction

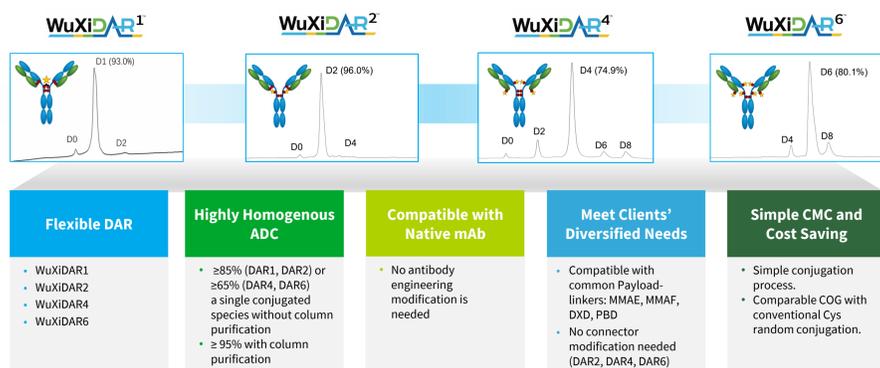
Antibody drug conjugates (ADCs) have garnered increasing attention over the past decade. Innovations in antibody development, such as the discovery of new targets and the selection of bispecific antibodies, have demonstrated significant potential in addressing previously untreatable diseases and expanding the therapeutic window beyond what is currently achieved by standard treatments. ADC pipelines built with these new antibodies involve various uncertainties, making it arguably better to use proven conjugation technologies and established payload-linkers to reduce the overall risks. However, clinically validated conjugation methods, such as cysteine and random lysine conjugation, often result in undesirable heterogeneity. Furthermore, the approved topoisomerase inhibitor linker-payloads, like deruxtecan, are proprietary. In addition, some developers, focusing on antibody innovation, lack expertise in conjugation and/or payload-linker capabilities, and starting from scratch could significantly delay the project timeline.

To address these needs, WuXi XDC has built a platform through internal development and external collaboration. This platform includes two parts:

- (1) Conjugation technologies featuring WuXiDARx™, X-LinC, CysLink, and AbClick
- (2) Novel payload-linker technologies

## WuXiDARx™

WuXiDARx™ conjugates at interchain cysteines which are the most clinical validated site, as 11 out of 15 commercial ADCs are developed through cysteine conjugation.



\*Technology in collaboration with MCLICK-DAR1-A1/MCLICK-DAR2-A1/MCLICK-DAR6-A1 from Bio-reinnovation Tech. Ltd.  
•Validated technologies: 7 ADCs in clinical trials, 10 CMC projects, up to > 2 kg batch size

## WuXi Dual-payload ADCs:



Fig 1. Overview of WuXiDARx

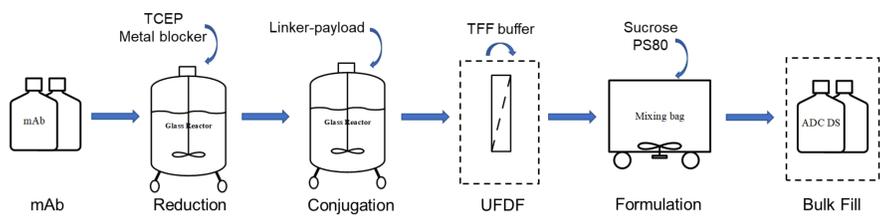


Fig 2. A simple and manufacturing friendly process using WuXiDAR4 technology

One major advantage of WuXiDARx is its ability to generate ADC molecules with homogeneous structural attributes and ideal developability characteristics, which allows for efficient CMC development and cost-effective manufacturing. Other advantages include a "one-pot" reaction and a single UF/DF step to remove the free linker-payloads and other small molecule impurities. Both the yield and the cost of ADCs produced with WuXiDARx are comparable to those of ADCs produced by stochastic cysteine conjugation.

## WuXiDAR4™

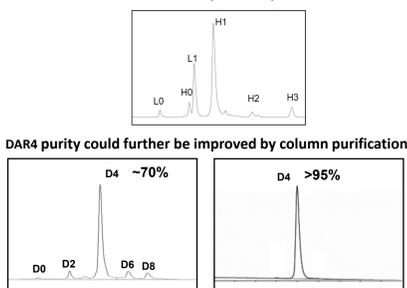
The WuXiDAR4 conjugation is suitable for various maleimide reacting linker-payloads and various human IgG1 (vcMMAE as the model linker-payload, trastuzumab as the mAb model.)

Product Name	DAR	D4%
Trastuzumab-MC-VC-PAB-MMAE	4.0	74.9
Trastuzumab-MC-MMAF	3.7	80.5
Trastuzumab-MC-GGFG-Dxd	4.1	71.0

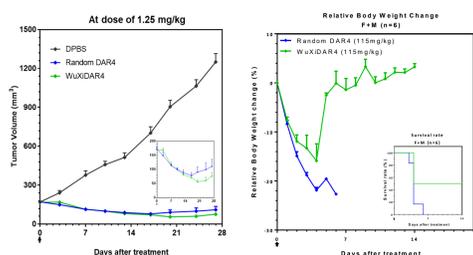
Product Name	DAR	D4%
Adalimumab, Anti TNF-α Antibody	4.0	71.7
Alemtuzumab, Anti CD52 Antibody	4.3	71.6
Atezolizumab, Anti PD-L1 Antibody	3.9	74.4
Basiliximab, Anti IL-2R α Antibody	4.2	80.4
Daclizumab, Anti CD25 Antibody	4.3	70.4
Trastuzumab, Anti HER2 Antibody	4.0	74.9
Rituximab, Anti CD20 antibody	4.0	73.8
Cetuximab, Anti EGFR antibody	3.8	81.4

Conjugation site at L-H interchain Cysteine (L1 & H1 are the dominating species) RP-HPLC (Reduced)



D4% may vary with different mAb and payload linker combinations.

Fig 3. WuXiDAR4 ADCs Physicochemical Characterizations



- WuXiDAR4-ADC shows stronger in vivo efficacy (N87-CDX)
- WuXiDAR4-ADC shows better tolerability (C57BL/6 mice, single dose)

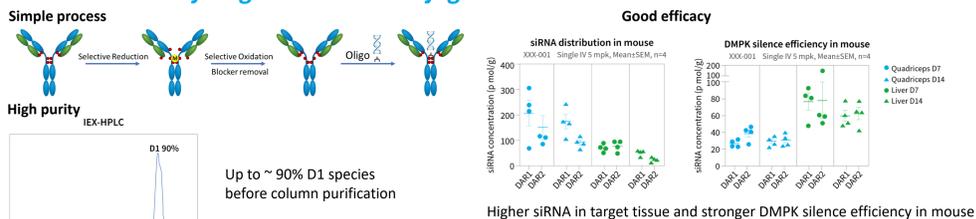
Fig 4. WuXiDAR4 ADCs in vivo Efficacy and Safety

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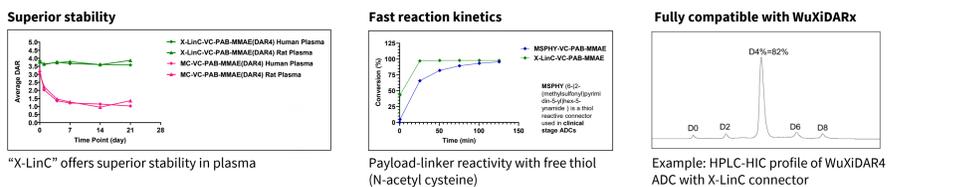
## WuXiDAR1™

### Ideal for antibody-oligonucleotide conjugates

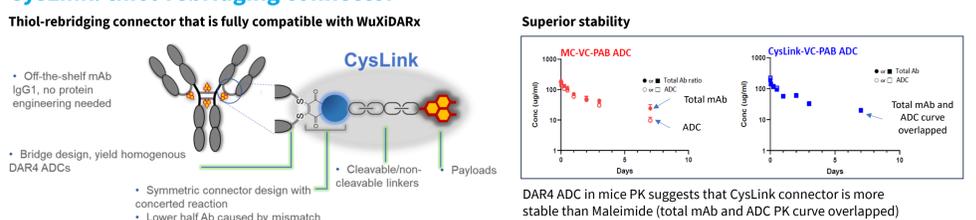


## Novel Connector Technologies

### X-LinC: novel thiol reactive connector



### CysLink: thiol-bridging connector

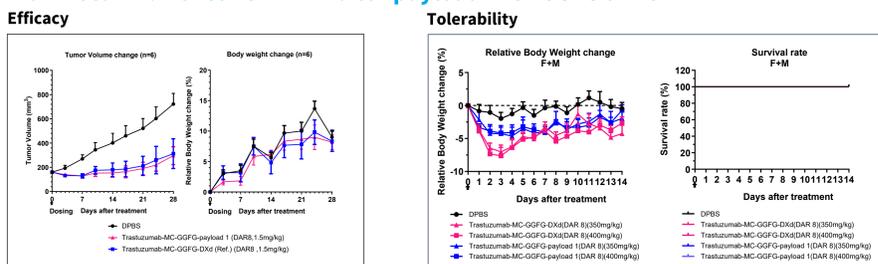


## Novel Payload-Linker Technologies

Topoisomerase I inhibitor payload-linkers are among the most popular choices in ADC development. Even though Enhertu and its linker-payload deruxtecan are successful, the best payload-linker may differ for each target or indication. Three payload-linker technologies from WuXi XDC partners are integrated into the platform. These technologies include diverse payloads (e.g., Exatecan and new payloads), a range of release mechanisms (e.g., peptidase, glucuronidase, TME enzymes), and innovative linker designs to improve hydrophilicity and stability. ADCs with these payload-linkers exhibit better efficacy and/or safety profiles compared to those with deruxtecan in preclinical stage.

	LP name	Connector	Release Mechanism	Payload	Cyno HNSTD	Design Strategy	Stage	Source
PL1	WuXiTecan-1	Mal	Peptidase (Lysosomal)	Novel payload (TOP1)	≥ 55 mpk (DAR8)	Novel payload	Preclinical	WuXi XDC
PL2	WuXiTecan-2	Mal	Peptidase (Lysosomal)	Exatecan	≥ 45 mpk (DAR8)	Novel linker	Preclinical	WuXi XDC
PL3	T1000-Exatecan	Mal	Peptidase (Lysosomal)	Exatecan	≥ 30 mpk (DAR8)	Novel linker	Phase 1	Partner
PL4	OHPAS-Nexatecan	Mal/IAA	Glucuronidase (Lysosomal)	Nexatecan (TOP1)	≥ 75 mpk (DAR8)	Novel linker + payload	CMC	Partner
PL5	Unilinker-Exatecan	Mal	Peptidase (Lysosomal & TME)	Exatecan	≥ 30 mpk (DAR8)	Novel linker	CMC	Partner
PL6	CPT113	Mal-bridge	Peptidase (Lysosomal)	CPT116 (TOP1)	≥ 20 mpk (DAR4)	Novel linker + payload	Phase 1	Partner

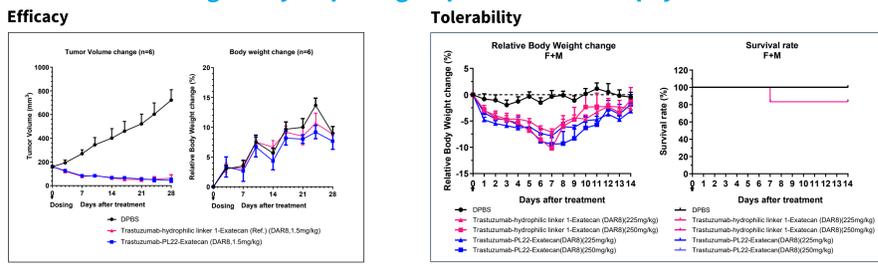
### WuXiTecan-1: Novel TOP1 inhibitor payload with GGFG linker



In Vivo Efficacy Study\_NCI-N87 in BALB/c Nude female mice

Single dose tolerability in C57BL/6 mice (Acute toxicity)

### WuXiTecan-2: Designed hydrophilic groups with Exatecan payload



In Vivo Efficacy Study\_NCI-N87 in BALB/c Nude female mice

Single dose tolerability in C57BL/6 mice (Acute toxicity)

Fig 5. ADCs prepared by novel linker-payloads

## Conclusion

The WuXiDARx conjugation platform, also utilizing inter-cysteine conjugation, offers a flexible target DAR, good homogeneity, compatibility with native IgG1, and proven linker-payloads, along with a simple process. The power of the WuXiDARx platform lies in its ability to help ADC development companies to dramatically reduce CMC development risks, allowing them to focus on selecting best-fitted connector or linker payload. As a dedicated CRDMO, WuXi XDC provides innovative technology platforms like WuXiDARx, new thiol reactive connectors, and advanced payload-linker solutions. Our goal is to help clients develop and produce high-quality bioconjugates more quickly and efficiently.

## Partners



## About WuXi XDC

WuXi XDC is a leading global CRDMO focused on ADCs and the broader bioconjugate market. It provides end-to-end contract research, development and manufacturing services for bioconjugates, including ADCs. Its services cover antibody intermediates and other biologics intermediates, chemical payloads and linkers, as well as bioconjugate drug substances and drug products.

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