CONJUGATES: DEVELOPMENT OVERVIEW AND RECENT DISCUSSIONS

JUNE 26, 2026

CASSS CMC STRATEGY FORUM EUROPE SHORT COURSE

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Lilly

Conjugates: then, now and future

The road ahead: current conversations

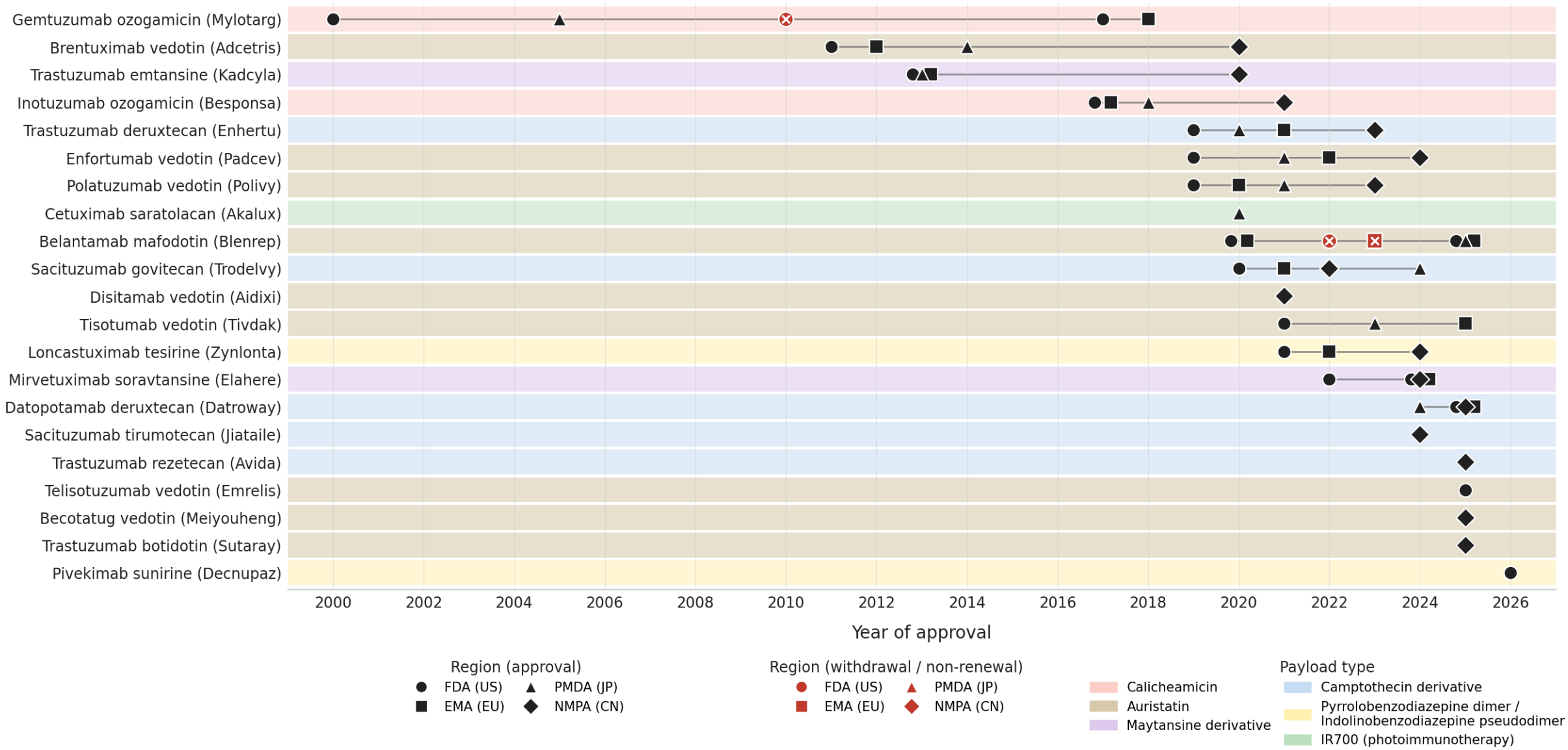
What are conjugates?

Combine targeting moiety with payload or cargo via a linker, enabling delivery of therapeutics to specific cells/tissues or new function.

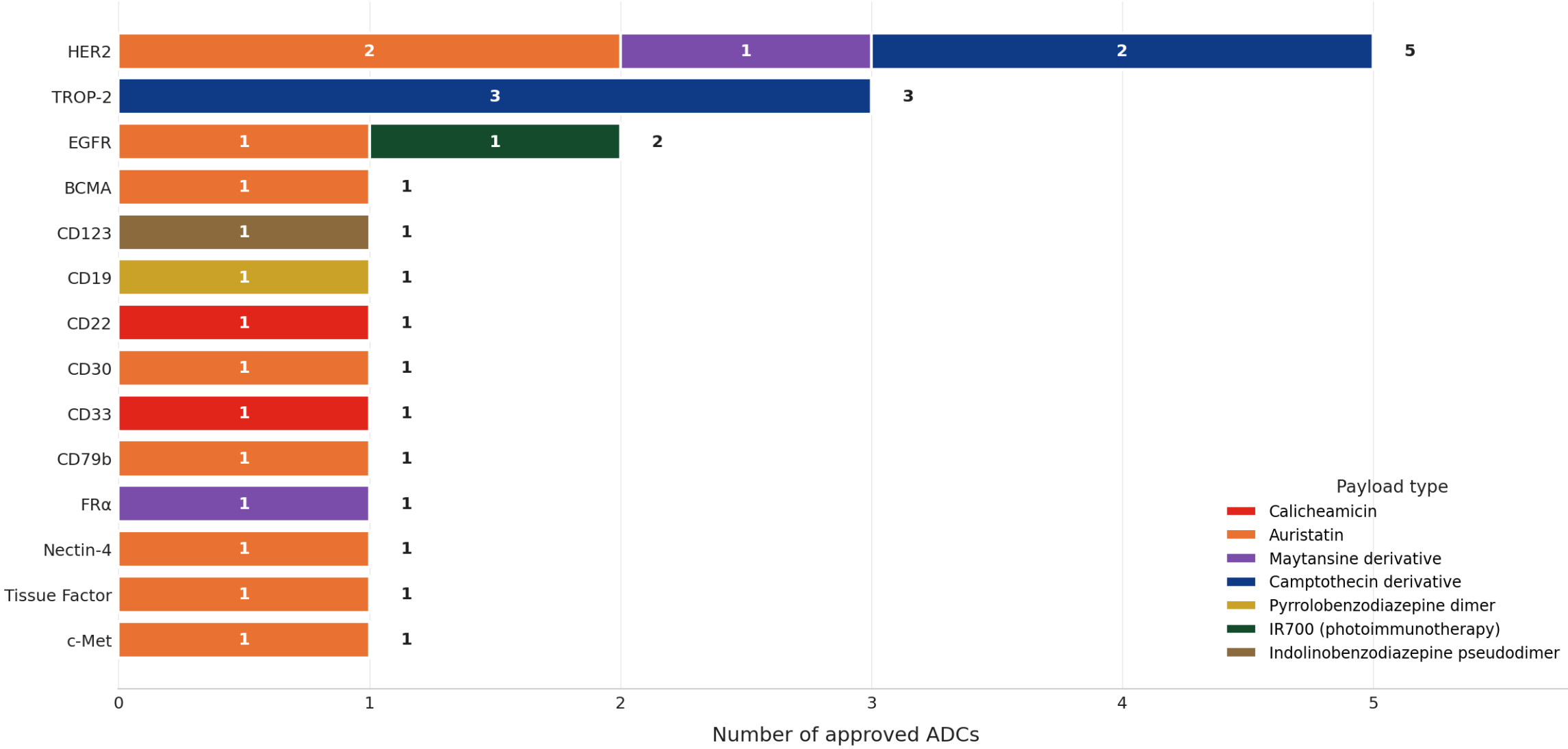
ADCs: Then and Now

	1980s–1990s **Early ADCs**	Late 1990s–2010 **1st Generation**	2010–2020 **2nd Generation**	2018–Present **3rd Generation**	Emerging **Next Generation**
mAb	Murine/chimeric antibodies • *Immunogenicity issues* • *Modest specificity* • *Low internalization*	Humanized mAb (CD33/CD22) • *Improved specificity* • *Better internalization*	Optimized humanized/ fully human mAb (CD30, HER2, CD70b) • *Strong affinity* • *Improved PK, targeting & internalization*	Fully humanized mAbs (HER2, TROP2, HER3) • *Optimized internalization* • *Heterogeneous-expression targets*	• Bispecific mAbs • Engineered residues for site-specific conjugation
Linker	Random lysine conjugation with unstable linkers • *Premature release* • *Heterogeneous (DAR 0-8+)*	Acid-labile hydrazone & disulfide linkers • *Partial plasma instability* • *Premature/inconsistent release*	Stable linkers: Protease-cleavable (Val-Cit) & non-cleavable (SMCC) • *Random heterogeneous conjugation* • *DAR ~3–4*	Highly stable cleavable linkers with site specific conjugation • *Higher DAR (~8)/ homogeneity* • *low-expression tumors*	• Improved site-specific conjugation • Multivalent: higher DAR/ multi-payload • Smart linkers
Payload	Conventional chemo drugs (doxorubicin, methotrexate, vinblastine) • *Low potency*	Calicheamicin • *Picomolar potency (1,000–10,000× vs. chemo)*	Auristatins & Maytansinoids • *Highly potent anti-tubulin payloads*	DNA damaging payloads (Topo1 inhibitors, PBD) • *Membrane-permeable, effective against slowly dividing tumors/solid tumors*	New classes: duocarmycins, immune-stimulating payloads (STING/TLR agonists), PROTACs/ molecular glues, multi-payload
Representative Products	vindesine-αCEA conjugate	Mylotarg, Besponsa	Kadcyla, Elahere, Adcetris, Padcev	Enhertu, Trodelvy, Datroway	

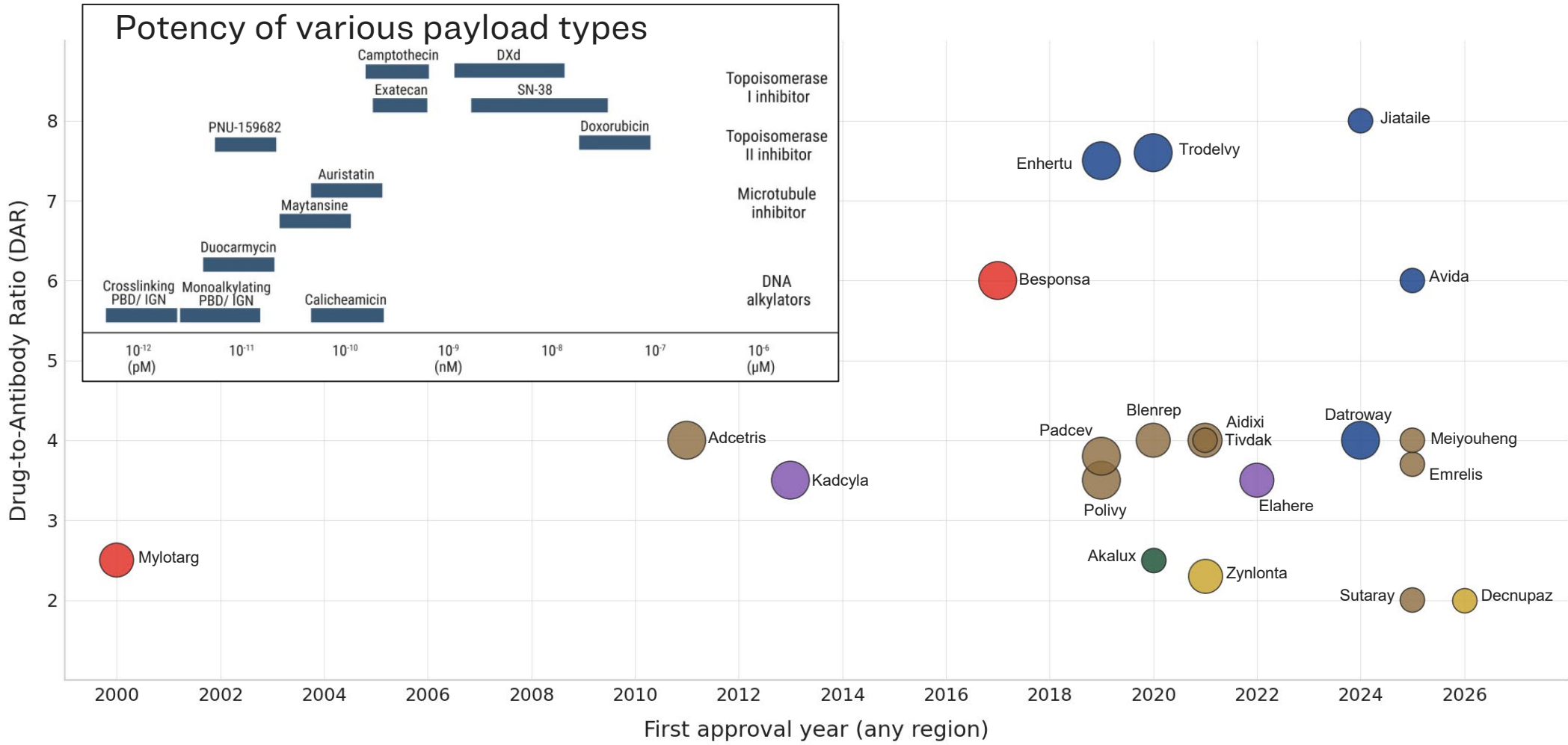
21 Globally Approved ADCs



Target vs. Payload for Approved ADCs



Evolution of DAR in Approved ADCs Over Time



Payload type:

- Calicheamicin
- Auristatin
- Maytansine derivative
- Camptothecin derivative
- Pyrrolobenzodiazepine dimer / Indolinobenzodiazepine pseudodimer
- IR700 (photoimmunotherapy)

 # regions approved:

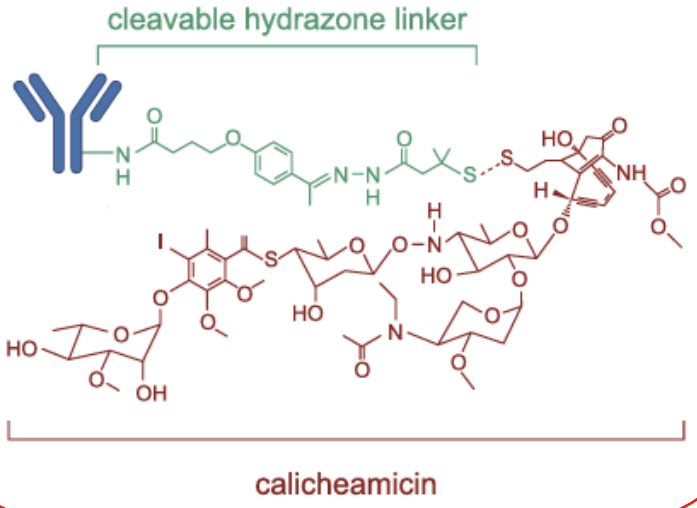
1 region · 2 regions · 3 regions · 4 regions

NJBio. Recent Advances in ADCs, January 2025

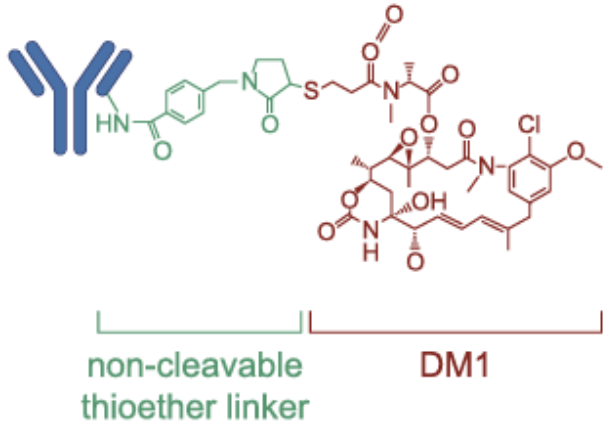
Payload Linkers in Approved ADCs

Chen et al. Molecular Cancer 2025, 24:279

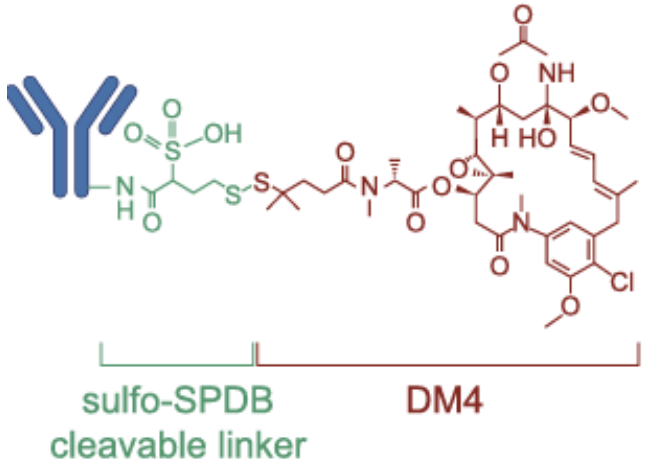
Ozogamicin (2)



Emtansine

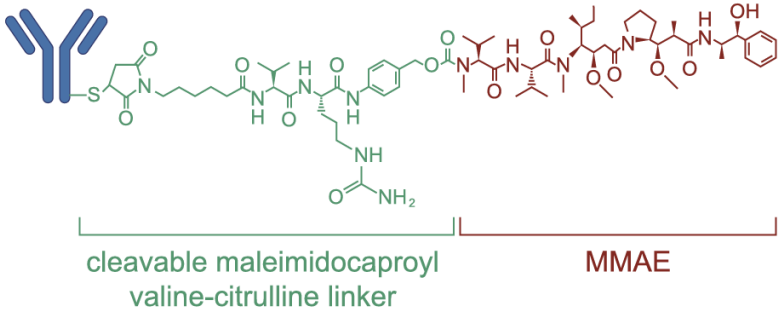


Soravtansine



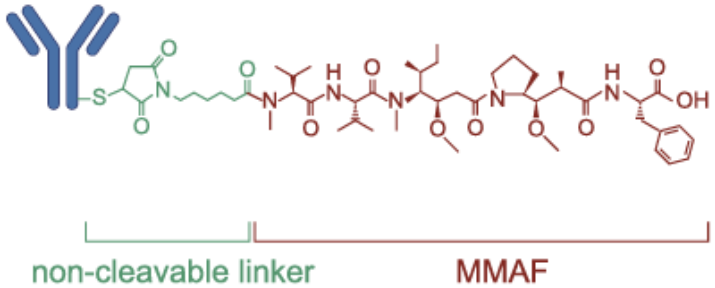
Maytansines

Vedotin (7)

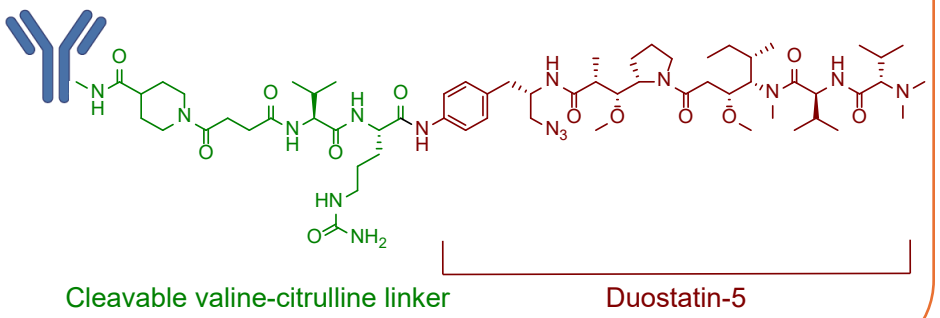


Auristatins

Mafodotin



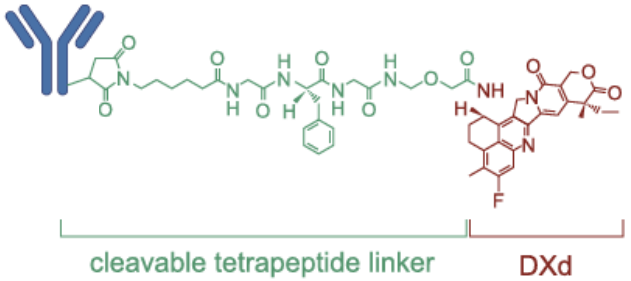
Botidotin



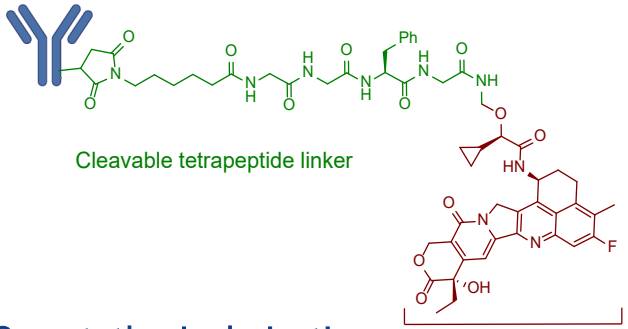
Payload Linkers in Approved ADCs

Chen et al. Molecular Cancer 2025, 24:279
JAN Database

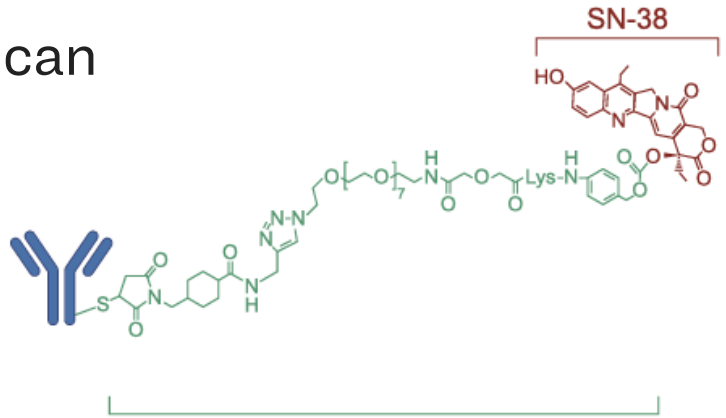
Deruxtecan (2)



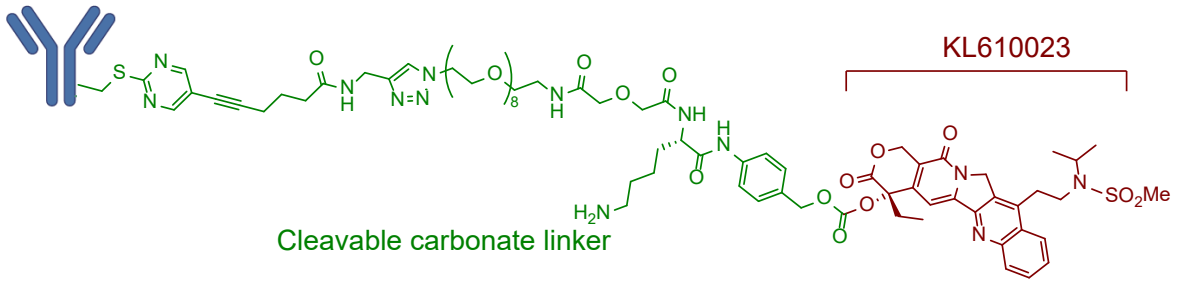
Rezetecan



Govitecan

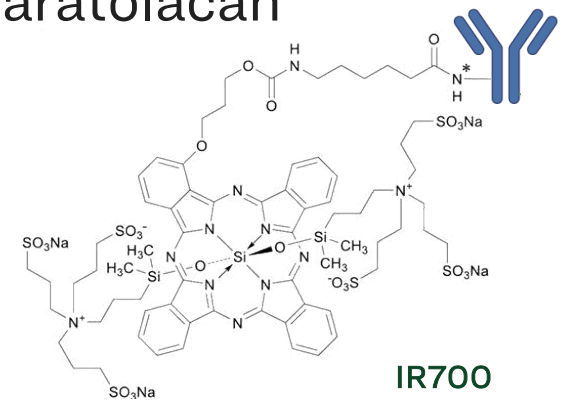


Tirumotecan

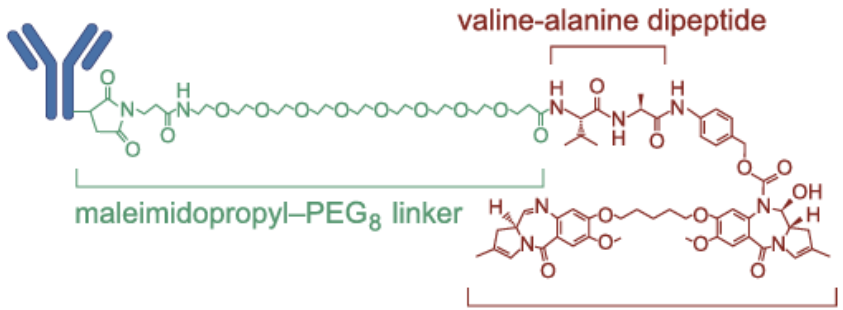


Camptothecin derivatives

Saratolacan

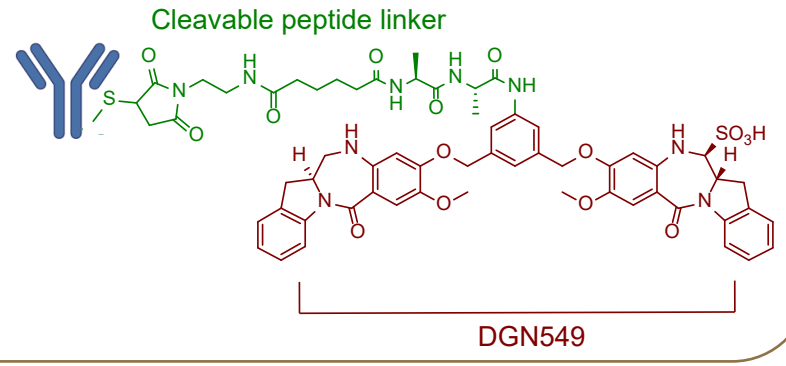


Tesirine



PBD/IBpDs

Sunirine



The Expanding AxCs, XDCs, Anything Drug Conjugates

TARGETING MOIETY

Antibody (mAb, antibody fragments, bsAb, etc.)

Peptides

Oligonucleotides

Polymers/Biopolymers

Small Molecules

GalNac

+

LINKER

Hydrophilic linkers (PEG, saccharides, ionizable groups to improve PK/aggregation)

New site-specific conjugations (enzymatic, biorthogonal)

Multi-valent linkers

+

PAYLOAD/CARGO

New cytotoxic classes

Oligonucleotides

Radionuclide

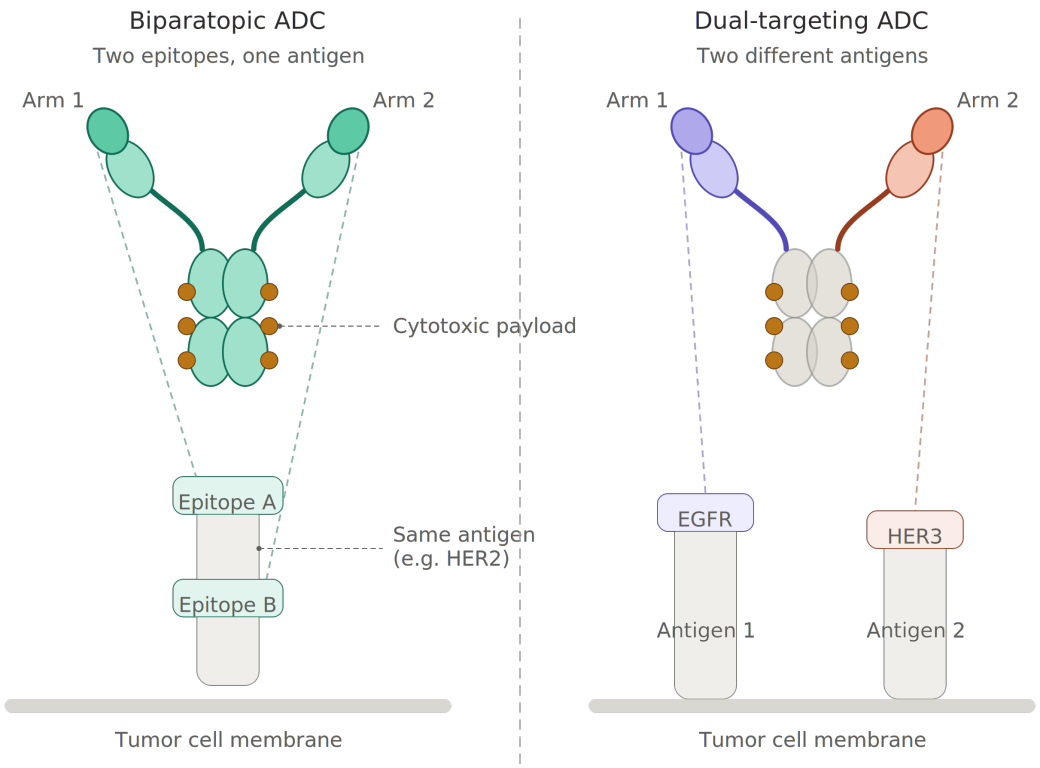
Peptides

PROTACs/Molecular glue

Immune-modulating agents

Multi-payloads

Multispecific ADCs



Clinical examples

Zanidatamab zovodotin
HER2 x HER2

REGN5093-M114
MET x MET

IMGN151
FRa x FRa

Key advantage
Enhanced internalization

Clinical examples

Iza-bren (BL-B01D1)
EGFR x HER3

M1231
EGFR x MUC1

AK146D1
Trop2 x Nectin4

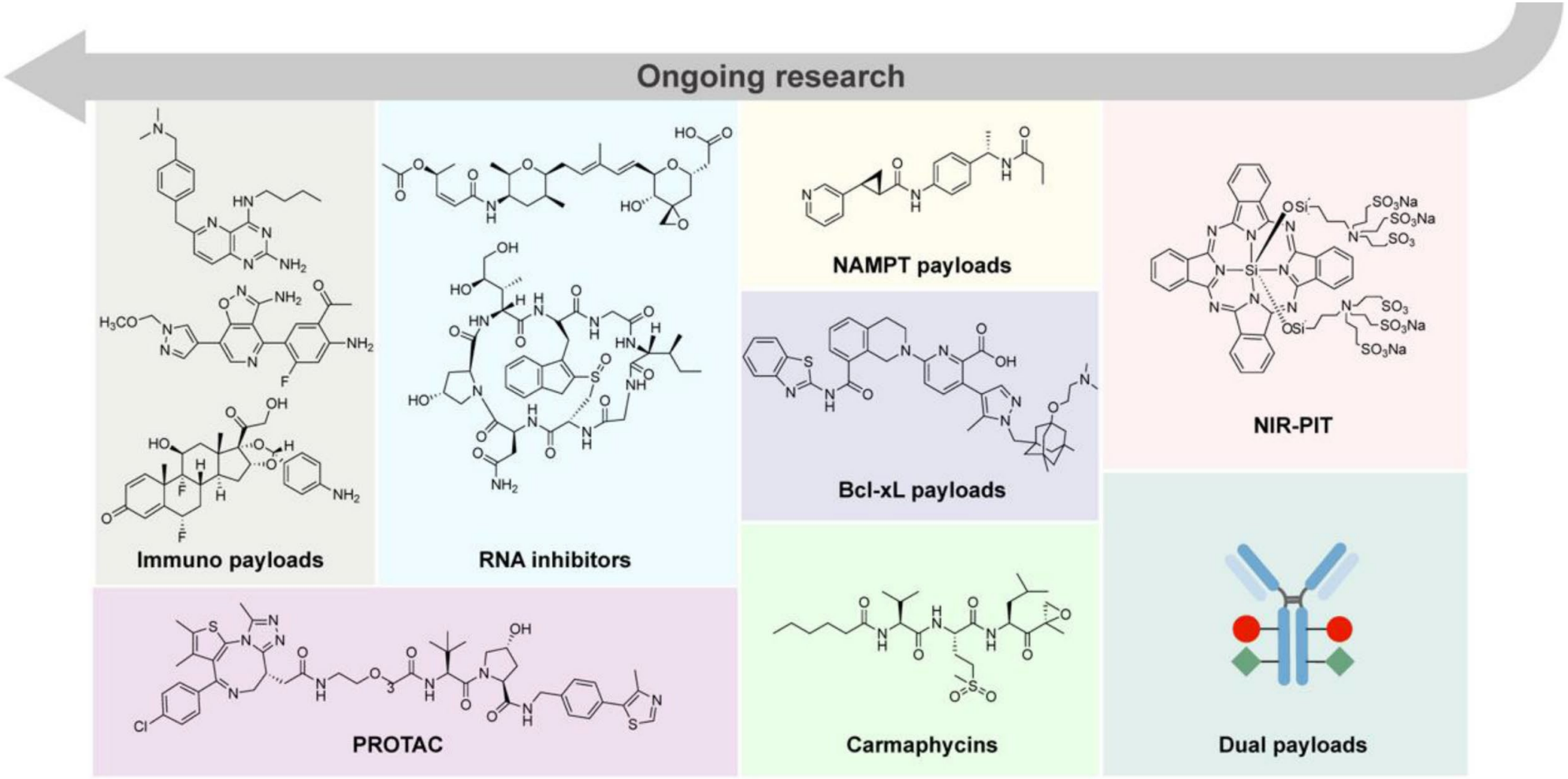
Key advantage
Overcomes antigen heterogeneity

Examples of BsAbs ADCs in the clinic

Type	Drug	Target	Payload	Phase	Country
EGFR	BL-B01D1	EGFR x HER3	TOPi	I/II/III	CN, US, EU, JP
	AZD9592	EGFR x c-MET	TOPi	I	US, EU, AU, CN, JP
	M1231	EGFR x MUC1	Hemiasterlin	I	US, CA
HER2	TQB-2102	HER2 x HER2	TOPi	I/III	CN
	JSKN003	HER2 x HER2	TOPi	I/II/III	AU, CN, US
	ZW-49	HER2 x HER2	Auristatin	I	US, CA, AU, SK
	MEDI4276	HER2 x HER2	Tubulysin	I	US
	KM501	HER2 x HER2	MTI	I	CN
MET	REGN5093-M114	MET x MET	Maytansinoid	I/II	US
FRα	IMGN151	FRα x FRα	DM21	I	US, EU, AU
TROP2	AK146D1	TROP2 x Nectin4	Not disclosed	I	US, AU, CN
PD-L1	DB-1419	B7-H3 x PD-L1	P1003	I/II	US, AU, CN

Gu, Y. et. al. Acta Pharmaceutica Sinica B 2024;14(5):1965-1986

ADC Payload Development



Multi-Payload ADCs

Dual-Payload ADCs showcased at AACR in April 2025

● Phase I ● IND Filing soon ● Preclinical

Payload mechanisms	Tubulin inhibitor	ATR inhibitor	Immune agonist	DDR / Tubulin inhibitor	Nucleoside analogue	RNA Pol II inhibitor	TOP1 inhibitor
TOP1 inhibitor	TROP2 *CATB-101*	HER2 *CLIO-8221*	Not disclosed *Undisclosed (Sutro)*	Not disclosed *STRO-00X/Y*	HER2 x HER2 *DXC018*	TROP2 *KH815*	NaPi2b *ARC-201*
	CDH6 x FRa *TJ102*	TROP2 *CBB-120*	Not disclosed *QHL-1096*				
	EGFR x HER3 *JSKN021*		TROP2 *BR-113*				
	Nectin-4 *Undisclosed (Araris)*						

Undisclosed

- CEACAM5 *IBI3020*
- TROP2 *ADC2192*
- HER2 *ADC2202*
- GPC3 *AD2C-Oncology*

Mullard A., Nature Reviews Drug Discovery 2025; **24:** 573-576

Conjugates: then, now and future

The road ahead: current conversations

CASSS VIRTUAL SUMMIT

May 28, 2026

TACKLING BIOCONJUGATE CHALLENGES

SESSION I: Control of Impurities

SESSION II: Comparability

There is no clear regulatory framework for ADCs and the next generation of bioconjugates; these newer modalities often require new science and regulatory approaches to product and process understanding.

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SESSION I: Control of Impurities

Chairs: Katie Duncan, Allison J Wolf

Impurity Qualification Requirements for Drug-Linkers Related Impurities Used to Generate ADCs

Osama Chahrour | AstraZeneca

Control of PMO-linker Impurities in Antibody-PMO Conjugates

Mitch Martini | Avidity Biosciences

Managing Bioconjugate Heterogeneity Related to Drug-Linkers

Kevin Cole | Eli Lilly and Company

Charge Variant Control Strategy for Late-Stage Antibody Drug Conjugates

Carrie Sowers | AstraZeneca

Panel Discussion

Additional Panelists: Steffen Gross | Paul-Ehrlich-Institut
Paresma (Pinky) Patel | Gilead Sciences

- As payload/linker complexity increases and improved analytical technologies enable better post-conjugation impurity detection and purging, should reassess:
  - applicability of small molecule number-based impurity thresholds for drug-linker intermediates
  - relevance of conventional biologics assays (like charge variants, bioassay) for conjugates
- With components spanning small and large molecule spaces and no established regulatory framework, control strategies for bioconjugate components should be phase appropriate and focus on ensuring quality, consistency and safety of final bioconjugate
- Leverage deep molecule understanding, prior knowledge and platform approaches to frame science- and risk-based strategy justifications, and engage health authorities early to discuss

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SESSION II: Comparability

Chairs: Hirendrasinh Parmar, Dawn Spiller

CMC Regulatory Considerations for ADCs - From the Biologics Perspective

Nailing Zhang | CDER, FDA

Analytical Comparability Approach for an Antibody Drug Conjugate

Tawnya Flick | Gilead Sciences

Comparability Risk Mitigation: Identification of a New Low-Level Heavy-Heavy Chain Variant in an ADC

Yazhe Wang | Merck & Co.

Designing Risk-Based Analytical Comparability: Strategic Considerations for ADCs in Late-Phase Development

Qingyuan Liu | AbbVie Inc.

Panel Discussion

Additional Panelists: Holly McCaleb | Pfizer
Isha Nasa | Health Canada

- Bioconjugate comparability follows ICH Q5E principles
  - For intermediates, also consider downstream impact. May need to forward process one batch to DS, especially for later-phase clinical and post-launch changes
  - Leverage accelerated and stressed stability studies with degradation-representative conditions
  - Given complexity, may face more characterization challenges than traditional mAbs
  - New modalities may bring novel challenges that require new analytics
- Understanding methods capability and use of orthogonal analytical methods can be essential to detect and understand change impacts
- Phase-appropriate approaches should be applied to set comparability criteria

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Moderators:
Helen Newton,
Stuart Finnie,
Karoline Bechtold-Peters

EFPIA Satellite Session Part 2 Comparability Assessment for Bioconjugates: Regulatory Expectations, Practical Experience, and Emerging Challenges

Additional Panelist:
Michelle Czajkowski | Gilead

Regulatory Perspectives on Comparability Evaluation of Antibody-Drug Conjugates

Pavel Šimek | SÚKL

Comparability Strategies for Bioconjugates

Thomas Pohl | Novartis

Beyond One-Size-Fits-All: Experiences with Comparability Strategies for ADCs

Katie Duncan | GSK

Prior Knowledge and Platform Approaches: How These Concepts Can Be Used for mAB Conjugates

Veronika Jekerle | EMA

- Bioconjugate comparability follows ICH Q5E principles
  - Assessment should follow risk-based approaches focused on the point of change (with impact to overall product quality assessed), supported by robust scientific evidence and process/product understanding
- There are diverse and at times inconsistent global expectations for ADC comparability.
  - Amount of data/number of batches to support a change depends on the product, process understanding, risk and predictability of change and stage of development. And being complex products, more data may be expected for bioconjugates than a typical DS
  - Open sharing of experiences and being transparent with regulatory agencies about the rationale behind other agencies' decisions may be helpful to drive global consistency. Don't be afraid to challenge agencies' decisions, if appropriate

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Topics/Questions for future exploration

- **What new types of bioconjugates are being developed, and are there any unique challenges associated with these new modalities?**
  - Challenges with charge variants method post-conjugation
  - Considerations for non-cytotoxic payloads
  - Approaches/analytical toolboxes to evaluate drug-linker impurities at DS stage
- **'Modernization' of regulatory expectations of bioconjugates given site specific conjugation control and advances in analytical capabilities and increasing diversity in modality**
  - Payload-linker related impurities identification/reporting thresholds
  - Bioassay requirements for oligonucleotides/synthetic peptides
  - Patient-centric control strategy for unavoidable drug-linker related species in the DS, particularly for species that pose no patient risk or efficacy impacts
- **Global harmonization of control strategies and RSM designations acceptance**
- **How to share knowledge/advice received/assessments across regulatory agencies?**
- **How to utilize platform or prior knowledge to support development** (esp. for investigational products)**?**
- **Considerations for biosimilar bioconjugates**
- **How is AI being leveraged in bioconjugate development?**

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