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Workshop III: Considerations for Pre-Approval of CMC Regulatory Strategies

CMC Considerations For Bioconjugates and Multi-specifics：A Regulator's Perspective

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The views expressed in this presentation are those of the author and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Outline

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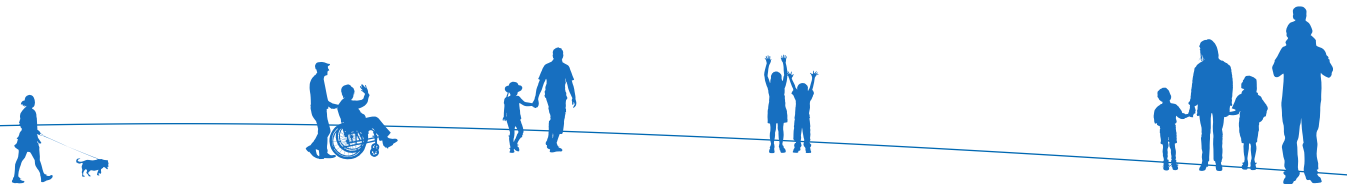
- Overview of bioconjugates and multi-specifics
- Our review experience
- Recommendations for Applicants



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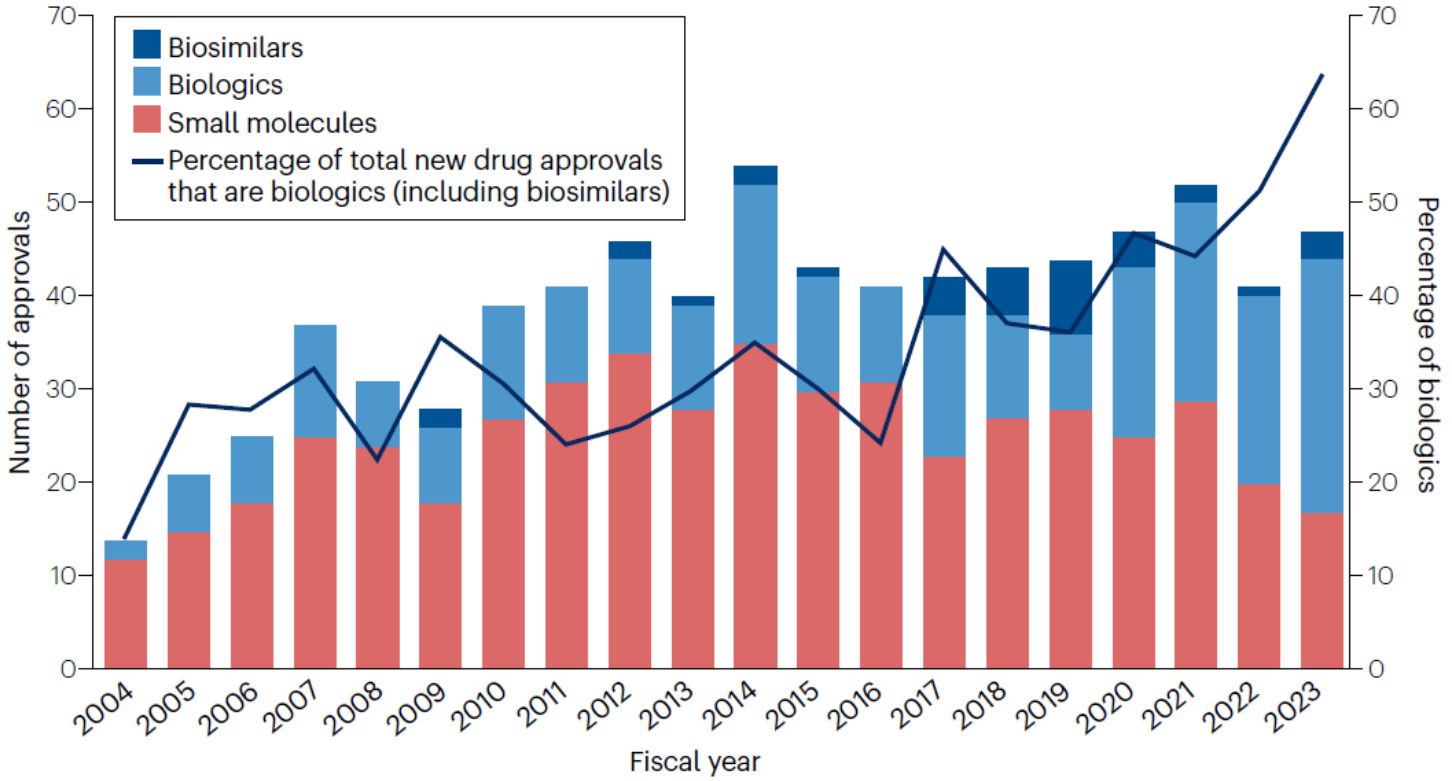
Trends in new drug approvals in Japan



Kuribayashi, R. et al.Nature Reviews Drug Discovery 24, 12-13 (2025)

- The proportion of biologics (light blue) in the new drug approved has increased.
- Two-thirds of the new drugs approved in Japan in FY2023 are biological drugs.

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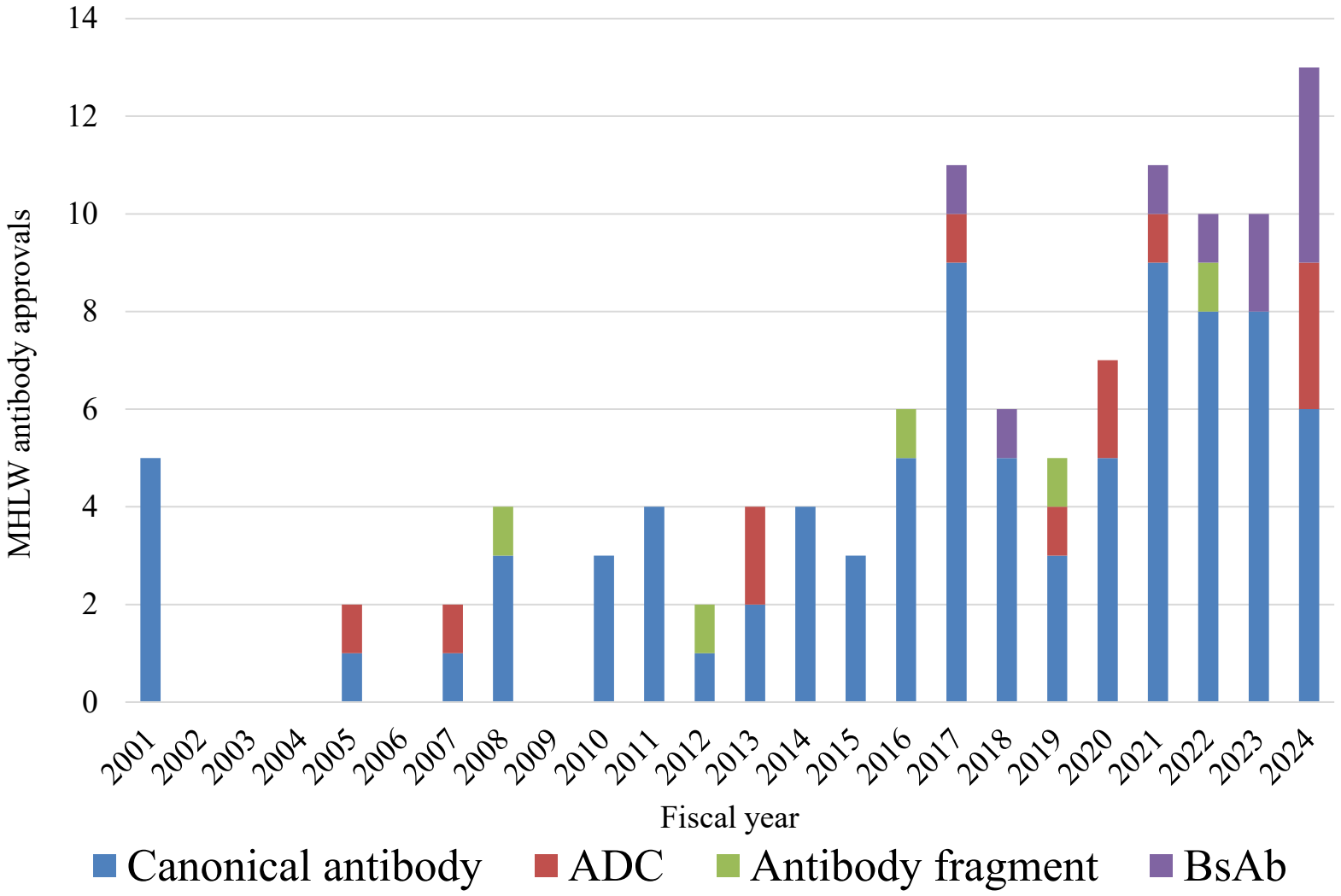
Trends in biologics approved in Japan

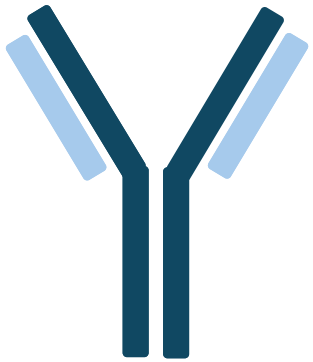


Adapted from Hariu, A. et al. AAPS J. 27: 105 (2025)

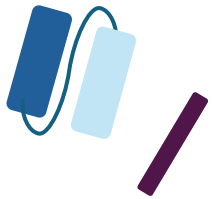
- ADCs and bi-specifics have been emerging as important contributors to overall approvals.
- It can be expected that the large number of ADCs and bi-specifics will be approved in 5-10 years in Japan.

Bioconjugate formats

Carriers



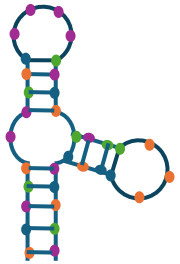
IgG (including Multi-specifics)



IgG fragment

Protein/peptides

Polymer



aptamer

Linkers

Cleavable linkers:

- Protease sensitivity
- pH sensitivity
- Glutathione sensitivity
- Disulfide linkage

Non-cleavable linkers

Chemically linked

Payloads

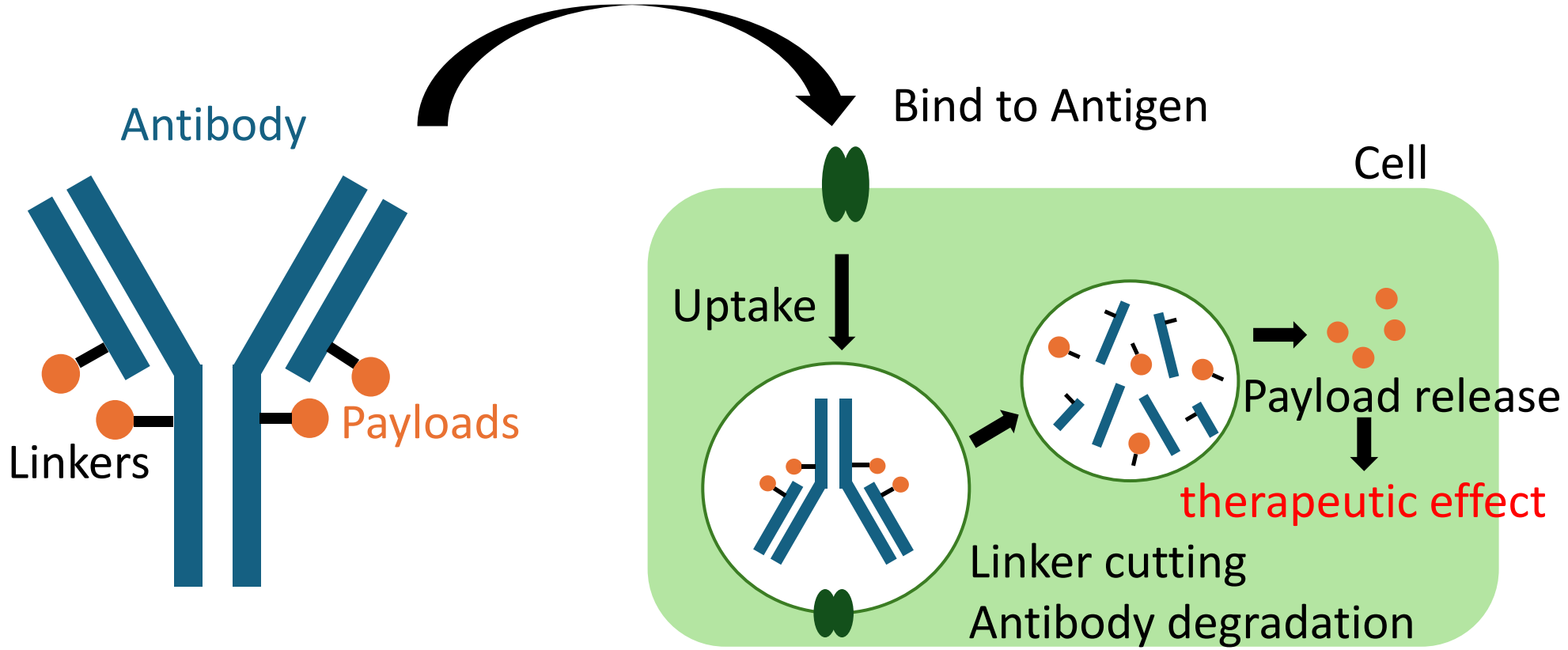
Small molecules
(ex. Cytotoxics, RI, Chelators, etc.)

Protein/peptides

Anti-sense Oligonucleotides

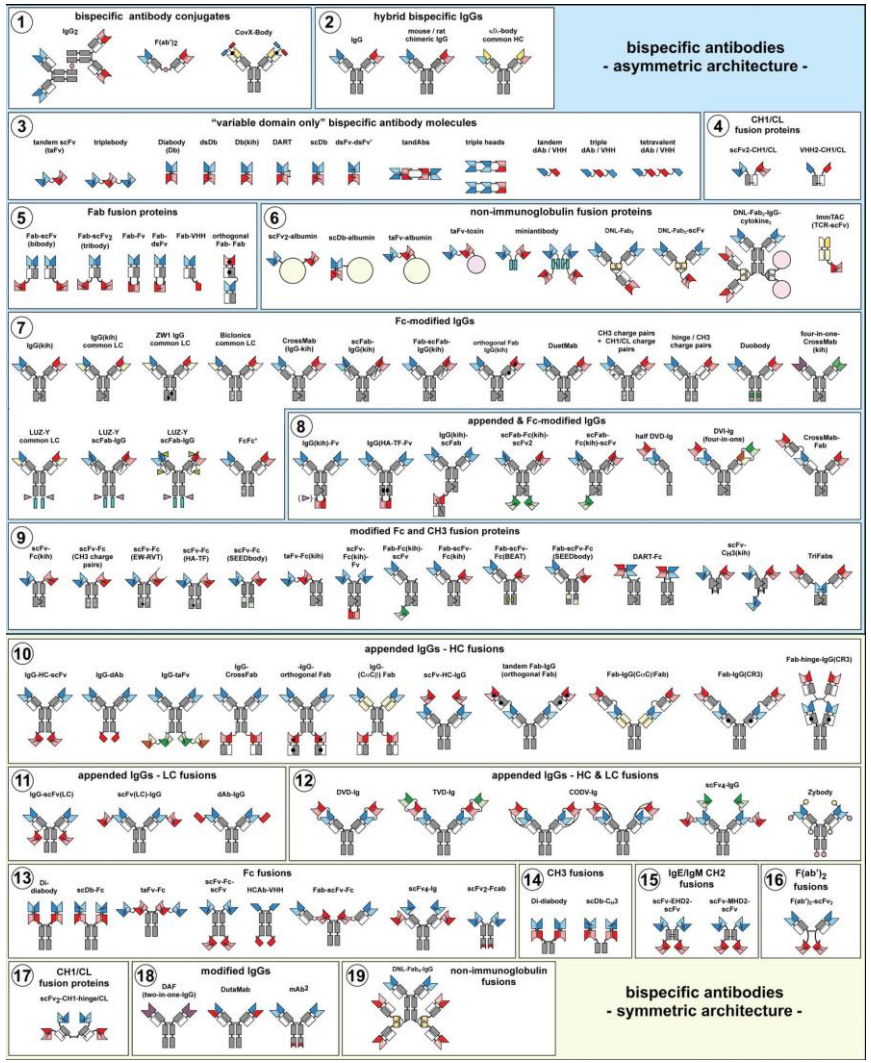
siRNA

Basic MOA of ADCs



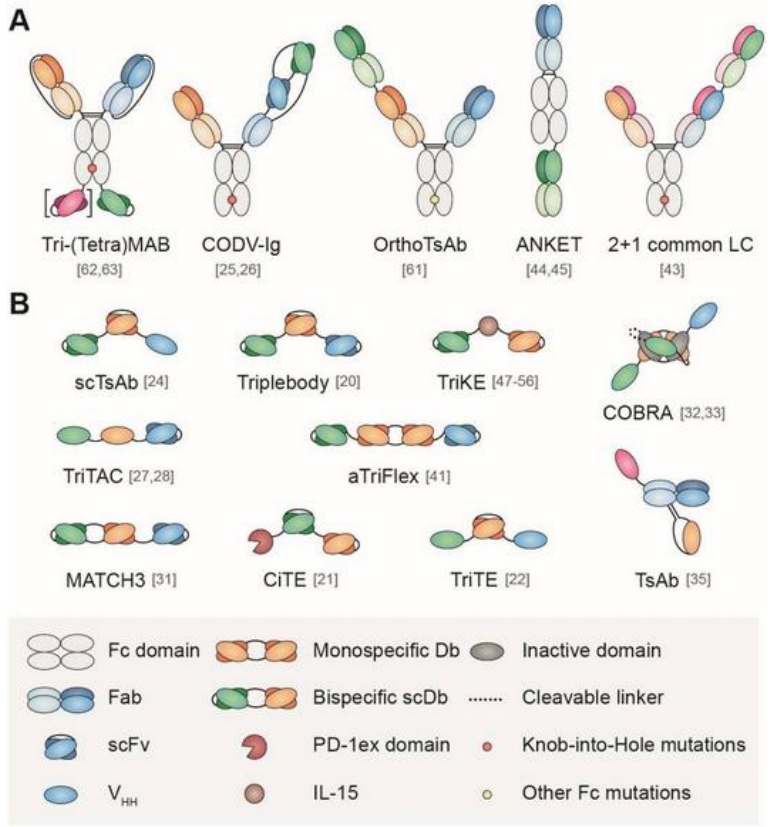
Multi-specific antibodies formats

Bi-specifics formats



Brinkmann, U. et al. MAbs. 9(2):182-212.

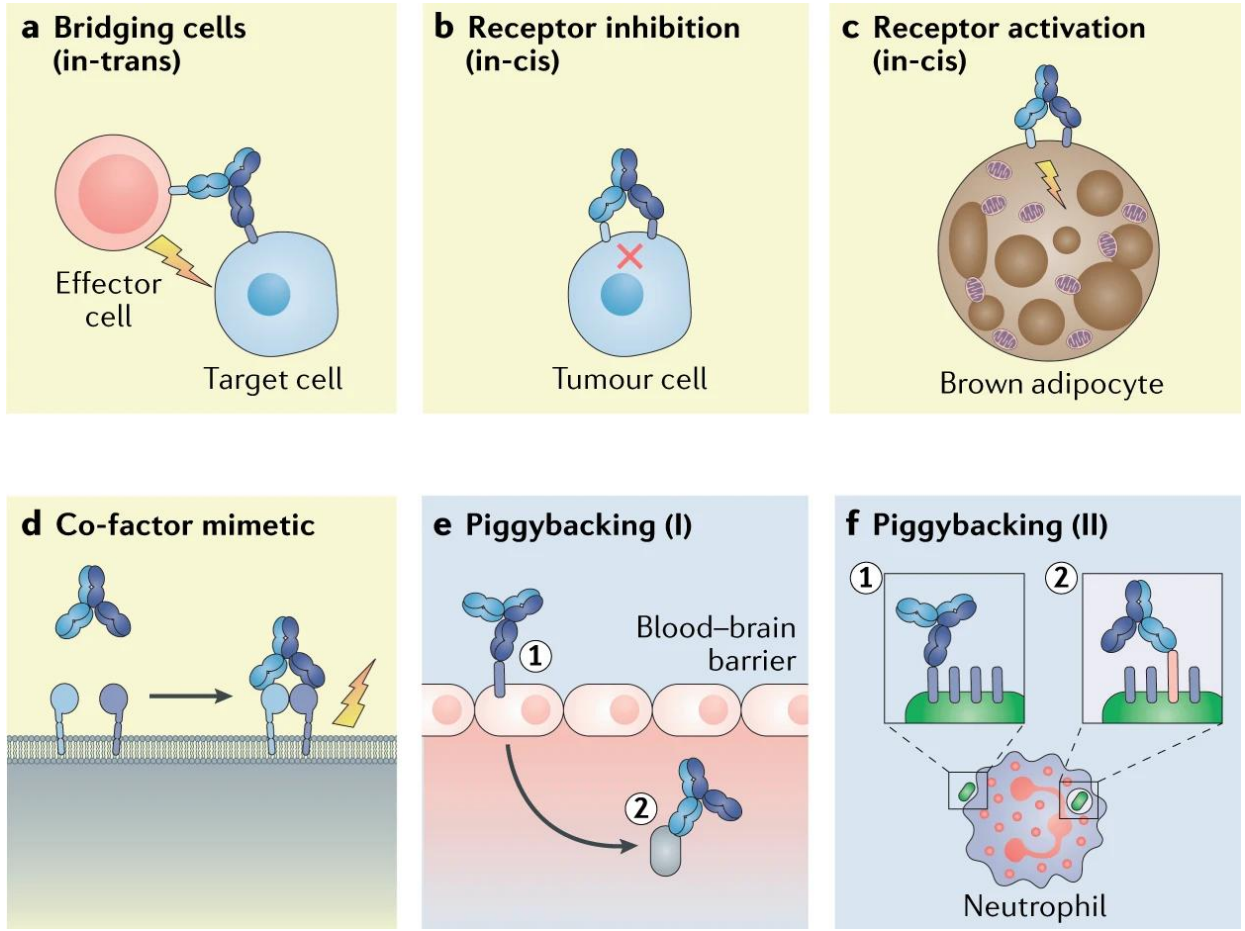
Tri-specifics formats



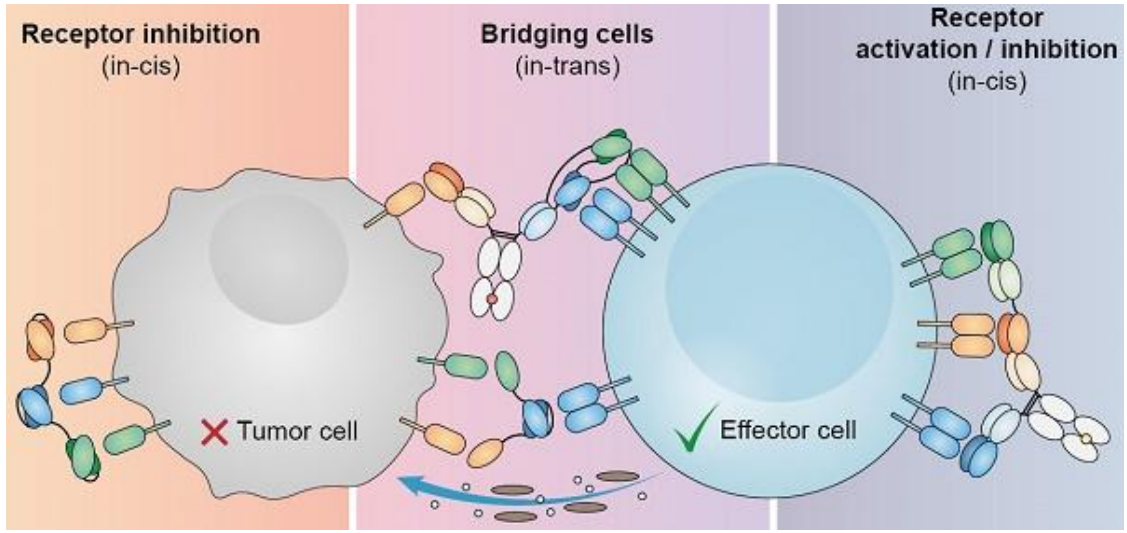
Tapia-Galisteo, A. et al. Theranostics. 22;13(3):1028-1041.

- Multi-specifics can simultaneously bind to two or more targets.

Basic MOA of Multi-specific antibodies



Labrijn, A.F. et al. Nat Rev Drug Discov 18, 585–608 (2019).



Tapia-Galisteo, A. et al. Theranostics. 22;13(3):1028-1041.

- Multi-specifics can bridge two cell types or to engage two or more molecules on the membrane of one cell.

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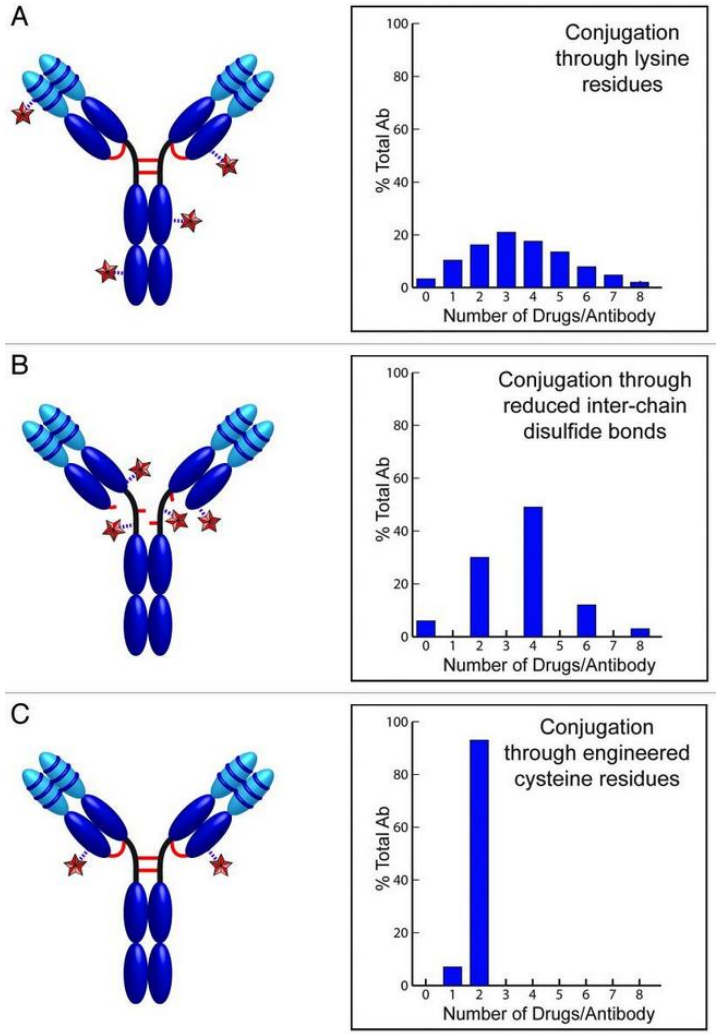
Approved Bioconjugates in Japan

Approval	Product（Brandname）	Target	Payloads	DAR
2005	Gemtuzumab ozogamicin (Mylotarg)	CD33	*N*-acetyl calichecheamicin	1.8-3.0
2008	Ibritumomab tiuxetan (Zevalin)	CD20	MX-DTPA + ^{90}Y or ^{111}In	-
2013	Trastuzumab emtansine (Kadcyla)	HER2	Maytasine	Average 3.5
2014	Brentuximab vedotin (Adcetris)	EGFR	MMAE	3-5
2018	Inotuzumab ozogamicin (Besponsa)	CD22	*N*-acetyl calichecheamicin	About 6
2019	Trastuzumab deruxtecan (Enhertu)	HER2	Extecan derivative	About 8
2020	Cetuximab sarotalocan (Akalux)	EGFR	Phthalocyanin derivative	2-3
2020	Polatuzumab vedotin (Polivy)	CD79b	MMAE	3-4
2021	Enfortumab vedotin (Padcev)	Nectin 4	MMAE	4
2024	Sacituzumab Govitecan (Trodelvy)	TROP-2	Camotothecin derivative	Average 8
2024	Datopotamab deruxtecan (Datroway)	TROP-2	Camotothecin derivative	Average 4
2025	Tisotumab vedotin (Tivdak)	TF	MMAE	Average 4
2025	Belantamab mafodotine (Blenrep)	BCMA	MMAF	Average 4

https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html

How are linker-drugs conjugated to an antibody?

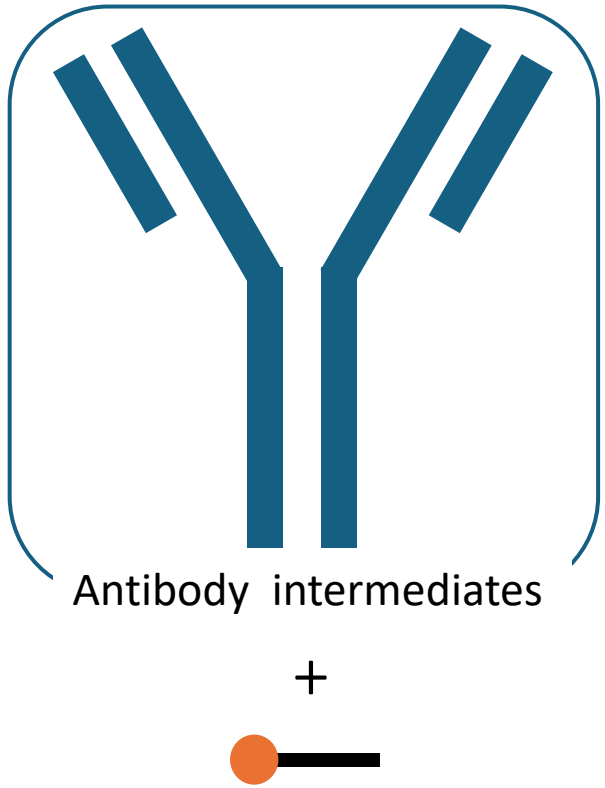


Panowski S. et al. MAbs. 6(1):34-45.

- ADC product using traditional conjugation(A or B) is known to results in high heterogeneity in both drug to antibody ratio (DAR) and location of conjugation site.
- Site-specific conjugation through such as engineered cysteine residues (c) tend to decrease this heterogeneity.
- DS specific QAs
  - Drug to antibody ratio (DAR)
  - Conjugation site of payload
  - Non-conjugated antibody
  - Free drug related impurities
  - Cytotoxicity assay, etc

Control strategy：antibody intermediates

- These specifications have to be established based on ICH Q6B.
- However, for low-risk QAs that are common to both the intermediate and the DS, it may be acceptable to only set specifications for either the intermediate or the DS if justified.



Case study：DAR affected ADCC activity

- An ADC that has ADCC activity as MOA.
- It has been observed that the effector function of DS is altered within the acceptance criteria for afcosylated glycans and the drug-antibody ratio.

How should they be managed?

We requested that the effector function of DS should be appropriately controlled.
The sponsor responded that the effector function would be controlled by setting FcγRI, FcγRIIa, and FcγRIIIa binding activity in the specification tests of the DS.

The above control strategy were accepted based on the following points.

- Binding to FcγR is necessary for the expression of effector function.
- FcγR binding activity correlated with effector function over a range of afcosylated glycan ratios and drug-antibody ratios
- DP process is unlikely to affect FcγR binding activity.

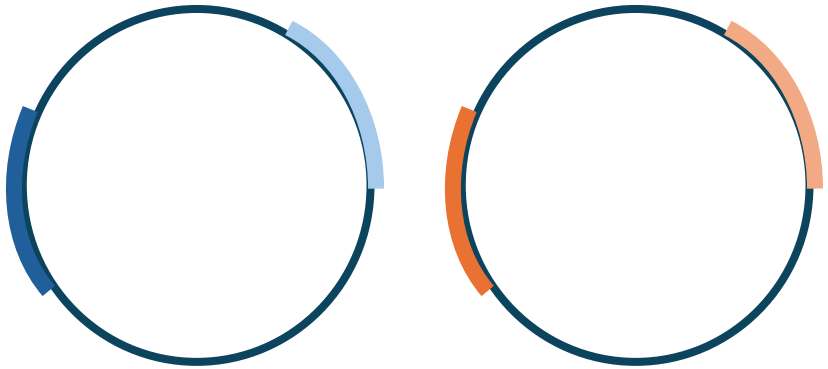
Approved Multi-specifics in Japan

Approval	Product （Brandname）	Targets		Valence and Formats	Producing method
2018	Emicizumab (Hemlibra)	FIXa	FX	1+1 ART-Ig	Genetic engineering
2018	Blinatumomab (Blincyto)	CD19	CD3	1+1 BiTE (scFv-scFv)	Genetic engineering
2022	Faricimab (Vabysmo)	VEGF-A	ANG2	1+1 CrossMab	Genetic engineering
2022	Ozoralizumab (Nanozora)	TNFα	HSA	2+1 Nanobody (VH-VH'-VH)	Genetic engineering
2023	Epcoritamab (Epkinly)	CD20	CD3	1+1 Duobody	Chain exchange
2024	Elranatamab (Elrexfio)	BCMA	CD3	1+1 BsAb	Chain exchange
2024	Amivantamab (Rybrevant)	EGFR	MET	1+1 Duobody	Chain exchange
2024	Tarlatamab (Imdelltra)	DLL3	CD3ε	1+1 Fc-(scFv)2, Fc-BiTE	Genetic engineering
2024	Teclistamab (Tecvayli)	BCMA	CD3ε	1+1 Duobody	Chain exchange
2024	Mosunetuzumab (Lunsumio)	CD20	CD3ε	1+1-KiH	Post-expression assembly
2025	Talquetamab (Talvey)	GPRC5D	CD3	1+1 Duobody	Chain exchange

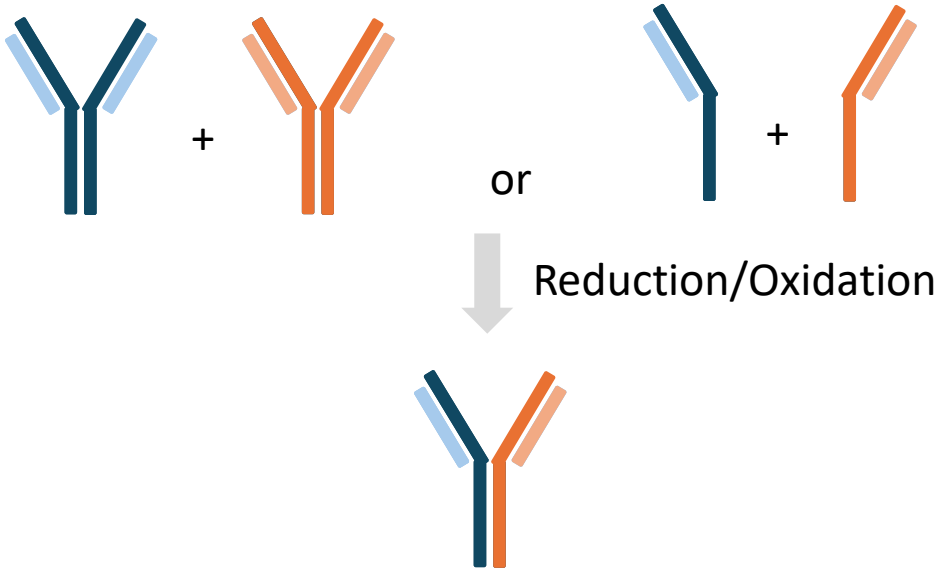
https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html

How are bispecific antibodies manufactured?

Genetic engineering

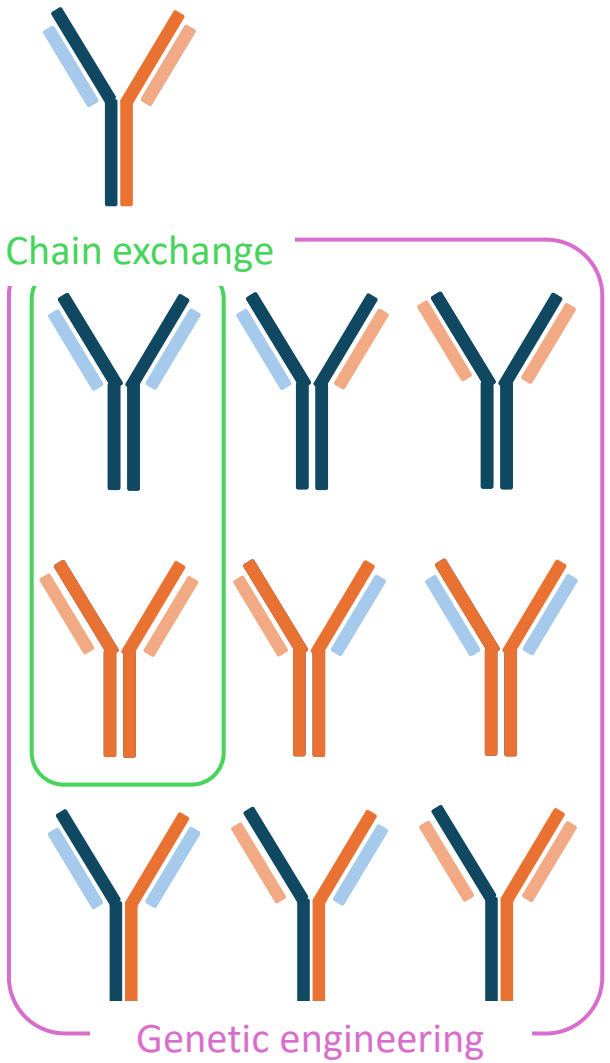


Chain exchange/Post-expression assembly

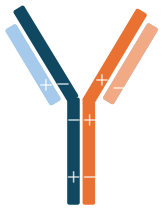


- There are two main manufacturing method.
- Chain exchange is currently more commonly used method for producing IgG-like bsAbs.

Control strategy：Mispairing of Multi-specifics




CrossMab

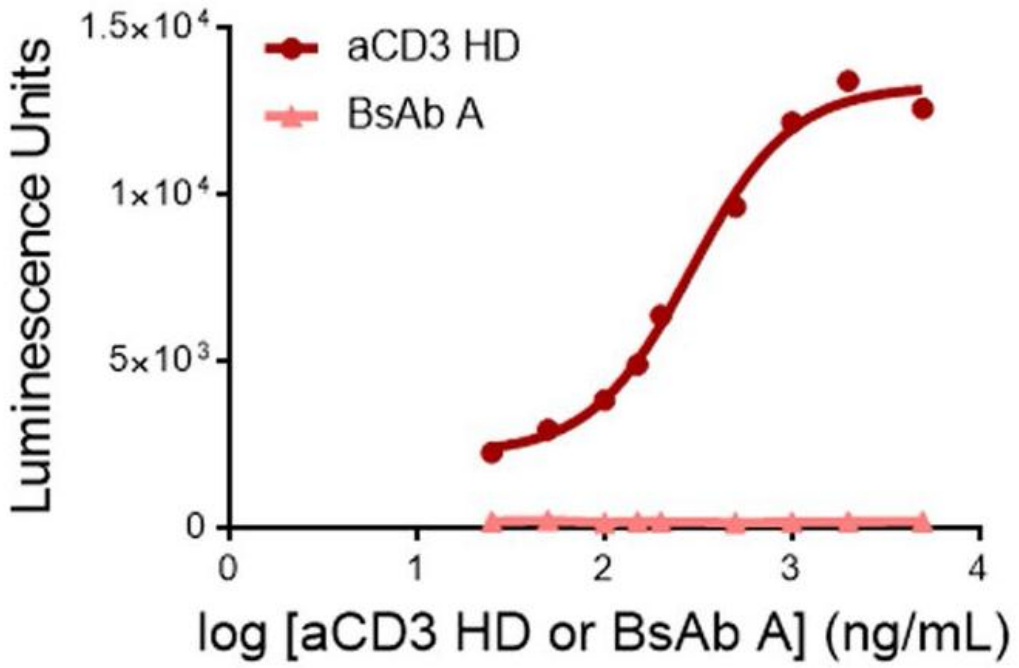

Charge-pairs


Knobs into Holes

- Nine undesirable mispairing forms are potentially generated.
- It is difficult to remove this mis-paired impurities by conventional purification processes because the target substance and mispairing forms have similar properties.
- To avoid mispairing, various strategy have been introduced in recent years.
- It is important to identify the potential mispairing forms at each manufacturing process and to establish a robust control strategy to control them.

Schaefer W, et al. Pro natl Acad Sci USA. 2011; 108(27): 11187-92, Bram E,et al. iScience.2021; 24(12):103447

Control strategy：impurities



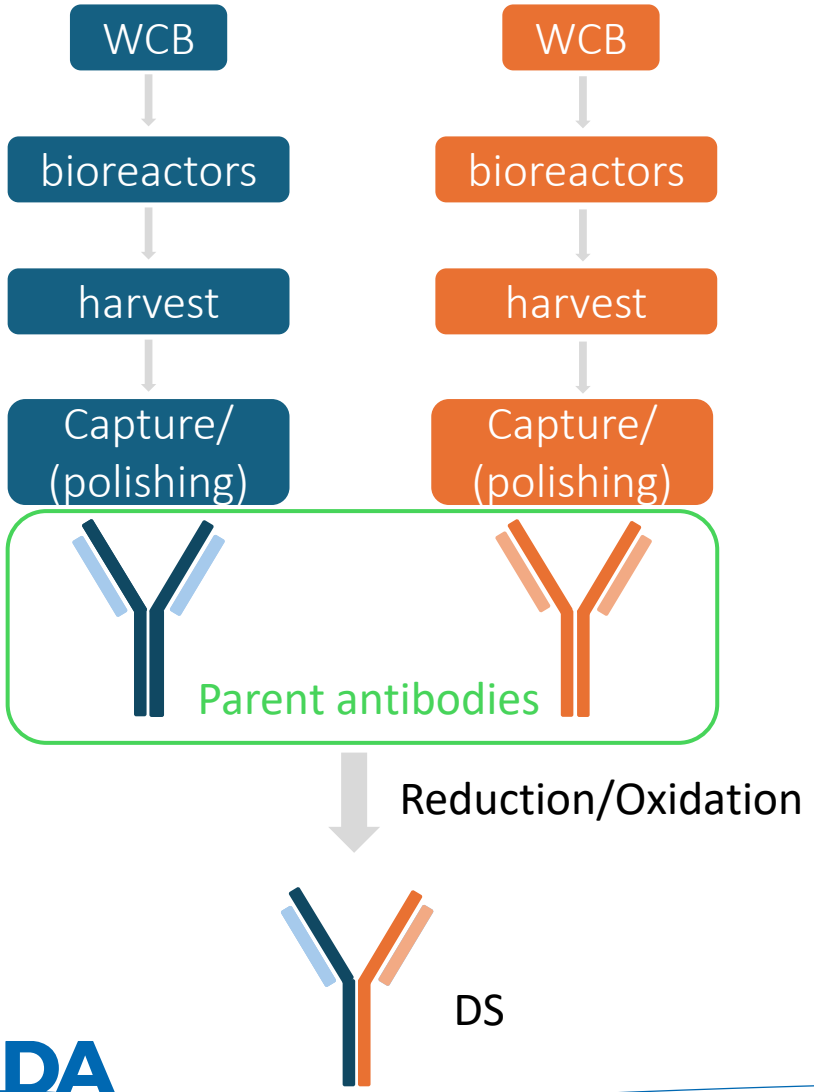
Standard dose-response curve of aCD3 HD(circle) and BsAb A (triangle) in T-cell-activation assay

Lee, H.Y. et al. Sci Rep 9, 3900 (2019).

- Anti-CD3 homodimer, one of mis-paired impurities of BsAbs having anti-CD3 arm is known to activate T-cell in absence of target tumor cell.
- This off-target T-cell activation can induce cytokine secretion, and it triggers an undesired immune response in patients.
- This impurity need to be properly controlled.

BsAb = Bispecific antibody

Control strategy：Parental antibodies



- We have accepted risk based approach at parental antibody point.
- This is because the properties of the parental antibodies are not necessarily carry over to the DS.
- Critical quality attributes that affect the final DP may need to be controlled at parental antibody stages.

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Case study：setting up biological activity test for bsAbs

- A bsAB that inhibits ligand binding to receptor A and receptor B, and mediates ADCC and FcR-mediated trogocytosis.

How should biological activities be managed?

The sponsor explained that they would manage biological activities that may contribute to efficacy as follows:

- ADCC activity and receptor A binding : ADCC activity assay using cells with high receptor A expression.
- receptor B binding : ELISA assay.
- Trogocytosis is Indirectly controlled by the above biological activity assays and by binding affinity to FcγR (through oligosaccharide analysis and CE-SDS).
- Oxidation forms and isomerization forms that contribute to receptor A or receptor B binding is controlled by specification.

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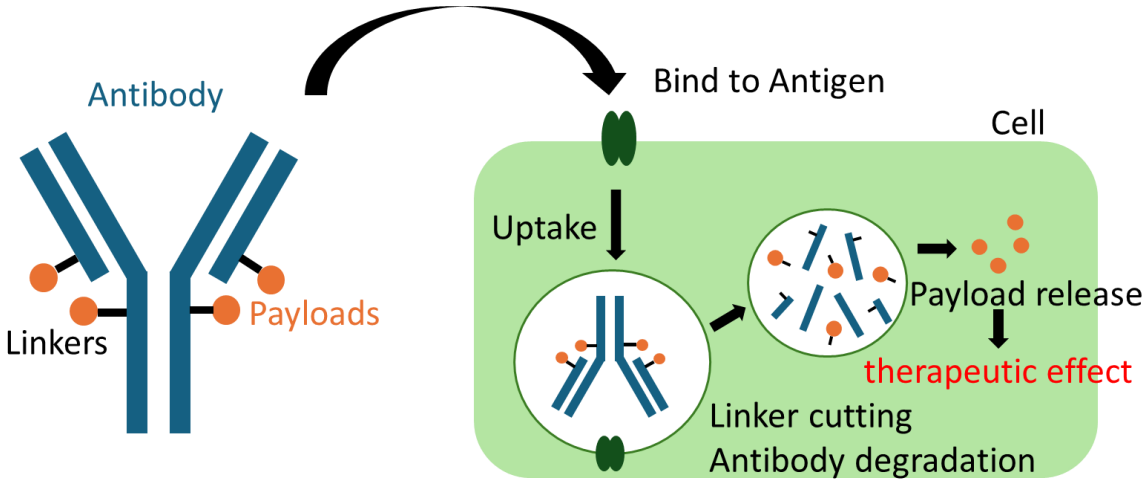
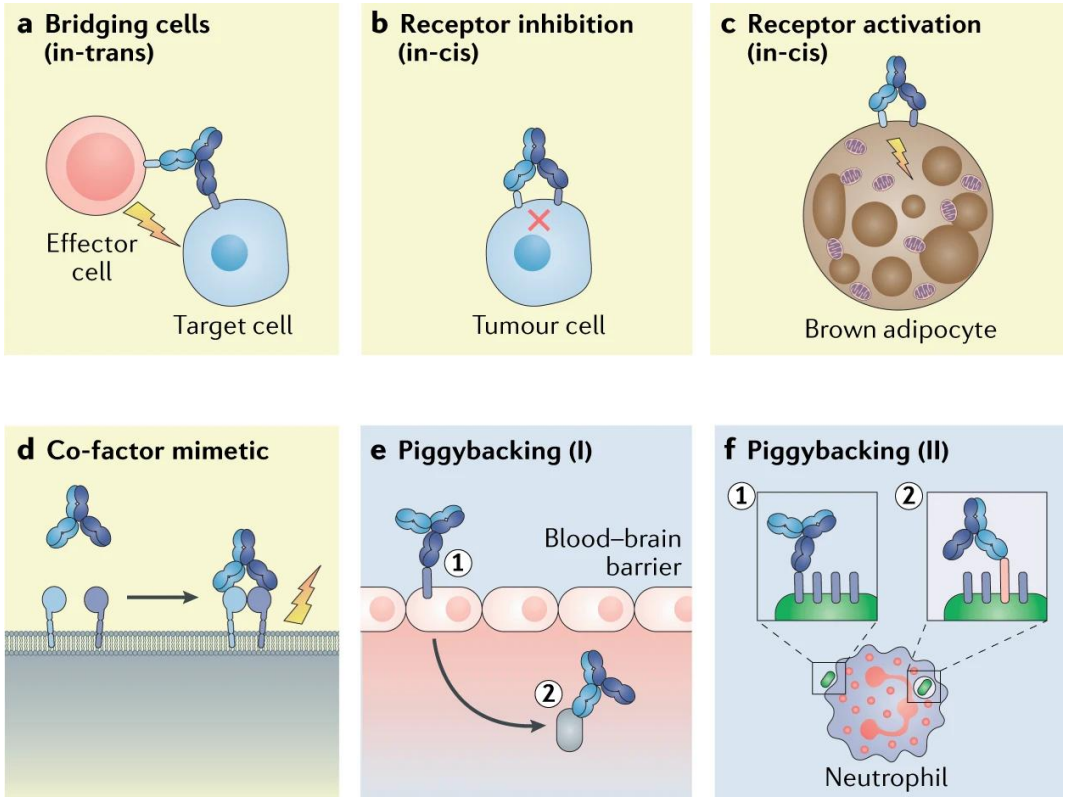
Biological activity testing as specifications

- Bioconjugates and multi-specifics must be evaluated comprehensively based on all mechanisms of action (MoAs), which may require multiple bioactivity testing setups.



Fc effecter function?



Labrijn, A.F. et al. Nat Rev Drug Discov 18, 585–608 (2019).

CTD

ADCs

- Antibodies and payloads are key intermediates, and require a comparable explanation to that for the DS, with the regard to the quality control, such as manufacturing processes, quality attribute analysis, and stability.
- It is recommended that CTDs are created for module 2 and 3 for payloads, antibodies, and DS separately.

Bi-specifics

- Provided there are no key intermediates, the composition should resemble that of a standard antibody.

Antibodies and Bi-specifics

- M2.3.S, M3.2.S – DS
- M2.3.P, M3.2.P – DP

ADCs

- M2.3.S, M3.2.S – payloads
- M2.3.S, M3.2.S – antibody
- M2.3.S, M3.2.S – DS
- M2.3.P, M3.2.S – DP

Ongoing public consultations on ICH M4Q（R2）

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Conclusion

- ✓Bioconjugates and multi-specifics represent the next generation antibody formats with a wide range of design possibilities, depending on how different components are cmbined.
- ✓Control strategy to minimize heterogeneity is the key to those molecule quality.
- ✓Biological activity testing must be tailored to each product MoA.

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Thank you for your attention!

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