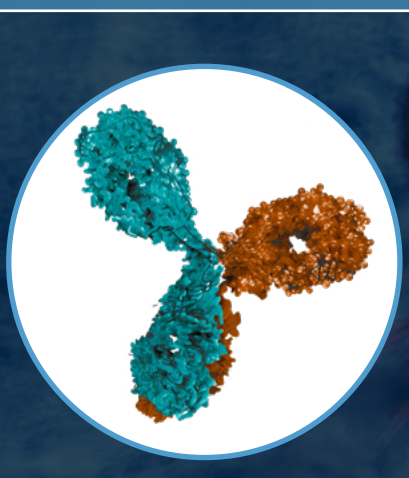
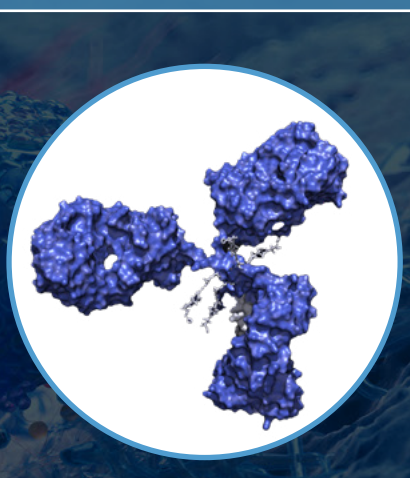
Introduction to Antibody Engineering

Molecular engineering is a long-standing approach to improving the safety and efficacy of therapeutic monoclonal antibodies (mAbs). Bispecific antibodies and antibody drug conjugates (ADCs) are two prominent examples of engineered mAbs. Such mAbs have benefits and limitations that require thorough study prior to choosing what is most appropriate for your application. This infographic presents an overview of the two main types of engineered mAbs, a brief historical timeline, advantages and disadvantages, recent safety and efficacy insights, as well as representative ongoing directions.



Bispecific antibodies



Antibody drug conjugates (ADCs)

Description[1-3]

What
Bind to two different epitopes (same antigen or different antigens)

Purpose
Commonly, tether immune cells to cancer cells

Total current FDA approvals by August 2023
9
(most for blood and solid cancers)

What
Commonly, pharmaceutical chemically linked to the mAb

Purpose
Targeted drug delivery

Total current FDA approvals by June 2023
11
(all for blood and solid cancers)

Historical Timeline[4,5]

- **1961** — **First reported:** for rabbit antibodies
- **1992** — **First clinical trial:** for $CD15^+$ tumors
- **2014** — **First FDA approval*:** blinatumomab for acute lymphoblastic leukemia
- **2021** — **First FDA approval for a solid cancer*:** amivantamab-vmjw for non-small cell lung cancer

**Still-active approvals. In 2009, the FDA approved catumaxomab for malignant ascites, but withdrew approval in 2013*

- **1983** — **First clinical trial:** for advanced renal and ovarian metastatic carcinoma
- **2000** — **First FDA approval:** anti-CD33–calicheamicin for acute myeloid leukemia
- **2019** — **First FDA approval for a solid cancer:** anti-HER2–maytansinoid for metastatic breast cancer

Advantages and Disadvantages[6,7]

Advantages
- Off-the shelf; no need to tailor to the patient as in CAR-T cell therapy
- Can attract additional immune cells, in addition to T cells, to the target

Disadvantages
- Can have a short half-life and thus require continuous IV infusion of >1 week
- Unpredictable success for patients with heavily pretreated cancer

Advantages
- Typically a longer half-life than unconjugated drugs
- Many chemical linkers available to help optimize drug release

Disadvantages
- Limited demonstration of clinical efficacy compared with unconjugated drugs
- Commonly, low delivery to the target and substantial off-target toxicity

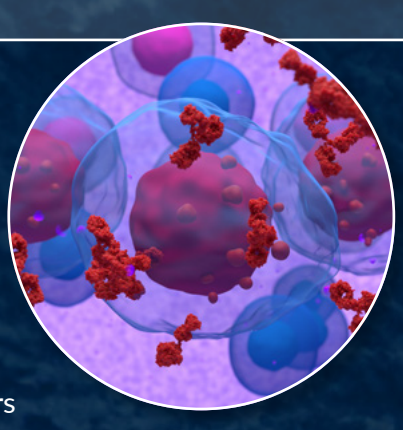
Safety and Efficacy[8,9]

A systematic review of eleven studies that used nine therapeutic bispecific antibodies for multiple myeloma indicates:

- Most frequent adverse event: anemia, **41%**
- Percentage patients who experienced cytokine release syndrome: **60%**
- Percentage patient deaths attributable to the therapy: **0.1%**
- Percentage patients who had a stringent complete response: **22.7%**

Representative modern means of improving the efficacy of ADCs:

- **Linkage chemistry:** PEGylation and peptide-based linkers
- **Masking:** Modifying antibodies with peptides for preferential activation within the tumor



Ongoing Directions[10,11]

Harvard University and Roche Innovation Center
- Preclinical kidney tissue model for assessing bispecific antibodies' on-target, off-tumor side effects
- Bispecific antibodies targeted the Wilms tumor 1 antigen present in podocytes (kidney cell subtype)
- Vascularized kidney model under development for more biologically relevant blood cell perfusion

AstraZeneca
- Phase 3 clinical trial of an ADC—datopotamab deruxtecan—for inoperable or metastatic HR-positive, HER2-negative breast cancer
- Under comparison against various small molecule drugs: eribulin, capecitabine, vinorelbine, and gemcitabine

Therapeutic antibody engineering has substantial scientific and regulatory hurdles, but they are not insurmountable and the FDA has provided considerable guidance.[12,13] Bispecific antibodies and ADCs differ from one another and thus have distinct utility and limitations, as well as distinct safety and efficacy considerations. Ongoing efforts at optimizing therapeutic engineered mAbs are essential to increasing their potential in basic research and clinical settings.[14]

References

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