BISPECIFIC ANTIBODIES

CHAN Cheuk Ka	1155174356
HO Cheuk Ting	1155191856
LEE Tsz Yeung	1155193424
LEE Wonji	1155155850

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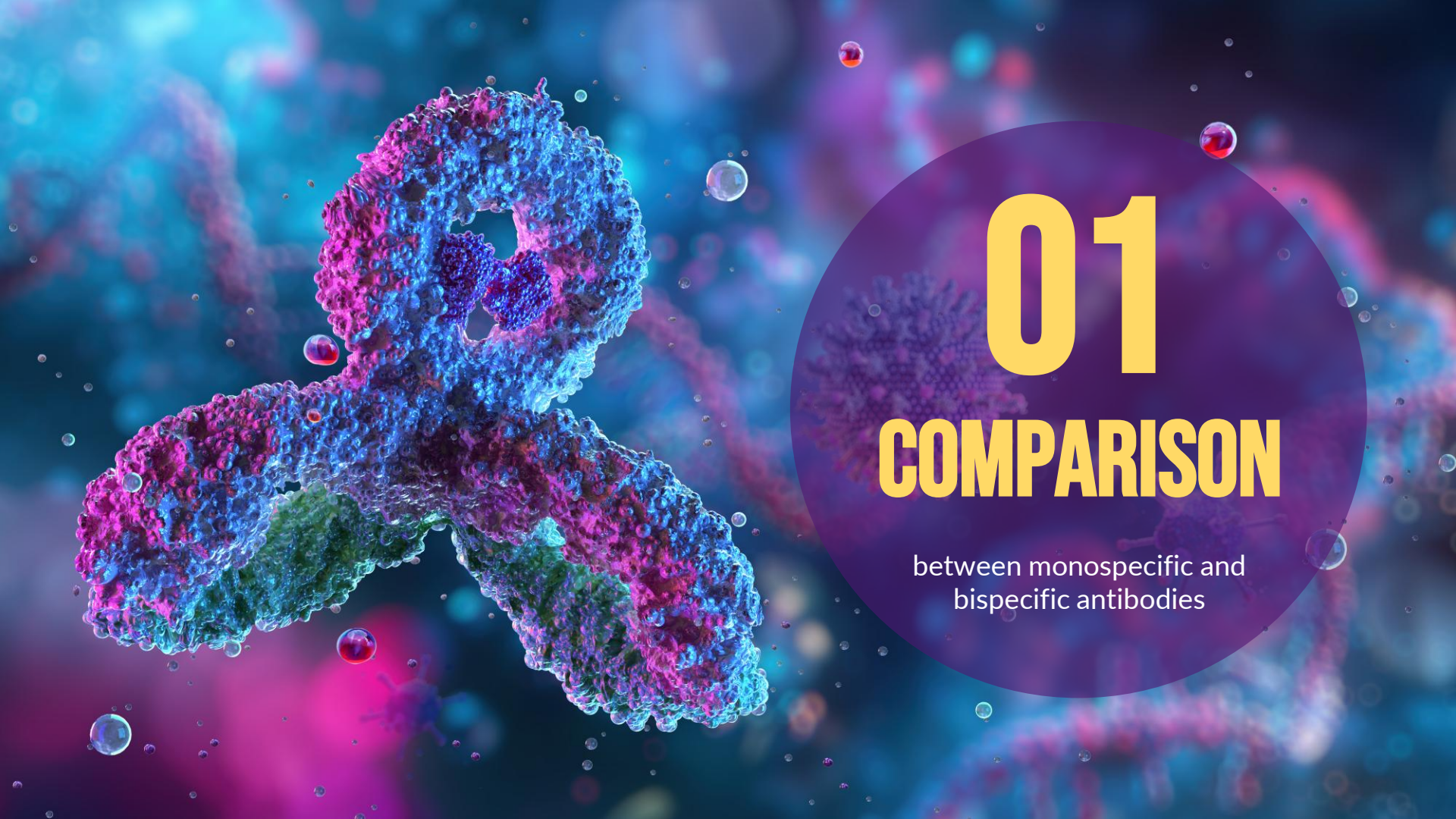
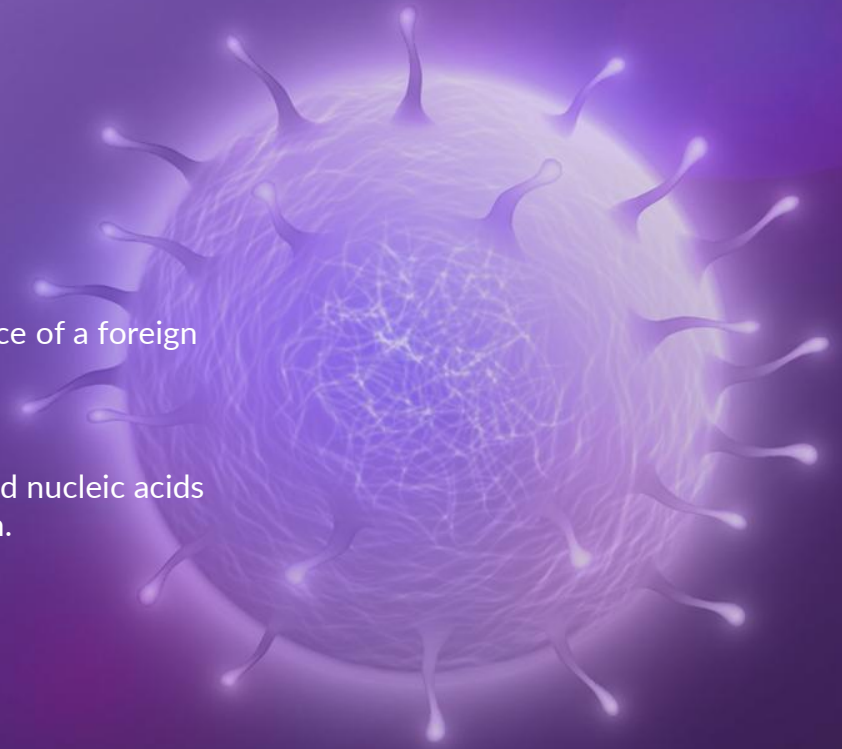

01
COMPARISON
between monospecific and
bispecific antibodies

ANTIBODY

- An animal-synthesized protein, in response to the presence of a foreign substance (e.g., bacteria, viruses), antigen
- Protect the animal from infection

- Has high affinity for the antigens, e.g. proteins, sugars, and nucleic acids
- Recognizes a specific group of amino acids on the antigen.
- Stimulates cells to form an antigen-recognizing antibody



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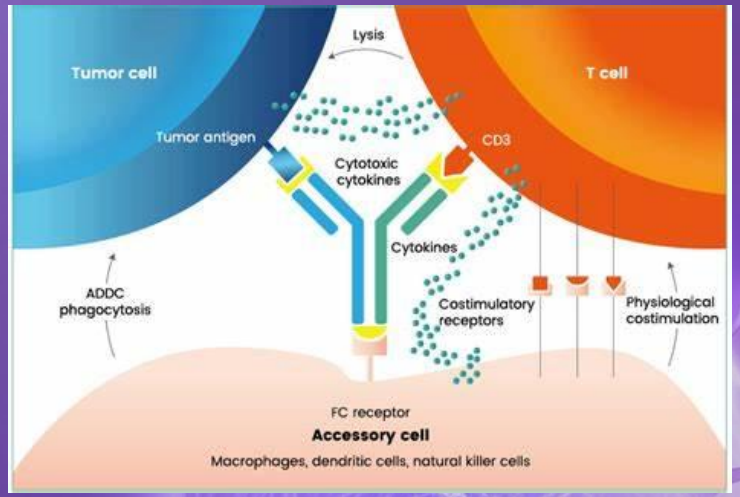
BISPECIFIC ANTIBODIES (BSABS)



https://www.sinobiological.com/resource/antibody-technical/bispecific-antibody

- can attach to two antigens or two epitopes (an antigen portion) of the same antigen at the same time because they have two different binding domains.

- IgG-like BsAbs: similar structure compared to natural antibodies, plus two antigen binding

- Non-IgG-like BsAb: different in structure, modifiable variables for designated applications over natural antibodies similarities

U.S. Food and Drug Administration. "Bispecific antibodies: An area of research and clinical applications." FDA, 14 Feb. 2024, https://www.fda.gov/drugs/spotlight-cder-science/bispecific-antibodies-area-research-and-clinical-applications.

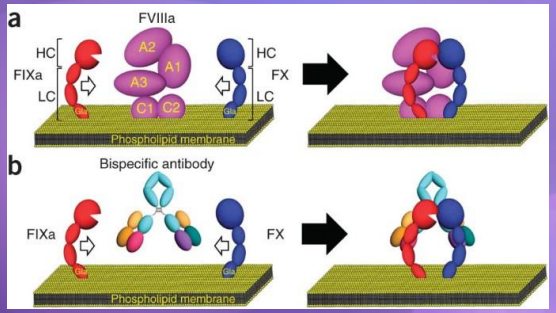
Liguori, L., Polcaro, G., Nigro, A., Conti, V., Sellitto, C., Perri, F., Ottaiano, A., Cascella, M., Zeppa, P., Caputo, A., Pepe, S., & Sabbatino, F. (2022). Bispecific Antibodies: A Novel Approach for the Treatment of Solid Tumors. Pharmaceutics, 14(11). https://doi.org/10.3390/pharmaceutics14112442

02 APPLICATIONS

in oncology

APPLICATIONS OF BISPECIFIC ANTIBODIES IN ONCOLOGY

- **Blinatumomab (CD3 x CD19)**:
  - Approved for acute lymphoblastic leukemia (ALL)
  - Redirects T cells to target malignant B cells
- **Emicizumab (Factor IXa x Factor X)**:
  - Approved for hemophilia A
  - Facilitates blood coagulation by binding both factors
- **Clinical Investigations**:
  - Targeting HER2-positive breast cancer
  - Targeting EGFR-mutant non-small cell lung cancer
  - **Mechanism of Action:**
- T-cell Engager Mechanism:
  - Binds CD3 on T cells and tumor antigens
  - Triggers MHC-independent T-cell mediated cytotoxicity



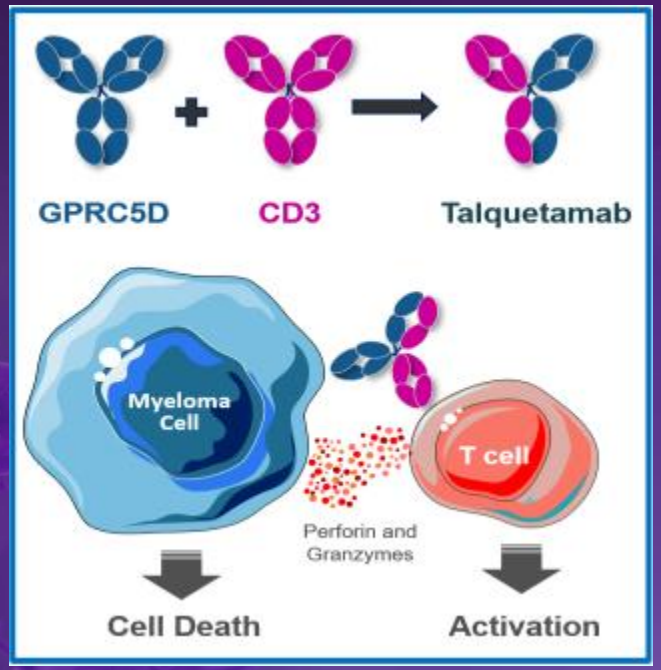
https://www.nature.com/articles/nm.2942

- C. Klein, U. Brinkmann, J. M. Reichert, and R. E. Kontermann, "The present and future of bispecific antibodies for cancer therapy," *Nature Reviews Drug Discovery*, vol. 23, pp. 301–319, Apr. 2024, doi: 10.1038/s41573-024-00896-6.


03
ADVANCES &
CHALLENGES

RECENT ADVANCES

Talquetamab



- **Target** : GPRC5D (multiple myeloma-associated antigen)

  CD3 (T-cell receptor complex)

- **Mechanism** : Binds GPRC5D on multiple myeloma (MM) cells and CD3 on T cells

  Redirects T cells to induce cytotoxicity against MM cells

  MHC-independent T-cell activation

(Approved in 2023)

RECENT ADVANCES

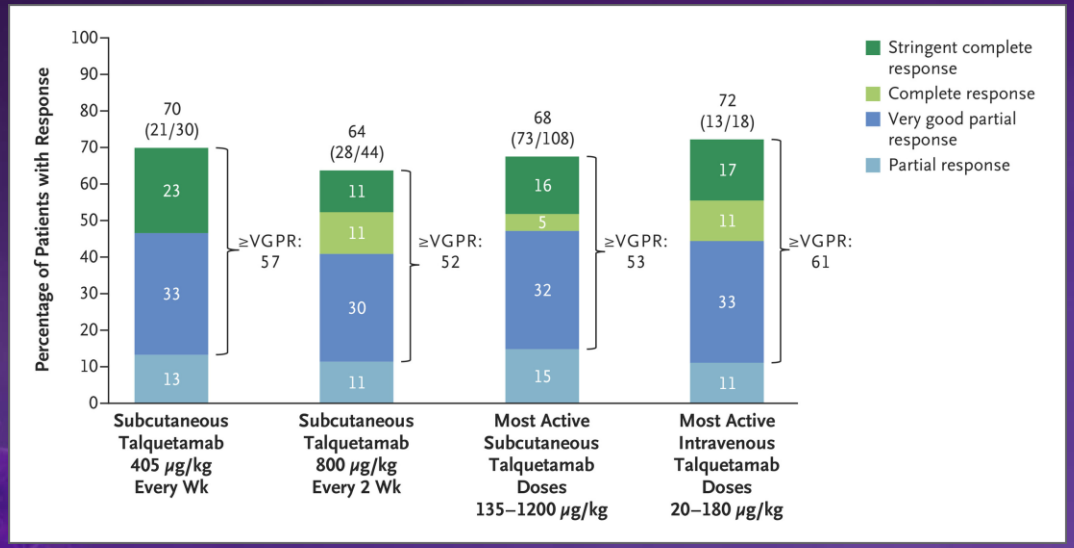


Figure 1. Response to Talquetamab Therapy in Patients with Relapsed or Refractory Multiple Myeloma.

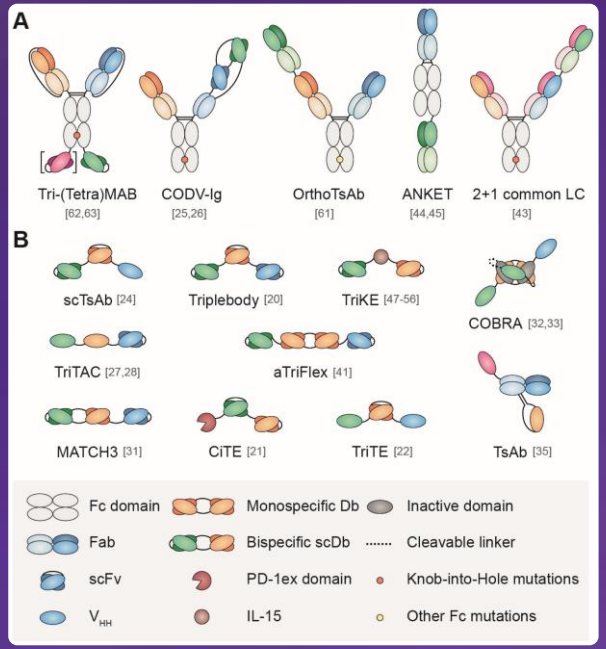
Key Concept :
Demonstrates strong dose-dependent clinical efficacy in relapsed/refractory multiple myeloma across both subcutaneous and intravenous regimens

Figure Analysis :

- High response rates (64–72%) across dose groups
- ≥VGPR in over 50% of patients
- Strong efficacy in heavily pretreated RRMM

A. Chari *et al.*, "Talquetamab, a T-Cell–Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma," *New England Journal of Medicine*, vol. 387, no. 24, pp. 2232–2244, Dec. 2022, doi: 10.1056/NEJMoa2204591.

TRISPECIFIC ANTIBODIES



A. Tapia-Galisteo, M. Compte, L. Álvarez-Vallina, and L. Sanz, "When three is not a crowd: trispecific antibodies for enhanced cancer immunotherapy," Theranostics, vol. 13, no. 3, pp. 1028–1041, Jan. 2023, doi: https://doi.org/10.7150/thno.81494

Schematic representation of some formats of multi-specific antibodies with (A) or without (B) Fc domain.

CHALLENGES

- ANTIGEN ESCAPE
- SHORT HALF-LIFE
- TOXICITY & IMMUNOGENECITY
- MANUFACTURING COMPLEXITY
- STABILITY CONCERNS

CHALLENGES

ANTIGEN ESCAPE

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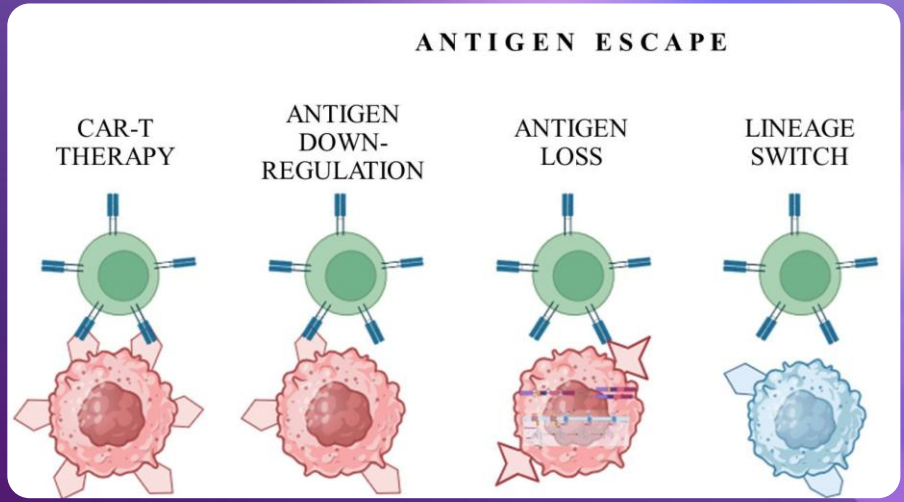
STABILITY CONCERNS



Elżbieta Bartoszewska et al., “Overcoming Antigen Escape and T-Cell Exhaustion in CAR-T Therapy for Leukemia,” Cells, vol. 13, no. 18, pp. 1596–1596, Sep. 2024, doi: https://doi.org/10.3390/cells13181596

CHALLENGES

- **ANTIGEN ESCAPE**
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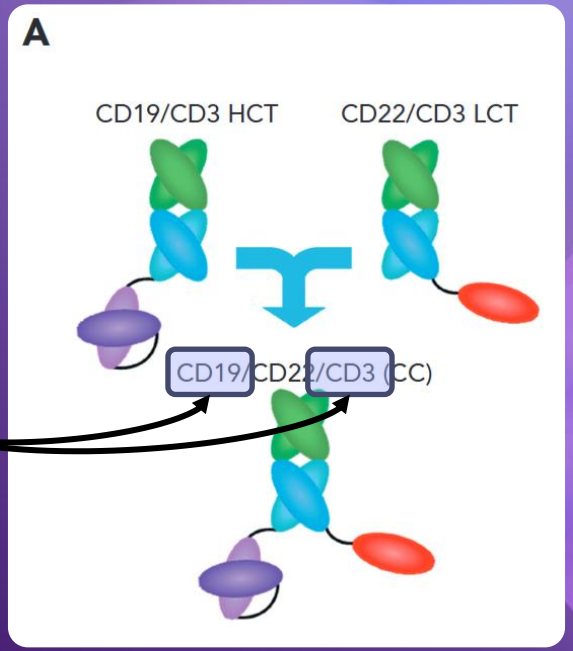
Tumour-associated antigen (TAA)

TRISPECIFIC ANTIBODIES



L. Zhao et al., "A novel CD19/CD22/CD3 trispecific antibody enhances therapeutic efficacy and overcomes immune escape against B-ALL," Blood, vol. 140, no. 16, pp. 1790–1802, Aug. 2022, doi: https://doi.org/10.1182/blood.2022016243

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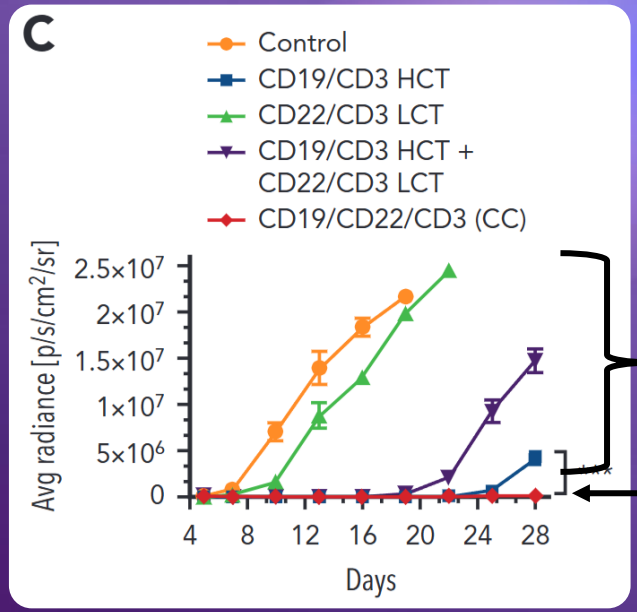

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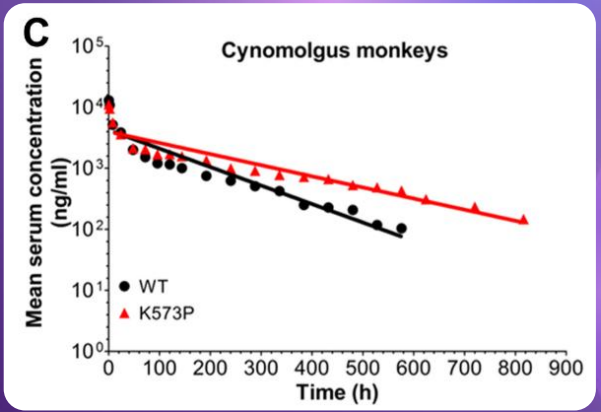
<2 hours serum half-life [1]

↓ Albumin binding

3 weeks serum half-life [2]

[2]



TRISPECIFIC ANTIBODIES

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[2] J. T. Andersen et al., "Extending Serum Half-life of Albumin by Engineering Neonatal Fc Receptor (FcRn) Binding," The Journal of Biological Chemistry, vol. 289, no. 19, pp. 13492–13502, May 2014, doi: https://doi.org/10.1074/jbc.M114.549832

CHALLENGES

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- SHORT HALF-LIFE
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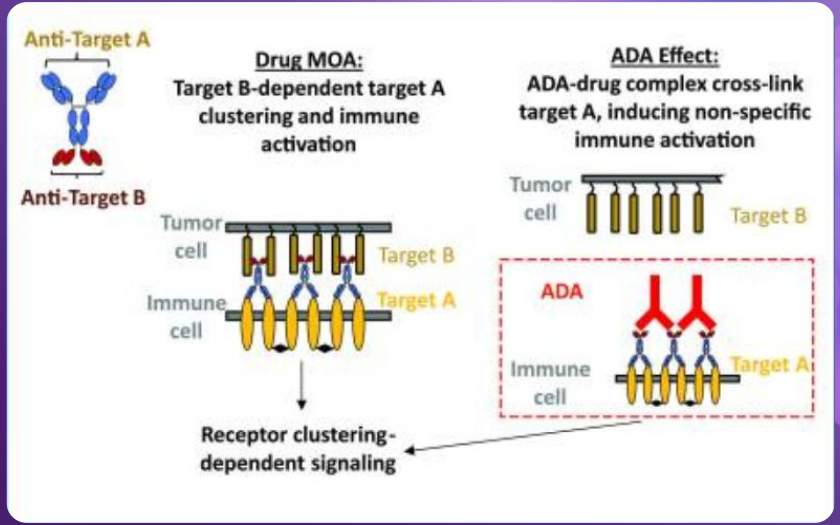
Immunogenicity (Prolonged use)
↓
Anti-drug antibodies
↓
Unintended clustering
↓
Off-target immune activation & toxicity



Y. Zhou et al., "Immunogenicity assessment of bispecific antibody-based immunotherapy in oncology," Journal for ImmunoTherapy of Cancer, vol. 10, no. 4, pp. e004225–e004225, Apr. 2022, doi: https://doi.org/10.1136/jitc-2021-004225

CHALLENGES

ANTIGEN ESCAPE

SHORT HALF-LIFE

TOXICITY & IMMUNOGENECITY

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TRISPECIFIC ANTIBODIES

- Effective at much lower concentrations [1]
- Longer-lasting tumour-suppressing effects [1]

[1] A. Tapia-Galisteo, M. Compte, L. Álvarez-Vallina, and L. Sanz, “When three is not a crowd: trispecific antibodies for enhanced cancer immunotherapy,” Theranostics, vol. 13, no. 3, pp. 1028–1041, Jan. 2023, doi: https://doi.org/10.7150/thno.81494.

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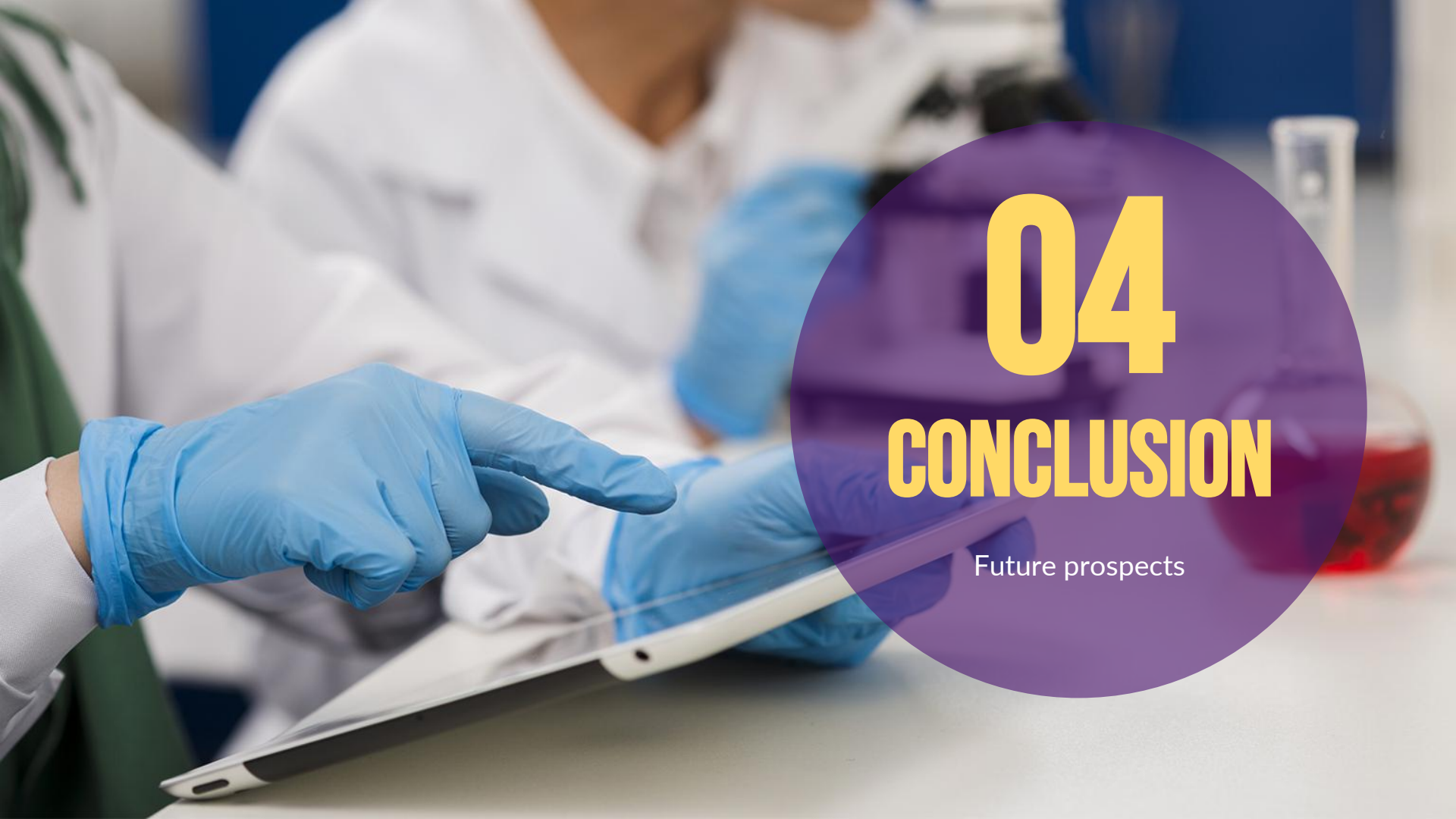

04

CONCLUSION

Future prospects

THANKS

Q & A SESSION