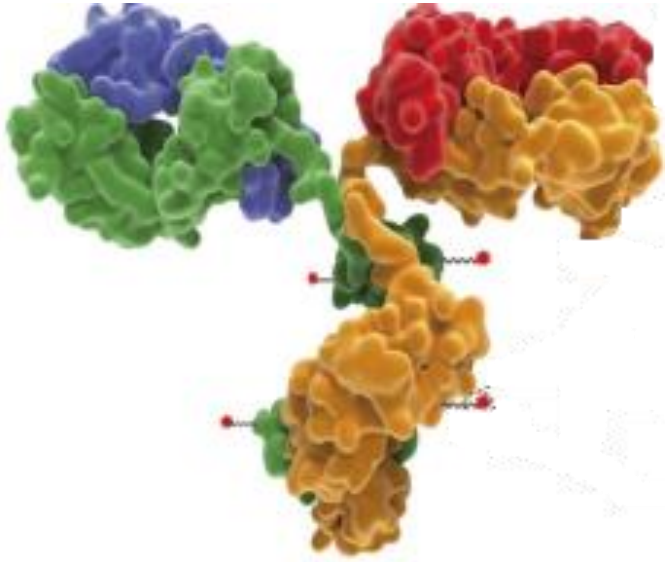
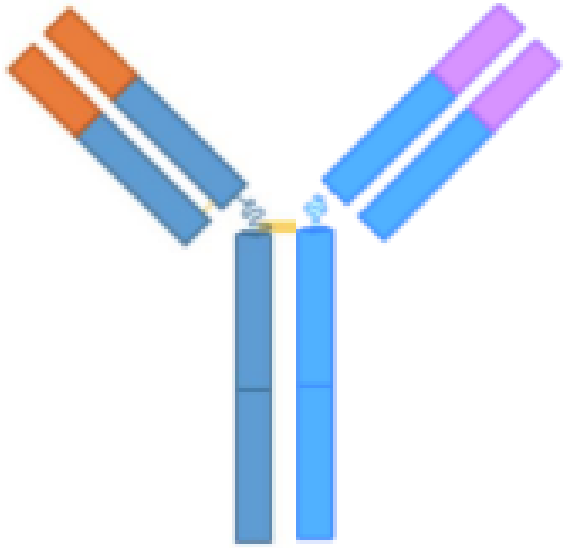


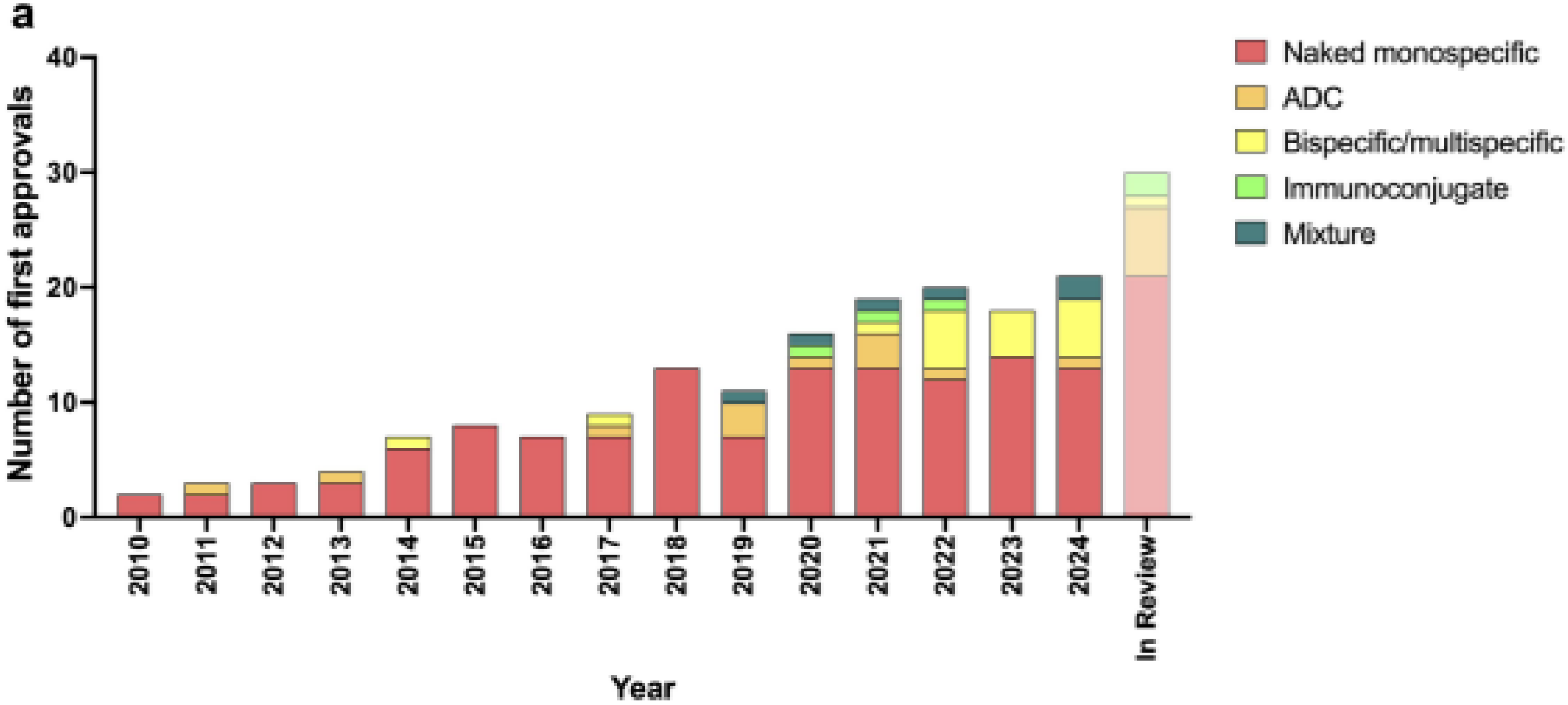


Antibody Drug Conjugates and Bispecific Antibodies

Maxine Handford
Oncology/Haematology Pharmacist
Waikato Hospital

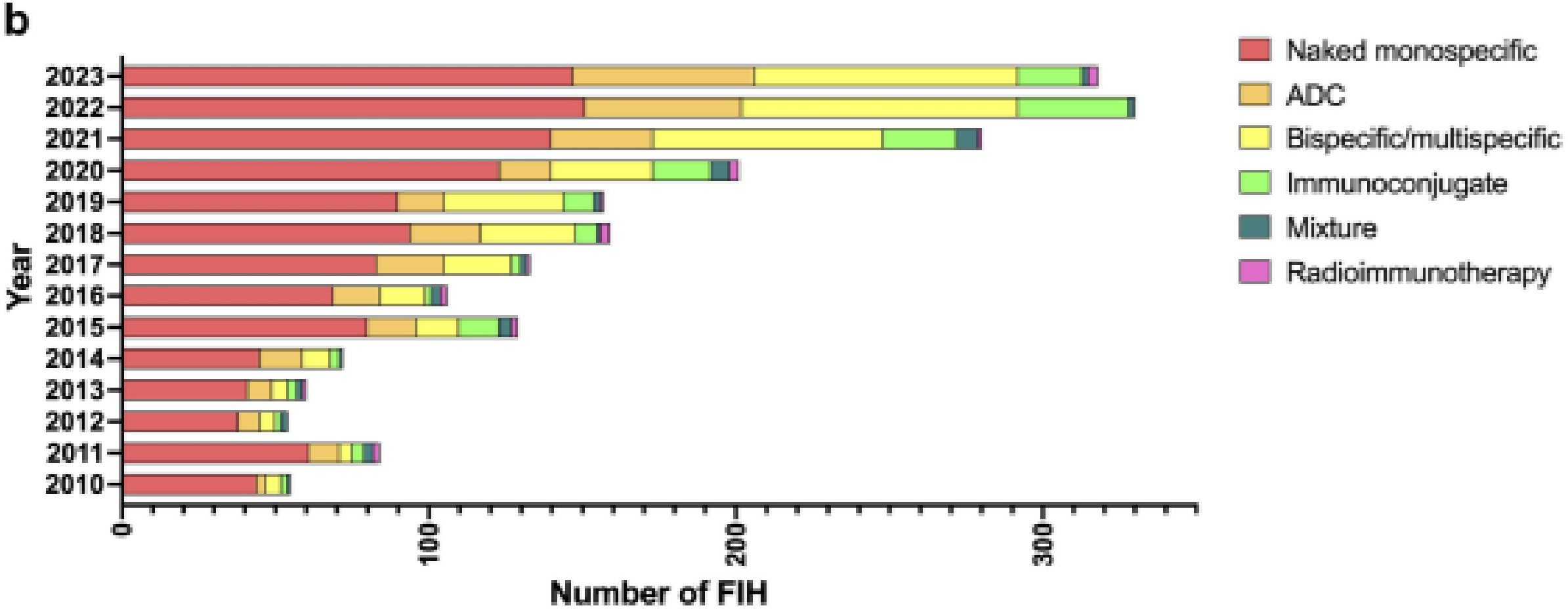
NZHPA CNO SIG Symposium
6 September 2025

Trends in First Approvals of Antibody Therapeutics in any country 2010-2024



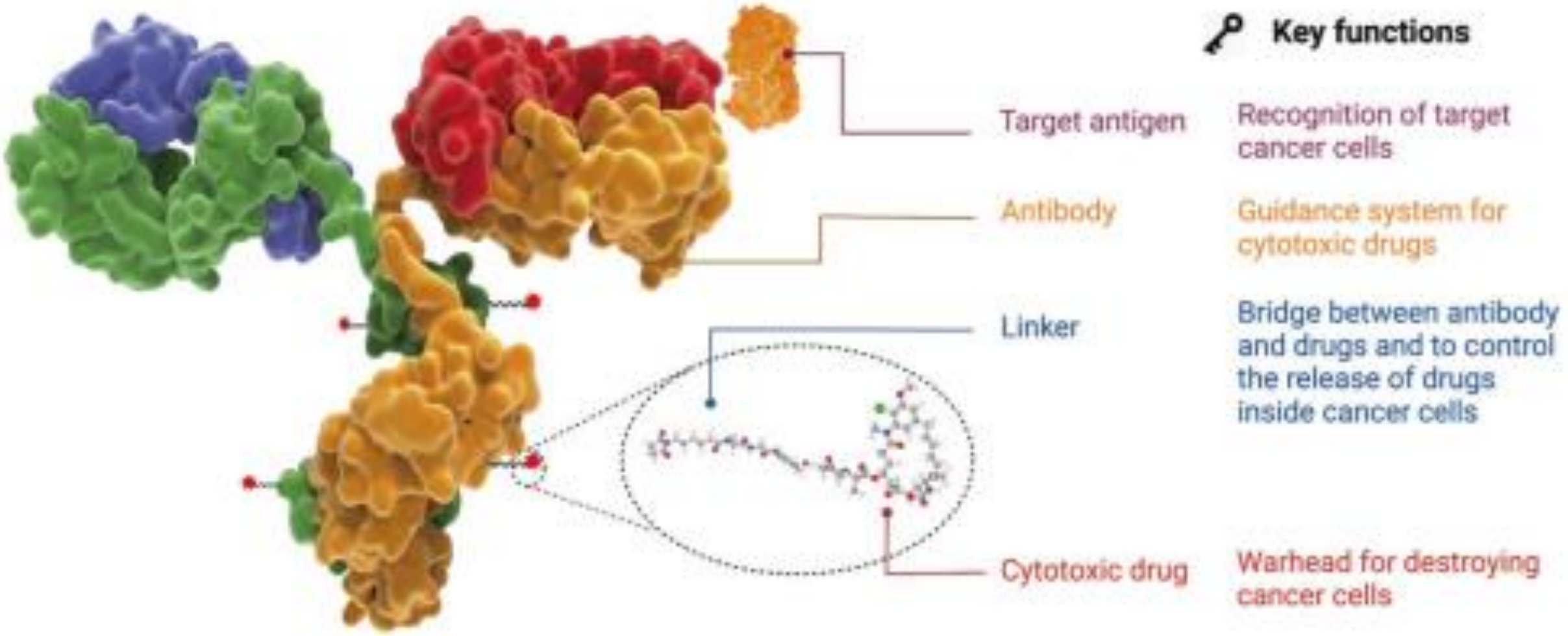
Crescioli, S., et al. mAbs, 2025; 17:1, 2443538

Trends in First-in-Human Studies of Antibody Therapeutics 2010-2024



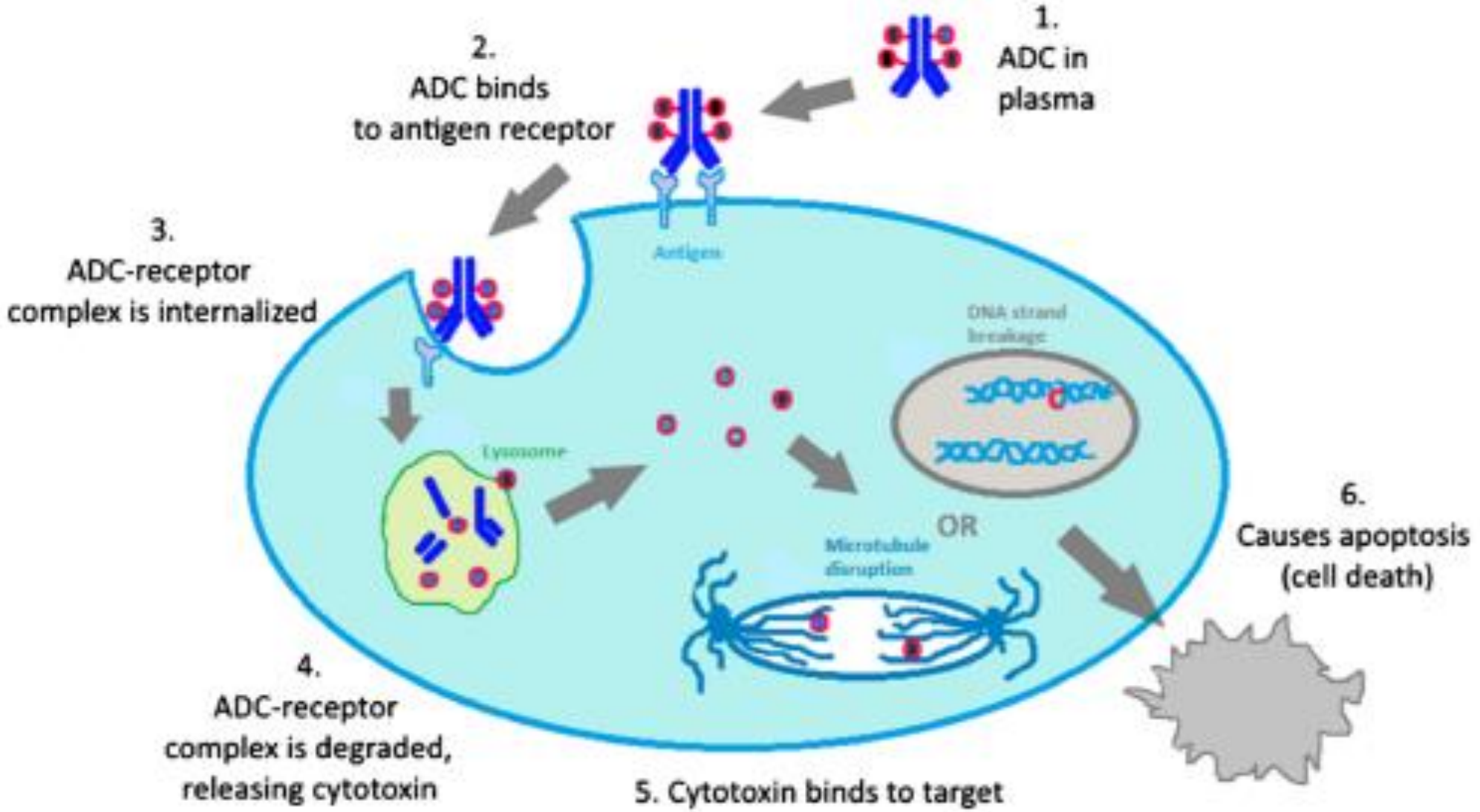
Crescioli, S., et al. mAbs 2025; 17:1, 2443538

Antibody Drug Conjugate (ADC): the “biological missile” for targeted cancer therapy



Fu, Z., et al. Signal Transduction and Targeted Therapy, 2022; 7: 93

Mechanism of Action of ADCs



Jain, N., et al., Pharm. Res.,. 2015; 32: 3526-3540

Selection of Target Antigen for ADCs

- Target antigens should be:
  - Expressed exclusively or predominantly in tumour cells (rare or low in normal tissues)
  - Surface (or extracellular) antigen with high copy numbers (>10^5/cell) on the target tumour cell
  - Non-secreted
  - Internalised upon binding with the corresponding antibody
  - Able to be processed by appropriate intracellular trafficking route → successful release of payload

Examples

- CD19, CD22, CD33, CD30, BCMA,CD79b for haematological malignancies
- HER2, TROP2, nectin4 and EGFR for solid tumours

Fu, Z., et al. Signal transduction and Targeted Therapy, 2022; 7: 93 Ritchie, M., et al. mAbs, 2013; 5: 13-21

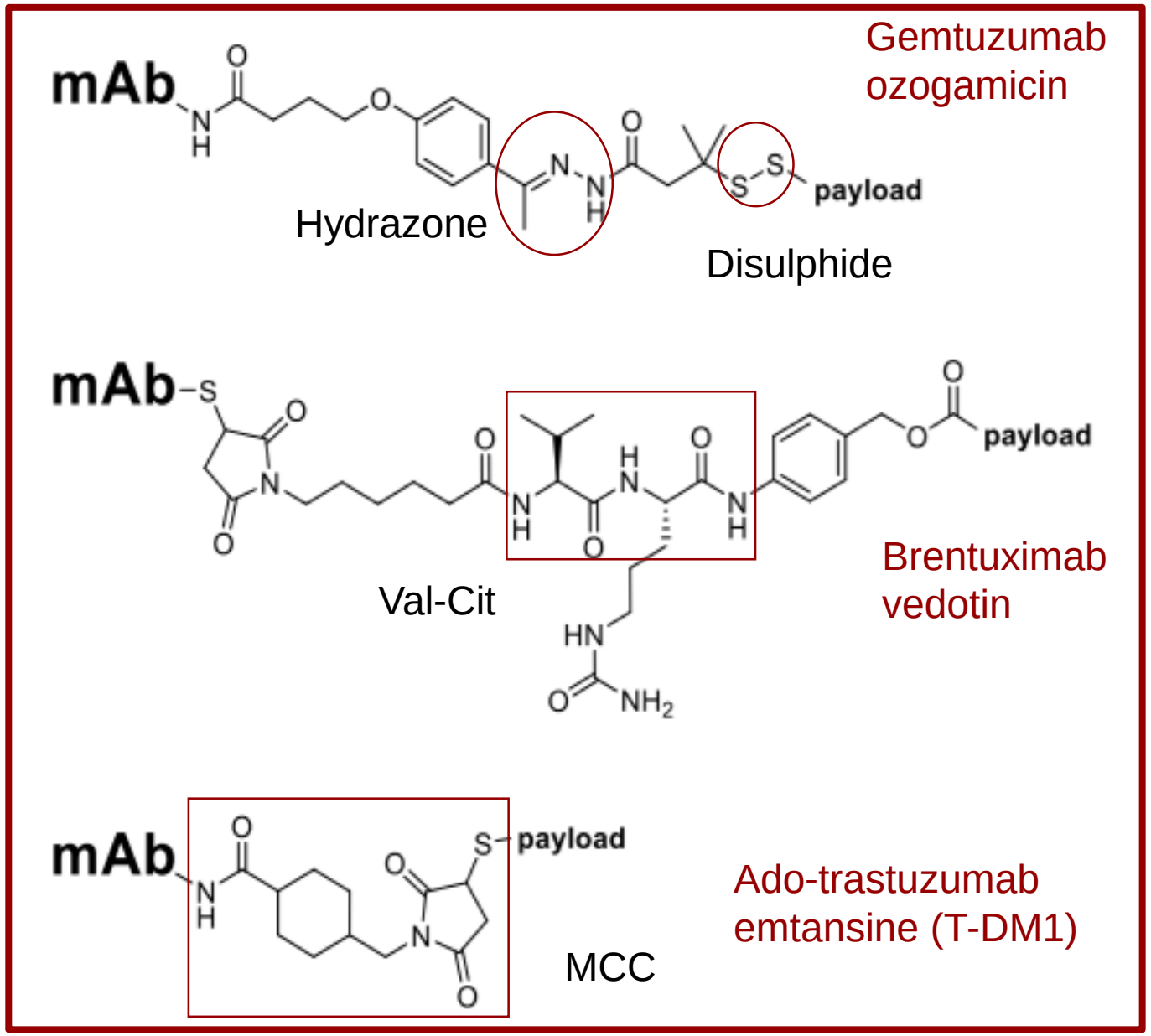
Important Considerations for Selection of Antibodies for ADCs

- Target antigen specificity
- Binding affinity to target antigen
- Ability to facilitate efficient internalisation into the target cell
- Size of antibody
- Immunogenicity
- Plasma half-life
- IgG isotype and subclass

Fu, Z., et al. Signal Transduction and targeted Therapy, 2022; 7:93.
Baah, S., et al. Molecules, 2021; 26: 2943
Hoffman, R.M., et al. Oncoimmunology, 2018; 7:3

Linkers for ADCs

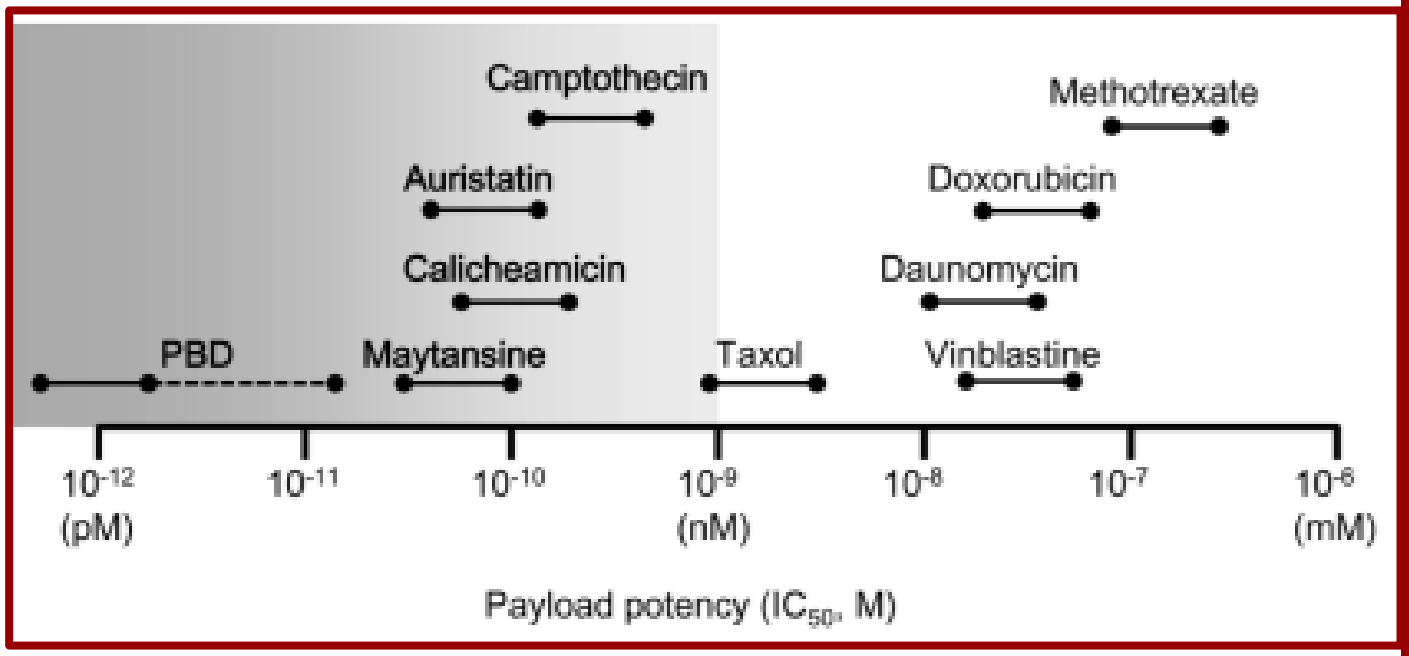
- Cleavable linkers → selective cleavage at the tumour site (e.g. by enzymes or change in pH)
  - Hydrazones
  - Disulphides
  - Peptide linkers (e.g. Val-Cit)
- Non-cleavable linkers depend on enzymatic hydrolysis of antibody → release of payload linked to amino acid residue e.g. lysine
  - Maleimide derivatives (e.g. MC, MCC)

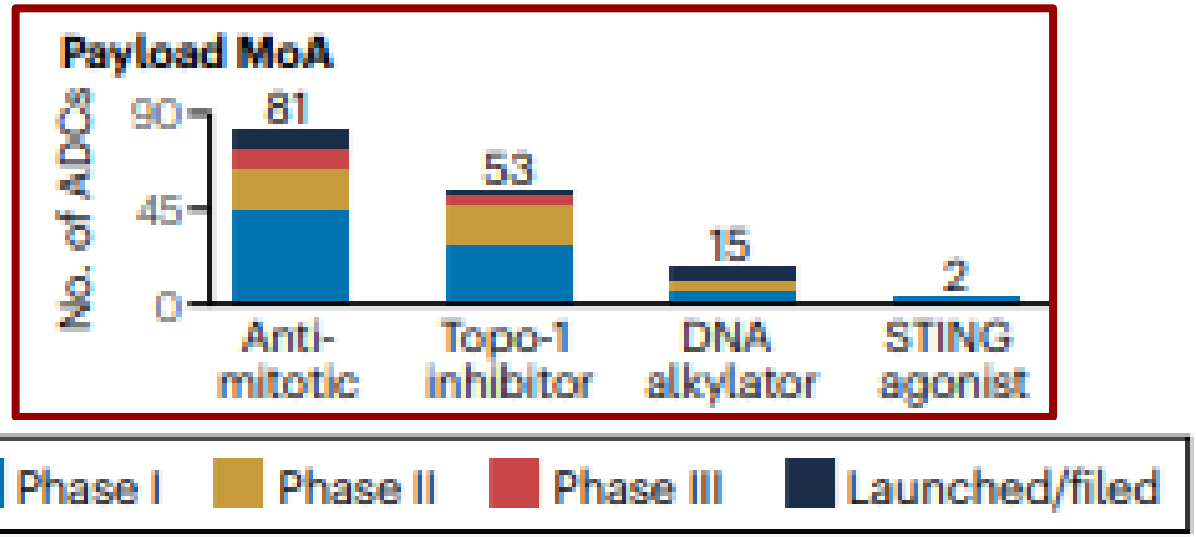


Baah, S., et al. Molecules, 2021; 26:2943. Fu, z., et al. Signal Transduction and targeted Therapy, 2022; 7:93.

Cytotoxic Payloads for ADCs

- Cytotoxic payloads must have:
  - High *in vitro* potency (IC_{50} in sub-nM range)
  - Good stability in physiological conditions
  - Functional groups for conjugating with the antibody
  - Mechanism of action providing selective toxicity toward cancer cells
- Payload classes most commonly used:
  - Auristatins (MMAE, MMAF)
  - Maytansinoids (DM1, DM4)
  - Calicheamicins
  - Camptothecin analogues (SN-38, DXd)
  - Pyrrolobenzodiazepine dimers (PBDs)
  - Duocarmycins

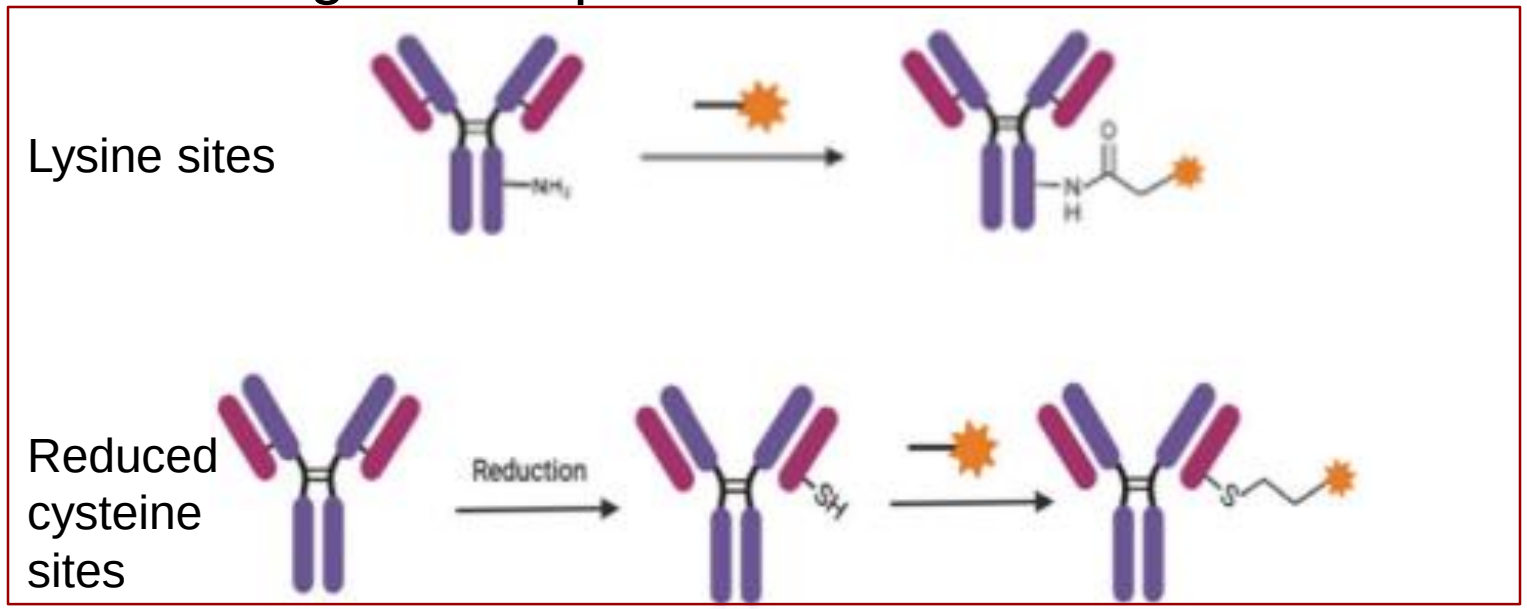


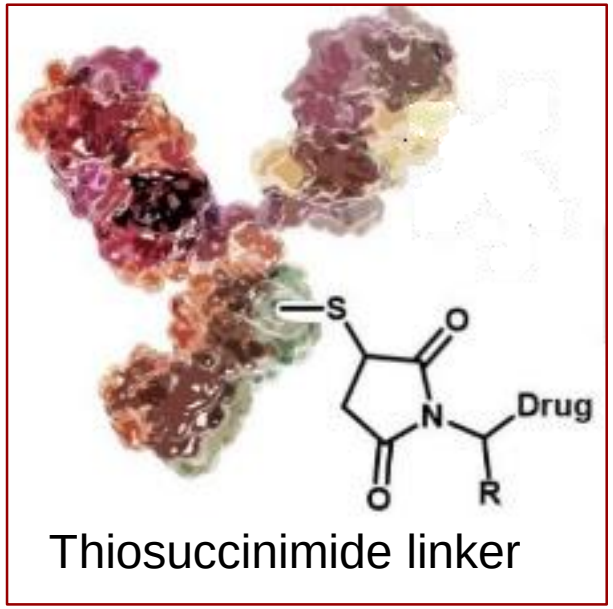


Nakada T., et al. Chem. Pharm. Bull., 2019;67:73-185 Flynn, P., et al., Nat. Rev. Drug Discovery, 2024;23:577-578

Drug-Antibody Ratio (DAR) and Homogeneity

- DAR = Av. No. of drug molecules per antibody; optimal DAR may be 2-4.
- Both DAR and homogeneity (consistency of sites of attachment) are dependent on method of conjugation of linker to antibody.
- Conjugation via pre-existing lysine (ε-amino) side chains of antibody → problems with heterogeneity and batch-to-batch variability.
- Conjugation via reduced cysteine sites and site-specific conjugation methods → more homogeneous products.





Thiosuccinimide linker

Jain, N., et al. Pharm. Res., 2015; 32: 3526-3540 Baah, S., et al. Molecules, 2021; 26; 2943
Fu, Z., et al. Signal Transduction and Targeted Therapy, 2022; 7: 93

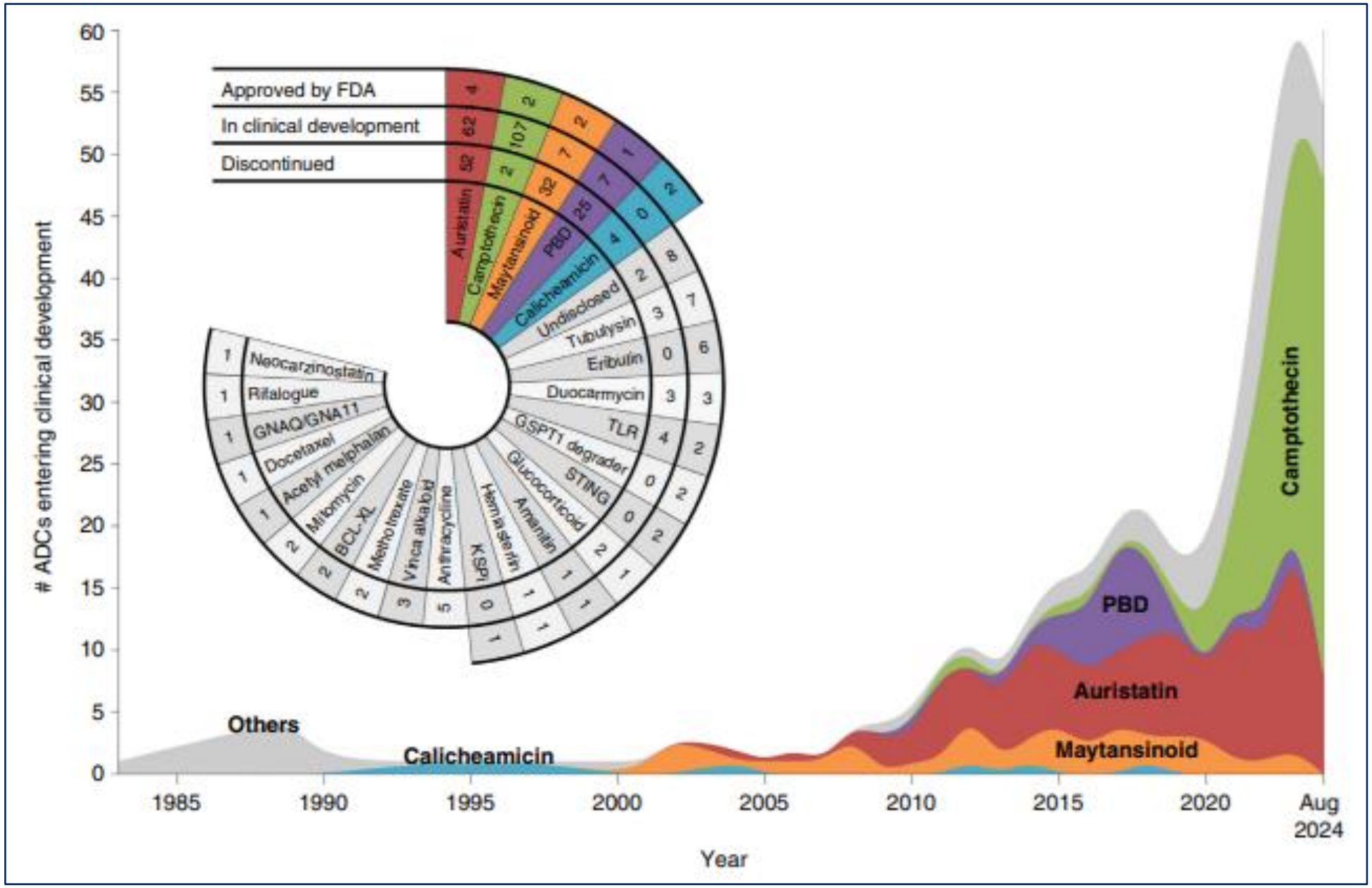
FDA-Approved ADCs and Availability in NZ (August 2025)

ADC	FDA-Approved Indications	Approved for funding in NZ
Haematological malignancies		
Gemtuzumab ozogamicin (CD33)	$CD33^+$ AML (2000, withdrawn 2011, reapproved 2017)	De novo $CD33^+$ AML, good or intermediate risk, in combination with standard anthracycline and cytarabine chemotherapy (1 July 2022)
Brentuximab vedotin (CD30)	Relapsed/refractory HL or systemic ALCL (2011), mycosis fungoides (2017), newly diagnosed stage III/IV cHL, systemic ALCL and CD30-expressing PTCL in combination with chemotherapy (2018), cHL in combination with chemotherapy in children (2022)	Relapsed/refractory $CD30^+$ Hodgkin Lymphoma, relapsed/refractory ALCL (1 December 2022)
Inotuzumab ozogamicin (CD19)	Relapsed/refractory B-cell ALL (2017)	Relapsed/refractory $CD22^+$ B-cell Acute Lymphoblastic Leukaemia / Lymphoma (1 April 2025)
Polatuzumab vedotin (CD79b)	Relapsed/refractory DLBCL (2019)	Not currently approved for funding*. Available via Roche CSP (July 2024)
Belantamab mafoditin (BCMA)	Relapsed/refractory multiple myeloma (2020, withdrawn November 2022)	–
Loncastuximab tesirine (CD19)	Relapsed/refractory DLBCL (2021)	–

FDA-Approved ADCs and Availability in NZ (August 2025)

ADC	FDA-Approved Indications	Approved for funding in NZ
Solid tumour malignancies		
Trastuzumab emtansine (HER-2)	$HER2^+$ breast cancer (2013)	Metastatic $HER2^+$ breast cancer (1 Dec 2019); Early $HER2^+$ breast cancer (1 July 2022)
Trastuzumab deruxtecan (HER-2)	$HER2^+$ breast cancer (2019), $HER2^+$ gastric cancer (2021), $HER2^{L0W}$ breast cancer (2022)	Metastatic $HER2^+$ breast cancer (1 Jan 2025)
Enfortumab vedotin (Nectin-4)	Urothelial carcinoma (2019), in combination with pembrolizumab (2023)	–
Sacituzumab govitecan (TROP-2)	Triple-negative breast cancer (2020), Urothelial carcinoma (2021), HR^+, $HER2^-$ breast cancer (2023)	–
Tisotumab vedotin (TF-011)	Cervical cancer (2021)	–
Mirvetuximab soravtansine (FRα)	$FR\alpha^+$, platinum-resistant epithelial ovarian, fallopian tube and peritoneal cancers (2022)	–
Datopotamab deruxtecan (TROP-2)	HR^+, $HER2^-$ breast cancer (2023)	–
Telisotuzumab vedotin (c-MET)	Non small cell lung cancer (2025)	–

Trends in ADC Development and Discontinuation Rates



Colombo, R., et al. Cancer Discov., 2024; 14: 2089-2108

Mechanisms for Toxicity of ADCs

- Toxic effects often driven by payload
- Target and linker may determine organ specificity of toxicity
- Low level expression of target antigen on normal cells → specific tissue toxicities
- Non-specific binding of antibody to Fc receptors or lectin receptors → toxicity toward cells expressing these receptors
- Early cleavage of linker → more widespread toxicities
- Variations in DAR of ADC can have also have significant effects on toxicity

Donaghy, H. mAbs, 2016; 8 (4); 659-671

Expected Adverse Effects of ADCs

Toxicity	ADC Payloads and Targets Associated with Toxicity	Examples
Off-Target Toxicities		
Gastro-intestinal	MMAE, calicheamicin, DXd, SN-38	Brentuximab vedotin Gemtuzumab ozogamicin Sacituzimab govitecan Fam-Trastuzumab deruxtecan (T-DXd)
Myeloid toxicity	Calicheamicin, PBD dimers	Gemtuzumab ozogamicin Inotuzumab ozogamicin Loncastuximab tesirine
Peripheral neuropathy	MMAE conjugates with a protease-cleavable linker (e.g. valine-citrulline)	Brentuxumab vedotin Polatuzumab vedotin
On-Target Off-Tumour Toxicities		
Cardiac toxicity	HER2-specific ADCs	Ado-Trastuzumab emtansine (T-DM1) Fam-Trastuzumab deruxtecan (T-DXd)
Myeloid toxicity	$CD33^{+}$-specific ADCs	Gemtuzumab ozogamicin

Donaghy, H., mAbs, 2016; 8: 659-671. Dumonet, C., et al. Nat. Rev. Drug Discov., 2023; 22; 641-661

Serious Unexpected Adverse Effects of ADCs

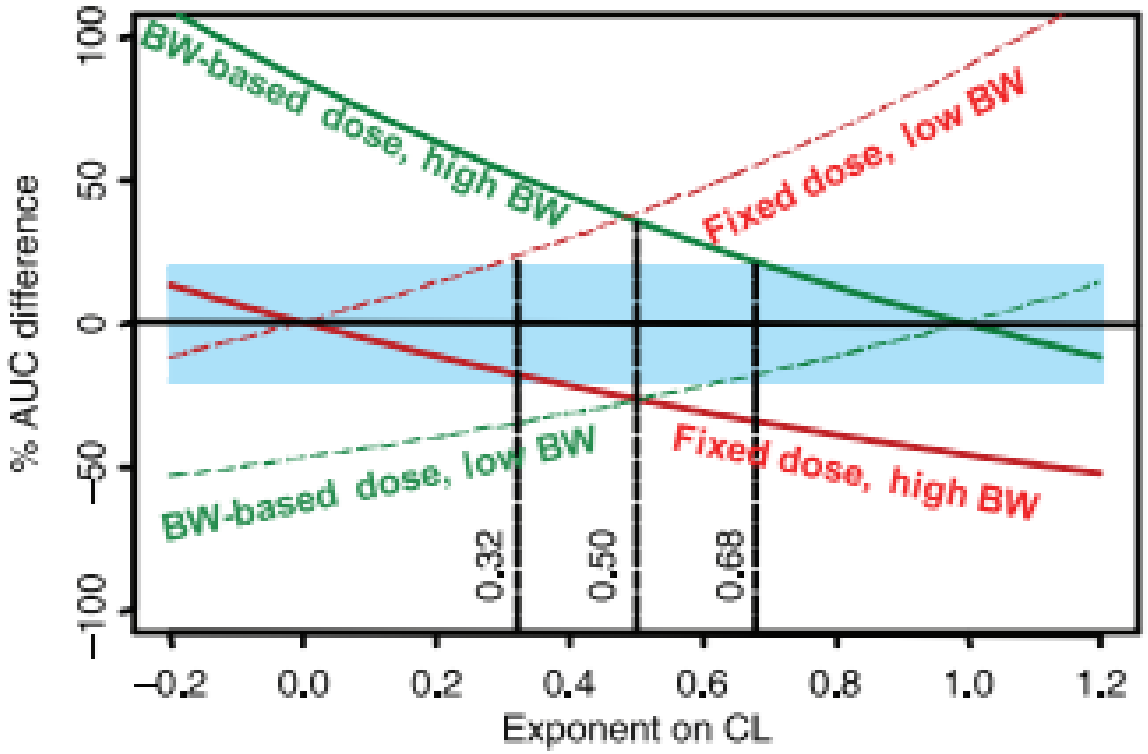
Toxicity	ADC Payloads and Targets Associated with Toxicity	Examples
Infusion reactions		Gemtuzumab ozogamicin Inotuzumab ozogamicin
Ocular toxicity	DM4 and MMAF	Belantomab mafoditin Mirvetuximab soravtansine
Thrombocytopenia*	Potent tubulin-inhibiting agents using non-cleavable linkers	Ado-trastuzumab emtansine (T-DM1) Belanatmab mafoditin
Neutropenia*	ADCs conjugated via protease-cleavable linkers to MMAE or DXd	Brentuxumab vedotin Polatuzumab vedotin Fam-trastuzumab deruxtecan (T-DXd)
Hepatic Toxicity including Sinusoidal Obstructive Syndrome (SOS) and ↑ LFTs*	Calicheamicin	Gemtuzumab ozogamicin Inotuzumab ozogamicin
Interstitial Lung Disease (ILD)* (Pneumonitis)	HER2-specific ADCs ADCs conjugated via protease-cleavable linkers to DXd	Fam-trastuzumab deruxtecan (T-DXd) Datopotamab deruxtecan

* Possibly due to phagocytosis or trogocytosis of ADC immune complexes (ICs) after non-specific binding to cells bearing Fcγ receptors → internalisation of ICs and release of cytotoxic payload → cell death.

Taylor, R.P., Lindorfer, M.A. Blood, 2024; 144 (2): 137-144

Dosing Strategies to Mitigate Risks of Toxicity from ADCs

- Body wt-based vs fixed dosing
- Body wt-based dose-capping
  (↓ risk of overdosing in heavier pts)
- Treatment duration capping
  (↓ risk of chronic AEs that emerge during repeated dosing)
- Fractionated dosing schedules
  (↓toxicity driven by C_{max})

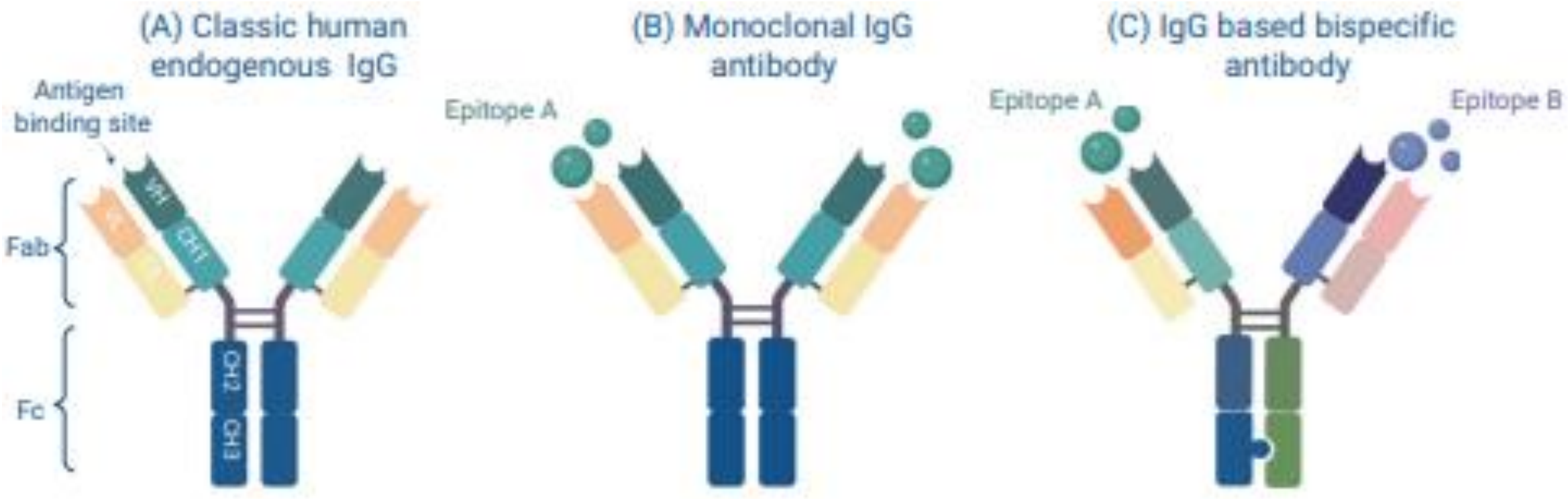


$$\left(\frac{BW}{BW_m}\right)^{exp}$$

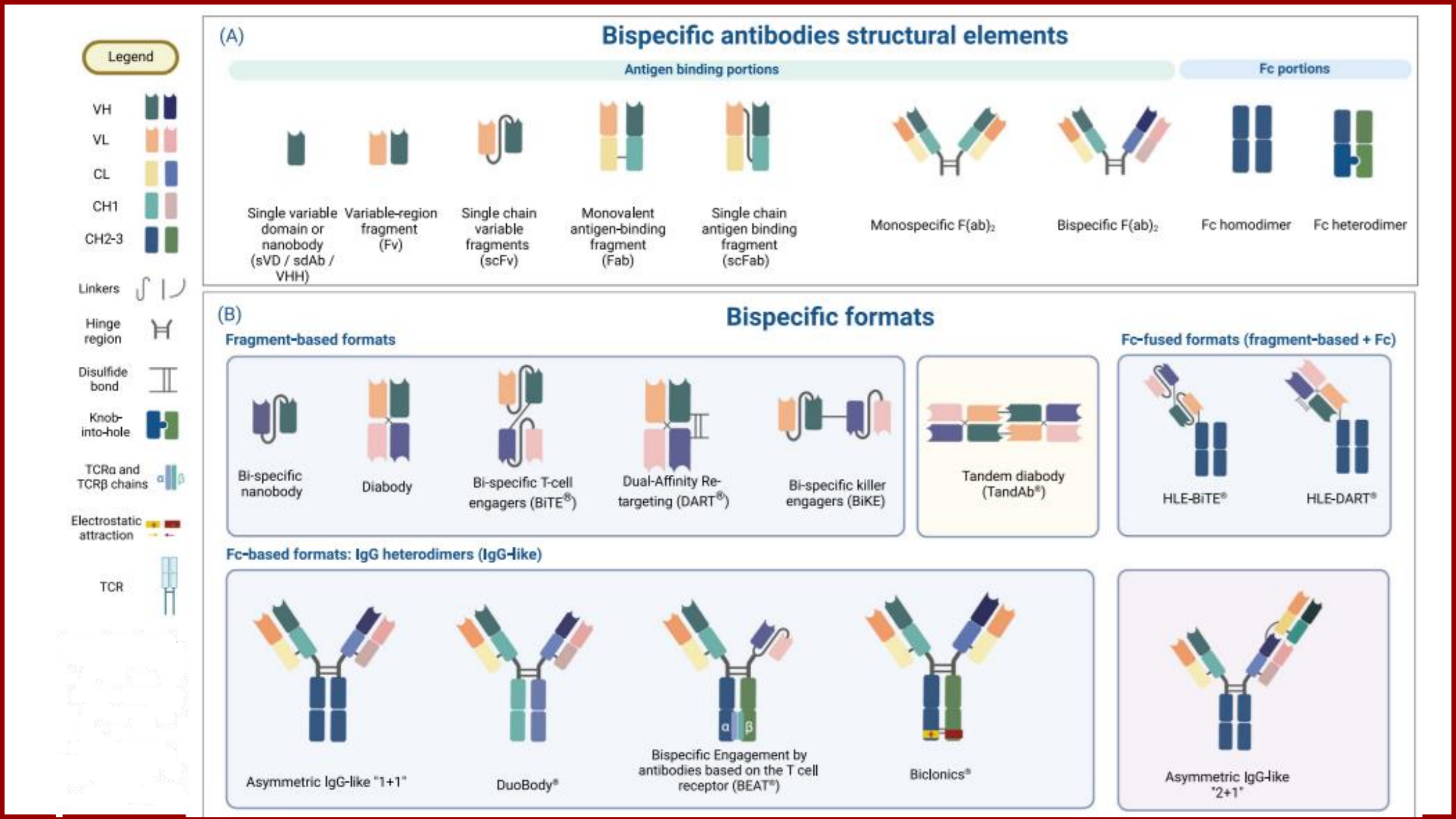
BW = Individual wt
BW_m = Typical body wt of normal wt pt

Liao, M.Z., et al. Clin. Pharmacol. Ther., 2021; 110 (5): 1216-1230

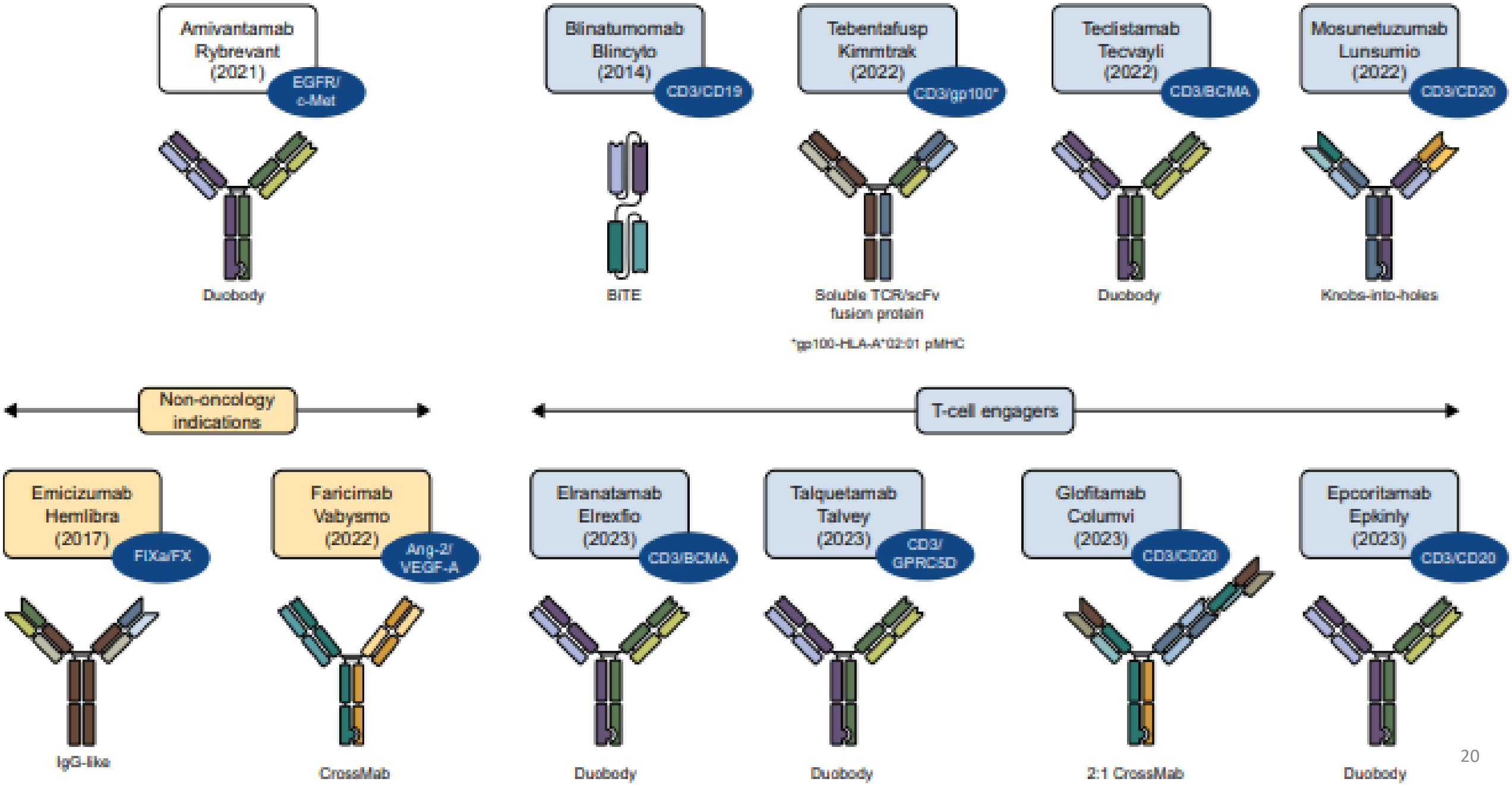
Bispecific Antibodies (BsAbs)



Herrera, M., et al. Trends in Cancer, 2024; 10 (10): 893-919


Legend
VH
VL
CL
CH1
CH2-3
Linkers
Hinge region
Disulfide bond
Knob-into-hole
TCRα and TCRβ chains
Electrostatic attraction
TCR
(A)
Bispecific antibodies structural elements
Antigen binding portions
Fc portions
Single variable domain or nanobody (sVD / sdAb / VHH)
Variable-region fragment (Fv)
Single chain variable fragments (scFv)
Monovalent antigen-binding fragment (Fab)
Single chain antigen binding fragment (scFab)
Monospecific F(ab)2
Bispecific F(ab)2
Fc homodimer
Fc heterodimer
(B)
Bispecific formats
Fragment-based formats
Bi-specific nanobody
Diabody
Bi-specific T-cell engagers (BiTE®)
Dual-Affinity Re-targeting (DART®)
Bi-specific killer engagers (BiKE)
Tandem diabody (TandAb®)
Fc-fused formats (fragment-based + Fc)
HLE-BiTE®
HLE-DART®
Fc-based formats: IgG heterodimers (IgG-like)
Asymmetric IgG-like "1+1"
DuoBody®
Bispecific Engagement by antibodies based on the T cell receptor (BEAT®)
Biclonics®
Asymmetric IgG-like "2+1"

FDA-Approved Bispecific Antibodies



FDA-Approved BsAbs and Availability in NZ (August 2025)

BsAb	Target	Mechanism of Action	FDA-Approved Indications	Approved for funding in NZ
Non-malignant conditions				
Emicizumab	Factor IXa x Factor X	Factor VIII mimetic	Haemophilia A (2017)	Prophylactic treatment of patients with severe haemophilia A and high-titre inhibitors of Factor VIII (Xpharm) (December 2020); extended to include all patients with severe haemophilia A and severe bleeding phenotype (endogenous Factor VIII activity ≤ 2%) (October 2023)
Faricimab	VEGF x Ang-2	Dual ligand inhibitor	Wet age-related macular degeneration, diabetic macular oedema, macular oedema following retinal vein occlusion (2022)	Application for second-line treatment of patients with neovascular (wet) age-related macular degeneration; and second-line treatment of patients with diabetic macular oedema (DMO)*
Ozoralizumab	TNFa x HAS	Half-life extended (HLE) Ligand inhibitor	Rheumatoid arthritis (2023)	–

Surowka,M., Klein, C. mAbs, 2024; 16:1. Herrera, M., et al. Trends in Cancer, 2024; 10 (10): 893-919

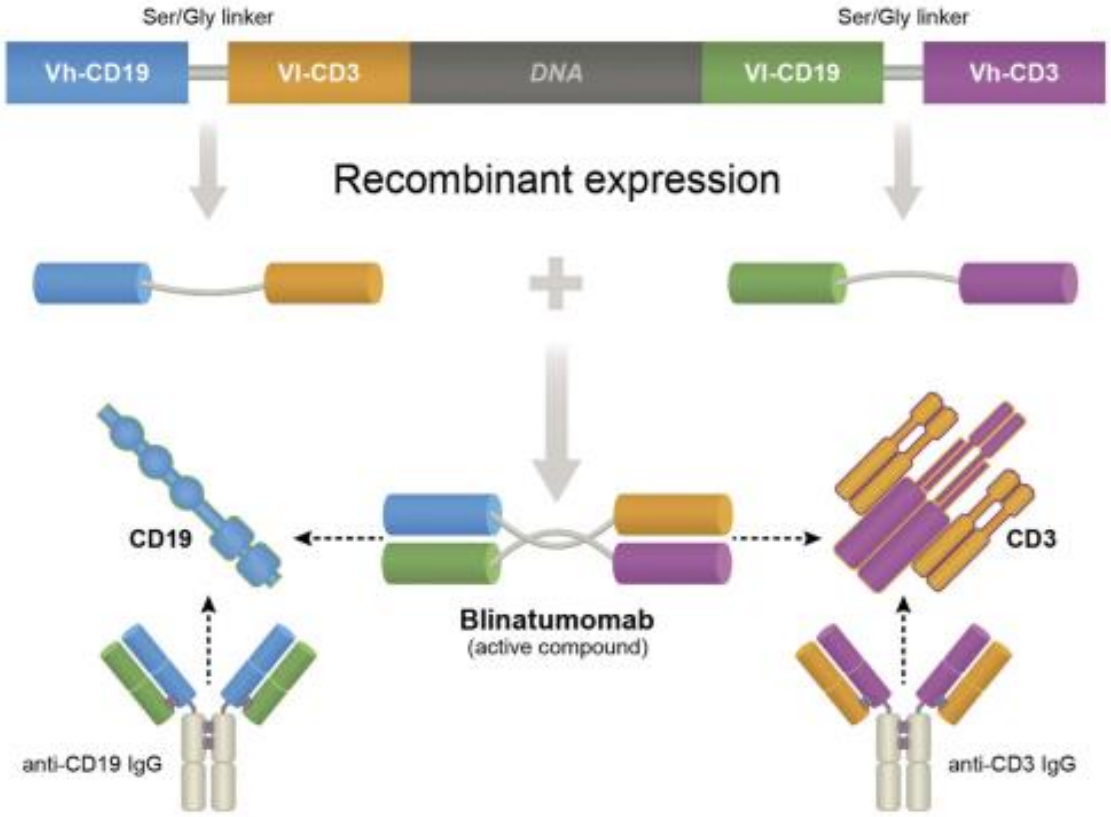
FDA-Approved BsAbs and Availability in NZ (August 2025)

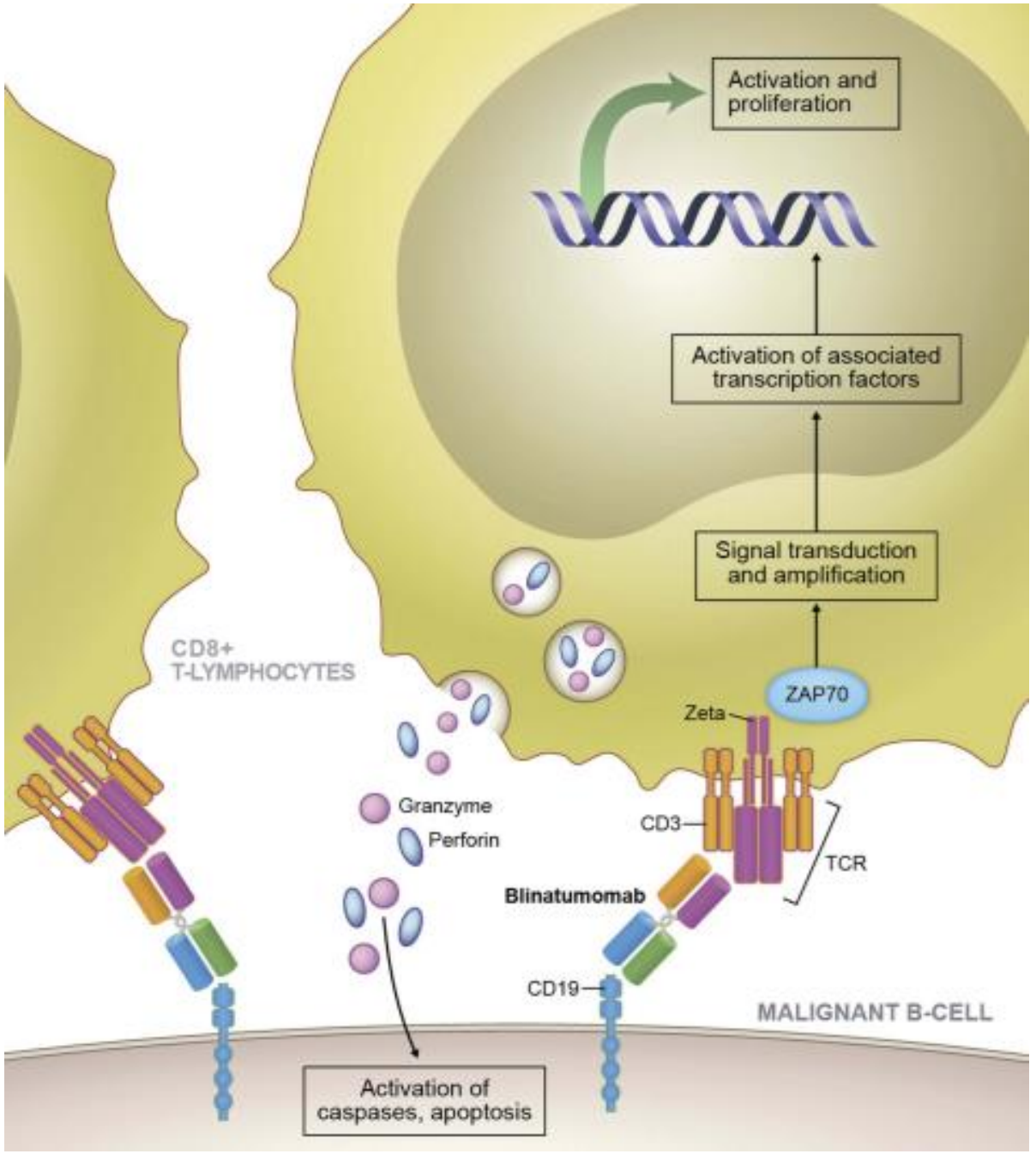
BsAb	Target	Mechanism of Action	FDA-Approved Indications	Availability in NZ
Solid tumour malignancies				
Catumaxomab	EpCAM x CD3ε	T-cell engager	Ovarian ascites (intraperitoneal) (2009); withdrawn (2013)	–
Amivantamab	EGFR x c-MET	Bispecific RTK inhibitor (BsRTKi) + ADCC	NSCLC with EGFR exon 20 insertion mutations (ex20ins) (2021)	–
Tebentafusp	gp100-HLA* A02 x CD3ε	T-cell engager	Uveal melanoma (2022)	–
Cadonilimab	PD-L1 x CTLA4	Dual checkpoint inhibitor	Cervical cancer after platinum-based chemotherapy (2022)	–
Tarlatamab	DLL3 x CD3ε	T-cell engager	ES-SCLC after platinum-based chemotherapy (2024)	–
Ivonescimab	PD-1 x VEGF	Dual checkpoint/Ligand inhibitor	NSCLC after progression following EGFR TKI (2024)	–
Zanidatamab	HER2-ECD2 x HER2-ECD4	Dual signalling inhibitor + ADCC + CDC	Biliary tract cancer (2024)	–
Zenocutuzumab	HER2 x HER3	Dual signalling inhibitor + ADCC	NSCLC and pancreatic adenocarcinoma with neuregulin 1 (NRG1) gene fusions (2024)	–

FDA-Approved BsAbs and Availability in NZ (August 2025)

BsAb	Target	Mechanism of Action	FDA-Approved Indications	Availability in NZ
Haematological malignancies				
Blinatumomab	CD19 x CD3ε	T-cell engager	R/R B-ALL (2014); MRD^+ B-ALL (2017) Consolidation of Ph^- ALL	NPPA Approvals for MRD^+ B-ALL (as bridge to Allo HSCT)*
Mosunetuzumab	CD20 x CD3ε	T-cell engager	R/R Follicular Lymphoma after ≥2 previous lines (2022)	Compassionate Use Programme (Roche)
Teclistamab	BCMA x CD3ε	T-cell engager	R/R MM after 4 previous lines (2022)	_
Glofitamab	CD20 x CD3ε	T-cell engager	R/R DLBCL after ≥ 2 previous lines (2023)	Compassionate Use Programme (Roche, closed May 2025)*
Epcoritamab	CD20 x CD3ε	T-cell engager	R/R DLBCL, high-grade B cell lymphoma, and Follicular Lymphoma after ≥ 2 previous lines (2023)	Pre-Approval Access Program (AbbVie, closed 31 Dec 2024)*
Elranatamab	BCMA x CD3ε	T-cell engager	R/R MM after 4 previous lines (2023)	Participation in MagnetisMM-5 clinical trial (closed)
Talquetamab	GPRC5D x CD3ε	T-cell engager	R/R MM after 4 previous lines (2023)	_

Mechanism of Action of Blinatumomab (BiTE®)

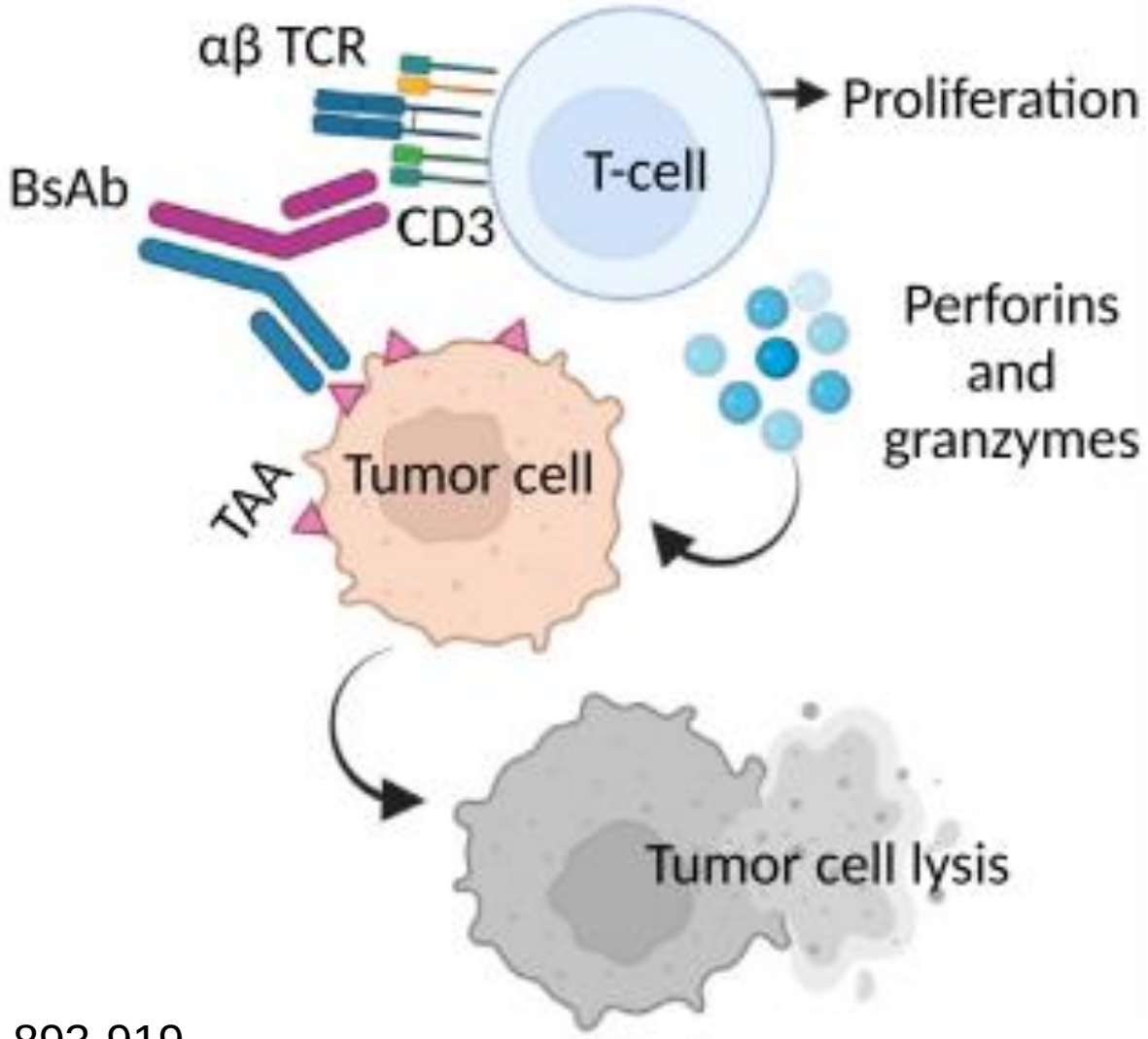




Franquiz, M.J., Short, N.J. Biologics: Targets and Therapy, 2020; 14: 23-34

Mechanism of Action of BsAb T-cell Engagers

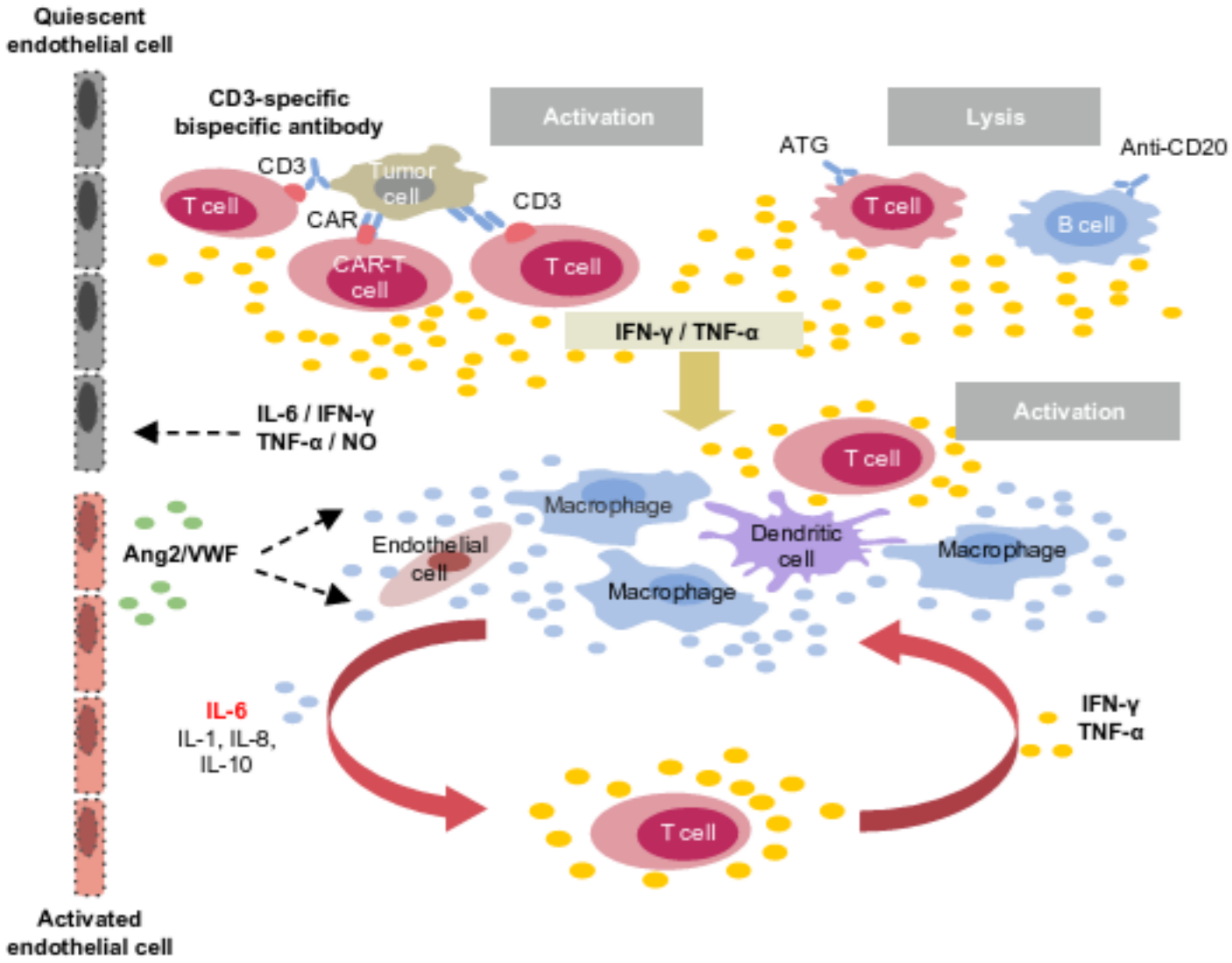
- Tumour-Associated Antigen (TAA) Targets for haematological cancers:
  - CD19; B-ALL
  - CD20; B-cell Non-Hodgkin Lymphoma
  - BCMA, GPRC5D; Multiple Myeloma



Herrera, M., et al. Trends in Cancer, 2024; 10 (10): 893-919
Van de Donk, N.W.C.J., Zweegman, S. Lancet, 2023; 402: 149-158.

Adverse Effects of BsAb T-Cell Engagers

- **Cytokine Release Syndrome (CRS)**
  - Risk of severe CRS reduced by:
    - Stepwise ↑ in dose (step up dosing)
    - Premedication with: antihistamine + paracetamol + dexamethasone
    - Subcut vs i.v. dosing



Shimabukuro-Vornhagen, A., et al. J. Immunother. Cancer, 6: 56

Leclercq-Cohen, G., et al. Clin. Cancer Res., 2023; 29 (21): 4449-4463

Grading and Management of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38ºC	Temperature ≥ 38ºC	Temperature ≥ 38ºC	Temperature ≥ 38ºC
		With		
Hypotension (SBP <90mmHg)	None	Not requiring vasopressors	Requiring vasopressor ± vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or		
Hypoxia	None	Requiring O_2 via nasal prongs (≤ 6L/min)	Requiring high-flow O_2 via nasal prongs (>6L/min), facemask, non-rebreather of venture mask	Requiring positive pressure O_2 e.g. CPAP, BiPAP, intubation and mechanical ventilation

- CRS Grades ≥2:
  - Consider using Tocilizumab 8mg/kg (max dose 800mg)
  - A second dose may be given after 8 hours if no response to first dose.
  - Consider addition of dexamethasone IV 10-20mg IV Q6H for 1-3 days
- CRS Grade 4:
  - Repeat dose of Tocilizumab 8mg/kg (max 2 additional doses)
  - Administer methylprednisolone IV 1000mg/day for 3 days, then taper.

Lee, D.W., et al. Biol. Blood Marrow Transplant, 2019; 25: 625-38
Yakoub-Agha, I., et al. Haematologica, 2020; 105: 297-316

Immune Effector Cell-Associated Neurotoxicity (ICANS)

- Hyperactivation of immune effector cells → release of cytokines and chemokines → endothelial cell activation, disruption of blood-brain barrier and neuronal cell injury by neurotoxin
- Early symptoms include tremors, mild aphasia, apraxia, dysgraphia.
- Dysphasia may be a specific, early marker of severe neurotoxicity
- Symptoms may progress to delirium, seizures or coma
- Incidence variable, but generally <5% with BsAbs
- Higher incidence with blinatumomab (all grades, 47-53%; grade ≥3, 7-13%)
- Requires close monitoring for early signs of neurotoxicity

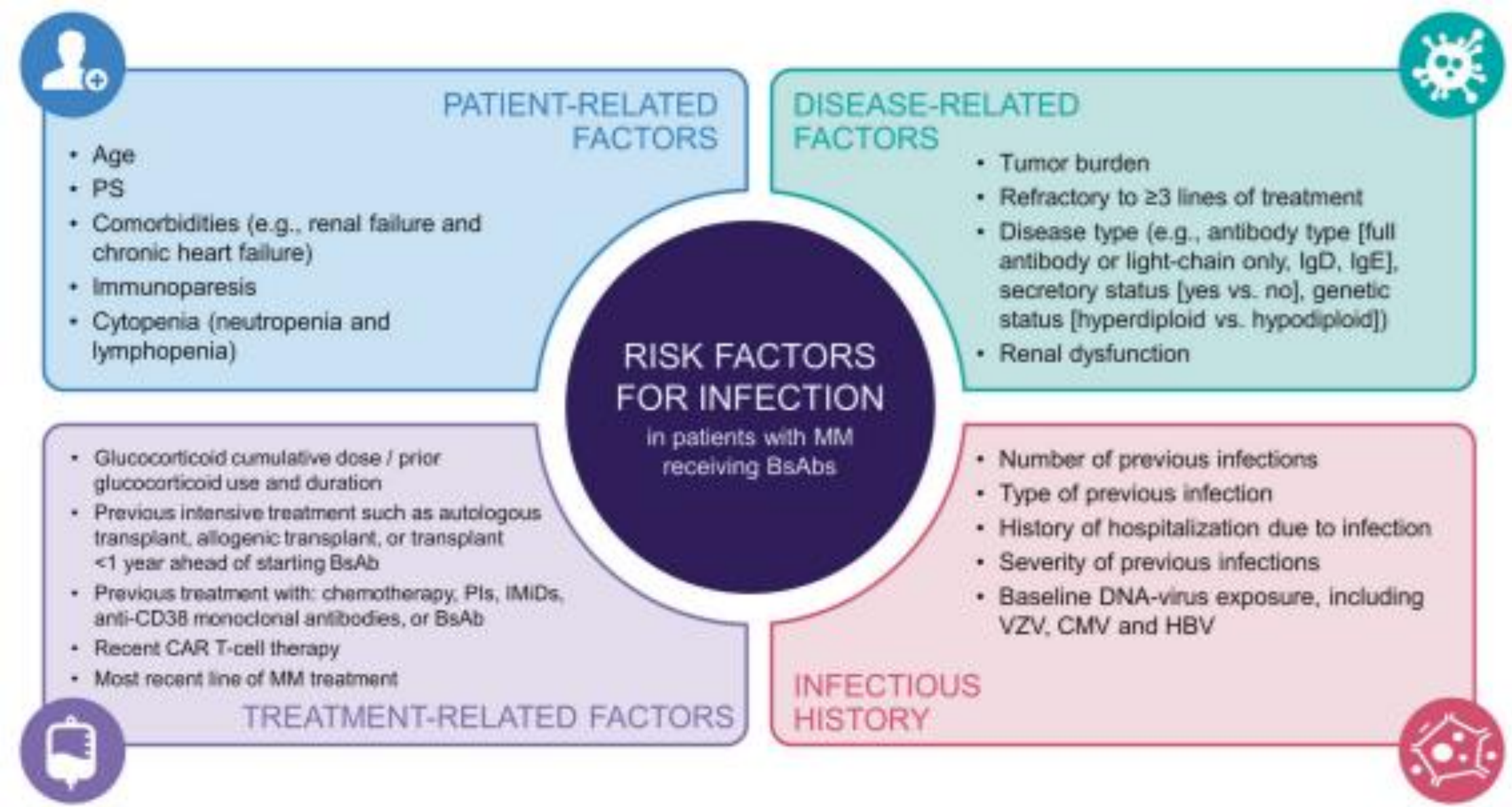
Immune Effector Cell Associated Encephalopathy (ICE) Assessment Tool

Grade	Total Points	Criteria
Orientation	4	• Ask patient to state the year, month, city, hospital (1 point each)
Naming	3	• Ask patient to name 3 objects you point to (e.g. point to clock, pen, button) (1 point each)
Following commands	1	• Assess ability for patient to follow simple commands (e.g. "show me 2 fingers", or "close your eyes and stick out your tongue")
Writing	1	• Assess ability for patient to write a standard sentence (e.g. ask patient to write 'my name is……')
Attention	1	• As patient to count backwards from 100 in 10s
ICE score 10/10 consistent with no neurocognitive impairment		

Use of ICE Score for Assessment of Neurologic Toxicity and Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE assessment score	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated cerebral oedema	N/A	N/A	Focal/local oedema on neuroimaging	Diffuse cerebral oedema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad (irregular/decreased respirations, bradycardia and systolic hypertension)

Increased Risk of Infections



Mechanisms for Resistance to Bispecific Antibodies

- Tumour-related features
  - Loss of target antigen expression
  - Presence of high-risk cytogenetic abnormalities
- T-cell dysfunction
  - Impaired T-cell fitness (T cell frequency) with cumulative exposure to immunosuppressive anticancer drugs
  - T-cell exhaustion (Upregulation of immune checkpoint proteins)
- Tumour microenvironment
  - Immune suppressor cells (e.g. Tregs)
  - Bone marrow stromal cells
- Anti-drug antibodies (ADAs)

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Conclusions

- Antibody-drug conjugates and bispecific antibodies have emerged as important new classes of therapeutic agents for treatment of cancer.
- They possess novel mechanisms of action and have demonstrated good clinical efficacy, when used for treatment of advanced disease.
- There are some significant adverse effects, but these are usually able to be managed with appropriate dosing schedules and supportive medications.
- These medications are expected to play an increasingly important role in management of both haematological malignancies and solid tumours when used in earlier stages of disease and in combination with other agents to overcome problems with resistance.

References

- Crescioli, S., Kaplon, H., Wang, L., et al. Antibodies to watch in 2025. mAbs, 2025; 17:1, 2443538. DOI: 10.1080/19420862.2024.2443538
- Strebhardt, K., Ullrich, A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat. Rev. Cancer, 2008: 8: 473-480.
- Fu, Z., Li, S., Han, S., et al. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. Signal transduction and Targeted Therapy, 2022; 7: 93
- Jain, N., Smith, S.W., Ghone, S., Tomczuk, B. et al. Current ADC linker chemistry. Pharm. Res., 2015; 32: 3526-3540.
- Ritchie, M., Tchistiakova, L., Scott, N. Implications of receptor-mediated endocytosis and intracellular trafficking dynamics in the development of antibody drug conjugates. mAbs, 2013; 5: 13-21.
- Baah, S., Laws, M., Rahman, M. Antibody-Drug Conjugates – A tutorial review. Molecules, 2021; 26: 2943.
- Hoffman, R.M., Coumbe, B.G.T., Josephs, D.H., et al. Antibody structure and engineering considerations for the design and function of Antibody Drug Conjugates (ADCs). Oncoimmunology, 2018; 7(3): e1395127
- Tsuchikama, K., An, Z. Antibody-drug conjugates: Recent advances in conjugation and linker chemistries. Protein Cell, 2018: 9: 33-46.

References

- Su, Z., Xiao, D., Xie, F., et al. Antibody-drug conjugates: Recent advances in linker chemistry. Acta Pharmaceutica Sinica B., 2021; 11: 3889-3907
- Beck, A., Goetsch, I., Dumontet, C., Corvalis, N. Strategies and challenges for the next generation of antibody-drug conjugates. Nat. Rev. Drug Discov., 2017; 16: 315-337.
- Flynn, P., Suryaprakash, S., Grossman, D., et al. The antibody-drug conjugate landscape. Nat. Rev. Drug Discovery, 2024; 23: 577-578.
- Nakada, T., Sugihara, K., Jikoh, T., et al. The latest research and development into the antibody-drug conjugate, [fam] Trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. Chem. Pharm. Bull., 2019; 67: 173-185.
- Pommier, Y., Thomas, A. New life of Topoisomerase I inhibitors as antibody-drug conjugate warheads. Clin. Cancer Res., 2023; 29 (6): 991-993.
- Tsuchikama, K., Anami, Y., Ha, S.Y.Y., Yamazaki, C.M. Exploring the next generation of antibody-drug conjugates. Nat. Rev. Clin. Oncol., 2024; 21: 203-223.
- Jain, N., Smith, S.W., Ghone, S., Tomczuk, B. Current ADC linker chemistry. Pharm. Res., 2015; 32: 3526-3540.
- Gogia, P., Ashraf, H., Bhasin, S., Xu, Y. Antibody-drug conjugates: A review of approved drugs and their clinical level of evidence. Cancers, 2023; 15: 3886.

References

- Jin, S., Sun, Y., Liang, X., et al. Emerging new therapeutic antibody derivatives for cancer treatment. Signal Transduction and Targeted Therapy, 2022; 7: 3
- Colombo, R., Tarantino, P., Rich, J.R., et al. The journey of antibody-drug conjugates: Lessons learned from 40 years of development. Cancer Discov., 2024; 14: 2089-2108.
- Donaghy, H. Effects of antibody, drug and linker on the preclinical and clinical toxicities of antibody-drug conjugates. mAbs, 2016; 8(4): 659-671.
- Dumontet, C., Reichert, J.M., Senter, P., et al. Antibody-drug conjugates come of age in oncology. Nat. Rev. Drug Discov., 2023; 22: 641-661.
- Zhu, Y., Liu, M.M., Wang, M.M., Zhu, H. Treatment-related adverse events of antibody-drug conjugates in clinical trials: A systematic review and meta-analysis. Cancer, 2023; 129: 283-295.
- Eaton, J.S., Miller, P.E., Mannis, M.J., Murphy, C.J. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J. Ocul. Pharmacol. Ther., 2015; 31: 589-604.
- Gorovits, B., Krinos-Farotti, C. Proposed mechanism of off-target toxicity for antibody-drug conjugates driven by mannose receptor uptake. Cancer Immunol. Immunother., 2013; 62: 217-223.
- Taylor, R.P., Lindorfer, M.A. Antibody-drug conjugate adverse effects can be understood and addressed based on immune complex mechanisms. Blood, 2024; 144 (2): 137-144.

References

- Liao, M.Z., Lu, D., Kågedal, M. Model-informed therapeutic dose optimization strategies for antibody-drug conjugates in oncology: What can we learn from US Foos and Drug Administration-approved antibody-drug conjugates? Clin. Pharmacol. Ther., 10 (5): 1216-1230
- Khoury, R., Saleh, K., Khalife, N., et al. Mechanisms of resistance to antibody-drug conjugates. Int. J. Mol. Sci., 2023; 24: 967
- Jabbour, E., Paul, S., Kantarjian, H. The clinical development of antibody-drug conjugates- lessons from leukaemia. Nat. Rev. Clin. Oncol., 2021; 18: 418-433.
- Herrera, M., Pretelli, G., Desai, J., et al. Bispecific antibodies: advancing precision oncology. Trends in Cancer, 2024; 10 (10); 893-919.
- Brinkman, U., Kontermann, R.E. The making of bispecific antibodies. mAbs, 2017; 9 (2): 182-212.
- Surowa, M., Klein, C. A pivotal decade for bispecific antibodies? mAbs, 2024; 16 (1): 2321635
- Lim, K-S., zhu, x., Zhou, D., et al. Clinical pharmacology strategies for bispecific antibody development: Learning from FDA-approved bispecific antibodies in oncology. Clin. Pharm. Ther., 2024; 116 (2): 315-327.
- Klein, C., Brinkmann, U., Reichert, J.M., Kontermann, R.E. The present and future of bispecific antibodies for cancer therapy. Nat. Rev. Drug Discov., 2024; 23: 301-319.
- Goebeler, M-E., Stuhler, G., Bargou, R. Bispecific and multispecific antibodies in oncology: opportunities and challenges. Nat. Rev. Clin. Oncol., 2024; 21: 539-560.

References

- Pyzik, M., et al. The therapeutic age of the neonatal Fc receptor. Nat. Rev. Immunol., 2023; 415-432.
- Jabbour, E., Zugmaier, G., Agrawal, V., et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. Am. J. Hematol., 2024; 99: 586-595.
- Jabbour, E., Lussano, .F., Martinéz-Sanchez, R., et al. Subcutaneous blinatumomab in adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: post-hoc safety and activity analysis from a multicentre, single-arm phase 1/2 trial. Lancet Haematol., 2025; 12 (7): E529-E541.
- Kitazawa, T., Igawa, T., sampei, z., et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat. Med., 2012; 18 (10); 1570-1574
- Lenting, P.J., Denis, C.V., Christophe. O.D. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood, 2017; 130 (23): 2463-2468.
- Cao, Y., Langer, R., Ferrara, N. Targeting angiogenesis in oncology, ophthalmology and beyond. Nat. Rev. Drug Discov., 2023; 22(6): 476-495.
- Huang, S., van Duijnhoven, S.M.J., Sijts, A.J.A.M., van Elsas, A. Bispecific antibodies targeting dual tumour-associated antigens in cancer therapy. J. Cancer Res. Clin. Oncol., 2020; 146; 3111-3122.
- Zhu, Y., Choi, S.H., Shah, K. Multifunctional receptor-targeting antibodies for cancer therapy. Lancet Oncol., 2015; 16: e543-e554.

References

- Lee, D., Sung, E.-S., Ahn, J.-H., et al. Development of antibody-based c-Met inhibitors for targeted cancer therapy. ImmunoTargets and Therapy, 2015; 4: 35-44
- Neijssen, J., Cardoso, R.M.F., Chevalier, K.M., et al. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. J. Biol. Chem., 2021; 29: 100641.
- Weisser, N.E., Sanches, M., Escobar-Cabrera, E., et al. An anti-HER2 biparatropic antibody that induces unique HER2 clustering and complement-dependent cytotoxicity. Nat. Commun., 2023; 14: 1394.
- Gandullo-Sánchez, L., Ocana, A., Pandiella, A. HER3 in cancer: from the bench to the bedside. J. Exp. Clin. Cancer Res., 2022; 41: 310.
- Schram, A.M., Odinstov, I., Epinosa-Cotton, M., et al. Zenotuzumab, a HER2xHER3 bispecific antibody is effective therapy for tumors driven by *NRG1* gene rearrangements. Cancer Discov., 2022;12: 1233-1247.
- Sun, Q., Hong, Z., Zhang, C., et al. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. Signal Transduct. Target Ther., 2023; 8: 320
- Zhang, T., Lin, Y., Gao, Q. Bispecific antibodies targeting immunomodulatory checkpoints for cancer therapy. Cancer Biol. Med., 2023; 20: 181-195.
- Farhanginia, P., Ghomi, S.M., Akbarpur, M., Delbandi, A-A. Bispecific antibodies targeting CTLA4: game-changer troopers in cancer immunotherapy. Front. Immunol., 2023; 14: 1155778.

References

- Burton, E.M., and Tawbi, H.A. Bispecific antibodies to PD-1 and CTLA-4: doubling down on T cells to decouple efficacy from toxicity. Cancer Discov., 2021; 11: 1008-1010
- Howlett, S., Carter, J.J., Shaw, H.M., Nathan, P.D. Tebentafusp: a first-in-class treatment for metastatic uveal melanoma. Ther. Adv. Med. Oncol., 2023; 15: 1-12.
- Stieglmaier, J., Benjamin, J., Nagorsen, D. Utilizing the BiTE (bispecific T-cell engager) platform for immunotherapy of cancer. Expert Opin. Biol. Ther., 2015; 15 (8): 1093-1099.
- Van de Donk, N.W.C.J., Zweegman, S. T-cell-engaging bispecific antibodies in cancer. Lancet, 2023; 402; 142-158.
- Buie, L.W.., Pecoraro, J.J., Horvat, T.Z., Daley, R.J. Blinatumomab: A first-in-class bispecific T-cell engager for precursor B-cell Acute Lymphoblastic Leukemia. Ann. Pharmacother., 2015; 49 (9): 1057-1067.
- Franquiz, M.J., Short, N.J. Blinatumomab for the treatment of adult B-cell acute lymphoblastic leukemia: toward a new era of targeted immunotherapy. Biologics, 2020; 14; 23-34.
- Salvaris, R., Ong, J., Gregory, G.P. Bispecific antibodies: a review of development, clinical efficacy and toxicity in B-cell Lymphomas. J. Pers. Med., 2021; 11: 355.
- Crombie, J.L., Graff, t., Falchi, L., et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. Blood, 2024; 143(16): 1565-1575.

References

- Tai, Y-T., Anderson, K.C. Targeting B-cell maturation antigen in multiple myeloma. Immunotherapy, 2015; 7 (11): 1187-1199.
- Strassl, I., Schreder, M., Steiner, N., et al. The agony of choice –where to place the wave of BCMA-targeted therapies in the multiple myeloma treatment puzzle in 2022 and beyond. Cancers, 2021; 13: 4701.
- Moore, D.C., Granger, K., Hill, H., et al. Elranatamab vs teliclistamab: battle of the BCMA bispecifics in relapsed/refractory multiple myeloma. Expert Rev. Hematol., 2024; 17 (6): 197-200.
- Shimabukuro-Vornahagen, A., Göbel, P., Sybklewe, M., et al. Cytokine Release Syndrome. J. Immunother., cancer, 2018; 6: 56.
- Leclercq-Cohen, Steinhoff, N., Servera, L.A., et al. Dissecting the mechanisms underlying the cytokine release syndrome. Clin. Cancer Res., 2023; 29 (21): 4449-4463.
- Lee, D.W., Santomasso, B.D., Locke, F.L., et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity associated with immune effector cells. Biol. Blood Marrow Transplant, 2019; 25: 625-638.
- Yakoub-Agha, I., Chabannon, C., Bader, P., et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy; best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). Haematologica, 2018; 105 (2): 297-316.

References

- Morris, E.C., et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat. Rev. Immunol., 2022; 22: 85-96.
- Stein, A.S., Schiller, G., Benjamin, R., et al. Neurologic adverse events in patients with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab: management and mitigating factors. Ann. Hematol. , 2019; 98: 159-167.
- Mohan, M., Nagavally, S., Dhakal, B., et al. Risk of infections with BCMA-directed immunotherapy in multiple myeloma. Blood, 2021; 138 (Suppl.1): 1626
- Raje, N., Anderson, K., Einsele, H., et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. Blood Cancer J., 2023; 13: 116.
- Ludwig, H., Terpos, E., van de Donk, N., et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Netwrok. Lancet Oncol., 2023; 24: e255-e269.
- Cao, L., Leclercq-Cohen, G., Klein, C., et al. Mechanistic insights into resistance mechanisms to T cell engagers. Front. Immunol., 2025; 16: 1583044.