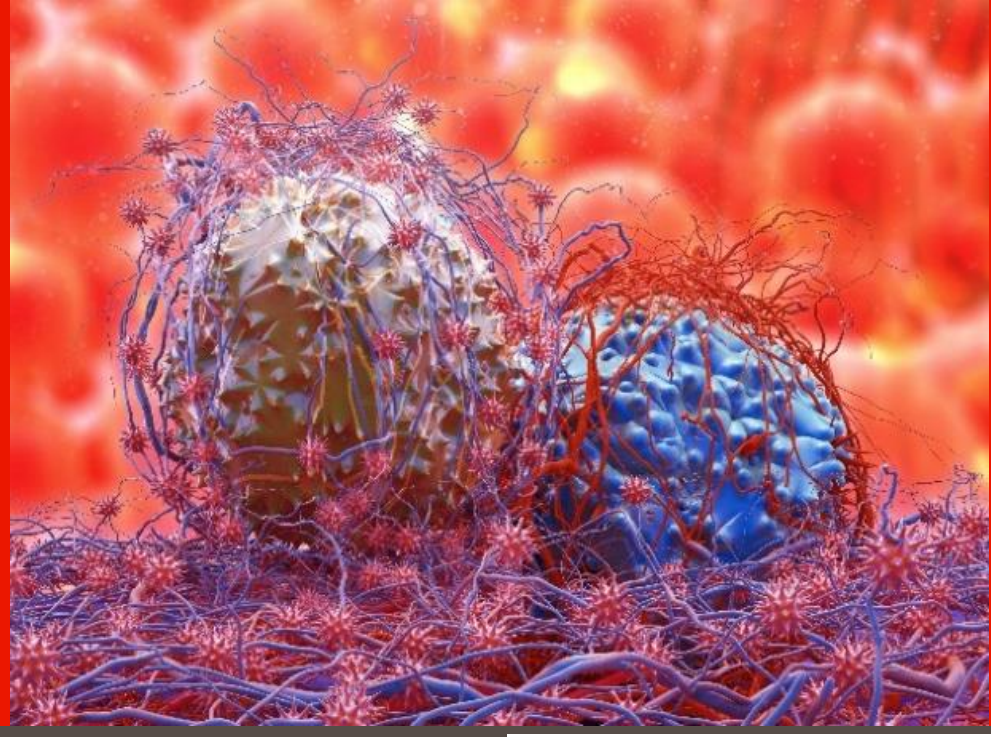
T Cell Engagers: Bispecific Antibodies & Beyond



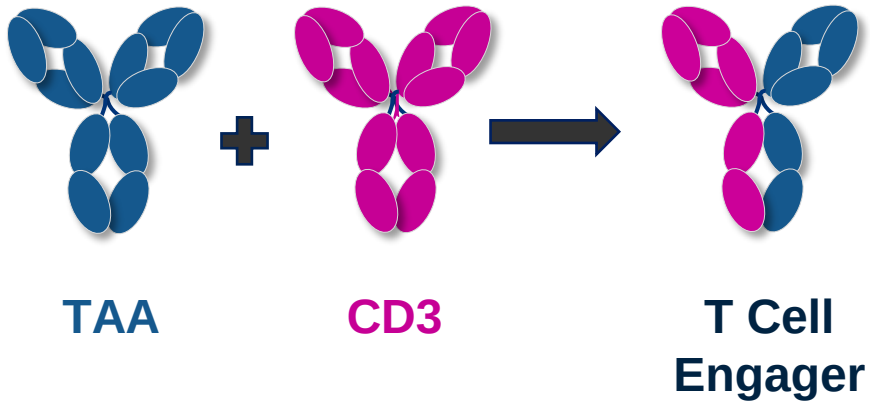
Ulrike Philippar, PhD

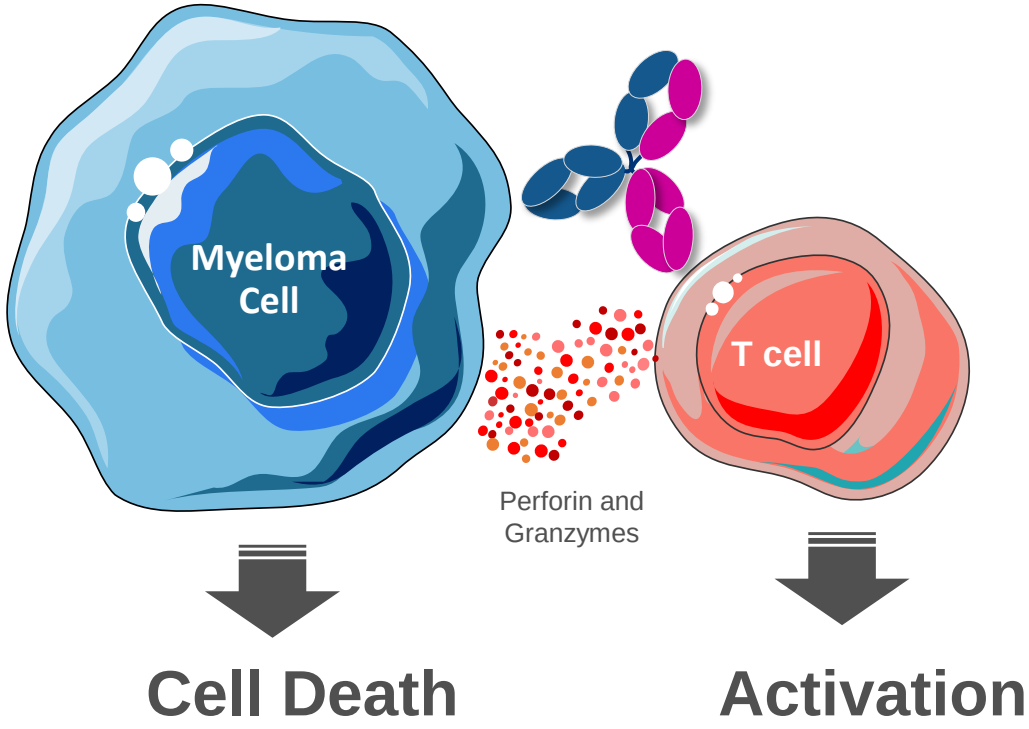
Vice President Oncology
Global Head of Discovery

J&J Innovative Medicine
Beerse, Belgium

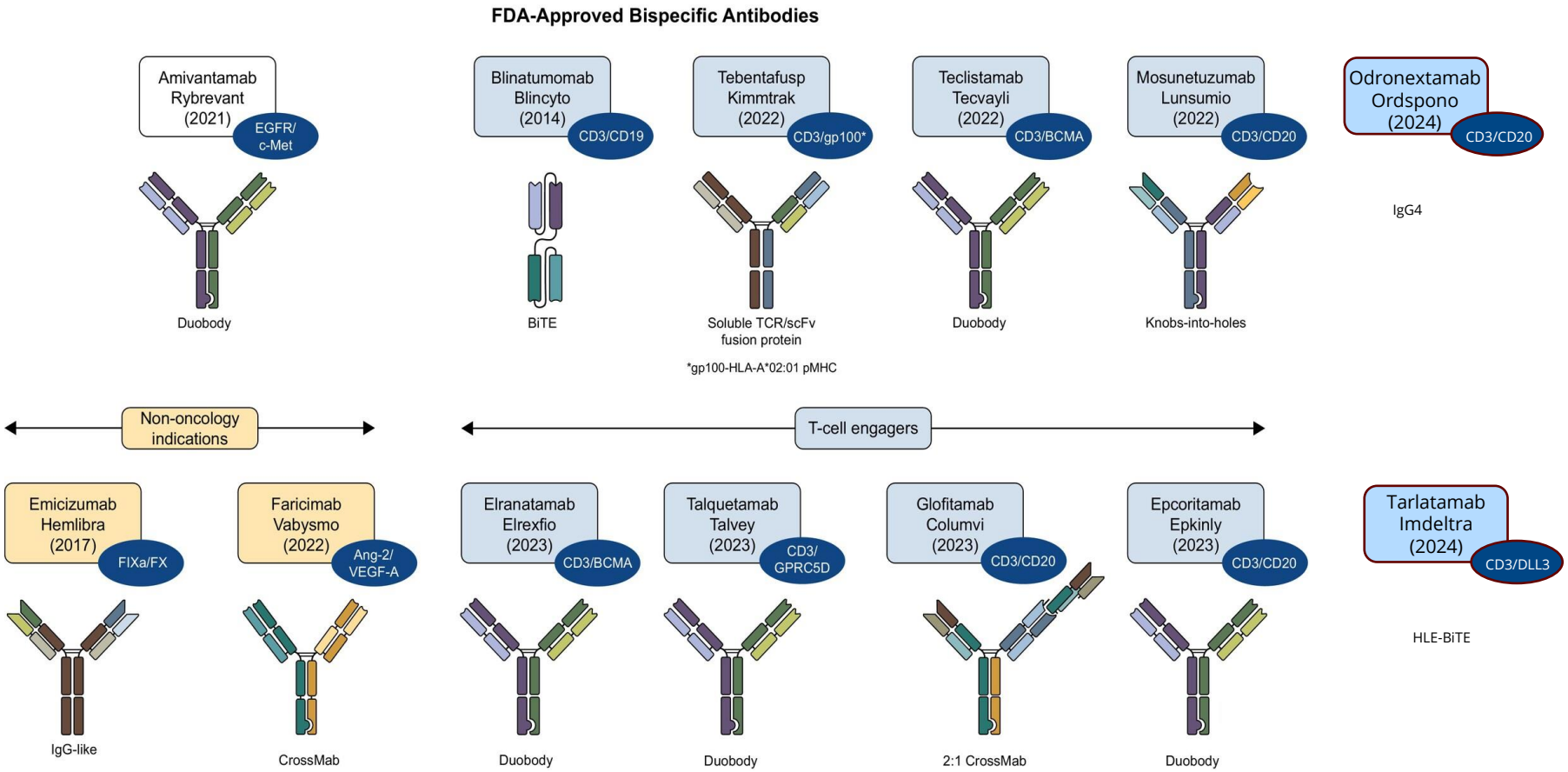
Presented by Ulrike Philippar at CDDF; March 31, 2025; Brussels, Belgium

T Cell Engagers Mechanism of Action



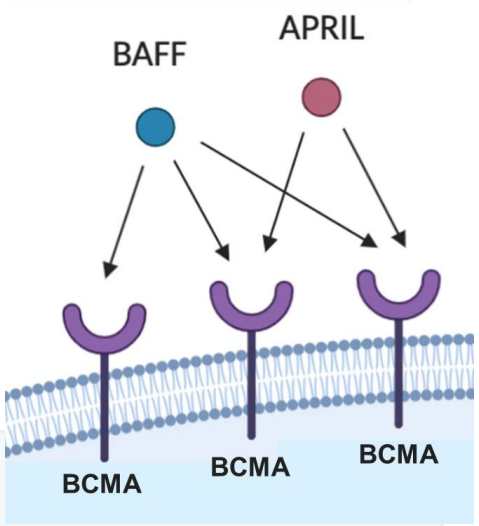


Approved T Cell Engagers



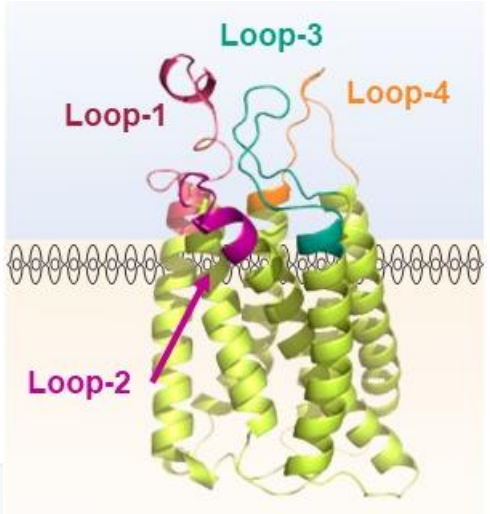
Adapted from Clin Pharma and Therapeutics, Volume: 116, Issue: 2, Pages: 315-327, First published: 02 June 2024, DOI: (10.1002/cpt.3308)

BCMA and GPRC5D are promising MM Targets



BCMA = B-Cell Maturation Antigen

- Type 3 transmembrane protein – tumor necrosis factor receptor superfamily 17 (TNFRSF17)
- BCMA expression is restricted to <u>B-cell lineage</u> and highly expressed in MM plasma cells
- Involved in B cell to plasma cell (PC) differentiation (but not required) and long-lived PC survival (required)



GPRC5D = G Protein-Coupled Receptor Class C Group 5 Member D

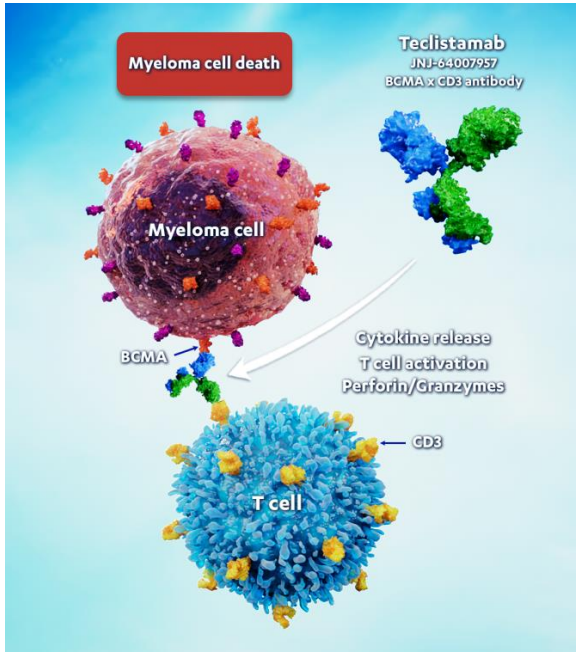
- Orphan G protein-coupled receptor of unknown function
- Limited expression in healthy human tissue, primarily in plasma cells and hair follicles[1-2]

Adapted from Yu B, Jiang T, Liu D. *Journal of Hematology & Oncology* 2020; 13; 125

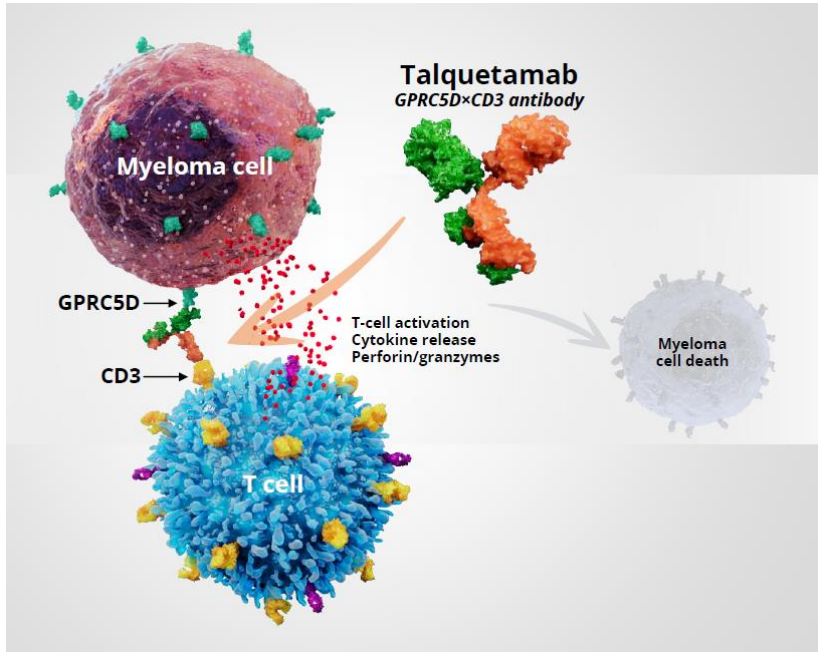
Cho SF, Anderson KC, Tai YT. Targeting B Cell Maturation Antigen (BCMA) in Multiple Myeloma: Potential Uses of BCMA-Based Immunotherapy. *Front Immunol*. 2018;9:1821. doi:10.3389/fimmu.2018.018

Teclistamab and Talquetamab

- **Teclistamab is the only approved BCMA×CD3 BsAb** with a weight-based dosing schedule for the treatment of triple class exposed RRMM[1]
  - ORR of 63% in MajesTEC-1[2]



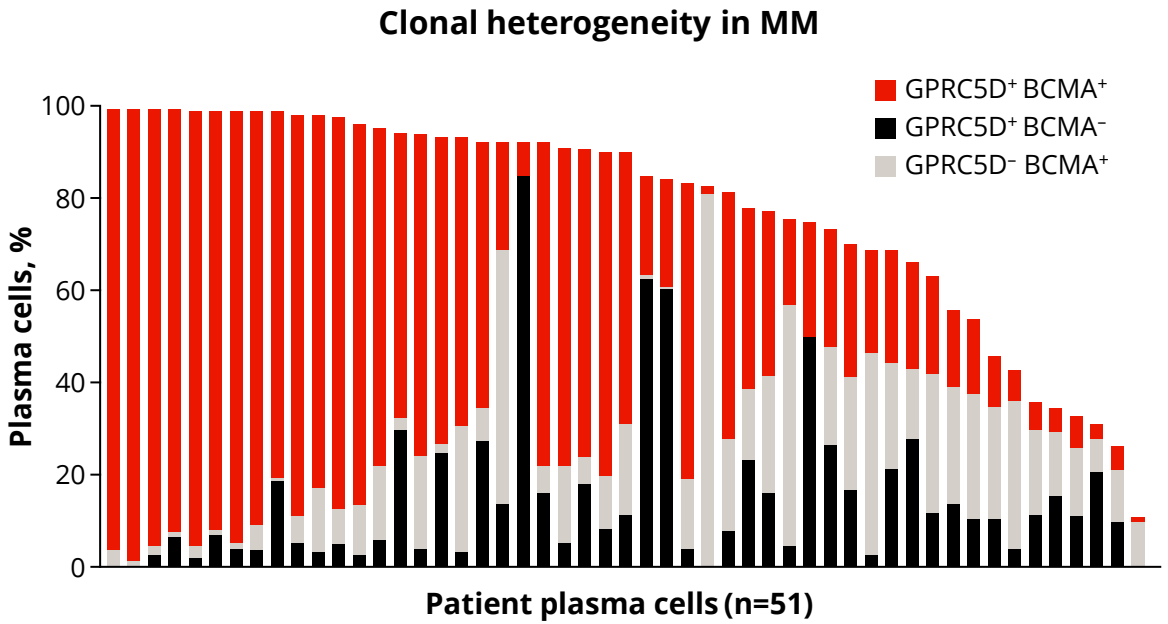
- **Talquetamab is the only approved GPRC5D×CD3 BsAb**, with promising efficacy in patients with RRMM[3]
  - ORR of >70% in MonumenTAL-1[3]



BCMA, B-cell maturation antigen; BsAb, bispecific antibody; EMD, extramedullary disease; GPRC5D, G protein–coupled receptor family C group 5 member D; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma; TCE, triple-class exposed. 1. TECVAYLI (teclistamab-cqyv). Prescribing information. Horsham, PA: Janssen Biotech, Inc; 2022. 2. Moreau P, et al. *New Engl J Med* 2022;387: 495-505. 3. Chari A, et al. *Blood* 2022;140 (suppl 1):384-7.

Dual Targeting of BCMA and GPRC5D May Avoid Antigen Escape and Clonal Resistance

- Due to antigen loss, antigen mutations, and presence of target heterogeneity, disease can recur, and new treatments are needed to overcome resistance and provide clinical benefit

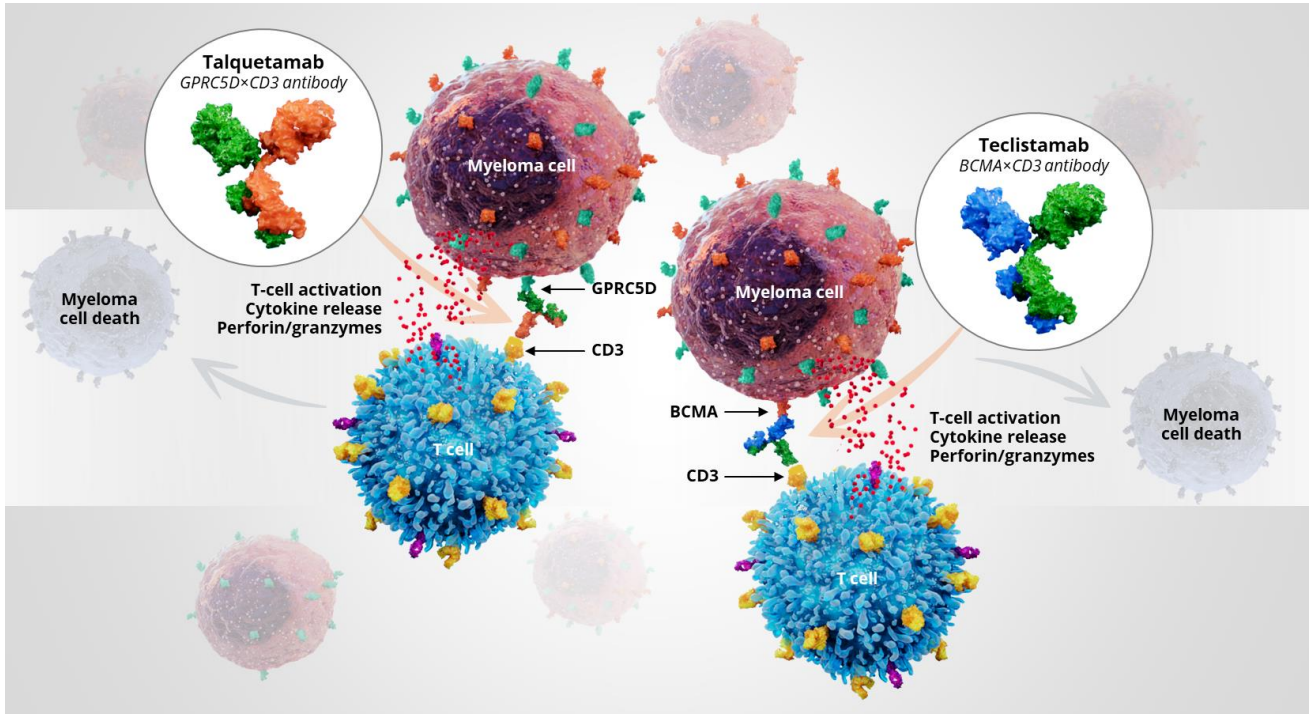


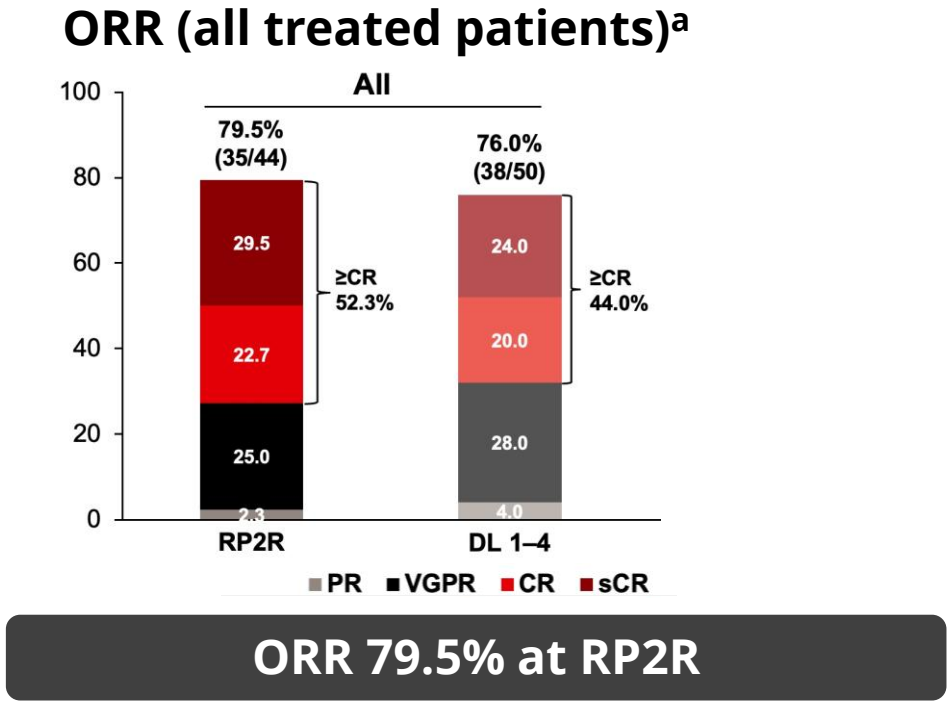
Adapted with permission from Pillarisetti K, et al[8]

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; GPRC5D, G protein–coupled receptor family C group 5 member D; MM, multiple myeloma; ORR, overall response rate; RRMM, relapsed/refractory multiple myeloma.

RedirecTT-1 Study with Dual Bispecific Combination of Teclistamab + Talquetamab in Relapsed/Refractory MM

- Dual antigen targeting may enhance tumor response
  - Potential to address tumor heterogeneity and circumvent antigen loss





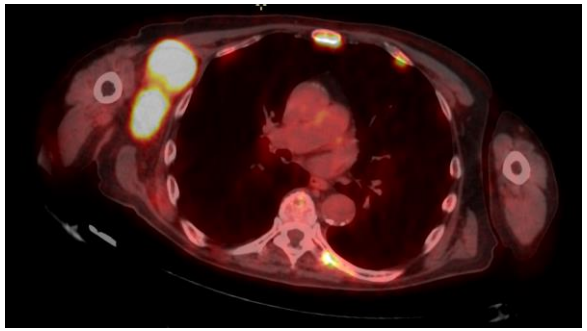
ORR 79.5% at RP2R

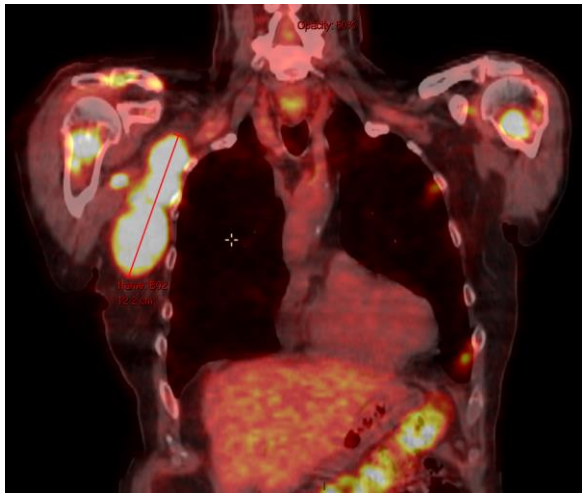
YC Cohen at the 21st International Myeloma Society (IMS) Annual Meeting; September 25–28, 2024; Rio de Janeiro, Brazil

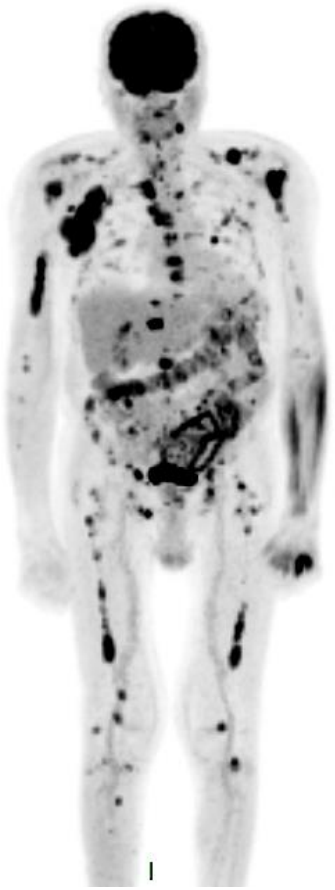
BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor family C group 5 member D;
Data cut-off date: March 15, 2024. [a]Responses were investigator-assessed per IMWG 2016 criteria. [b]EMD defined as ≥1 nonradiated, bone-independent lesion ≥2 cm. CR, complete response; DL, dose level; EMD, extramedullary disease; IMWG, International Myeloma Working Group; ORR, overall response rate; PR, partial response; RP2R, recommended phase 2 regimen; sCR, stringent complete response; tal, talquetamab; tec, teclistamab; VGPR, very good partial response.
RP2R = Tal 0.8 mg/kg + Tec 3.0 mg/kg Q2W

RedirecTT-1: EMD Case Study

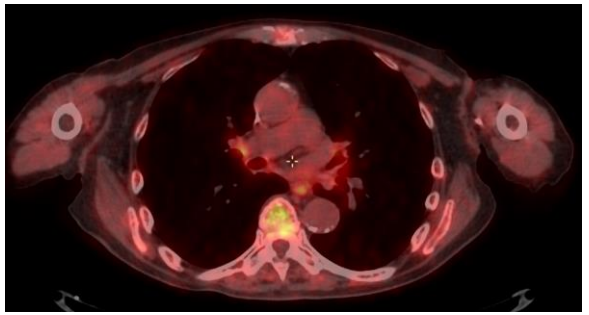
- 74-year-old male, penta refractory, 6 prior LOT including ASCT, belantamab mafodotin, and prior RT to humerus

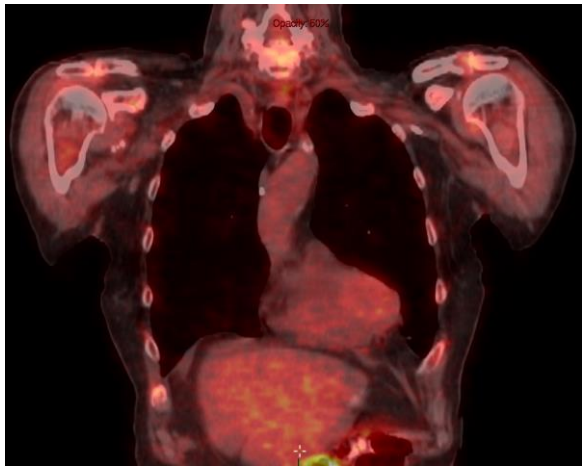






October 25, 2021





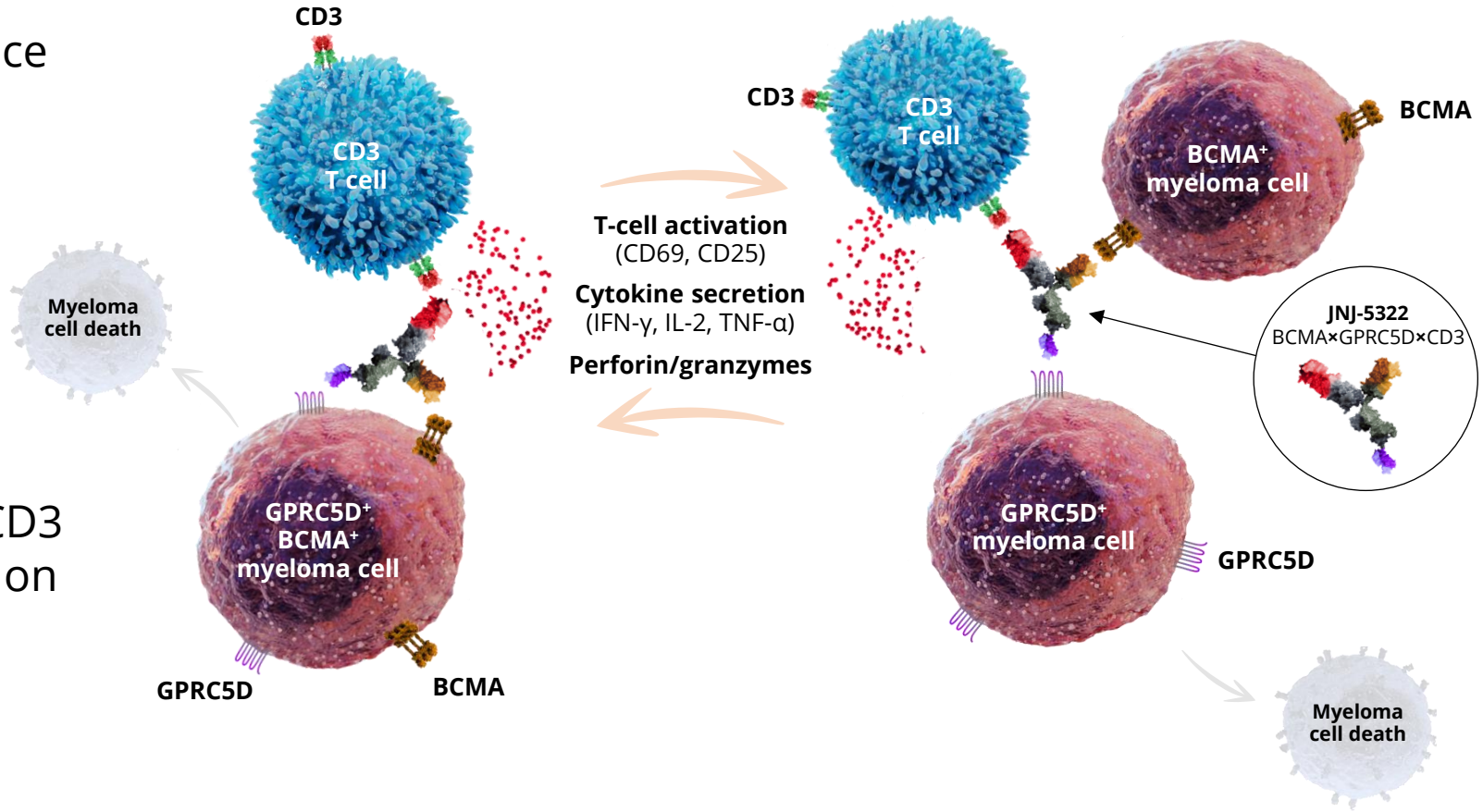
January 2022

ASCT, autologous stem cell transplant; LOT, line of therapy; RT, radiotherapy.

Presented by Ulrike Philippar at CDDF; March 31, 2025; Brussels, Belgium

JNJ-79635322 Is a Potential First-in-Class Trispecific Antibody Targeting BCMA, GPRC5D, and CD3

- Dual antigen targeting may enhance tumor response by circumventing tumor heterogeneity and antigen loss and improving potency due to antigen binding avidity
- JNJ-79635322 (JNJ-5322) is an IgG1 trispecific antibody that binds to CD3 on T cells and BCMA and GPRC5D on MM cells

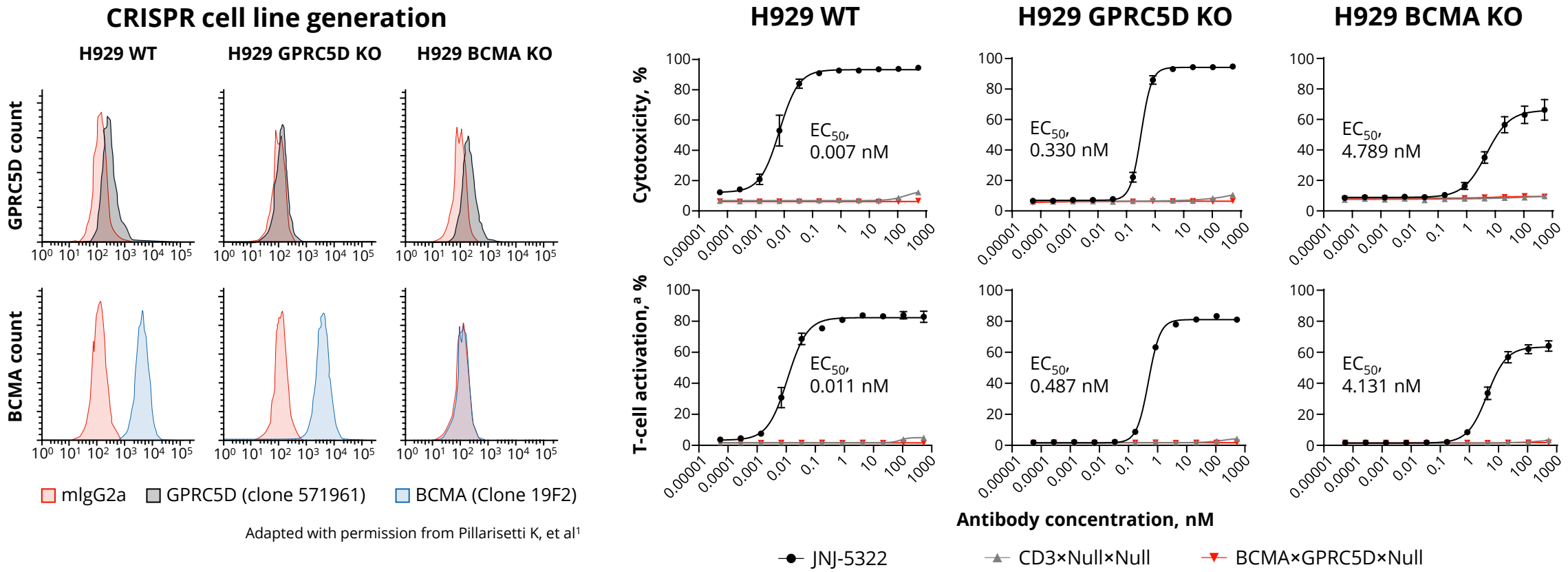


BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor family C group 5 member D; IFN-γ, interferon-gamma; IgG, immunoglobulin G; IL, interleukin; MM, multiple myeloma; TNF, tumor necrosis factor.

Presented by Ulrike Philippar at CDDF; March 31, 2025; Brussels, Belgium

JNJ-79635322 Induces T-Cell–Mediated Cytotoxicity of Dual- and Single-Target–Positive MM Cell Lines

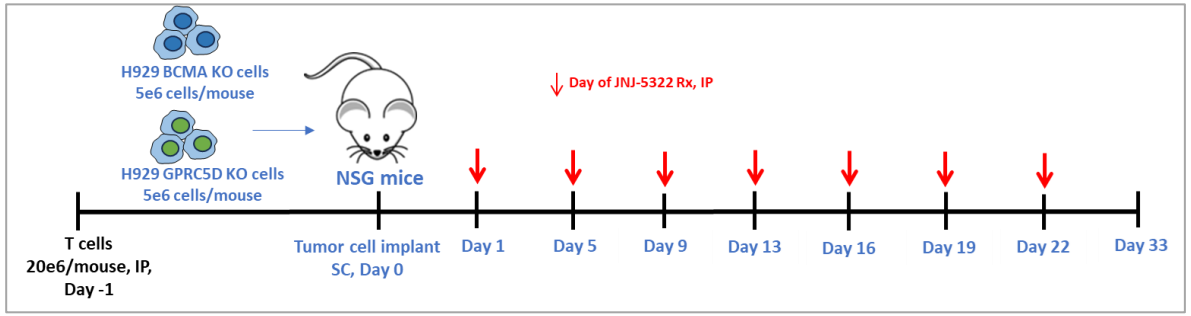
- Dual-target binding (avidity) on H929 WT cells resulted in potent cytotoxicity



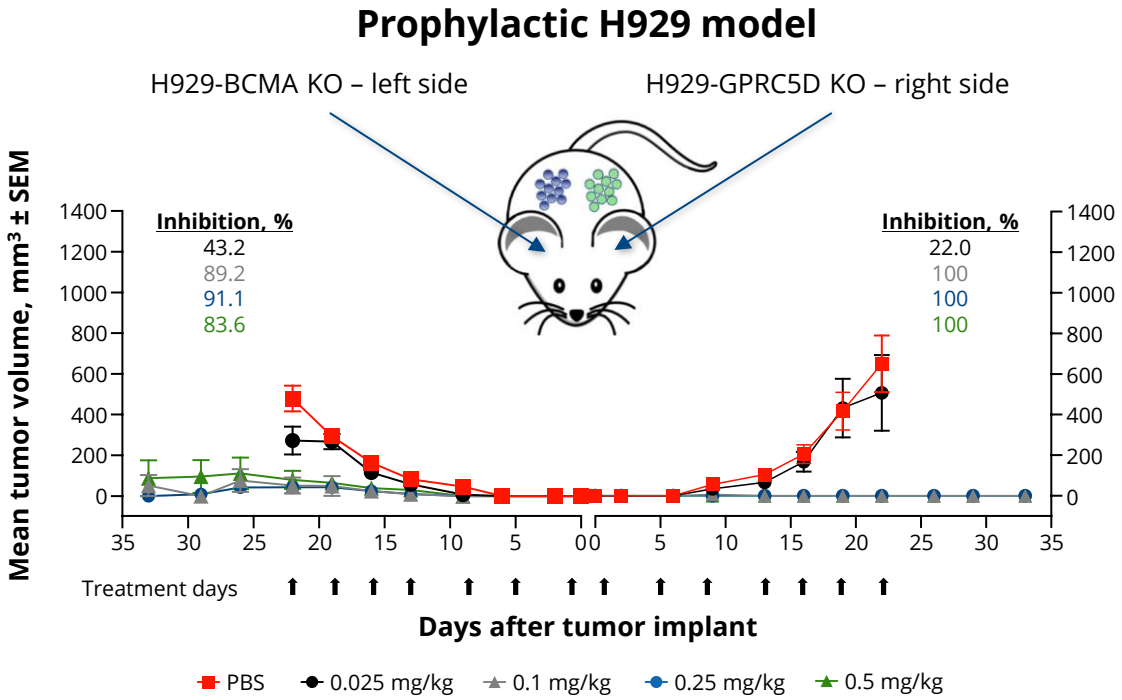
Adapted with permission from Pillarisetti K, et al[1]

Number of healthy T-cell donors = 4; average values plotted.
[a]T-cell activation measured by % of $CD25^+$ $CD3^+$ T cells.
1. Pillarisetti K, et al. *Blood* 2020;135:1232-43.
BCMA, B-cell maturation antigen; EC_{50}, half-maximal effective concentration; GPRC5D, G protein–coupled receptor family C group 5 member D; KO, knock out; MM, multiple myeloma; WT, wild-type.

JNJ-79635322 Prevents Tumor Progression in H929 Single Target Mouse Model



	Antigen	BCMA KO	GPRC5D KO
Receptor density per cell	BCMA	1	3926
	GPRC5D	957	19



- Efficacy at 0.1, 0.25, and 0.5 mg/kg with each group *P*<0.05 vs PBS control

BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor family C group 5 member D; KO, knock out; PBS, phosphate-buffered saline; SEM, standard error of the mean.

Presented by Ulrike Philippar at CDDF; March 31, 2025; Brussels, Belgium

Bispecific and Trispecific T Cell Engagers in MM

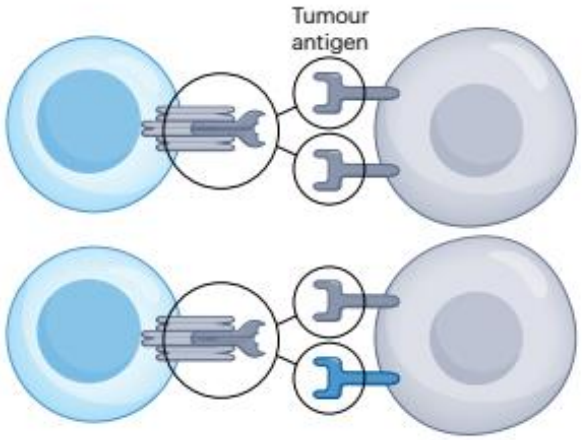
- Bispecific antibodies like Teclistamab and Talquetamab can efficiently engage T cells and show promising clinical activity in MM patients
- Combination of two bispecific antibodies shows promising clinical results
- Trispecific antibodies may provide further advantages

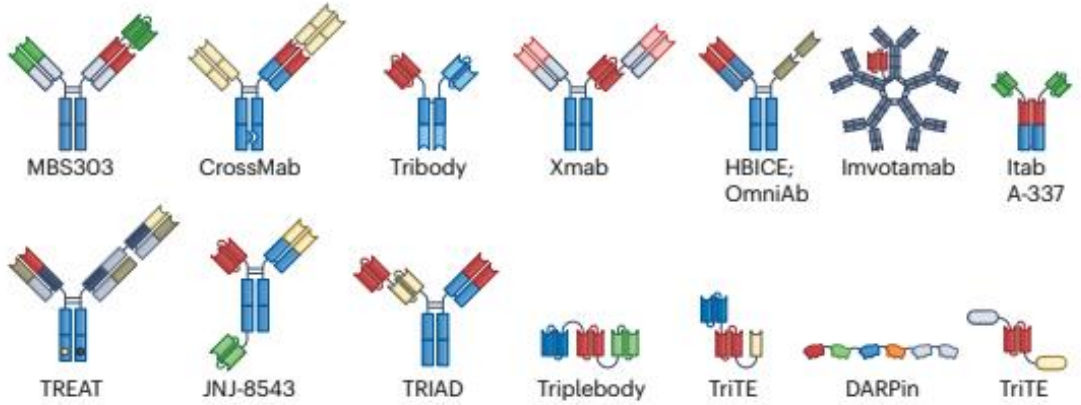
Phase 1/1b dose-escalating studies of JNJ-79635322 in patients with RRMM are ongoing (NCT05652335 and NCT06768489)

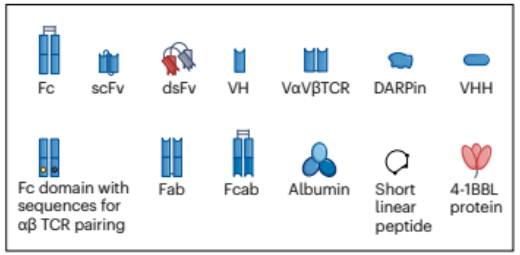
BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor family C group 5 member D; RRMM, relapsed/refractory multiple myeloma.

Next Generation T Cell Engagers

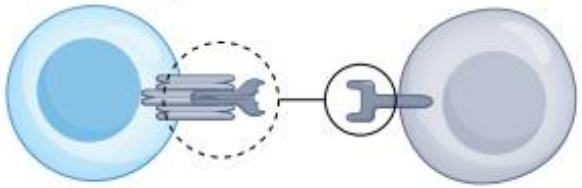
Improve valency for tumor antigen:

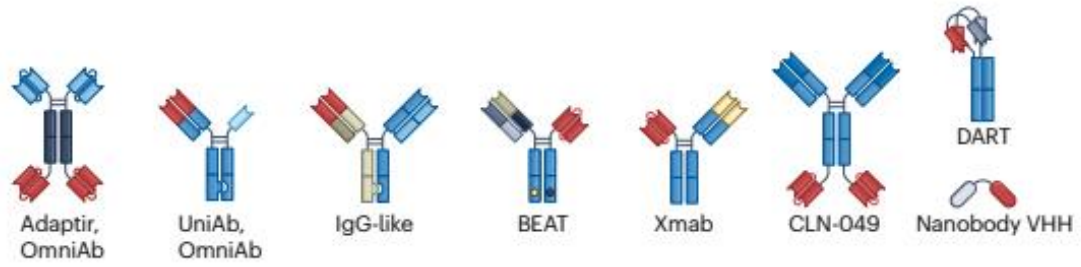






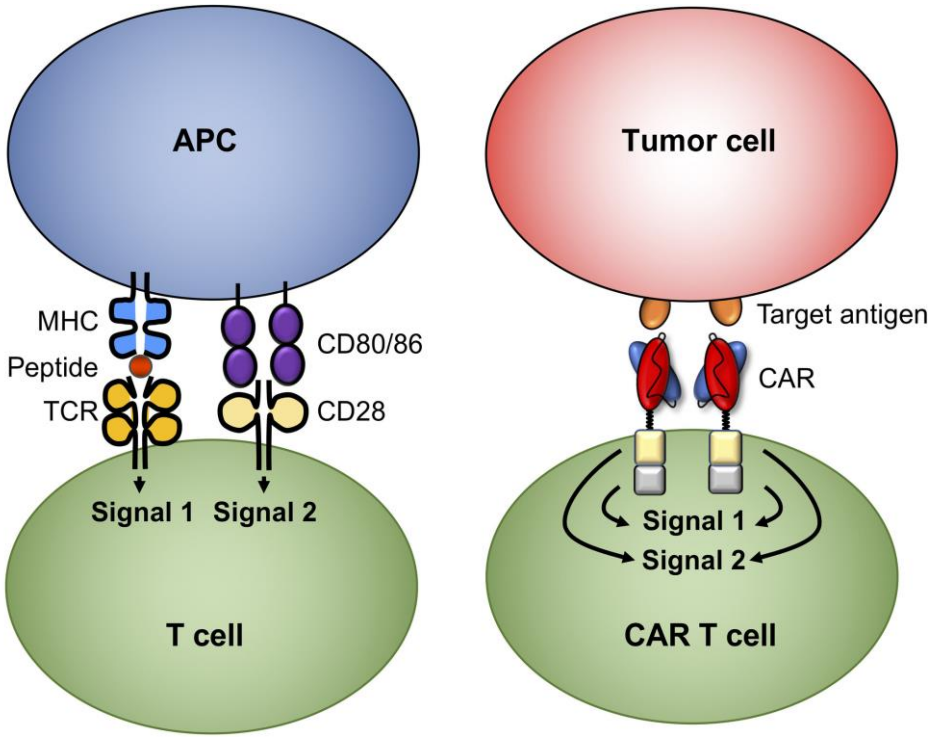
Low affinity for CD3:





Adapted from Nature Reviews Immunology, Vol 24, July 2024, 471-486

Co-stimulation to Provide Signal 2



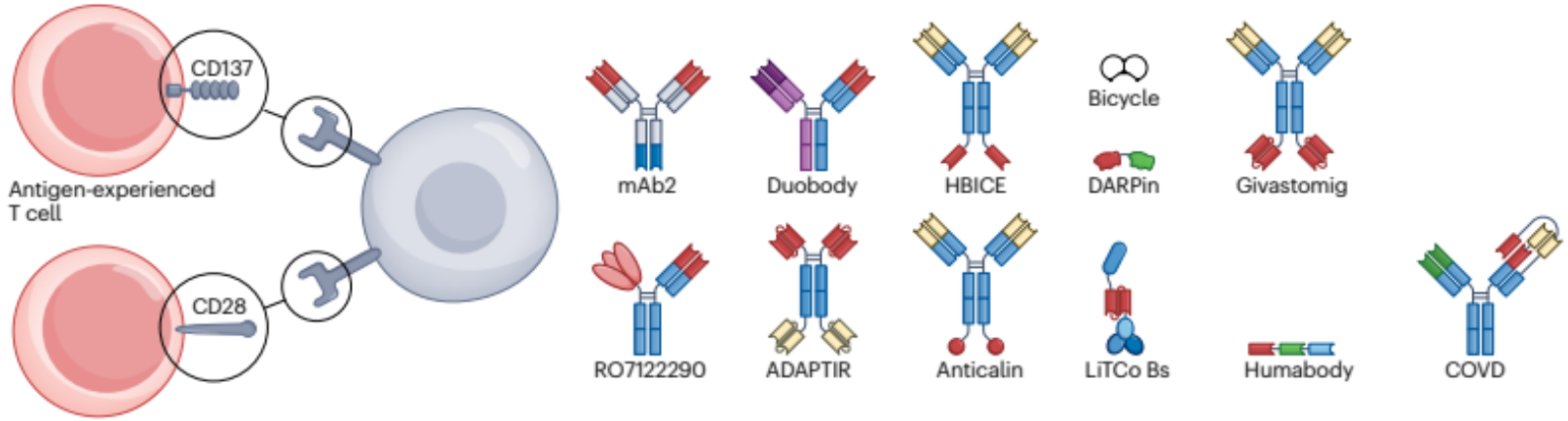
- Effective T-cell activation requires activation by 2 signals:
  - Signal 1: TCR and Signal 2: co-stimulatory receptor
  - T-cells receiving only Signal 1 become anergic and/or undergo apoptosis
- Co-stimulatory receptors:
  - CD28: classical immune synapse component, constitutively expressed on T cells
  - 41BB (CD137): enhanced co-stimulation & metabolic fitness, potential to drive memory generation, inducible T cell expression
  - CD2: interacts with CD58, CD58 lost in many tumor types, constitutively expressed on T cells

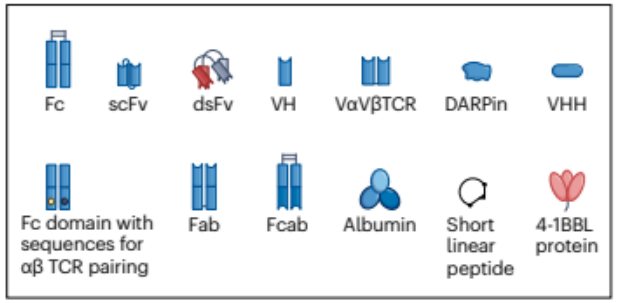
Clin & Trans Imm, Volume: 8, Issue: 5, First published: 11 May 2019, DOI: (10.1002/cti2.1049)

Next Generation T Cell Engagers in Combination with Co-Stim

Costimulatory antibodies may enhance the activity of T-cell Engagers

Target co-stimulatory molecules:





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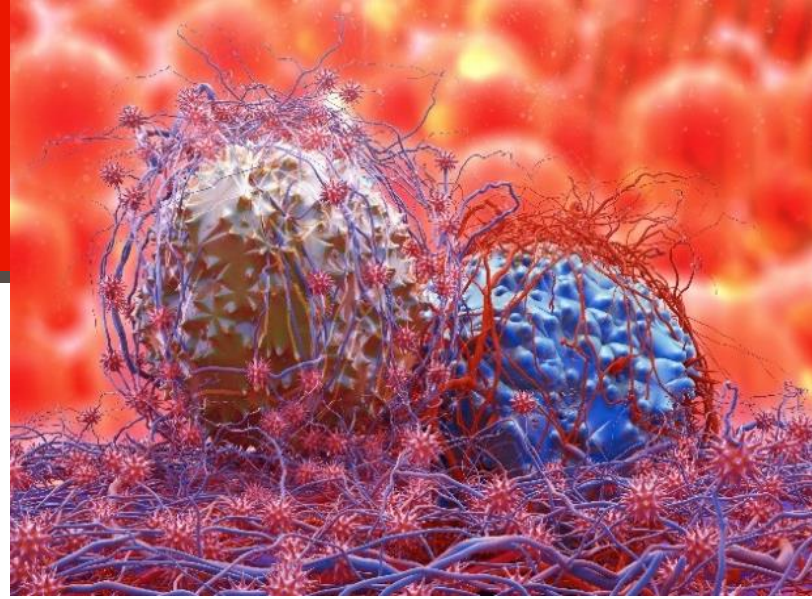

- Patients
- Clinical Sites
- Johnson & Johnson Innovative Medicine R&D Discovery & Compound Development Teams