Proceedings of ICMMGH 2026 Symposium: Environmental Engineering and Climate Change
DOI: 10.54254/2753-8818/2026.PJ30561

Multi-specific T Cell Engager And Multi-specific Natural Killer Engager, the Novel Immunotherapy Approaches for Cancer Treatment

Yuhong Chen

Ocean University of China, Qingdao, China
448621232@qq.com

Abstract. T cell engagers and NK cell engagers are the specialized multi-specific antibodies for cancer treatment. They recruit the immune cells to attack cancer issues, simultaneously induce tumor cell lyse activity by targeting their surface antigens. This article discussed the mechanism and development of multi-specific T cell engager and multi-specific NK engagers, as well as their current applications in tumor treatment and outlook on the future development. It might serve as a useful review for understanding the immune therapeutic approaches and shedding light on the development of more promising approaches for cancer therapy.

Keywords: Immunotherapy, Multi-specific T cell engager, Multi-specific Natural Killer engager

1. Introduction

Cancers currently remain the most dangerous disease. Reports from World Health Organization(WHO) have shown that nearly 20 million people diagnostic positive and approximately 9.7 million people death caused by cancer in 2022 [1]. The total global death due to cancer is expected to increase from 18% to 25% till 2050 [2]. Due to the seriousness of cancer, the development of cancer treatment methods has become one of the top priorities for human health. In the past decades, tumor treatments have developed rapidly, like the chemotherapy and radiation therapy, etc. Nevertheless, none of these traditional therapies achieved the ideal therapeutic efficacy and safety during clinical trials and treatments [3]. Utilizing tumor immune escaping theory, cancer immune-therapeutic approaches have been developed in the past decades. Due to their improved safety and efficiency, immunotherapy has emerged as a groundbreaking approach for cancer treatment [4]. Among different immunotherapeutic approaches, Bi-specific T cell engager(BiTE) and Bi-specific Natural killer engager(BiKE) antibodies are two of the most potential cancer treatment approaches. They are designed to re-recruit T cells and NK cells to trigger an immune response against tumor cells that escaped from the monitoring of our innate immune system [5]. This review discussed the current applications of BiTE & BiKE for cancer treatment.

DOI: 10.54254/2753-8818/2026.PJ30561

2. Novel Immunotherapy: BiTE

2.1. Development of bispecific antibody to BiTEs

In the past decades, the development of therapeutic antibodies enabled the breakthrough in tumor treatment. Inspired by the advances in immune oncology(IO), numerous types of monoclonal antibodies (mAb) have been developed for cancer treatment [6-7]. However, the mono specificity of mAb is the major limitation for its application in IO-based treatment. Current application is limited to immune checkpoint inhibitor and adoptive cell therapies. T cell being the robust defender of immune system have been increasingly considered as the potent weapon against the cancer. However, due to the lack of Fc receptors on T cells, the induction of tumor killing activity via T cell cannot be achieved by mAb [8]. Recently breakthrough in bispecifc antibodies enables the development of BiTE [9]. The first-in-class BiTE, Blinatumomab, consists of two variable chains which recognize CD19 of B cell and CD3 of T cell [10]. The killing of tumor over-expressing CD19 is achieved by the recruitment of and activation of T cell via the CD3 binding arm. This BiTE not only showed high response rates in refractory or relapsed patient population, but also cause acutely adverse event involved pyrexia, neurological, etc. [11]. The discovery of various tumor-enriched antigens in the past decades leads to a spike in the number of BiTE for cancer treatment moving to preclinic and clinic trials [12]. For example, Tarlatamab(DLL3-targeted BiTE) against to Small-Cell Lung Cancer, a Pronectin^{TM}-based BiTE(pAXL×CD3ε) makes a great progress in preclinical models of human soft tissue and bone sarcomas, and Teclistamab-cqyv(CD3-BCMA) caters to multiple myeloma(MM) [13-15].

2.2. Structure of BiTE

Antibody is composed of several structurally independent submits with defined functions. The two variable regions (VH, VL) are involved in target recognition and Fc regions regulates corresponding downstream immune responses [16,17]. A bispecific antibody can be engineered to recognize two different targets by grafting their sequences in the variable regions into the two binding arms of an antibody. A BiTE that consists of two binding arms is able to simultaneously recognize TAA and T cell receptors such as CD3 and CD28. Via these two binding arms, BiTE can recruit T cells, redirect T cells to target tumor antigens and induce the proliferation of T cell [18,19], figure1(a).

DOI: 10.54254/2753-8818/2026.PJ30561

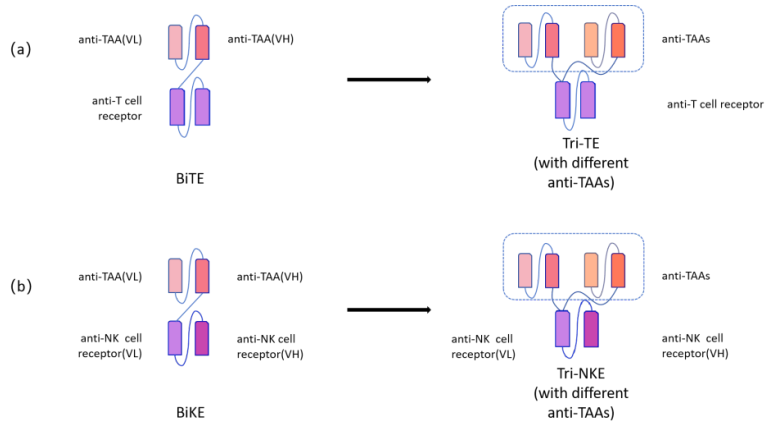

Figure 1. The structure of BiTE(a) and BiKE(b): Bispecific antibodies with binding domains for TAA and T cell/NK cell receptors could recruit T cell or NK cell to eliminate cancers by targeting TAA. Tri-TE and Tri-NKE contain an additional binding domain for TAA and might recognize a broader range of cancer cells

2.2.1. T cell receptors

The most popular receptor to be used for T cell engager(TCE) design is CD3. The activation of CD3 can promote the maturation of T cells into CD4+T cells and CD8+T cells after binding to co-stimulatory receptors [20] and induce complement-dependent cytotoxicity (CDC) for tumor cell elimination [21], figure2. CD28 can also be used as the receptor for engaging T cells. CD28 interacts with B7 molecule(CD80/CD86) from dendritic cell(DC) and subsequently regulates immune responses and the extracellular elicitation of ADCC [22]. The crucial role of B7:CD28 signaling pathway in immunotherapies for cancer makes CD28 another promising receptor for T cell engagers [23].

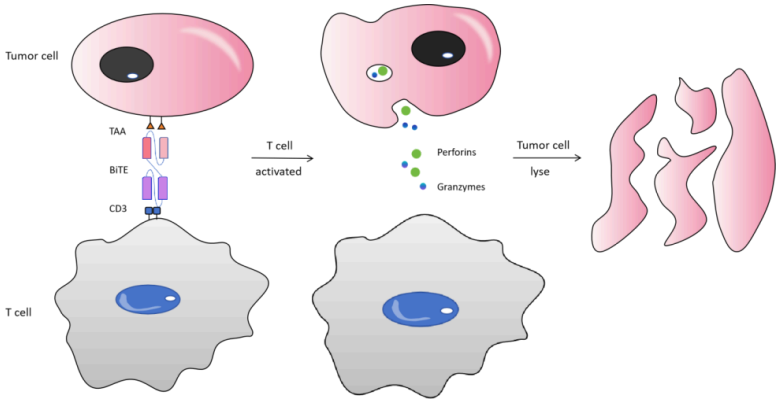

Figure 2. The mechanism of action for BiTE: BiTE targets tumor cell antigen and CD3 to induce T cell dependent killing of tumor cells. Perforins and granzymes released by activated T cells are internalized by tumor cells through endocytosis and lyses the tumor cells

2.2.2. Tumor antigens

There are numerous solid tumor associated antigens that can be used as targets for BiTE. One of the most remarkably targets is Human Epidermal Growth Receptor 2(HER2, gene ERBB2), which has predicted to be utilized in therapeutic target for breast or gastric cancer for decades [24-26].

DOI: 10.54254/2753-8818/2026.PJ30561

Meanwhile, HER3 is another the significant member in epidermal growth factor receptor(EGFR) family associated with cancer progression. The up-regulation of HER3 leads to resistance on epidermal growth factor receptor(EGFR) and HER2-targeted therapy. Other popular TAA targets for Antibody-drug conjugates (ADCs) like Trop2/TACSTD2, Folate Receptor-α(FLOR1), Nectin-4 EFNA4, cMET, B7-H3/CD276, NECTIN4, and PTK7, are also suitable to be used for the treatment of pancreatic, lung, breast, oesophageal, and head and neck cancers for BiTE [27].

2.2.3. Fragment- crystallizable (Fc) regions

The half-life span of an antibody, as well as its ability to activate immune systems, is determined by the Fc region. Two major classes of BiTE have been designed based on the presence and absence of the Fc region [22-23,28]. BiTEs without the Fc regions consist of two covalently linked variable regions. Due to its simple structure, they might be able to penetrate regions which are inaccessible to large molecules within solid tumor. Therefore, this type of BiTE might have better diffusivity within the high condensed tumor matrix and better killing efficacy against tumor [22]. However, due to the lack of the Fc region, this type of BiTE might have shorter half-life in vivo. On the contrary, BiTE with the Fc region can not only inherit the specificity and sensitivity of BiTE without Fc region, but also mediate the ADCC effect due to the presence of Fc region, further enhance the killing efficacy of cancer cells. At the same time, the existence of Fc region makes the whole molecule more stable and has a longer half-life [23].

2.3. Preclinic and clinic landscape of BiTE

A series of promising drug candidates utilizing the T cell engager mechanism have been developed by Amgen. AMG 757, a novel BiTE, has demonstrated the ability in killing small cell lung cancer(SCLC) cells by simultaneously targeting the Notch ligand Delta-like ligand 3(DLL3) and CD3 on T cell [29]. AMG 420, which recognizes B cell maturation antigens(BCMA) expressed on multiple myeloma cells, plasma cells, and mature B cells, had shown promising efficacy in preclinical and clinical studies [30]. In pancreatic adenocarcinoma and gastric cancer, Claudin 18(CLDN18) is a specifically expressed tumor cell antigen. AMG910 is designed to target CLDN18.2 for the treatment of pancreatic adenocarcinoma and gastric cancer [31]. Furthermore, DR30318, which targets CLDN18.2 and CD3, has about 3 weeks' more life span in vivo due to the addition of human serum albumin (HSA) fragment. Its subsequently in vitro and in vivo studies indicated a robust efficacy in suppressing tumor proliferation [32-33].

In addition to the examples above, numerous promising BiTEs for tumor treatment have entered clinic stages. For instance, AMG330(CD33/CD3 without Fc region), AMG673(CD33/CD3 with Fc region), JNJ-63709178(CD123/CD3), MCLA-117(CLEC12A/CD3) are utilized on Acute myeloid leukemia(AML) treatment. Meanwhile, Solitomab (EpCAM/CD3) has been tested against several types of solid tumors. AMG211(CEA/CD3), AMG596(EGFRvIII/CD3), BAT2010112(PSMA/CD3), BI764532(DLL3/CD3, which is similar to AMG757), Tebentafusp(HLA-A*02:01/CD3), SAR442257(CD3/CD28/CD38) are used for the treatment of gastrointestinal adenocarcinomas, glioblastoma, prostate cancer, neuroendocrine carcinomas, uveal melanoma, and non-hodgkin lymphoma, respectively [34]. Moreover, a bi-specific T cell engager Tb535H, which engages tumor-associated antigen 5T4, have shown progress in preclinic studies for multiple tumor models [35]. Furthermore, inspired by the idea of the BiTE, several tri-specific T cell engagers(TriTEs) have also been designed to target a broad range of tumor cells with variable TAA expression [19,36-37]. One

DOI: 10.54254/2753-8818/2026.PJ30561

of the examples is a novel tri-specific antibody(tsAb) architecture composed of CD19/CD22/CD3 that showed improved efficacy comparing to Blinatumomab (CD19/CD3) [38].

3. BiKE

3.1. Development and biology of BiKE

Inspired by the success of BiTE in cancer treatment, NK cell engager(NKE) is developed as an alternative approach under similar immunotherapeutic mechanism [39]. NK cells belong to group 1 innate lymphoid cell(ILC) family and are known for their vital role in native immune system as the first line defense. NK cells can mediate the cytotoxic activity without co-stimulatory signals. Upon activation, NK cells could release releasing interferon gamma(IFN-γ) and tumor necrosis factor alpha(TNF-α) and induce the lysis of malignant tumor cells [40]. Unlike BiTE, monoclonal antibody is able to recruit and activate NK cell via Fc binding to the Fc receptors, like CD16a, on the NK cells [36]. Afucosylation of a monoclonal antibody can enhance the binding affinity to CD16a thus expediting ADCC-dependent killing of tumor cells [41,42]. To further improve the killing efficacy for tumor cells, Bi-specific NK engager(BiKE) is designed based on the idea of BiTE. An additional binding arm targeting other NK cell stimulatory receptors can be employed (eg. NKp46, NKp30) and enhance the activity of NK cells. NKp46 is the most studied NK cell receptor for inducing ADCC effect. Therefore, an additional NKp46 binding domain within an antibody could occupate NKp46 caps with externalized calreticulin(ecto-CRT) in synapses between NK and ecto-CRT, further enhance the ADCC effect [43]. NKp30 is another promising NK cell receptor for BiKE-mediated ADCC. The activation of NKp30 accelerates the cytokines like interleukin-2 to release and enhance the NKp30-denpentent NK cells cytotoxicity [44,45]. NKp40 and NKp44 are currently also being tested as alternative activation receptors for NK cells engagers [46,47]. In addition, ligands that activate NK cells can also be used for NK cell engagement. For example, NKG2C and NKG2D are known for their essential roles in NK activation and promising alternative targets for engaging NK cells [46,48]. Furthermore, due to the inhibitory effect on NK cell-dependent cytotoxic process, HLA family inhibitors are promising binding domains for BiKE.

3.2. BiKEs' structure and its clinical landscape

The structures of BiKEs are similar with those of BiTE. BiKEs also consist of two binding arm target NK cell receptor and TAAs, with half-life expanding region additionally [figure1(b)]. For example, AFM13 is a BiKE without Fc domains and recognizes human CD16A on NK cells and CD30 expressed on Hodgkin Reed–Sternberg cells. In additions, other BiKEs, like AFM28 (CD123/CD16a), LAVA-051(CD1d/NKTTCR), IPH6101/SAR443579 (CD123/CD16/NKp46) and IPH6401/SAR445514 (BCMA/CD16/NKp46), have shown promising results in preclinic and clinic studies for hematological malignancies treatment [49]. Moreover, to further enhance the kill activity of NK cell, a fusion antibody composed of a single chain variable fragment(scFV) which targets CD16 as well as a scFV targets tumor antigen and a moiety of IL-15, had shown better tumor kill efficacy than IL-15 alone [50].

4. Conclusion and outlook

Immunotherapeutic approaches for cancer treatment have been developed rapidly and robustly in the past few decades. Both TCEs and NKEs have made outstanding contributions and shown great potential in the clinical treatments of both invasive and solid tumors at present. However, only

DOI: 10.54254/2753-8818/2026.PJ30561

limited numbers of TCEs have been approved so far [51-54]. Advancing new TCE and NKE based drug into clinic treatment remains challenging due to the limited accessibility of antibodies to the cell-surface TAAs in solid tumor issues [55], as well as the complications of cancer immune biology and resistance from tumor [56]. Therapeutic approaches combing drugs with different mechanism of actions might be a better cure for cancer [57].

References

[1] Cancer today. https: //gco.iarc.who.int/today/en/fact-sheets-cancers

[2] Cancer tomorrow. https: //gco.iarc.who.int/tomorrow/en/dataviz/trends?multiple_populations=1

[3] Immunotherapy vs. Chemotherapy: What's the Difference? https: //www.cancerresearch.org/blog/difference-cancer-immunotherapy-and-chemotherapy#: ~: text=The%20primary%20distinction%20between%20immunotherapy%20and%20chemotherapy%20lies, of%20action.%20Immunotherapy%20doesn%E2%80%99t%20target%20cancer%20cells%20direct

[4] Dougan M, Dranoff G. Immune therapy for cancer [J]. Annual review of immunology, 2009, 27(1): 83-117.

[5] Miyazato K, Hayakawa Y. Pharmacological targeting of natural killer cells for cancer immunotherapy. Cancer Sci (2020) 111: 1869–75. doi: 10.1111/cas.14418

[6] Shim H. Bispecific Antibodies and Antibody-Drug Conjugates for Cancer Therapy: Technological Considerations. Biomolecules. 2020 Feb 26; 10(3): 360. doi: 10.3390/biom10030360. PMID: 32111076; PMCID: PMC7175114.

[7] Wojtukiewicz MZ, Rek MM, Karpowicz K, Górska M, Polityńska B, Wojtukiewicz AM, Moniuszko M, Radziwon P, Tucker SC, Honn KV. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4-new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer Metastasis Rev. 2021 Sep; 40(3): 949-982. doi: 10.1007/s10555-021-09976-0. Epub 2021 Jul 8. PMID: 34236546; PMCID: PMC8556173.

[8] Gill J, Gorlick R. Advancing therapy for osteosarcoma. Nat Rev Clin Oncol. 2021 Oct; 18(10): 609-624. doi: 10.1038/s41571-021-00519-8. Epub 2021 Jun 15. PMID: 34131316.

[9] Ball K, Dovedi SJ, Vajjah P, Phipps A. Strategies for clinical dose optimization of T cell-engaging therapies in oncology. MAbs. 2023 Jan-Dec; 15(1): 2181016. doi: 10.1080/19420862.2023.2181016. PMID: 36823042; PMCID: PMC9980545.

[10] Cech P, Skórka K, Dziki L, Giannopoulos K. T-Cell Engagers-The Structure and Functional Principle and Application in Hematological Malignancies. Cancers (Basel). 2024 Apr 20; 16(8): 1580. doi: 10.3390/cancers16081580. PMID: 38672662; PMCID: PMC11048836.

[11] Buie LW, Pecoraro JJ, Horvat TZ, Daley RJ. Blinatumomab: A First-in-Class Bispecific T-Cell Engager for Precursor B-Cell Acute Lymphoblastic Leukemia. Ann Pharmacother. 2015 Sep; 49(9): 1057-67. doi: 10.1177/1060028015588555. Epub 2015 Jun 3. Erratum in: Ann Pharmacother. 2016 Jan; 50(1): 74. doi: 10.1177/1060028015621161. PMID: 26041811.

[12] Guo, Z.S.; Lotze, M.T.; Zhu, Z.; Storkus, W.J.; Song, X.-T. Bi- and Tri-Specific T Cell Engager-Armed Oncolytic Viruses: Next-Generation Cancer Immunotherapy. Biomedicines 2020, 8, 204. https: //doi.org/10.3390/biomedicines8070204

[13] Paz-Ares L, Champiat S, Lai WV, Izumi H, Govindan R, Boyer M, Hummel HD, Borghaei H, Johnson ML, Steeghs N, Blackhall F, Dowlati A, Reguart N, Yoshida T, He K, Gadgeel SM, Felip E, Zhang Y, Pati A, Minocha M, Mukherjee S, Goldrick A, Nagorsen D, Hashemi Sadraei N, Owonikoko TK. Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study. J Clin Oncol. 2023 Jun 1; 41(16): 2893-2903. doi: 10.1200/JCO.22.02823. Epub 2023 Jan 23. PMID: 36689692; PMCID: PMC10414718.

[14] Polerà N, Mancuso A, Riillo C, Caracciolo D, Signorelli S, Grillone K, Ascrizzi S, Hokanson CA, Conforti F, Staropoli N, Gervasi L, Di Martino MT, Arbitrio M, Nisticò G, Crea R, Tagliaferri P, Juli G, Tassone P. The First-In-Class Anti-AXL×CD3ε Pronectin™-Based Bispecific T-Cell Engager Is Active in Preclinical Models of Human Soft Tissue and Bone Sarcomas. Cancers (Basel). 2023 Mar 8; 15(6): 1647. doi: 10.3390/cancers15061647. PMID: 36980534; PMCID: PMC10046451.

[15] Hua G, Scanlan R, Straining R, Carlson DS. Teclistamab-cqyv: The First Bispecific T-Cell Engager Antibody for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma. J Adv Pract Oncol. 2023 Mar; 14(2): 163-171. doi: 10.6004/jadpro.2023.14.2.7. Epub 2023 Mar 1. PMID: 37009408; PMCID: PMC10062534.

[16] Acc. Chem. Res. 1993, 26, 8, 421–427. https: //doi.org/10.1021/ar00032a005

[17] Gerald M. Edelman , Antibody Structure and Molecular Immunology.Science180, 830-840(1973).DOI: 10.1126/science.180.4088.830.

DOI: 10.54254/2753-8818/2026.PJ30561

[18] Passariello, M., Yoshioka, A., Takahashi, K. et al. Novel tri-specific tribodies induce strong T cell activation and anti-tumor effects in vitro and in vivo. J Exp Clin Cancer Res 41, 269 (2022). https: //doi.org/10.1186/s13046-022-02474-3.
[19] Tapia-Galisteo, A., Álvarez-Vallina, L. & Sanz, L. Bi- and trispecific immune cell engagers for immunotherapy of hematological malignancies. J Hematol Oncol 16, 83 (2023). https: //doi.org/10.1186/s13045-023-01482-w
[20] Clevers J C, Alarcon B, Wileman T, et al. The T cell receptor/CD3 complex: a dynamic protein ensemble [J]. Annual review of immunology, 1988, 6: 629-662.
[21] Burke KP, Chaudhri A, Freeman GJ, Sharpe AH. The B7: CD28 family and friends: Unraveling coinhibitory interactions. Immunity. 2024 Feb 13; 57(2): 223-244. doi: 10.1016/j.immuni.2024.01.013. PMID: 38354702; PMCID: PMC10889489.
[22] Axelrod ML, Cook RS, Johnson DB, Balko JM. Biological Consequences of MHC-II Expression by Tumor Cells in Cancer. Clin Cancer Res. 2019 Apr 15; 25(8): 2392-2402. doi: 10.1158/1078-0432.CCR-18-3200. Epub 2018 Nov 21. PMID: 30463850; PMCID: PMC6467754.
[23] Schildberg FA, Klein SR, Freeman GJ, Sharpe AH. Coinhibitory Pathways in the B7-CD28 Ligand-Receptor Family. Immunity. 2016 May 17; 44(5): 955-72. doi: 10.1016/j.immuni.2016.05.002. PMID: 27192563; PMCID: PMC4905708.
[24] Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol. 2001; 12 Suppl 1: S3-8. doi: 10.1093/annonc/12.suppl_1.s3. PMID: 11521719.
[25] Lohrisch C, Piccart M. An overview of HER2. Semin Oncol. 2001 Dec; 28(6 Suppl 18): 3-11. PMID: 11774200.
[26] Rüschoff J, Hanna W, Bilous M, Hofmann M, Osamura RY, Penault-Llorca F, van de Vijver M, Viale G. HER2 testing in gastric cancer: a practical approach. Mod Pathol. 2012 May; 25(5): 637-50. doi: 10.1038/modpathol.2011.198. Epub 2012 Jan 6. PMID: 22222640.
[27] Bosi C, Bartha Á, Galbardi B, et al. Pan-cancer analysis of antibody-drug conjugate targets and putative predictors of treatment response [J]. European Journal of Cancer, 2023, 195: 113379.
[28] Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020 Mar 1; 10(3): 727-742. PMID: 32266087; PMCID: PMC7136921.
[29] Giffin MJ, Cooke K, Lobenhofer EK, Estrada J, Zhan J, Deegen P, Thomas M, Murawsky CM, Werner J, Liu S, Lee F, Homann O, Friedrich M, Pearson JT, Raum T, Yang Y, Caenepeel S, Stevens J, Beltran PJ, Canon J, Coxon A, Bailis JM, Hughes PE. AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and Sensitivity in Preclinical Models of Small-Cell Lung Cancer. Clin Cancer Res. 2021 Mar 1; 27(5): 1526-1537. doi: 10.1158/1078-0432.CCR-20-2845. Epub 2020 Nov 17. PMID: 33203642.
[30] Topp MS, Duell J, Zugmaier G, Attal M, Moreau P, Langer C, Krönke J, Facon T, Salnikov AV, Lesley R, Beutner K, Kalabus J, Rasmussen E, Riemann K, Minella AC, Munzert G, Einsele H. Anti-B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma. J Clin Oncol. 2020 Mar 10; 38(8): 775-783. doi: 10.1200/JCO.19.02657. Epub 2020 Jan 2. PMID: 31895611.
[31] Cao W, Xing H, Li Y, Tian W, Song Y, Jiang Z, Yu J. Claudin18.2 is a novel molecular biomarker for tumor-targeted immunotherapy. Biomark Res. 2022 May 31; 10(1): 38. doi: 10.1186/s40364-022-00385-1. PMID: 35642043; PMCID: PMC9153115.
[32] Zhu G, Foletti D, Liu X, et al. Targeting CLDN18. 2 by CD3 bispecific and ADC modalities for the treatments of gastric and pancreatic cancer [J]. Scientific Reports, 2019, 9(1): 8420.
[33] Ma Z, Zhou Z, Duan W, Yao G, Sheng S, Zong S, Zhang X, Li C, Liu Y, Ou F, Dahar MR, Huang Y, Yu L. DR30318, a novel tri-specific T cell engager for Claudin 18.2 positive cancers immunotherapy. Cancer Immunol Immunother. 2024 Mar 30; 73(5): 82. doi: 10.1007/s00262-024-03673-x. PMID: 38554200; PMCID: PMC10981630.
[34] Zarezadeh Mehrabadi A, Tat M, Ghorbani Alvanegh A, Roozbahani F, Esmaeili Gouvarchin Ghaleh H. Revolutionizing cancer treatment: the power of bi- and tri-specific T-cell engagers in oncolytic virotherapy. Front Immunol. 2024 Feb 22; 15: 1343378. doi: 10.3389/fimmu.2024.1343378. PMID: 38464532; PMCID: PMC10921556.
[35] Dahlman A, Nelson M, Bannink J, Johnson S, Werchau D, Nilsson A, et al. Preclinical safety and efficacy of a tumor-directed T cell activating 4–1BB x 5T4 ADAPTIR™ bispecific antibody. Cancer Res. 2019; 79: 2380–2380.
[36] Ding Z, Sun S, Wang X, et al. Nanobody-based trispecific T cell engager (Nb-TriTE) enhances therapeutic efficacy by overcoming tumor-mediated immunosuppression [J]. Journal of Hematology & Oncology, 2023, 16(1): 115.
[37] Guo Z S, Lotze M T, Zhu Z, et al. Bi-and tri-specific T cell engager-armed oncolytic viruses: next-generation cancer immunotherapy [J]. Biomedicines, 2020, 8(7): 204.
[38] Zhao L, Li S, Wei X, et al. A novel CD19/CD22/CD3 trispecific antibody enhances therapeutic efficacy and overcomes immune escape against B-ALL [J]. Blood, The Journal of the American Society of Hematology, 2022,

DOI: 10.54254/2753-8818/2026.PJ30561

140(16): 1790-1802.
[39] Zhang M, Lam KP, Xu S. Natural Killer Cell Engagers (NKCEs): a new frontier in cancer immunotherapy. Front Immunol. 2023 Aug 9; 14: 1207276. doi: 10.3389/fimmu.2023.1207276. PMID: 37638058; PMCID: PMC10450036.
[40] Wu S Y, Fu T, Jiang Y Z, et al. Natural killer cells in cancer biology and therapy [J]. Molecular cancer, 2020, 19(1): 120.
[41] Huan T, Guan B, Li H, Tu X, Zhang C, Tang B. Principles and current clinical landscape of NK cell engaging bispecific antibody against cancer. Hum Vaccin Immunother. 2023 Aug; 19(2): 2256904. doi: 10.1080/21645515.2023.2256904. Epub 2023 Sep 29. PMID: 37772505; PMCID: PMC10543353.
[42] Liu S, Galat V, Galat Y, Lee YKA, Wainwright D, Wu J. NK cell-based cancer immunotherapy: from basic biology to clinical development. J Hematol Oncol. 2021 Jan 6; 14(1): 7. doi: 10.1186/s13045-020-01014-w. PMID: 33407739; PMCID: PMC7788999.
[43] Oosterhoff JJ, Larsen MD, van der Schoot CE, Vidarsson G. Afucosylated IgG responses in humans - structural clues to the regulation of humoral immunity. Trends Immunol. 2022 Oct; 43(10): 800-814. doi: 10.1016/j.it.2022.08.001. Epub 2022 Aug 22. PMID: 36008258; PMCID: PMC9395167.
[44] Pahl JHW, Koch J, Götz JJ, Arnold A, Reusch U, Gantke T, Rajkovic E, Treder M, Cerwenka A. CD16A Activation of NK Cells Promotes NK Cell Proliferation and Memory-Like Cytotoxicity against Cancer Cells. Cancer Immunol Res. 2018 May; 6(5): 517-527. doi: 10.1158/2326-6066.CIR-17-0550. Epub 2018 Mar 7. PMID: 29514797.
[45] Coënon L, Villalba M. From CD16a Biology to Antibody-Dependent Cell-Mediated Cytotoxicity Improvement. Front Immunol. 2022 Jun 3; 13: 913215. doi: 10.3389/fimmu.2022.913215. PMID: 35720368; PMCID: PMC9203678.
[46] Cocker ATH, Guethlein LA, Parham P. The CD56-CD16+ NK cell subset in chronic infections. Biochem Soc Trans. 2023 Jun 28; 51(3): 1201-1212. doi: 10.1042/BST20221374. PMID: 37140380.
[47] Fang F, Xie S, Chen M, Li Y, Yue J, Ma J, Shu X, He Y, Xiao W, Tian Z. Advances in NK cell production. Cell Mol Immunol. 2022 Apr; 19(4): 460-481. doi: 10.1038/s41423-021-00808-3. Epub 2022 Jan 5. PMID: 34983953; PMCID: PMC8975878.
[48] Berrien-Elliott MM, Jacobs MT, Fehniger TA. Allogeneic natural killer cell therapy. Blood. 2023 Feb 23; 141(8): 856-868. doi: 10.1182/blood.2022016200. PMID: 36416736; PMCID: PMC10023727.
[49] Tapia-Galisteo A, Álvarez-Vallina L, Sanz L. Bi- and trispecific immune cell engagers for immunotherapy of hematological malignancies. J Hematol Oncol. 2023 Jul 27; 16(1): 83. doi: 10.1186/s13045-023-01482-w. PMID: 37501154; PMCID: PMC10373336.
[50] Vallera, D.A.; Ferrone, S.; Kodal, B.; Hinderlie, P.; Bendzick, L.; Ettestad, B.; Hallstrom, C.; Zorko, N.A.; Rao, A.; Fujioka, N.; et al. NK-Cell-Mediated Targeting of Various Solid Tumors Using a B7-H3 Tri-Specific Killer Engager In Vitro and In Vivo. Cancers 2020, 12, 2659. https: //doi.org/10.3390/cancers12092659
[51] Einsele H, Borghaei H, Orlowski RZ, Subklewe M, Roboz GJ, Zugmaier G, Kufer P, Iskander K, Kantarjian HM. The BiTE (bispecific T-cell engager) platform: Development and future potential of a targeted immuno-oncology therapy across tumor types. Cancer. 2020 Jul 15; 126(14): 3192-3201. doi: 10.1002/cncr.32909. Epub 2020 May 13. PMID: 32401342.
[52] Subklewe M, Magno G, Gebhardt C, Bücklein V, Szelinski F, Arévalo HJR, Hänel G, Dörner T, Zugmaier G, von Bergwelt-Baildon M, Skapenko A, Schulze-Koops H. Application of blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, in treating severe systemic sclerosis: A case study. Eur J Cancer. 2024 Jun; 204: 114071. doi: 10.1016/j.ejca.2024.114071. Epub 2024 Apr 22. PMID: 38691878.
[53] Cayatte C, Ciucci T, Lin W, Lara A, Jafarzadeh N, Foreman T, et al. 1093 Development of TITAN: a new CD8-guided T cell engager platform for hematological and solid tumor applications. Journal for ImmunoTherapy of Cancer. 2024; 12: . https: //doi.org/10.1136/jitc-2024-SITC2024.1093
[54] Shanshal M, Caimi PF, Adjei AA, Ma WW. T-Cell Engagers in Solid Cancers-Current Landscape and Future Directions. Cancers (Basel). 2023 May 18; 15(10): 2824. doi: 10.3390/cancers15102824. PMID: 37345160; PMCID: PMC10216491.
[55] Simao D C, Zarrabi K K, Mendes J L, et al. Bispecific T-cell engagers therapies in solid tumors: focusing on prostate cancer [J]. Cancers, 2023, 15(5): 1412.
[56] Chandran S S, Klebanoff C A. T cell receptor-based cancer immunotherapy: emerging efficacy and pathways of resistance [J]. Immunological reviews, 2019, 290(1): 127-147.
[57] Fan Y, Duan Y, Chen J, Wang Y, Shang K, Jiang J, Su L, Zhou C, Sadelain M, Huang H, Sun J. Bispecific killer cell engager-secreting CAR-T cells redirect natural killer specificity to enhance antitumour responses. Nat Biomed Eng. 2025 Jul 14. doi: 10.1038/s41551-025-01450-4. Epub ahead of print. PMID: 40659834.