Adoptive cell therapy is a treatment modality that leverages the power of the immune system to combat cancer. Cell-based therapies are constantly evolving, and rapidly providing new therapeutic approaches for cancer patients. Since the U.S. Food and Drug Administration approved Tisageniecleucel (CTL019, Imimria) in 2018, chimeric antigen receptor (CAR) T cell therapy has ushered in a new era of personalized cancer treatment, becoming a powerful therapeutic strategy for effective cancer therapy [1].

CAR-T cells are engineered T lymphocytes with hybrid receptors comprising a tumor antigen-binding moiety, typically a single-chain variable fragment (scFv), a hinge region, a transmembrane domain, and various combinations of intracellular signaling domains. Several generations of CAR have been developed in an effort to enhance the immune response against programmed targets. For example, first-generation CAR includes the endodomain of the cluster of differentiation 3ζ (CD3ζ) but exhibited limited clinical efficacy. Second- and third-generation CARs have one or more costimulatory endodomains, such as CD28 and/or 4-1BB, to enhance T cell activation. More recently, fourth-generation CARs are further modified to express cytokines or immunomodulatory molecules (Fig. 1A) [2].

Various therapeutic targets in hematological tumors have been validated for CAR-T cell therapy through extensive preclinical and, subsequent, clinical trials. For the treatment of B-cell malignancies, currently approved CAR-T products include Tisageniecleucel and axicabtagene ciloleucel (KTE-C19, Yescarta). Other CAR-T products presently under development include lisocabtagene maraleucel (JCAR017) and UCART19, also specifically target the B-cell antigen CD19 [3]. Furthermore, CD20 and CD22 are other potential therapeutic targets for CAR-T development to treat B-cell malignancies [4, 5]. More recently, several potential therapeutic targets for treating hematological tumors other than B-cell malignancies have been identified. For example, B-cell maturation antigen (BCMA) for multiple myeloma, CD30 for Hodgkin’s lymphoma, and CD123 for acute myeloid leukemia are promising targets for CAR-T cell development (Fig. 1B) [6, 7].

One of the persistent challenges in immunoncology is targeting solid tumors. While the groundbreaking clinical success of CAR-T cell therapy in treating hematological tumors is clear, using this approach to treat solid tumors has presented numerous challenges. While preclinical and clinical studies in solid tumors have revealed many potential therapeutic targets, including carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2), mesothelin, disialoganglioside GD2 (GD2), glypican-3 (GPC-3), CD133, epidermal growth factor receptor variant III (EGFRvIII), and interleukin 13 receptor subunit alpha 2 (IL13RA2) [8–14], CAR-T therapy in solid tumors has yet to prove efficacious and improve clinical outcomes for patients with solid tumors (Fig. 1B) [15].

Another challenge to the use of CAR-T cell therapy are life-threatening toxicities, such as cytokine release syndrome and neurotoxicity. Despite limiting CAR-T cell therapy to patients who have failed other therapeutic options, efforts to improve CAR-T cell safety profiles are currently being conducted with therapeutic antibodies specifically targeting interleukin-6 or interleukin-6 receptors to promptly mitigate such side effects. Another major limitation in the CAR-T field is cost and clinical effectiveness. In this regard, recent studies have focused on the development of off-the-shelf CAR-T cells using an allogeneic engraftment approach. Simultaneously, T cell receptor (TCR) modulation strategies, such as gene editing or knockout, are currently being investigated to reduce TCR-mediated graft-versus-host disease, a form of allogeneic transplantation rejection [2].
At present, CAR-T technology is one of the fastest-growing markets in the field of immuno-oncology. Although current technologies are not yet optimized to address unmet needs in both clinical and commercial development of CAR-T cell therapy, this cell-based therapy remains a promising therapeutic approach and offers hope for terminally-ill cancer patients. Additionally, as CAR-T strategies and potential solutions continue to evolve, new avenues for more effective and safer cell-based therapies are likely to be identified.

1. Author contributions

JWK and SL collected and analyzed the information, discussed and commented on the manuscript, and wrote the paper. SL supervised the project. All authors have read and agree with the published version of the manuscript.

2. Ethics approval and consent to participate

Not applicable.

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5. Conflict of interest

The authors declare no conflicts of interest. The funders have no role in the design of the study, nor in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results. SL is serving as one of the Editorial Board members and Guest editors of this journal. We declare that BR had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GP.
6. References


Abbreviations: BCMA, B-cell maturation antigen; CAR, Chimeric antigen receptor; CAR-T, cells Chimeric antigen receptor T cells; CD, Cluster of differentiation; CEA, Carcinoembryonic antigen; EGFRvIII, Epidermal growth factor receptor variant III; GD2, Disialoganglioside GD2; GPC-3, Glypican-3; HER2, Human epidermal growth factor receptor 2; IL13RA2, Interleukin 13 receptor subunit alpha 2; ScFv, Single-chain variable fragment; TCR, T cell receptor.

Send correspondence to: Sukmook Lee, Biopharmaceutical Chemistry Major, School of Applied Chemistry, Kookmin University, 02707 Seoul, Republic of Korea, E-mail: Lees2018@kookmin.ac.kr