WHITE PAPER

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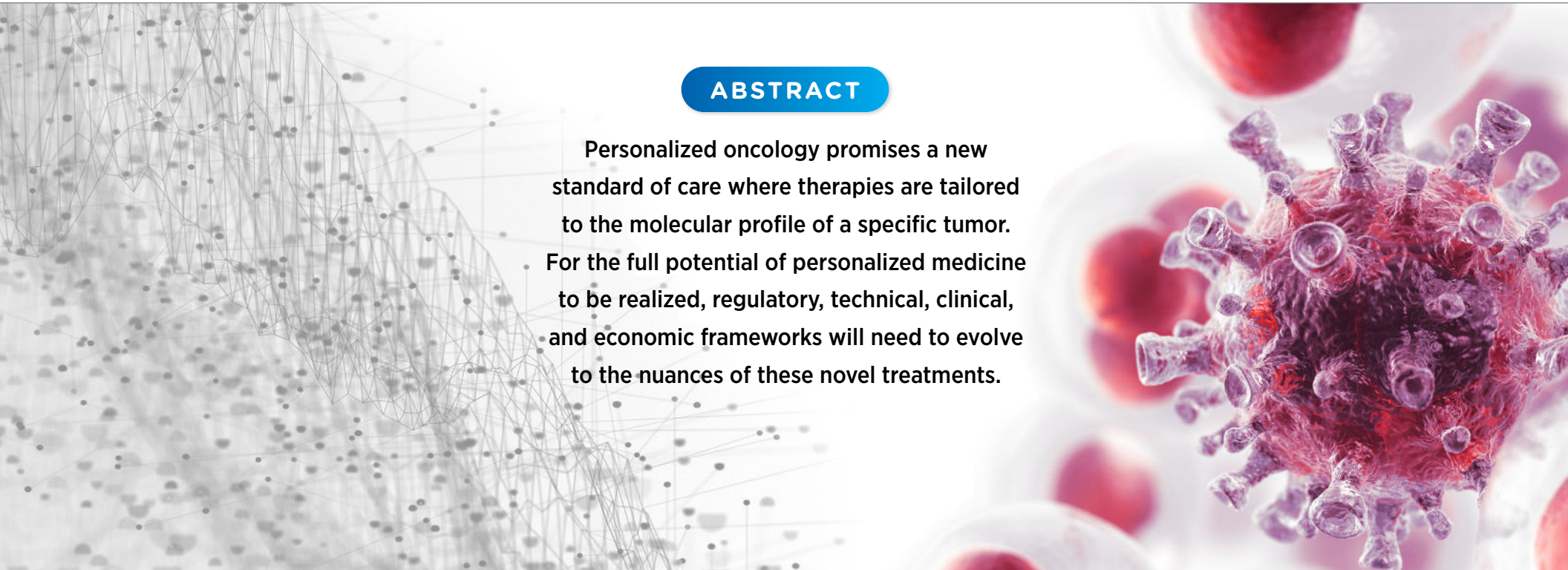
ONCOLOGY

Unlocking the Full Potential of Personalized Medicine in Oncology

ABSTRACT

Personalized oncology promises a new standard of care where therapies are tailored to the molecular profile of a specific tumor. For the full potential of personalized medicine to be realized, regulatory, technical, clinical, and economic frameworks will need to evolve to the nuances of these novel treatments.



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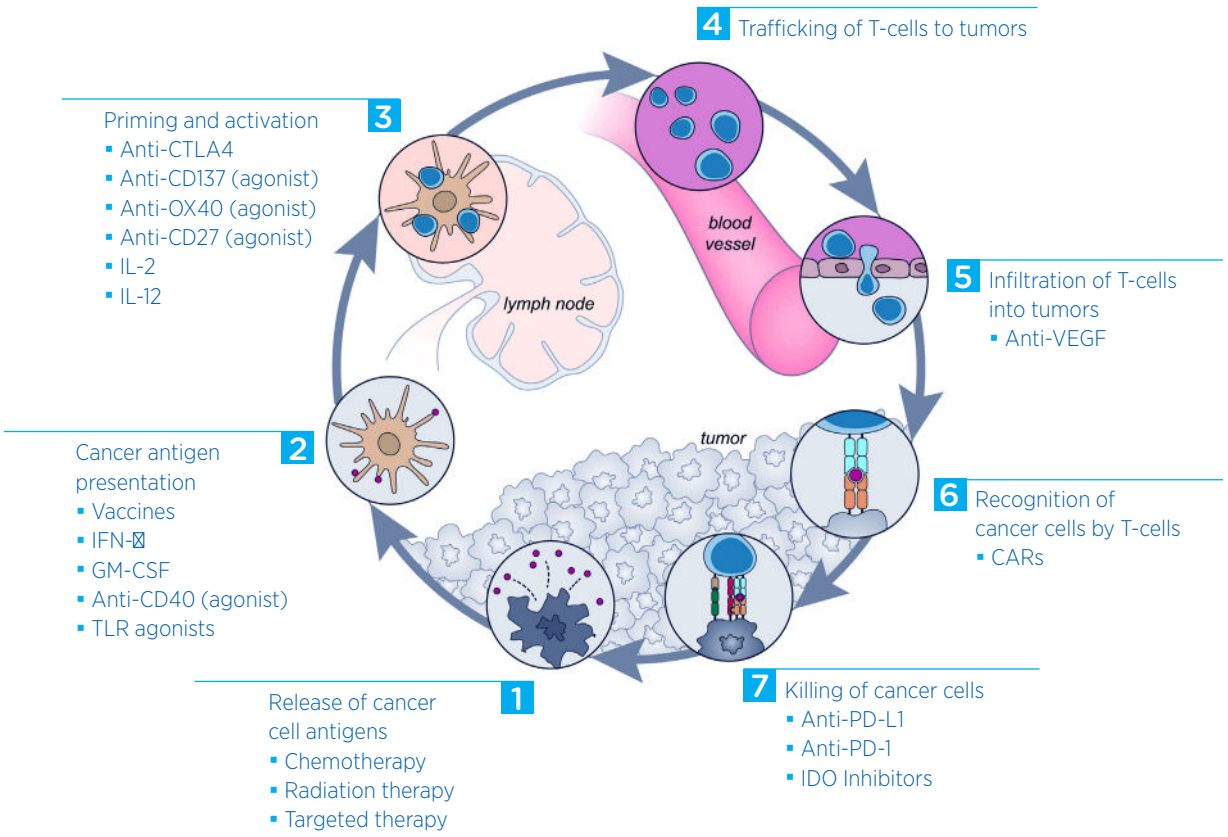
Introduction

In recent years, innovation in oncology drug development has been dominated by advancements in immunotherapy and stepwise progress toward the promise of personalized medicine. To date, the immune checkpoint inhibitors – PD-1/PD-L1 and CTLA-4 inhibitors – have transformed the treatment landscape for certain hematologic malignancies and solid tumors and have been approved for more than 15 indications. With the approvals of tisagenlecleucel (KYMRIAH™) and axicabtagene ciloleucel (YESCARTA™) in 2017, we officially entered the era of chimeric antigen receptor (CAR) T-cell therapies and next-generation biotherapies.

Personalized oncology promises a new standard of cancer care where therapies are tailored to the molecular profile of a specific tumor, in the context of a holistic view of the patient. Currently, CAR T-cell therapies are among the most powerful – and expensive – tools in oncology and one of the most-studied types of investigative products. According to the Alliance for Regenerative Medicine's Q1 2019 Data Report, there are 642 cell therapy or gene-modified cell therapy trials underway worldwide.[1] Accompanying this research fervor is intense interest from patients and providers seeking to gain access to these treatments. But for the full potential of personalized medicine to be realized, regulatory, technical, clinical, and economic frameworks will need to evolve or be adapted to the nuances of these novel treatments.

In this white paper, we provide a brief background on cancer immunotherapy and explore key challenges which must be overcome to deliver on the promise of personalized medicine in oncology.

Figure 1. Potential opportunities to intervene in the cancer-immunity cycle[3]



Background on cancer immunotherapy

The fundamental role of the immune system is to distinguish self from non-self. Being able to identify and attack the non-self without turning on the self and triggering autoimmunity requires a delicate balance of immune system responses. In cancer, the immune system may mistakenly recognize cancer as self and develop tolerance to tumor cells. To further complicate the matter, tumors employ a variety of tactics to overcome host immunity. The complex interactions between cancer and the immune system, sometimes referred to as the Cancer-Immunity Cycle (see Figure 1), involve a multitude of both stimulatory and inhibitory factors, each of which represents a potential opportunity for therapeutic intervention.

Ideal targets for cancer immunotherapy should have the following features:

- Selective expression on malignant cells or non-vital tissue
- A functional protein
- Ability to break tolerance and help the immune system recognize the cancer as non-self

Approaches to cancer immunotherapy

The goal of cancer immunotherapy is to stack the odds by stimulating a patient's immune system so that it can launch a sustained attack against tumor cells.[2] Given that tumors have various mechanisms of evading host immunity, there are multiple approaches to cancer immunotherapy, including:

- **Monoclonal antibodies**: Artificial versions of large proteins with unique antigen specificity which allows them to bind to cancer cells or target the tumor microenvironment. Immune checkpoint inhibitors fall into this category.
- **Cytokines**: Naturally-produced immune modulators that can directly enhance or suppress T-cell responses against cancer cells.[2]

- **Cancer vaccines**: Vaccines that encourage the body to develop antibodies that target tumor cells. These vaccines may contain whole cancer cells, parts of cancer cells, or purified antigens that enhance the immune response against the cancer. A variety of approaches have been investigated for cancer vaccines, ranging from peptide- and immune cell-based to virus- and DNA-based.
- **Cell-based immunotherapy**: Unlike other approaches which are designed to stimulate an immune response, cell-based immunotherapies contain intrinsic anti-tumor properties.[3] CAR T-cell therapy and therapeutic tumor-infiltrating lymphocytes fall into this category.

As with other cancer treatment modalities, the development of resistance will diminish the efficacy of immunotherapies.

Combining cancer treatment modalities

As with other cancer treatment modalities, the development of resistance will diminish the efficacy of immunotherapies. With CAR T-cell therapies, resistance may be due to poor persistence of CAR T-cells following infusion or due to antigen loss of the target receptor. Thus, strategies for optimizing response and minimizing resistance must be considered early in the development process.

The complexity of the immune response to cancer provides a strong rationale for combination therapies. Examples of combination treatments may include:

- **Immunotherapy/Immunotherapy**: Two immunotherapies targeting different immune checkpoints
- **Immunotherapy/Chemotherapy**: Direct killing of tumor cells with chemotherapy may help activate the immune system, potentially leading to an additive effect for immunotherapy
- **Immunotherapy/Targeted therapy**: For example, anti-vascular endothelial growth factor (VEGF) therapy may stimulate the immune system and inhibit tumor vascularization, creating a possible synergistic effect with immunotherapy

CAR T-cell therapy

CAR T-cell therapy involves re-engineering a patient's own T-cells to recognize and eradicate cancer. These T-cells are genetically altered to express artificial receptors which enable them to bind to a specific antigen on the patient's tumor cells and kill them. Unlike T-cell receptor-mediated immune reactions, CAR T-cell mediated immune reactions lead to direct recognition of extracellular tumor-associated antigens; however, immunogenicity can be challenging.

Figure 2. Normal vs. CAR T-cell[4]

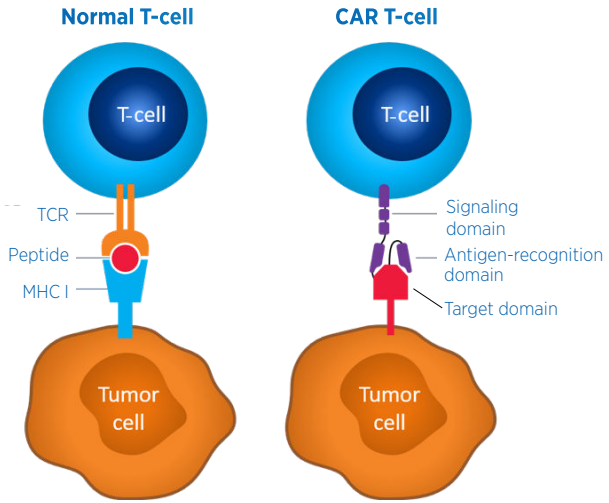
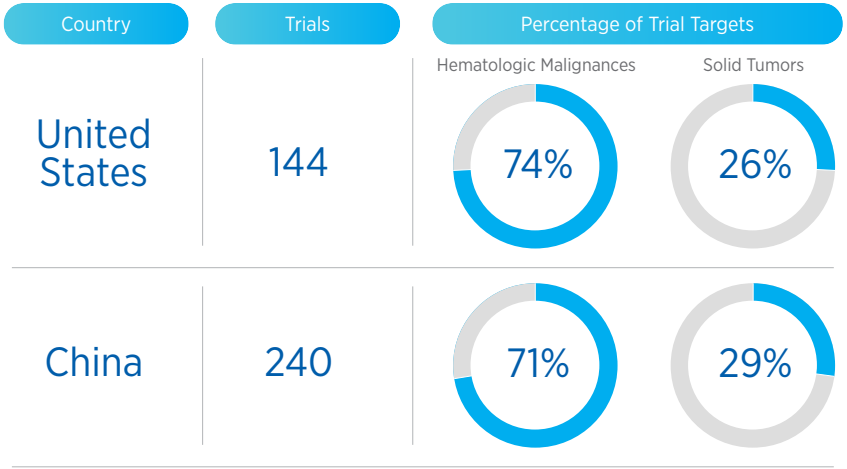


Figure 3. CAR T-cell trials in the U.S. and China[5]



Current CAR T-cell therapy landscape

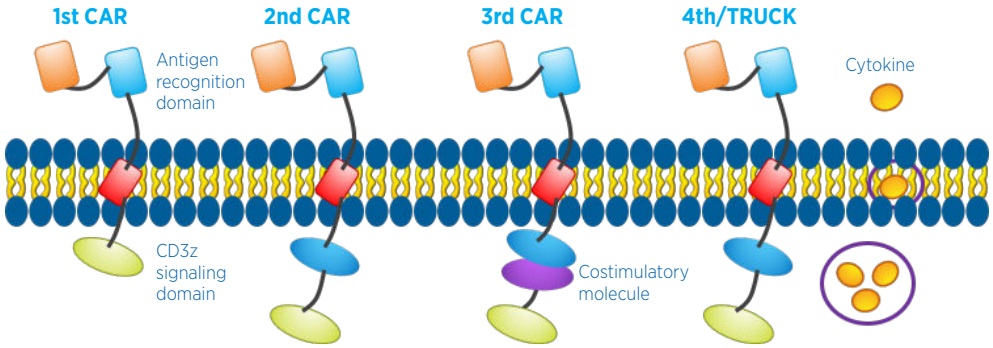
As of September 2019, two CAR T-cell therapies have been approved by the FDA:

- **Tisagenlecleucel**. Approved for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma as well as young adult patients up to age 25 with relapsed or refractor acute lymphoblastic leukemia
- **Axicabtagene ciloleucel**. Approved for the treatment of adults with certain types of B-cell lymphoma who have either not responded to or have relapsed following two or more lines of systemic therapy

CAR T-cell therapy clinical development has accelerated significantly over the past decade, with 144 ongoing trials in the U.S. alone as of August 2018.[5]

In recent years, researchers have been making efforts to enhance the efficacy of CAR T-cell-based therapies, such as improving the structures of CAR T-cells (see Figure 4) or developing mechanisms to make these treatments safer. These mechanisms include suicide switches or elimination genes that trigger selective destruction of CAR T-cells, as well as remote-controlled CARs that include a molecular on/off switch that enables precise regulation of the location, duration, and intensity of the cells' behavior.[6]

Figure 4. Evolution in CAR T-cell design for improved safety or efficacy[7]



Clinical pros and cons of CAR T-cell therapy[8,9,10]

CAR T-cell therapy has a number of advantages compared to other immuno-oncology treatments:

- HLA-independent antigen recognition, enabling universal application
- Selective modification of specific T-cell subtypes
- Rapid generation of tumor-specific T-cells
- Minimal risk of graft-versus-host disease
- Potential for lasting immunity even after a single infusion since it is a living "drug"
- Additional modification capability of the CAR construct

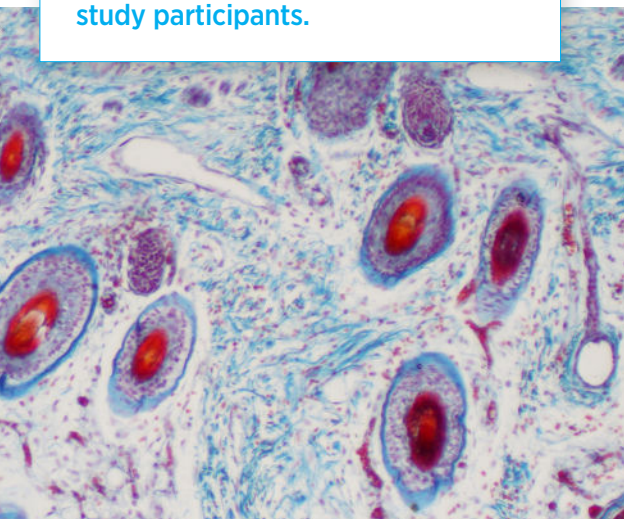
However, CAR T-cell therapy is also associated with a variety of clinical challenges, including:

- Length of time required for T-cell processing and modification
- Adverse events, including cytokine release syndrome (CRS), tumor lysis syndrome, and neurologic toxicity
- On-target, off-tumor toxicity (e.g., B-cell aplasia)
- Off-target, off-tumor toxicity (e.g., agammaglobulinemia)

Managing CRS

The reported incidence of CRS in recent trials ranges from 50 to 93 percent,[11] with symptoms ranging from mild, flu-like symptoms to severe life-threatening systemic inflammatory responses. Currently, the first-line treatment for mitigating moderate to severe CRS is tocilizumab, a monoclonal antibody that competitively inhibits the binding of interleukin-6 (IL-6) to its receptor and hinders IL-6 from exerting its pro-inflammatory effects.[12] In cases where tocilizumab is not effective, steroids have been used. Humanized immunoglobulin (IG)-1 anti-human immunoglobulin (anti-hIL)-6R was also approved by the FDA in August 2017 for treatment of CRS. To date, prophylaxis with tocilizumab has not been shown to reduce the incidence of CRS.

With the robust research activity in this space, sponsors may face fierce competition for sites and study participants.



Conducting clinical trials of CAR T-cell therapies

Sponsors of CAR T-cell clinical trials – particularly global multi-center trials – must deal with unique study-related challenges. The global regulatory environment is not harmonized and certain countries – and even individual sites within the same country – may have different requirements. In addition, with the robust research activity in this space, sponsors may face fierce competition for sites and study participants.

As with any multi-center trial, integrating the study processes of a CAR T-cell trial into each site's standard processes can be time-consuming. Given that the raw material for CAR T-cell therapies must be collected from individual patients and is inherently unique, sponsors should proactively plan for inter- and even intra-site variations in how the cells are collected and processed, as this could affect the quality and efficacy of the final product.

Challenges of commercializing CAR T-cell therapies

Sponsors seeking to commercialize CAR T-cell therapies must overcome a number of critical challenges including:

1. **Scaling manufacturing**. CAR T-cell manufacturing does not fit into the traditional manufacturing mold, and successful bench-to-bedside translation may require sponsors to evolve their manufacturing platform during the course of development.
2. **Managing chain of custody**. Given the complexity of the manufacturing process, which begins with T-cell collection and ends with infusion of engineered T-cells back into the patient, proactive planning around logistics is also critical for managing all aspects of chain of custody.
3. **Obtaining reimbursement**. Most traditional health insurance models are not structured to reimburse for CAR T-cell therapies. Values- or outcomes-based pricing models may be needed to address the challenge of reimbursement and will likely require sponsors to develop patient-selection tools.[13]

Applying CAR T-cell therapies to solid tumors

So far, CAR T-cell therapies have failed to demonstrate significant efficacy in solid malignancies. Barriers to CAR T-cell efficacy in solid tumors include:[14]

- Identifying target antigens that are expressed homogeneously throughout the tumor but are not present in normal vital tissues
- Trafficking to and infiltrating the tumor
- Overcoming immunosuppressive factors in the tumor microenvironment

Bi-specific CAR T-cells that target multiple antigens may be one approach for circumventing tumor escape and optimizing CAR T-cell function in solid tumors. Researchers are also investigating strategies for enhancing CAR T-cell persistence or modulating the tumor microenvironment.[14]

Next steps in CAR T-cell therapy

Looking forward, we are seeing continued investment in CAR T-cell therapies as researchers seek to answer key clinical questions such as:

- Can CAR T-cell therapy be used earlier in the course of treatment?
- Can CAR T-cell treatment replace autologous transplant?
- What is the role of CAR T-cell therapy in maintenance?
- How can CAR T-cell treatment be made safer?
- Will CAR T-cell therapy become an off-the-shelf treatment?

With ongoing research, we hope to see faster, more cost-effective manufacturing and cell expansion using off-the-shelf products with improved safety profiles, making CAR T-cell therapy more accessible to the patients who need it.

References

1. Alliance for Regenerative Medicine. Q1 2019 Data Report. Available at https://alliancerm.org/publication/q1-2019-data-report/.
2. Ventola CL. Cancer Immunotherapy, Part 1: Current Strategies and Agents. PT 2017/42(6):375-383.
3. Zugazagoitia J, et al. Current challenges in cancer treatment. Clin Ther 2016;38(7):1551-1566.
4. Hinrichs CS, Restifo NP. Reassessing target antigens for adoptive T-cell therapy. Biotechnol 2013;31:999-1008. Referenced in Locke, F. L., MD, Gardner, R., MD, & Neelapu, S. S., MD. (2017, December 20). Test Driving CARs: Optimizing Outcomes. Retrieved from https://www.medscape.org/viewarticle/890215_transcript.
5. The-Scientist.com. Cell and Gene Therapy Tracker: Global CAR T-Cell Trials. Available at https://www.the-scientist.com/infographics/cell-and-gene-therapy-tracker-64450. Infographic created with data compiled by CellTrials.org. Accessed April 19, 2019.
6. Sun S, et al. Immunotherapy with CAR-modified T cells: toxicities and overcoming strategies. J Immunol Res 2018;2386187.
7. Xu D, et al. The development of CAR design for tumor CAR-T cell therapy. Oncotarget 2018;9(17):13991-14004.
8. Zhao Q, et al. The application of CAR-T cell therapy in hematological malignancies: advantages and challenges. Acta Pharm Sin B 2018;8(4):539-551.
9. Gauthier J, Yakoub-Agha I. Chimeric antigen-receptor T-cell therapy for hematological malignancies and solid tumors: Clinical data to data, current limitations and perspectives. Curr Res Transl Med 2017;65(3):93-102.
10. Salmikangas P, Kinsella N, Chamberlain P. Chimeric antigen receptor T-cells (CAR T-cells) for cancer immunotherapy – moving target for industry? Pharm Res 2018;35(8):152.
11. Shimabukuro-Vornhagen A, et al. Cytokine release syndrome. J ImmunoTher Cancer 2018;6:56.
12. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. Am J Health Syst Pharm 2008;65(15):1413-1418.
13. Blue Latitude Health. Precision Medicine from Concept to Clinic. Available at https://www.bluelatitude.com/how-we-think/precision-medicine-from-concept-to-clinic/.
14. Srivastava S, Riddell SR. CAR T cell therapy: challenges to bench-to-bedside efficacy. J Immunol 2018;200(2):459-468.

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