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EDITORIAL

Advances and challenges in CAR-T cell-mediated immunotherapy

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Immuno-oncology approaches involving engineered T cell-mediated immunotherapies have revolutionized anti-cancer clinical research in recent years. Among these, Chimeric Antigen Receptor (CAR)-T cell-based therapies have taken center stage in the field of immuno-therapeutics. The strategy involves *ex-vivo* engineering of T cells with CAR molecules, whose external domains are designed to recognize tumor-expressed antigens. Following the infusion of engineered CAR-T cells in patients, upon antigen recognition the internal signaling events initiated from the remaining intracellular CAR domains result in the activation of T cells, and finally elimination of tumor cells take place. The key advantages of this immuno-therapy are the selective recognition of tumor antigens and the elimination of tumor cells by autologous engineered T cells. In this special issue of *International Reviews of Immunology*, we present five comprehensive review articles that summarize key advances in basic and translational aspects of CAR-T cell research (Figure 1).

First, Zhang *et al*. provide an overall summary of the current progress and challenges in the field. The authors initiate their discussion by starting with the evolution of CAR-T cell engineering strategies, pointing out the scientific and clinical hurdles that prompted researchers to develop four generations of CAR-T cells. The authors then go on to discuss cutting-edge strategies such as dual antigen-specific CARs and the co- or sequential administration of pooled CAR-T cells, which are being developed currently to ensure persistent CAR-T cell activity in the long run. Patient immune system-mediated immunological rejection of the CAR transgene is a major issue that precludes the efficient therapeutic efficacy of CAR-T cells. The authors look into this issue further, as well as the strategies currently underway to minimize CAR-T cell-mediated toxicity as a means to overcome tumor immune suppression, as well as possible methodologies to develop universal CAR-T cells that can circumvent the long-standing problem of the enhanced propensity of the exhaustion of T cells that are isolated from patients for *in vitro* manipulation. Finally, the authors discuss cutting-edge research that several laboratories are undertaking to generate CAR-T cells in vivo, directly in patients. Successful achievement of this feat will indeed be a milestone in CAR-T cell-based cancer immunotherapy (Figure 1).

While CAR-T cell-mediated therapeutic approaches have shown enormous promise against hematological malignancies, their efficacy against solid tumors remains relatively unsatisfactory due to the lack of appropriate tumor-specific antigens (TSAs) that have been identified as targets. For example, glioblastoma (GBM), one of the most common types of brain cancer, is associated with an extremely unfavorable prognosis and a two-year survival rate of less than 30%. Despite being refractory to different kinds of treatments, novel therapeutic approaches pursued using CAR-T cell technology in recent years have shown considerable promise. Two articles in this special issue by long-term collaborators, the Goda and Purwar groups, cover this topic. The article by Chatterjee & Asija *et al*. discusses the features of GBM that make it challenging to treat. Following this, the authors describe in-depth the strategies used currently to treat the disease, and finally present their perspective on clinical regime and combinatorial treatment plans that may prove to be beneficial in the foreseeable future. In the subsequent article, Chatterjee et al. primarily discuss the advances in CAR-T cell-mediated targeting of brain tumors, with a specific focus on GBM. The

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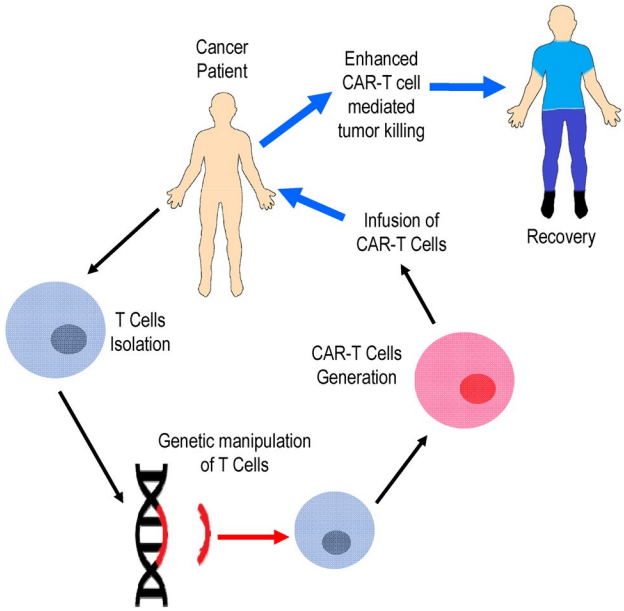

Figure 1. Fundamental and translational aspects of CAR-T cell cancer immune-therapy.

authors sum up their discussion with additional perspectives on dendritic cell vaccines, immune checkpoint inhibitors, oncolytic virus-based therapies, and nanoparticle-based gene-editing technologies that are currently being pursued in clinic as future therapeutic artilleries against various forms of brain cancer (Figure 1).

B7 homolog proteins, exemplified by the widely targeted checkpoint inhibitor PD-L1 (the alias for B7-H1), are a family of ligands with immune cell co-activation or co-repressor properties. One of the members of this family, highly expressed in different kinds of tumors, and consequently increasingly pursued as a viable target tumor-associated antigen (TAA) in cancer research, is the protein B7-H3 (also known as CD276). B7-H3 is known to exert both co-stimulatory and co-inhibitory effects on the immune system, and is known to exist both in membrane-bound and soluble form, the latter generated upon cleavage by metallopeptidase enzymes or through alternative splicing. TREM-like transcript 2 (TLT2) has recently been identified as a receptor of B7-H3, although, provided the multifunctional properties of B7-H3 are as reported, other potential receptors are anticipated to be awaiting discovery in the future. The article by Li et al. discusses the progress and challenges of B7-H3-targeting CAR-T cell therapy for solid tumors of the types found in lung cancer, ovarian cancer, GBM, and pediatric tumors, among others (Figure 1).

As for advances in other fields of biomedical innovation, the in-depth protocols and manufacturing technologies for engineering T cells have gone through different phases of modifications throughout the past several years. Modules of automated systems have been developed for the large-scale expansion and purification of modified T cells, with intact functional identities. The final review by Song *et al.* extensively covers the current advances and latest techniques used at different phases in the CAR-T and TCR-T cell manufacturing processes, from cell isolation and transduction to expansion and harvest. Further, the authors present three case studies to share their own experience in the clinical application of the techniques, and categorically discuss the major questions that one should consider when choosing optimal manufacturing platforms based on clinical specifications (Figure 1). Collectively, all the articles of this special issue will surely be of immense technical and fundamental benefit for a broad readership in various disciplines of immunology and clinical/translational oncology.

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