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Editorial

Adoptive T Cell Transfer-Based Cancer Immunotherapy is a Promising Strategy for Cancer Treatment

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Editorial

Cancer is a leading cause of death worldwide [1]. According to the World Cancer Report 2014, the global burden of cancer rose to an estimated 14 million new cancer cases in 2012, and this figure is expected to rise to 22 million annually within the next two decades. Over the same period, cancer deaths are predicted to rise from an estimated 8.2 million to 13 million per year. Traditional cancer treatments, including surgery, chemotherapy, and radiation therapy, have demonstrated very limited efficacy for cancer patients with late-stage disease.

The innate and acquired immune systems play a critical role in immune surveillance and immune defense [2,3]. Therefore, the use of the immune system to eliminate cancer is a very promising approach for cancer treatment [4, 5]. Indeed, immunotherapy has demonstrated great potential for cancer treatment [6-9], especially for disease refractory to traditional treatments. Recent FDA approval of immunotherapy-based vaccines/drugs sipuleucel-T (Provenge) [10] and ipilimumab (Yervoy) [11] represent milestones in the field of cancer immunotherapy for advanced prostate cancer and metastatic melanoma, respectively [8]. Furthermore, a phase III clinical trial of gp100 peptide vaccine in patients with advanced melanoma has shown encouraging results [12]. Thus, cancer immunotherapy has become an important part of treating cancer patients with advanced or refractory disease.

Cancer immunotherapy approaches include active immunization, reversal of immune suppression, nonspecific immune stimulation, and Adoptive Cell Transfer (ACT). To date, ACT has been demonstrated to be the most effective immunotherapy method for cancer treatment and has achieved very promising results in cancer clinical trials [13-17]. In the Tumor Infiltrating Lymphocyte (TIL)-based ACT approach, TILs are isolated from the tumor tissues of cancer patients, expanded *in vitro* using a high concentration of Interleukin (IL)-2 (6000 U/ml), and then infused back into the patient. The feasibility of the TIL-based ACT approach was first demonstrated in melanoma [18], with a current objective response rate of 49% to 72% when lymph depleting preparative regimen is performed prior to TIL infusion [7,19]. Despite the clinical benefits of TIL-based therapy, there are limitations to its successful implementation. TIL-based therapy is an individualized treatment that requires surgical removal of tumor tissues for TIL cultivation. Furthermore, few medical centers worldwide provide TIL-based therapy as it requires a highly skilled medical staff to isolate and cultivate TILs. To overcome these barriers, genetically modified cancer-specific T cells, such as T Cell Receptor (TCR)- and Chimeric Antigen Receptor (CAR)-transduced T cells are being developed to augment ACT-mediated immunotherapeutic responses against various types of cancer and have already shown encouraging therapeutic effects in clinical trials [13-17,20]. TCRs expressed on T cells can be genetically engineered in vitro to specifically recognize and kill cancer cells [15]. Cancer regression in patients with metastatic melanoma following administration of autologous T cells genetically engineered to express a TCR against MART1 was first reported in 2006 by Rosenberg et al. at the NIH [21]. TCR-transduced T cells against several tumor antigens including MART1, CEA, gp100, NY-ESO-1, and MAGEA3 have been tested in clinical trials [15]. The results from these clinical trials have shown great promise in treating various types of cancers including metastatic melanoma, metastatic colorectal cancer, metastatic synovial cell sarcoma, and epithelial malignancies. Importantly, CAR-transduced T cell based immunotherapy has been producing exciting clinical results. The concept of CAR was firstly introduced by Eshhar et al [22] and the CAR structure is composed of an extracellular single-chain variable fragment (scFv) of an antibody, a transmembrane domain, and intracellular signaling domains derived from molecules involved in T cell signaling. Although CAR-transduced T cells have been used to treat patients with various types of cancer in clinical trials, the most promising results from CAR-transduced T cell therapy have been with CD19-based targeting of B cell malignancies [23-27]. Several recent clinical trials performed by NIH, University of Pennsylvania, Memorial Sloan-Kettering Cancer Center have demonstrated positive clinical outcomes with anti-CD19 CAR T cell therapy in patients with B cell malignancies [6].

Although ACT-based cancer immunotherapy has exhibited encouraging results in clinical trials, this success has only been observed in a few types of cancer, predominantly in hematological cancers and melanoma. To develop safe and efficient ACT-based immunotherapy with broad efficacy against a wide range of cancer types, future research in ACT-based cancer immunotherapy should be focused on the following aspects: (1) to identify ideal cancer antigens. Currently, most clinical trials of ACT–based immunotherapy have used self-antigens that are over expressed in malignant cells compared with normal cells. Thus, infused antigen-specific T cells can target not only antigen-positive cancer cells in vivo but also normal tissues expressing the shared cancer antigen. The biggest challenge to overcome remains the identification of antigens with a strictly cancer cell-restricted expression, such as NY-ESO-1, to achieve selective tumor targeting while sparing normal

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tissues. Mutated cancer antigens have been suggested as ideal targets for immune-based therapies, and such mutated cancer antigens can be identified by using a whole-exomic-sequencing-based approach [28,29]. (2) To enhance in vivo persistence and survival of adoptively transferred T cells. Results from clinical trials have suggested that cancer regression is positively associated with the long-term survival and persistence of adoptively transferred T cells *in vivo*. Strategies to enhance in vivo persistence and survival of transferred T cells can lead to improved anticancer efficacy. This may be achieved by exposure of T cells to IL-21 during in vitro culture [30], using Naïve CD8+ T cells or human stem cell-like memory T cells for adoptive immunotherapy [31,32], and by shRNA-mediated silencing of genes that inhibit T cell function in the tumor microenvironment [33]. Another alternative is to generate rejuvenated antigen-specific T cells that have a high proliferative capacity by reprogramming to pluripotency and redifferentiation [34,35]. (3) To identify cancer biomarkers for ACT-based therapy. Cancer biomarkers can support and guide clinical cancer treatment and development of the candidate products [36]. Thus, identification of biological correlates of response, either TILs or tumor characteristics, will help not only to select the most efficacious cell types for infusion but also patients who are most likely to respond to ACT-based therapy. (4) To use combinational immunotherapy**.** Although emerging techniques allow for the generation of high affinity antigen-specific T cells capable of targeting cancer cells *in vitro*, immune suppression and negative regulation at tumor sites can impede the induction of effective anticancer immune responses *in vivo*. Suppressive cytokines/agents such as IL-10, transforming growth factor-β, and indoleamine 2,3-dioxygenase and cell populations such as MDSCs and Treg cells present in the tumor microenvironment induce immunosuppression, thereby blocking T cell function [37,38] and leading to poor antitumor efficacy of immunotherapy. Therefore, combining ACT therapy with other strategies that block negative regulators may induce potentially profound immune antitumor responses.

In conclusion, ACT-based cancer immunotherapy has achieved encouraging results in clinical trials and has curative potential in some cancer patients. These promising results obtained from clinical trials have earned cancer immunotherapy being named as the *Science* 'Breakthrough of the Year' in 2013 [39]. For the first time in many years, a number of pharmaceutical industries are investing heavily to facilitate the development of ACT-based cancer immunotherapy to treat various cancer types. We believe that the increasing interest and investments from pharmaceutical industries will accelerate research and development of ACT-based cancer immunotherapy to benefit patients with various types of cancers.

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