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Editorial
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Nanoparticles could Improve the Efficiency of CAR-T Immunotherapy for Cancer

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Editorial

CAR-T immunotherapies are the cutting-edge topics of research and investment recently. The emerging leukemia treatments have had amazing success in the past few years, even curing patients with progressive and terminal phase of the disease. Chimeric Antigen Receptors (CARs) are a type of antigen-targeted receptor composed of intracellular T-cell signaling domains fused to extracellular tumor-binding moieties, most commonly single-chain variable fragments (scFvs) from monoclonal antibodies. CARs directly recognize antigens on the cell surface, independent of MHC-mediated presentation, approving the use of a single receptor specific for any given antigen in all patients. Initial CARs fused antigen-recognition domains to the CD3 activation chain of the T-Cell Receptor (TCR) complex. CAR-expressing T cells have demonstrated potent clinical efficacy in patients with B cell malignancies. To date, it has been most widely studied and most successful in that group of patients, targeting the differentiation antigen CD19 expressed by normal B-lymphocytes at the National Cancer Institute (NCI), Memorial Sloan-Kettering Cancer Center (MSKCC), the University of Pennsylvania (UPenn), and University of California San Diego [1]. The first report of antitumor activity occurred at the NCI in a patient with follicular lymphoma using second-generation CAR-T cells derived from the murine FMC63 antibody specific for human CD19 and a CD28 costimulatory signaling domain [2].

However, the CAR-T cell therapy targeting other cancers, it has been limited by both the induction of antigen-specific toxicities targeting normal tissues expressing the target-antigen, and the extreme potency of CAR-T cell treatments resulting in life-threatening cytokine-release syndromes. While the first generation CARs were largely limited by poor antitumor efficacy *in vivo*, the second and third generation CARs dramatically improved antitumor efficacy [3]. In some cases they led to complete remissions in patients with advanced cancer [2,4-7]. The increased potency of second and third generation CARs is obvious; however it might also increase the risk of severe toxicities.

The first report of clinical use CAR-T cell treatment as well as toxicities following occurred in a study of first generation CAR-T cells targeting carboxy-anhydrase-IX (CAIX) in three patients with metastatic clear cell Renal Carcinoma (RCC). Unfortunately, the treatment causing CAIX-targeted destruction of these cells produced the hepatotoxicity [8]. The next reported a third-generation CAR-T cell treatment targeting epidermal growth factor receptor 2 (ERBB2, HER2) occurred in a patient with colorectal cancer metastatic to the lung and liver [9]. The patient developed severe side effect such as respiratory distress within 15 minutes of receiving a single dose of 10^{10} CAR-T cells. Second-generation CARs have recently been explored targeting mesothelin, an antigen overexpressed by Malignant Pleural Mesotheliomas (MPM), pancreatic, ovarian, and a subset of lung cancers [10]. To decrease the severe side effects of CAR-T therapy the clinical trial (NCT02159716) has been ongoing using lentivirus -engineered CARTmeso cells.

Bringing CAR-T immunotherapies into solid tumors is the next cutting edge of the technology, and a new approach from the Fred Hutchinson Cancer Research Center may help it along the way. The research team led by Dr. Matthias Stephan demonstrated how they used nanotechnology to solve the tumor-targeting problem and decrease the price of therapy. They demonstrated that once they adapted with lymphocyte-targeting ligands, polymeric nanocarriers can selectively deliver leukemia-specific CAR genes into host T cells *in situ* [11]. To achieve effective nucleic acid delivery into T cells, genes carriers must be taken up by T cells, and import their DNA cargo into the cell nucleus.

Recently, the researchers used tiny, biodegradable nanoparticles to deliver two drugs directly and simultaneously into solid tumors. The drugs worked together to shut down the tumors' defense

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mechanisms and rally the immune system. That opens the door for CAR-T treatments, which are made up of genetically modified immune cells, to come in and attack the cancer cells. The finding is important because it could help target CAR-T treatments directly at tumors instead of sending them coursing throughout a patient's body, which leads to potentially dangerous side effects.

We are the witnesses of the new era of medications. CAR-T therapy already proved its superiority to the other therapies. CAR-T cells showed already clear therapeutic benefits in patients with $CD19^{+}$ malignancies. The ability to engineer T cells with a desired specificity through the use of CARs has induced a profound effort to extend this approach to other antigen targets and solid tumors. Expanded clinical use of CAR-T cells will provide further insights into proper dosing regimens and patient monitoring strategies that will provide safe administration, while maximizing clinical benefit.

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