Designer Immunotherapy Specific for Cancer

Shengwen Calvin Li* and Mustafa H Kabeer*

CHOC Children's Hospital, University of California Irvine, Orange, CA 92868, USA

In the USA, cancer affected over 1.4 million people in 2007 and we spent over $206 billion, one third of the total healthcare expenditure of $686 billion, to develop cancer therapies (NCI). Much is known about gene mutations and yet this has not been successfully translated into meaningful therapy for cancer patients. This unmet need urgently demands for new therapies to be developed. A promising subset of cancer therapy is immunotherapy. Cancer immunotherapy aims at inducing, enhancing, or suppressing an immune response to reject and destroy tumors.

Cancer immunotherapeutic agents include immunomodulators (often cytokines [1] or chemokines) and immune effector cells (lymphocytes, macrophages, dendritic cells, natural killer cells (NK Cell), cytotoxic T lymphocytes (CTL), etc.). Many forms of these therapeutic strategies have showed efficacy in animal models; unfortunately, they did not translate well during human clinical trials. Surprisingly, a recent report showed that immune T-cell therapy for the treatment of chronic lymphocytic leukemia (CLL) works better in humans than it does in mice (ClinicalTrials.gov number NCT01029366) [2]. It shed new light on the treatment of CLL, a highly lethal disease. What made it succeed?

In this study, June et al. address the issue of the horrendous side effects of conventional cancer therapy utilizing techniques such as bone marrow transplantation to treat CLL. Many patients developed graft-versus-host disease upon undergoing allogeneic hematopoietic stem cell transplantation and still faced a high relapse rate with limited chances for cure [3]. June's group developed a technology to create gene-modified T cells that do not cause graft versus host disease and target malignant CLL cancer cells with high specificity [2].

This technology uses a patient's own T cells subjected to the designer engineering specific for killing CLL cancer cells. They engineered T-cells expressing CD19-specific chimeric antigen receptor (CART-19) [4]. The designer T-cells recognize CD19 antigen on the surface of cells such as non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and chronic lymphocytic leukemia. This modification enables the designer T-cells to recognize the cancer and become activated thus triggering tumoricidal activity. In the clinical trial on leukemia patients, each patient had between 3 to 7 pounds of tumor burden that was eradicated by these designer T cells. The first treated patients remain leukemia-free for more than three years. Potential drawbacks remain to be determined since the T-cell targeted CD19 is not only expressed by cancer cells but also by normal B cells. CD19 is not expressed by hematopoietic stem cells or other tissues.

In principle, this concept may be expanded to a wide spectrum of other human cancers [5]. CART-19 used in June's study, is a chimeric molecule that has both the binding domain of an antibody on the cell surface as well as the T cell receptor complex and costimulating signaling modules within the cell [2]. This modular construction allows for changing the antibody binding domain, allowing these engineered T cells to recognize molecules on other types of cancer cells, such as CD3-specific single-chain antibody fragment (scFv) [6,7], PDL1 [8], NY-ESO-1 and LAGE-1, or mesothelin in prostate and breast cancers [5,9]. Indeed, June's group has tested this idea for treating pancreatic cancer as well with optimistic but preliminarily results [7]. The long-term benefit of this platform providing clinical translation of promising advances in immunotherapy remains to be seen by clinical trials monitoring outcomes of patients with other types of cancer.

References

*Corresponding authors: Shengwen Calvin Li, CHOC Children's Hospital, University of California Irvine, Orange, CA 92868, USA, E-mail: shengwei@uci.edu
Mustafa H Kabeer, CHOC Children's Hospital, University of California Irvine, Orange, CA 92868, USA, E-mail: kabeer135@hotmail.com

Received January 16, 2013; Accepted January 16, 2013; Published January 18, 2013


Copyright: © 2013 Li SC, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.