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Molecular Therapy

A New Era of Innovation for CAR T-cell Therapy

The field of chimeric antigen receptor (CAR) T-cell therapies has entered a new stage of development, and the tremendous promise of this new cancer treatment was evident at the recent CAR-T Summit held in Boston 12–13 November 2015. The meeting was organized by Hanson-Wade, a commercial enterprise specializing in business conferences, including some within the biotechnology and life-sciences sectors. The aim of the conference was to bring together diverse stakeholders to discuss how to facilitate the commercial development of this rapidly evolving field. The larger part of the meeting was dedicated to issues of efficiency, cost, logistics, and quality control of product manufacturing, in addition to regulatory challenges and prospects for reimbursement by health-care payers. Although these issues pose important hurdles to the field, there was collective optimism among the attendees that they would eventually be surmounted.

The concept of CAR T-cell therapy dates to the 1980s, when Zelig Eshhar and colleagues engineered and expressed chimeric T-cell receptor (TcR) genes comprising the TcR constant domains fused to the variable domain from an antibody molecule.[1] The aim was to redirect the specificity of the engineered T cells toward an antigen of choice—such as a tumor-specific antigen—in a manner independent of the major histocompatibility complex. Assuming the selection of an appropriate target antigen restricted to tumor cells, the idea is to thus direct a patient's own T cells to express the chimeric receptor and then to reinfuse the cells into the patient to attack and kill the antigen-bearing tumor. In the intervening years, second- and third-generation chimeric receptors have been developed that augment the potency of the therapy.

A pertinent question is whether we might be witnessing another rush toward commercialization that might end in disappointment. The biotechnology industry has seen several boom-and-bust cycles with the development of a number of promising platforms—antisense technology, RNA interference, and oncolytic virotherapy being easy examples. What distinguishes CAR T-cell technology from these platforms, however, is the robustness of the early preclinical and clinical data—at least for therapy targeting the B-cell CD19 antigen. Several laboratories and centers have reported success in early trials, at this point primarily for hematological malignancies. The challenge now is establishing and putting into place manufacturing technology that can meet the anticipated demand for the treatment, and in a fashion that is economically sustainable.[2]

CAR T-cell therapy would not be the first cell therapy to hit the market. Dendreon's Provenge—an autologous cell therapy product for prostate cancer—was approved by the US Food and Drug Administration in 2010. Unfortunately, the expensive therapy afforded only modest benefit, and Dendreon was bankrupt by the end of 2014. Despite the failure of Provenge, Dendron's example shows that cell therapy products can be brought to market, but that cost and efficacy, and the balance between the two, will be important factors determining their success or failure.

As noted by Usman Azam, the Global Head of the Cell & Gene Therapies Unit at Novartis Pharmaceuticals, "We have moved on from the era of a "cottage industry" in relation to manufacturing science and now realizing true scalability of therapies like CAR-T. But much more will need to be done to ensure all stakeholders can meet the demand globally and ensure consistent and quality products for our patients." Indeed, the number of cellular products available for patients should rise with increased automation of what is currently a manual process dependent on highly trained technicians.

Other challenges and opportunities remain. Efforts are under way to engineer cells to create allogeneic "off-the-shelf" products, which obviate the need for a personalized therapy. At the December meeting of the American Society of Hematology, a report was recently presented on the first clinical application of "universal" CD19-targeted CAR T cells modified by transcription activator–like effector nucleases to knock out both the endogenous T-cell receptors and CD52, which effectively eliminates the risk of graft-versus-host disease.[3] The

therapy was used on a compassionate basis under UK special-therapy regulations for an infant with refractory, relapsed B-cell acute lymphocytic leukemia. Although the follow-up period is still quite short, the intervention, comprising lymphodepletion and infusion of the universal CAR T cells, has induced molecular remission where all other treatments had failed.

Both on-target and off-target recognition of normal tissue can occur with engineered T cells, and adverse events and toxicities have been observed in the clinic. These effects are being mitigated through the development of genetic safety switches and increasing the potency of the cell therapy so as to limit the doses required. Others are adapting the technology for solid tumors and other disease indications (see the Research Highlights in this issue). What is clear is that we can expect a continuing stream of encouraging clinical results that should help drive innovation in the manufacturing process as well as further refinement of the technology itself so that the ultimate aim of bringing this life-saving therapy to patients is realized.

Robert M Frederickson
Executive Editor

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