



## A Revolution in Cancer Care

### *AACI's New Initiative Will Establish Best Practices in CAR T Therapy*

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### Commentary Overview

- CAR T therapy is a rapidly evolving form of cellular immunotherapy.
- CAR T has shown promising results in clinical trials, but it presents technical and financial challenges.
- By early 2018, nearly half of AACI's 98 cancer centers were approved to provide CAR T therapies.
- AACI recently established a CAR T Initiative to develop clinical best practices and address barriers to delivering the treatment.

**Advances in chimeric antigen receptor T-cell (CAR T) technology are revolutionizing cancer treatment. By early 2018, nearly half of AACI cancer centers were approved to provide CAR T therapies. To establish best practices, AACI spearheaded a CAR T working group that became an initiative this fall. As steering committee chair, I am pleased to take the lead as we usher in the next phase of the initiative.**

CAR T is a form of cellular immunotherapy – a rapidly evolving approach that harnesses a patient's immune system to fight cancer. Immunotherapy is now considered the “fifth pillar” of cancer care, alongside surgery, chemotherapy, radiation, and targeted therapy. It gained significant attention earlier this year, when James Allison, PhD, an immunologist at MD Anderson Cancer Center in Houston and the recipient of AACI's 2016 Distinguished Scientist Award, jointly received the 2018 Nobel Prize in Physiology or Medicine with Tasuku Honjo, MD, PhD, of Kyoto University in Japan, for advancing the study of checkpoint inhibitors.

### **Building on Decades of Discovery**

The history of cellular immunotherapy reaches back to the 1960s, when researchers were

encouraged by early successes with allogeneic stem cell transplantation. In the 1980s, cancer immunotherapy pioneer Steven Rosenberg, MD, PhD, identified tumor infiltrating lymphocytes—immune cells in tumors with cancer-fighting properties—which he isolated in the laboratory, expanded, and re-infused in patients. He reported durable, complete responses in patients with melanoma in a 1985 article in the *New England Journal of Medicine (NEJM)*. Dr. Rosenberg later discovered that T cells could be modified to eradicate melanoma and published the updated findings in a 1990 *NEJM* article.

That year, in the journal *Blood*, Mary Horowitz, MD, MS, published a retrospective analysis of graft-versus-leukemia in hematologic malignancies, leading to donor leukocyte infusion for relapse following allogeneic stem cell transplantation. Early breakthroughs like these have enhanced our understanding of the ability of T cells to eliminate cancer. However, the mechanisms that drove these processes remained largely unknown for years.

Subsequent decades of scientific investigation have further improved our understanding of T-cell immunobiology. Scientists have used this body of knowledge to genetically manipulate T cells, giving rise to the development of CAR T and other cellular therapies, including T-cell receptor-modified constructs.

### **Promising Results, But Challenges Remain**

CAR T has shown promising results in clinical studies, specifically related to chronic lymphocytic leukemia, diffuse large B-cell lymphoma (DLBCL), acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). In fact, in 2017, the Food and Drug Administration (FDA) approved CAR T for the treatment of DLBCL and ALL. Another AACI Distinguished Scientist—Carl June, MD, director of translational research at the University of Pennsylvania’s Abramson Cancer Center—played a key role in the development of Kymriah, the first FDA-approved therapy based on gene transfer. Yet despite a remarkable expansion of CAR T clinical trials for a broad array of hematologic malignancies—and, increasingly, solid tumors—many challenges remain.

Chief among them are identifying tumor-restricted antigens to minimize on-target, off-tumor toxicities; optimizing tumor eradication; and developing strategies to ameliorate toxicities associated with CAR T, particularly cytokine release syndrome and CAR T-related encephalopathy syndrome. Areas for further study include identifying optimal sub-populations of T cells for transductions and adapting new gene manipulation technologies, such as CRISPR-CAS9, to specifically direct the placement of the CAR-T genes in the genome. Another major focus of research involves the development of “safety switches,” which can inactivate CAR T in the event of severe toxicity through the transduction of so-called “suicide genes.”

### **Ensuring Access to All Patients**

It is also important to limit toxicities in the financial realm. CAR T is associated with significant costs, which must be addressed as the therapies are more broadly applied. A cost-effectiveness analysis has demonstrated that commercial CAR T is a feasible treatment option for ALL and DLBCL. However, the financial burden is sure to increase as CAR T is indicated for more applications, particularly in treating solid tumors, including breast, lung, colon, and gynecologic cancers.

Appropriate reimbursement models will be essential to ensuring equitable access to CAR T therapies and their associated supportive care and hospitalization – especially important to patients insured by Medicare and Medicaid. FDA Commissioner Scott Gottlieb recently voiced concerns that the current reimbursement system could stifle development of novel treatments, noting that the FDA may soon allow CAR T products to be administered in outpatient settings to reduce costs.

Other strategies, such as the development of “off-the-shelf” third-party CAR T-cell lines, are being studied in clinical trials, but they pose major technical challenges. Though their immediate availability could potentially keep costs down, these third-party allogeneic cells are more likely to either be rejected by a patient’s body or result in lethal graft-versus-host disease. Researchers are examining the use of CRISPR-CAS9 to edit out the molecules that increase the risk of these outcomes.

### **Tackling Challenges Head-On**

Additional pressing issues include improving the CAR T education offered to practitioners; forming national research networks to expedite clinical trials; and mandating a centralized system to track and report patient outcomes. The FDA currently requires all patients undergoing allogeneic stem cell transplantation in the U.S. to participate in such a registry, managed by the Center for International Blood and Marrow Transplant Research. The resulting data has led to dramatic improvements in the field; a similar infrastructure, currently under development, will greatly benefit the field of CAR T research.

Addressing these challenges is a tall order, but AACI is tackling them head-on. Through the CAR T Initiative, AACI will convene experts from across North America to improve access to CAR T therapies. This year alone, approximately 8,500 patients should have qualified for CAR T to treat DLBCL; however, only a small fraction of that number utilized the therapies. Closing this gap is a major priority of the initiative.

Although CAR T has become standard of care for some cancers, technological developments are still outpacing oncologists' education on the therapies. AACI's CAR T Initiative will help establish a baseline of knowledge on the topic and implement uniform best practices across North America, ensuring that referral processes and indications for the treatment are consistent.

With membership spanning the U.S. and Canada, AACI is positioned remarkably well to facilitate communication of novel ideas among academic cancer centers and to broaden clinical research to advance CAR T therapies. AACI has also been instrumental in advocacy, presenting recommendations for CAR T reimbursement to the Centers for Medicaid & Medicare Services to help eliminate the financial barriers that stand in the way of patients' access to these lifesaving treatments.

In 2019, members of the AACI CAR T Initiative will focus on assembling working groups to address the above issues, ultimately helping cancer centers build and sustain robust CAR T therapy programs.

Learn more about the **AACI CAR T Initiative**.

## Our Mission

Representing 98 of North America's premier academic and freestanding cancer centers, the Association of American Cancer Institutes is dedicated to reducing the burden of cancer by enhancing the impact of leading cancer centers.

## About AACI Commentary

To promote the work of its members, AACI publishes Commentary, an editorial series focusing on major issues of common interest to North American cancer centers, authored by cancer center leaders.

