

'Super T cells' engineered for optimal performance drive new gene-therapy approach

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From left, Drs. Richard Koya, Kunle Odunsi and Thinle Chodon with genetically engineered T cells to be given to a patient as part of a new adoptive cell therapy clinical trial at Roswell Park Cancer Institute. Credit: Roswell Park Cancer Institute

Researchers at Roswell Park Cancer Institute have initiated a clinical

trial based on a unique two-pronged strategy for arming the immune system to more effectively attack cancer cells. Patients treated through this early-stage clinical trial, which is available only at Roswell Park, will receive one-time injections of their own cells—"super T cells" reprogrammed to make them more effective at targeting tumor cells, and armed with an added element to help them to evade one of cancer's most resilient defenses.

The "TGF beta" clinical trial, named for one of the elements that distinguish this approach, is part of an emerging class of immunotherapies that employ adoptive cell transfer. These so-called "living drugs"—injected T cells genetically modified to better recognize and kill [tumor](#) cells through a perpetual process of cell renewal and expansion—are revolutionizing [cancer](#) treatment, with the first two FDA approvals of such gene-altering therapies occurring in just the last two months. But efforts to develop adoptive T cell therapies for solid tumors have hit upon a number of challenges; the only gene therapies to show significant benefit for patients have been in liquid tumors—forms of leukemia and lymphoma.

"What we see over and over in trying to treat some of the most aggressive and intractable cancers, including many lung, brain, ovarian, breast, melanoma and sarcoma tumors, is that the tumor fights back. The area around the tumor is a hostile environment that disarms [immune cells](#) and deprives them of the ability to kill [tumor cells](#). We have identified a major pathway by which these kinds of cells try to disable immune cells, and formulated a strategy for exploiting that weakness," says the study's principal investigator, Kunle Odunsi, MD, PhD, FRCOG, FACOG, Deputy Director and Chair of Gynecology at Roswell Park, and Executive Director of its Center for Immunotherapy.

The roughly 24 patients to be treated through this phase I/IIa study will have their T cells removed in a process that's similar to platelet removal,

and takes about two hours. Approximately one week later, they will receive a single injection of those T cells, now modified with two strategic enhancements: insertion of one gene that forces them to produce a T cell receptor (TCR) that hones in on the target antigen, NY-ESO-1, and another that blocks a protein that allows cancers to grow and suppress the immune system—transforming growth factor beta (TGF-beta).

"It's an approach that allows the immune system to be on the offense and on the defense at the same time," says the study's scientific lead, Richard Koya, MD, PhD, Associate Director of the Roswell Park Center for Immunotherapy. "First we arm the T cells with a receptor to help them hunt down the cancer cells, and then we add a TGF-beta blocker to suppress the suppressor. The result of this two-step gene modification—forcing expression of the receptor for NY-ESO-1, and adding a blocker gene to nullify the effect of TGF-beta—is a super T cell engineered to both more effectively kill target [cancer cells](#) and to resist the tumor's attack."

While preclinical studies suggest that this treatment may be effective, long-lasting and well-tolerated, the study now underway at Roswell Park marks the first time this strategy will be assessed in humans.

It is also the first time a Roswell Park team has produced a genetically engineered T cell therapy in-house. The immune [cells](#) that play such a central role in this therapy are never frozen or shipped, as they are drawn, re-engineered and reinjected within Roswell Park facilities.

More information: For more information on this study (ClinicalTrials.gov identifier no. NCT02650986), which is open to adult patients with various types of advanced cancer whose tumors express NY-ESO-1, or other clinical trials available at Roswell Park, please call 1-877-ASK-RPCI (1-877-275-7724) or send an e-mail

inquiry to ASKRPCI@roswellpark.org

Provided by Roswell Park Cancer Institute

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