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Spotlight

This is the second article in a two-part series on a form of immunotherapy for cancer called adoptive cell transfer (ACT). The first article described a type of ACT that uses tumor-infiltrating lymphocytes to treat advanced melanoma. The second article describes genetically engineered T cells that are being studied for the treatment of a variety of cancers, as well as hurdles in translating ACT from an experimental treatment to one commonly used in the clinic.

Complex Immune-Based Cancer Treatment Shows Signs of Progress

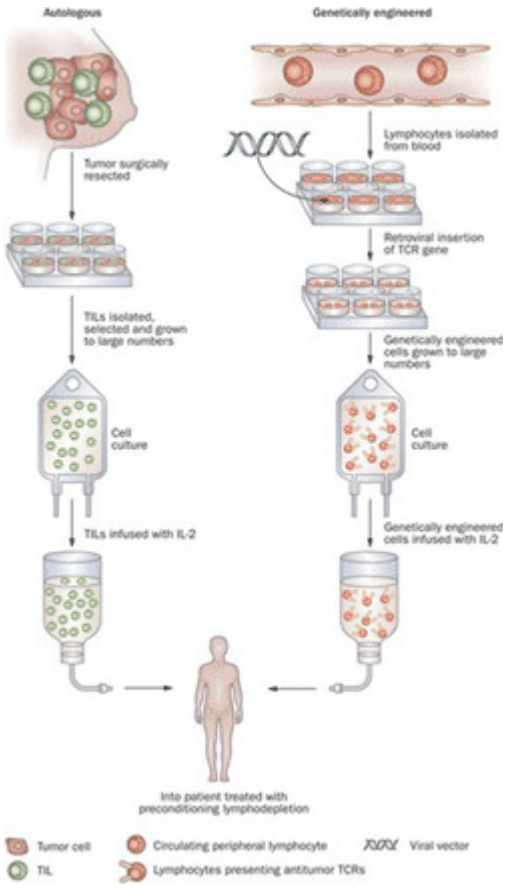
Published in *Science* in 2006, the results of a 15-patient clinical trial conducted by NCI researchers represented a milestone of sorts for the burgeoning field of adoptive cell transfer (ACT) as a treatment for cancer.

Two of the patients in the trial had a complete remission of their advanced melanoma following the one-time only treatment, which consisted of collecting lymphocytes from a trial participant, genetically modifying and growing the lymphocytes in the laboratory until the cells numbered in the billions, and then infusing the cultured cells into the patient a short time later.

At the time, Dr. Steven Rosenberg of the Surgery Branch in NCI's Center for Cancer Research and his colleagues had already had some remarkable successes in treating patients with advanced melanoma using a similar form of ACT, in which patients were treated with T cells, known as tumor-infiltrating lymphocytes (TILs), that had been taken directly from the patients' own tumor samples.

But with this publication in *Science*, Surgery Branch researchers were announcing the first reported use of T cells—collected from patients' blood, not their tumors—that had been genetically engineered to enhance their antitumor capabilities before being infused into the patient.

In large part because melanoma seems to elicit a stronger immune



Adoptive cell transfer therapy involves collecting T cells from a patient, growing them in cell culture, and infusing them into the patient. Enlarge the image to read the

response than most cancers, it has been a proving ground for ACT. But with advances in the genetic engineering of T cells, that has rapidly started to change.

full caption. (Image from S. Rosenberg [2011] Nature Reviews Clinical Oncology, 8:577-585) [Enlarge]

"[These advances have] really expanded the number of cancers for which ACT could be a viable treatment option," said Dr. Richard Morgan of the Surgery Branch, which has performed the most trials of ACT as a cancer treatment to date.

Serious hurdles must be overcome, however, if any form of ACT is to become widely available, acknowledged Dr. Michel Sadelain of Memorial Sloan-Kettering Cancer Center, who is involved in several ACT trials at his institution. After all, these therapies consist of live immune-system cells that have been altered in the laboratory by highly complex processes, not mass-produced pills or injectable drugs that can be stored for long periods on a shelf or in a refrigerator, ready to be administered to multiple patients.

Although there are still many skeptics, "the number of people who are starting to believe in the potential of these types of cell-based therapies is growing," Dr. Sadelain said.

Building a Better T Cell

TIL therapy is the most extensively tested type of ACT to date, but approaches using genetically engineered T cells are slowly catching up.

T cells collected from melanoma tumors are often already primed to attack cancer cells. But in other tumor types, infiltrating T cells are too few or difficult to isolate, Dr. Sadelain explained.

That fact led researchers to investigate whether they could introduce specific genes into T cells to augment their tumor-attacking capabilities, with a focus on engineering the cells to express antitumor receptors. These receptors act like docking stations on a T cell's surface, recognizing and binding to specific targets (antigens) on or within cancer cells—and, ideally, only cancer cells.

The first efforts to genetically modify T cells, which date back nearly two decades, "didn't work at all," Dr. Sadelain said. "Now it's much more effective, and we have a plethora of methods available to modify patients' T cells."

Much of the work has focused on engineering the cells to express T-cell receptors (TCRs) or chimeric-antigen receptors (CARs). The genetic material the T cells need to produce these receptors is typically delivered by viral vectors—viruses stripped of their ability to cause illness but that retain the capacity to integrate into cells' DNA.

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>
> *—Dr. Sadelain*

Both receptor types have their limitations. Because the primary components of CARs are bits of an antibody, they can bind only to antigens that reside on the surface of cancer cells. TCRs, on the other hand, can be used to target antigens on the surface of and inside cells. However, TCRs need to be genetically matched to bits of patient-specific immune system proteins on cancer cells, adding another layer of complexity and potential restriction.

"Which [receptor type] you use is fundamentally an issue of biology," Dr. Morgan said.

Finding the right antigen targets—those that are commonly expressed on cancer cells but not on healthy cells—is "a significant barrier," he added, and remains a rate-limiting step in ACT research.

Regardless, both approaches are being put to the test.

Since the 2006 melanoma trial, which used TCR-expressing T cells, NCI researchers have reported excellent responses in several pilot trials. In 2010, they reported the first trial using CAR-expressing T cells that target the antigen CD19 (which they developed, based in part, on work from Dr. Sadelain's laboratory) in a patient with follicular lymphoma. Having received two cycles of treatment, this patient has been responding for nearly 3 years, Dr. Rosenberg said. Another eight patients with lymphoma or leukemia have also been treated, seven of whom have had tumor regressions, including three complete remissions.

Researchers at the Baylor College of Medicine, led by Dr. Malcolm Brenner, have reported results of a trial in which several children with neuroblastoma achieved complete remissions following treatment with CAR-expressing T cells targeted to the antigen GD2.

And late last year, Dr. Carl June of the University of Pennsylvania Abramson Cancer Center reported early findings from three patients with chronic lymphocytic leukemia who were treated with CD19-targeted CAR T cells. Two of the patients had complete remission, and one had a partial remission.

The groups leading this research have intensively studied their patients after treatment to better understand exactly how the infused T cells behave in the body, with some intriguing results.

In the patients in the Abramson trial, Dr. June explained, "We found that each infused CAR T cell or progeny from those T cells killed between 1,000 and 93,000 tumor cells." This massive tumor cell die-off represented anywhere from 3 to 7 pounds of tumor "melting away," he said.

Researchers have found that a small percentage of the engineered T cells remains in the body for some time, some taking up residence in the bone marrow, where they presumably can be spurred into action should the cancer try to resurrect itself.

Although recent experience with ACT has been positive, like other therapies it's not universally effective and it has side effects, including high fevers and other problems that have required prolonged hospitalizations. In one instance, a patient with advanced colorectal cancer died within days of treatment, apparently as a result of a cytokine storm—a massive, unchecked immune response initiated by the ACT infusion.

Transitioning to a Larger Setting

A number of things must happen if ACT is to become a broadly available therapy, many in the field agree. Expanding its use is one of the most critical, said Dr. Brenner, who directs Baylor's Center for Cell and Gene Therapy.

"Until we can show that we can treat a wider range of diseases, we're not going to get the resources we need...to treat a wider range of diseases," he quipped last fall at an NCI-sponsored conference on immunotherapy. With a number of ACT trials under way, progress is being made on that front. (See the table.)

Examples of Human Trials Testing ACT with TCRs/CARs

Institution	Cancer Types
NCI	Melanoma, glioblastoma, sarcoma, pancreatic cancer, mesothelioma
Abramson Cancer Center	Leukemia, multiple myeloma, mesothelioma, ovarian cancer, sarcoma
Baylor College of Medicine	Glioblastoma, head and neck cancers
City of Hope Cancer Center	Glioma, lymphoma
Memorial Sloan-Kettering	Leukemia, lymphoma, prostate cancer

Researchers are also beginning to get buy-in from pharmaceutical and biotechnology companies, which have the resources and infrastructure to bring new therapies to market.

NCI, for example, has a research agreement with Genesis Biopharma, Inc., to develop production-scale manufacturing processes for TILs and advance the treatment into larger clinical trials. Other researchers in the field say that they've discussed commercial development with companies and hope to reach agreements in the near future.

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>
> *—Dr. Carl June*

Dr. Rosenberg believes one potential clinical model for ACT that wouldn't necessarily require industry involvement is bone marrow transplantation, which is available around the country at centers with dedicated transplant programs.

The Food and Drug Administration's 2010 approval of the prostate cancer vaccine sipuleucel-T (Provenge), meanwhile, has provided a successful industry model to follow, Dr. Morgan noted.

As the process for engineering and growing cells becomes more efficient and streamlined, ACT may also be a highly cost-effective treatment. At Abramson, the research team can now produce 10 billion CAR-expressing T cells in 10 days at a cost of approximately $15,000—a price, Dr. June pointed out, that compares favorably with many of the newer targeted therapies, which can cost twice that amount for one month's treatment.

"There is definitely room for improvement," Dr. June said. The technology for engineering and growing the cells will improve, he continued, and with more research and funding, new methods for identifying target antigens will be developed as well.

—Carmen Phillips