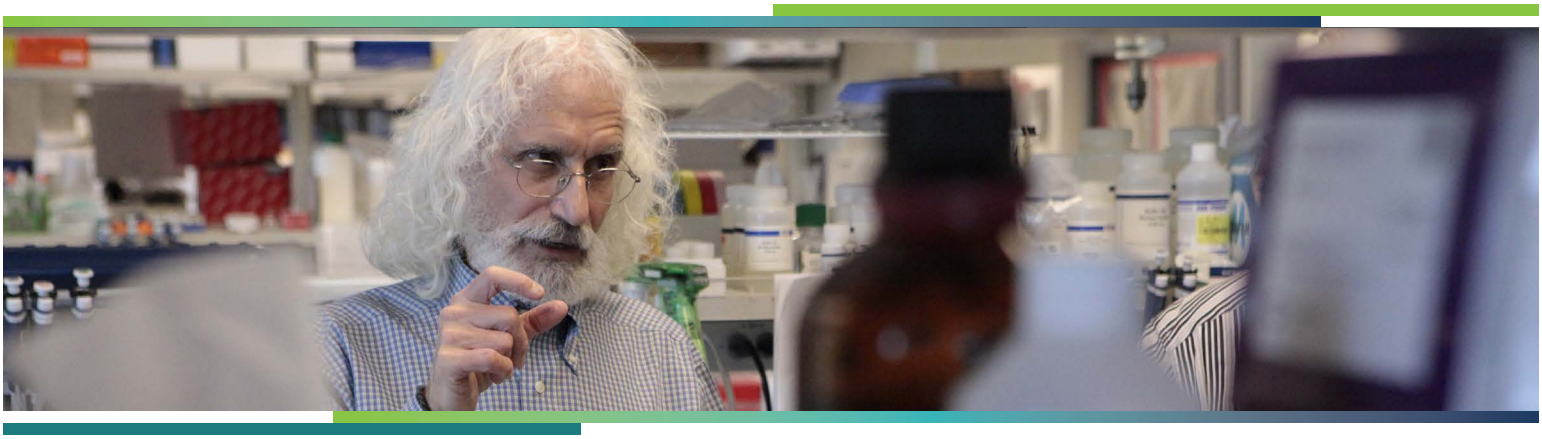
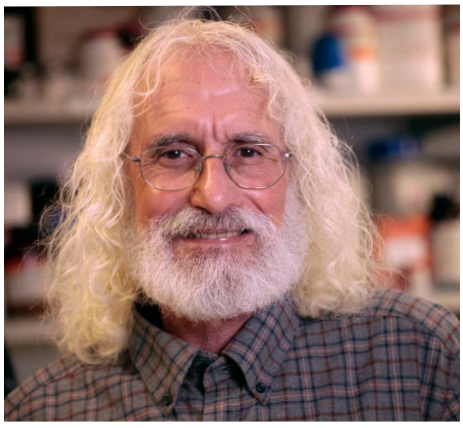


T-cell receptor therapy for patients with cancer

World-renowned scientists at Fred Hutchinson Cancer Research Center are harnessing the power of the immune system to create cancer cures. Right now, our teams are developing living immunotherapies, composed of genetically reprogrammed immune cells, designed to eradicate tumors.

Though it's still early, results so far in patients with certain blood cancers have been unlike anything researchers have ever seen. Tumors that had stopped responding to other therapies have melted away after just one dose of engineered T cells. Patients who would otherwise have had just weeks or months to live are now in sustained remissions.

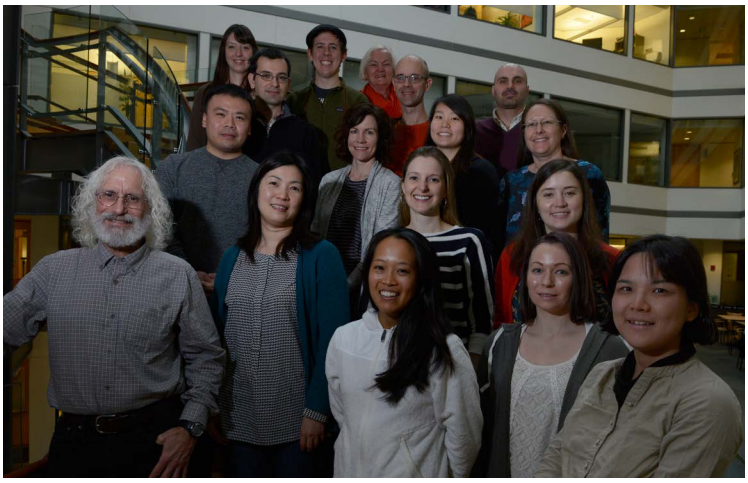
One of the pioneers in this field is Dr. Phil Greenberg. His expertise in using immune cells known as T cells for therapy has earned him the proudly worn moniker "Dr. T cell." Dr. Greenberg joined Fred Hutch three decades ago to develop new cancer therapies. At the time, only Fred Hutch offered bone marrow transplants for patients with certain leukemias and other blood disorders. "People came to us to try to live," says Dr. Greenberg.



Dr. Phil Greenberg
PHOTO BY ROBERT HOOD / FRED HUTCH

The Hutch's Nobel Prize–winning work on transplantation provided the first definitive and reproducible example of the power of the human immune system to cure cancer, but the damaging side effects of the treatment were often too much for critically ill patients to face. Dr. Greenberg resolved to create a safer, more effective cancer therapy by leveraging the immune system to do what bone marrow transplants do — but better.

Over the past 30 years, Fred Hutch, singularly among cancer research centers, has remained focused on developing such a treatment for acute myeloid leukemia (AML). Now, thanks to Dr. Greenberg's perseverance and the dedication of so many other Hutch researchers, scientific knowledge and technology have caught up with that vision, and



Members of the Greenberg Lab at Fred Hutch
PHOTO BY BO JUNGMAYER / FRED HUTCH

a promising treatment for AML, and possibly many other cancers, is within our grasp.

These targeted cellular immunotherapies have the potential to one day **replace blood stem cell transplantation** as a cure for many blood cancers and become the **first cures** for what have historically been some of the most challenging solid tumors, including advanced lung, pancreatic and ovarian cancers. **With the partnership of private supporters we can speed this research, give more patients and their families hope, and, ultimately, save more lives.**

T-cell therapy for cancer

Adoptive T-cell therapy is a form of immunotherapy that uses intact living immune cells to specifically and selectively attack tumors. Early attempts, particularly in the treatment of melanoma, hinted at the power of this approach, but the responses in patients were usually temporary and incomplete. A recent revolution in molecular biology has resulted in new methods that dramatically improve adoptive T-cell therapy. One of those is the development of **T-cell receptor, or TCR, therapy**, which involves a method of genetically reprogramming T cells to bind to and destroy a patient's cancer.

In TCR therapy, scientists insert into the T cells a gene that encodes an engineered T-cell receptor. This TCR binds to molecules displayed on the surface of other cells. By targeting molecules displayed by cancer cells — but rarely if ever by healthy cells — these therapies have the potential to cause far fewer side effects than conventional treatments like chemotherapy and radiation, which kill malignant and healthy tissues alike.

Dr. Greenberg and his team have worked tirelessly to bring this approach to the clinic, including optimizing both the T cells and the TCR molecules used in the therapy. The first target they chose to study was WT1, a protein seen almost universally in acute myeloid leukemia.

Dr. Dan Egan
PHOTO BY BO JUNGMAYER / FRED HUTCH

In their ongoing trial, the team, which includes Drs. Aude Chapuis and Dan Egan, has treated 20 patients with AML who received blood stem cell transplants and either relapsed or were at high risk for doing so, and additional patients are enrolled and awaiting treatment on the trial. So far, they are very encouraged by the responses they are seeing. They plan to publish a paper describing their results in early 2016, and they are extending the clinical trial based on their interim findings. In September 2015, the researchers enrolled and treated their first pediatric leukemia patient. The group also plans to open a new trial soon that hopefully will take them one step closer to making T-cell therapy a frontline treatment for myeloid leukemias.

Fueling the next advances in TCR therapy

Generous private contributions have been critical to the Greenberg team's incredible progress to date. To continue fueling their efforts, donations are needed to:

- **Make TCR therapy for AML available to more patients**. TCR therapy offers the potential to make tumor-reactive T cells available for many patients, but it does require matching the artificial receptor to the HLA type (also known as tissue type) of the patient. The Greenberg team's first TCR is specific for the most common HLA type, but the researchers are actively working to build libraries of TCRs that could be used in patients with any HLA type.

- **Enhance the TCR molecules used for this therapy.** To eradicate patients' tumors, engineered T cells must live and function for extended periods once they've been infused. This can be particularly challenging with advanced cancers that commonly suppress T-cell responses. The Greenberg team is developing strategies for engineering TCRs that can overcome these obstacles, possibly even turning the inhibitory "off" signals cancer cells send out into activating "on" signals. The most effective of these strategies could then be incorporated into TCR therapies for patients with a wide range of cancers, including blood cancers like AML and the solid-tumor cancers described below.

- **Apply TCR therapy to more types of cancer.** The research team is already extending TCR therapy beyond blood cancers. They recently opened a clinical trial, led by Dr. Sylvia Lee, of anti-WT1 T cells for patients with advanced **non-small cell lung cancer or mesothelioma** that is resistant to treatment with prior therapy. A strategy for treating patients with **pancreatic cancer** is also advancing toward clinic trials: In October 2015, the researchers published important preclinical data showing that, even when used without chemotherapy or radiation, the new T-cell therapy can boost survival by more than 75 percent in mice that develop pancreas tumors very similar to those found in humans. Another version of the TCR therapy is being developed for patients with **ovarian cancer**.

Dr. Sylvia Lee
PHOTO BY SCOTT STREBLE FOR FRED HUTCH

This is an unprecedented time in cancer research. A new era of therapies that are not only easier on patients but that also yield better outcomes is now within reach.

To learn more about Dr. Greenberg's research — and how you can help accelerate it and have a profound impact on the lives of countless cancer patients and their loved ones — please contact Nicole Pratapas at 206.667.5190 or npratapa@fredhutch.org.

The clinical trials referenced in this report involve investigational products and/or therapies that have not been approved for commercial marketing by the U.S. Food and Drug Administration or any other regulatory authority. Encouraging results from early stage clinical trials may not be supported in later stage clinical trials. No conclusions should be drawn from the information in this report about the safety, efficacy, or likelihood of regulatory approval of these investigational products and/or therapies.