CAR T-Cell Therapy

A new era in cancer treatment

LEUKEMIA & LYMPHOMA SOCIETY®

Harnessing a Patient's Immune Cells to Fight Cancer

Over the past several years, immunotherapy – harnessing a patient's immune system to attack cancer – has emerged as an innovative treatment option. This had long been a dream of the medical community. Today, that dream is a reality.

In fact, the scientific community has been pursuing research in this area for more than a century. William B. Coley, MD, first attempted to harness the immune system for treating cancer in 1891.

One emerging immunotherapy approach is called adoptive cell transfer (ACT), which describes the various ways by which a patient's T cells, the soldiers of the immune system, are removed, grown in a laboratory and then returned to the patient's body to help fight cancer.

There are different types of ACT, but one revolutionary, lifesaving therapy is called CAR (chimeric antigen receptor) T-cell immunotherapy. In this therapy, the patient's T cells are extracted, genetically engineered and multiplied, and infused back into the patient's body where they continue to multiple, recognize and destroy cancer.

This therapy has proven to be effective in clinical trials and has now been approved in patients with certain types of leukemia and lymphoma. Many adults and children near death are now in remission, and some remain healthy more than five years after treatment.

One CAR T-cell therapy, tisagenlecleucel-T (Kymriah™) received approval from the U.S. Food and Drug Administration (FDA) on August 30, 2017, for the treatment of children and young adults 25 and younger with relapsed and refractory acute lymphoblastic leukemia (ALL). Another CAR-T, axicabtagene ciloleucel (Yescarta™) for adults with relapsed and refractory non-Hodgkin lymphoma was approved on October 18, 2017.

Over the past twenty years, LLS has invested

$40 million in CAR T-cell immunotherapy, supporting the development of this revolutionary therapy by funding more than fifteen researchers and companies across the world.

History of CAR-T: Sixty Years in Development

What many people might not realize is that this innovative therapy is the culmination of more than sixty years of dedicated research utilizing knowledge of the immune system, genetic engineering, antibody therapy, and a deep understanding of the underpinnings of blood cancers.

In the 1950s, our understanding of the procedure known as bone marrow transplantation laid the groundwork for developing this therapy. This was the first concept of infusing cells into blood cancer patients to control cancer and understanding that T cells have the power to kill cancer cells.

In 1953, LLS awarded its first research grant. This was the start of LLS's vast research portfolio, which, through 4000 grants to date, has funded more than

$1 billion in research.

LLS has supported the development of some of the most effective and widely used therapies – from the early days of bone marrow transplants to immunotherapies today.

Homing In On The Cancer Cells

As early as the early 1900s, researchers have sought to figure out how to make T cells better at finding and recognizing cancer cells. While T cells are good at killing cancer cells, they need a guide to direct them to the tumors.

That guide is an "antibody." Antibodies are a protein that serve as a natural homing mechanism – they recognize and attack foreign substances in the body, such as bacteria or viruses. **In 1975, Georges Köhler, PhD, and César Milstein, PhD,** laid the groundwork for developing **"monoclonal antibodies,"** which are proteins that bind specifically to only one type of molecule and can be mass produced in the laboratory.

In 1997, the first monoclonal antibody used as a cancer therapeutic, rituximab (Rituxan®), was approved for the treatment of certain types of lymphoma. The antibody binds to the surface of lymphoma cells and leads to tumor cell death. The discovery of rituximab paved the way for targeted cancer treatments, transforming cancer care and significantly improving patient survival.

LLS supported this breakthrough by funding early research

that led to its development and later research that led to FDA approval for additional diseases.

The Ultimate Breakthrough: Genetically Engineering T Cells

In 1987, an Israeli immunologist, **Zelig Eshhar, PhD**, from The Weizmann Institute of Science, created the first "chimeric antigen receptor," an engineered receptor that does not exist in nature. The DNA encoding the receptor was implanted in the T cells so they could fight and kill cancer. This newly created receptor has an antibody fragment that allows the T cells to home in on the tumor. Once it attaches to the tumor cell, this tells the T cells to multiply as well as kill the attached tumor cell. Moreover, the engineered T cells can persist in the body for years and remain like a guard at the gate – ready to call the troops out to kill any stray tumor cells if they are detected.

In the 1980s, researchers began experimenting with the concept of genetically engineering T cells to fight cancer. Early developers include **Steven Rosenberg, MD**, of National Cancer Institute, **Carl June, MD**, University of Pennsylvania, **Michel Sadelain, MD**, Memorial Sloan Kettering Cancer Center, and **Dario Campana, MD, PhD**, St. Jude Children's Research Hospital.

In the late 1990s, the laboratories of **June** and **Sadelain** discovered how to optimally multiply the T cells in vast numbers in the lab and return these super-stimulated T cells to the body where they became serial killers of cancer cells.

LLS has been a key engine advancing the game-changing CAR T-cell therapy. LLS began funding June and his team in 1998, and has invested approximately $20 million over two decades to support their work. Overall since 1998,

LLS has funded $40 million specifically for CAR-T development

funding more than fifteen researchers and companies across the world.

From Bench to Bedside: CAR-T Clinical Trials Show Great Promise

The first successful cancer treatment with CAR-T was for an advanced follicular lymphoma patient and was reported by the lab of Steven Rosenberg, M.D., Ph.D., chief of the Surgery Branch in NCI's Center for Cancer Research.

In 2011, study results were published under the guidance of June's colleague at University of Pennsylvania, **David Porter, M.D**, who showed two of three relapsed or refractory chronic lymphocytic leukemia (CLL) patients went into complete remission. Some of these patients are still alive and disease-free to this day.

Around the same time, clinicians at the University of Pennsylvania, Memorial Sloan Kettering Cancer Center, and National Cancer Institute reported on the next patients, who were children or adults with B-cell acute lymphoblastic leukemia (ALL).

The response rates in children and adolescents with ALL, who had failed all previous therapies and were out of options, were astonishing. Approximately 90% of the ALL patients had a complete and rapid response, including many patients whose disease can no longer be detected after receiving CAR T cells. This clinical trial was conducted under the leadership of **Stephan Grupp, M.D.**, Children's Hospital of Philadelphia, and a member of June's team. The toxicities from the therapy were equally stunning. This life-threatening immune response is called a "cytokine release syndrome." But based on quick thinking by June's team, researchers have developed treatments to mitigate the problem without blocking the ability of the CAR T cells to kill tumor cells.

In addition to their participation on June's LLS-funded CAR-T team,

Grupp and Porter were both funded in the 1990s through LLS's Career Development Program.

Designed to help investigators early in their careers.

A New Day in Cancer Treatment: CAR T-Cell Immunotherapy

In 2017 we witnessed a historic victory for cancer patients when this revolutionary, innovative immunotherapy was approved, ushering in a new era in the treatment of cancer.

On August 30, 2017, tisagenlecleucel (Kymriah) was the first CAR T-cell immunotherapy approved by the FDA. It was approved for children and young adults aged 25 and under who relapsed or were not responding to therapy for acute lymphoblastic leukemia (ALL).

LLS funded much of the research advancing this therapy at the University of Pennsylvania for over two decades. Novartis licensed that therapy in 2012 and replicated these dramatic clinical results in children and adolescents with ALL in further studies. In March 2017, Novartis submitted the therapy for FDA review and in July 2017, a committee of the FDA unanimously recommended therapy for approval.

The FDA approved axicabtagene ciloleucel (Yescarta), on October 18, 2017 for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and other rare large B-cell lymphomas. The therapy was initially developed at the National Cancer Institute under the guidance of Steven Rosenberg, MD, and Terry Fry, MD, and was expanded by the biopharmaceutical company, Kite, a Gilead Company. LLS supported the clinical trial leading to the approval of Yescarta since 2015 through its Therapy Acceleration Program® (TAP).

LLS has provided $2.5 million in support for Kite's CAR-T clinical trial,

testing axicabtagene ciloleucel (Yescarta), since 2015 through LLS's Therapy Acceleration Program (TAP). Through TAP, LLS partners directly with biotechnology companies to help advance the development of promising therapies.

The Future of CAR-T: Targeting other Cancers

Based on the initial success of CAR-T, the therapy is being tested in other blood cancers, including myeloma and acute myeloid leukemia. Researchers continue to investigate how to improve the utility and effectiveness of CAR-T, and LLS is supporting much of this work.

As part of its Specialized Center of Research (SCOR) grant program, LLS recently awarded $5 million for a five-year program to **Anas Younes, MD**, and his colleagues at Memorial Sloan Kettering Cancer Center. The goal of their research is to develop even more powerful "armored" CAR-Ts, and enhance their effectiveness. They are studying how CAR-Ts can secrete a genetically engineered protein to further reduce tumor cell growth, and how CAR-T works combined with other immunotherapeutic approaches.

Additionally, researchers are studying other approaches to CAR-T. They are working to: identify new targets on the surface of the cancer cells; develop "off the shelf" versions that do not require removing the patient's own T cells; and genetically engineer switches that turn the activated T cells "off" if they are not needed anymore or produce severe side effects.

Based on the success of CAR-T in blood cancers, CAR-Ts are now being tested in solid tumors including glioblastoma, liver, lung, colon, esophageal, pancreatic, prostate, gastric and hepatic carcinoma. While the results haven't been as promising to date, some of these next generation CAR-Ts, or combinations with other therapeutic approaches, may hold the key to effectiveness in solid tumors.

LLS is funding work

in all of these areas at institutions such as University of Pennsylvania, University of California San Diego, The Ohio State University, Baylor College of Medicine and the Dana-Farber Cancer Institute.

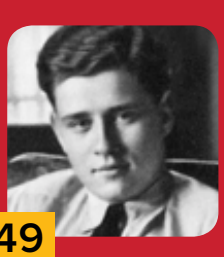
The Leukemia & Lymphoma Society (LLS) has invested more than

$70 million in adoptive cellular therapy

programs since our founding in 1949.

1891

William B. Coley, MD, now known as the Father of Immunotherapy, first attempted to harness the immune system for treating cancer.



1949

Rudolph and Antoinette Roseler de Villiers, who lost their teenage son, **Robert**, to leukemia in 1944, established the first incarnation of what became The Leukemia & Lymphoma Society. The impact was felt right away and the 1950s and 1960s saw some major treatment advances that were revolutionary for the time, which paved the way for today's innovative immunotherapies.

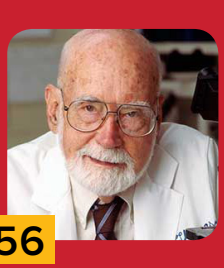


Photo: Susie Fitzhugh

1956

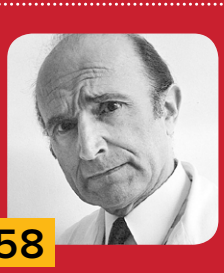
First Bone Marrow Transplant

E. Donnall Thomas, MD, conducted the first successful bone marrow transplant. This involved identical twins, one of whom had leukemia. This was the first concept of infusing cells into blood cancer patients to control leukemia.

1953

LLS Awards First Research Grant

This was the start of LLS's vast research portfolio, which has funded $1 billion in research to date. LLS has supported the development of some of the most effective and widely used therapies – from the early days of bone marrow transplants to immunotherapies today.



1958

First Allogeneic Bone Marrow Transplant

The first successful bone marrow transplant for unrelated donors (allogeneic) was completed by **George Mathé, MD**. This led him to predict and then demonstrate that immune cells from an unrelated donor can fight cancer.

1975

Monoclonal Antibodies Discovered

Georges Köhler, PhD, and César Milstein, PhD laid the groundwork for developing "monoclonal antibodies," which are proteins that bind to a molecule (for example, another protein) at a specific site.

1987

CAR-T Concept Discovered

Dr. Zelig Eshhar discovered the first "chimeric antigen receptor," an engineered receptor that was placed into T cells, the soldiers of the immune system, to fight and kill cancer.

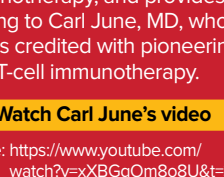
1998

LLS Funds Carl June, MD

The Leukemia & Lymphoma Society recognizes the early promise of the CAR T-cell immunotherapy, and provides funding to Carl June, MD, who later is credited with pioneering CAR T-cell immunotherapy.

Watch Carl June's video

Source: https://www.youtube.com/watch?v=xXBGgOm8o8U&t=34s



2010

The first successful cancer treatment with CAR-T for a lymphoma patient was reported by the lab of **Steven Rosenberg, M.D., Ph.D.**, chief of the Surgery Branch in NCI's Center for Cancer Research (CCR).

Watch Dr. Rosenberg's video

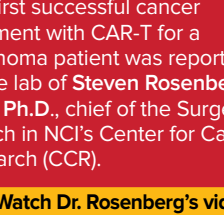
Source: https://www.youtube.com/watch?v=ZrEbAOqoGuM&t=56s

2011

Under the guidance of Carl June, MD, David Porter, MD, whose work was funded by LLS, published a study in which two of three leukemia patients went into complete remission after CAR T-cell treatment. One patient was **Doug Olson**, who is still in remission today.

Watch Doug Olson's video

Source: https://www.youtube.com/watch?v=__PUhj8thr0



2017

On August 30, 2017, Kymriah (tisagenlecleucel) **was the first CAR T-cell immunotherapy approved by the FDA.** It was approved for certain children and adults with ALL who have run out of other treatment options. Today, 7-year-old Kaitlyn, like many other children who received this treatment, is cancer free.

www.LLS.org

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