Axicabtagene Ciloleucel (YESCARTA®)

Kite Pharma's CAR T-Cell Therapy for Non-Hodgkin Lymphoma

Contributions of investigators from National Cancer Institute (NCI), NCI Technology Transfer Center's (TTC's) facilitation of a cooperative research and development agreement (CRADA), and the subsequent collaboration between Kite Pharma and NCI investigators paved the way for FDA approval of Axicabtagene Ciloleucel (Yescarta®). NIH is solely responsible for the content of these materials.

Context/Background

Chemotherapy, radiation, and stem-cell transplantation have been the standard line of treatment for certain leukemias and lymphomas for decades. Some patients with relapsed or refractory lymphoma do not respond to initial treatment. In fact, approximately 30%–40% of patients will develop relapsed/ refractory diffuse large B-cell lymphoma, the most common type of non-Hodgkin lymphoma (NHL). However, separate new insights into the genetic composition of leukemic cells have given rise to the development of chimeric antigen receptor (CAR) T-cell therapy.[1] CAR T-cell therapy uses a patient's own T cells to treat their cancer.[2] T cells, which play a role in initiating immune responses against invading pathogens, are harvested from a patient's blood and modified in the lab to add a new molecule (i.e., CAR) on their surface, turning T cells into CAR T cells. A breakthrough trial in 2010 led NCI scientists Dr. Steven Rosenberg and Dr. James Kochenderfer to demonstrate that CAR T cells recognizing the CD19 receptor were successful in the treatment of some types of B-cell malignancies. Research and clinical contributions of NCI investigators paved the way for the early work that led to FDA approval of Axicabtagene Ciloleucel.

Axicabtagene Ciloleucel was the first CAR T-cell therapy to treat adults with certain types of B-cell lymphomas.[3] Axicabtagene Ciloleucel, which is marketed as Yescarta®, is indicated to treat two types of NHL: (1) large B-cell lymphoma, when a patient's first cancer treatment did not work, the cancer returned within a year of first treatment, or when at least two kinds of treatment have failed to control the cancer, and (2) follicular lymphoma, when at least two kinds of treatment have failed to control the cancer. Early results from Phase 3 trials indicate that Yescarta® is 60% more effective than the current standard line of treatment for patients with large B-cell lymphoma who did not respond well to, or relapsed after, the first line of treatment.[4]

The Discovery of the Technology (inventor story)

The origins of discovery of Yescarta date back to the 1970s, when NCI scientist Dr. Steven Rosenberg, widely considered the father of cancer immunotherapy, wanted to understand immune response to growing cancer in humans that might then lead to an effective cancer immunotherapy. For decades, Rosenberg's lab contributed to foundational research on using T cells for immunotherapy. In the 1990s, Zelig Eshhar of the Weizmann institute in Israel came to the NCI on sabbatical to work with

[1] Marion Subklewe et al. "Chimeric Antigen Receptor T Cells: a race to revolutionize cancer therapy." *Transfusion medicine and hemotherapy* 46, no 1 (2019): 15–24. https://doi.org10.1159/000496870

[2] Lymphoma Research Foundation. "CAR T Cell Therapy for Lymphoma." (2021). https://lymphoma.org/wp-content/uploads/2021/12/LRF-CAR-T-Cell-Therapy_Factsheet.pdf

[3] U.S. Food and Drug Administration. "FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma." (October 18, 2017). https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma

[4] Kristi Birch. "Early trial results indicate Yescarta CAR-T therapy improves survival for adults who relapse from large B-cell lymphoma." KU Medical Center. (August 4, 2021). https://www.kumc.edu/about/news/news-archive/yescarta-car-t-therapy.html

Dr. Rosenberg.[5] He had helped develop the first CAR designs in 1989.[6] Drs. Eshhar and Rosenberg collaborated on advancing the usage of T cells as immunotherapy, specifically, the use of CAR T cells.[7] This collaboration enabled multiple patent filings, including applications that later issued as foundational patents in the CAR-T space.

Through the late 1990s and early 2000s, the field experienced a period of stagnancy. In 2007, Dr. James Kochenderfer, a medical oncology/hematology fellow at NCI, approached Dr. Rosenberg about leveraging his work on T-cell receptor transfer and CAR T-cell transfer to target CD19 to treat patients with advanced lymphomas. Up until this point, Dr. Rosenberg's work focused mostly on solid tumor cancers, like melanoma and breast cancer. Drs. Kochenderfer and Rosenberg shifted their focus to the anti-CD19 CAR. They hypothesized that CD19 would be an ideal target because it is not expressed on any critical cells in the human body except B cells, which patients can live without, and is very well expressed on malignant B-cell cancers, such as lymphoma and leukemia. Leveraging learnings from Dr. Rosenberg's previous work, Dr. Kochenderfer constructed two CARs containing a mouse-anti-human-CD19 antibody chain derived from the FMC63 hybridoma.[8] He selected the CAR that showed the "greatest potency in vitro when transduced into CD8 + and CD4 + T cells and showed highly specific activity against CD19 expressing tumor cells."[9] In 2009, the team went on to use its constructed CD19 CAR to treat the first patient with autologous peripheral lymphocytes.[10] This is the same CAR used in axicabtagene ciloleucel.

Role of NCI Technology Transfer Center (tech transfer story)

Despite demonstrating significant clinical success, manufacturing CAR T cells at scale presented inherent challenges. It is a delicate process that is done on a per-patient basis. After T cells are isolated from a patient, they are genetically modified and expanded and subsequently introduced back into the body via transfusion. Drs. Kochenderfer and Rosenberg successfully demonstrated this process in clinical trials, which saw six of eight patients achieve remission of their advanced B-cell malignancies.[11] Although the drug had shown significant clinical value, the doctors needed to determine how to take the therapy that worked in Dr. Rosenberg's 600 sq. ft. manufacturing space in his lab into a commercially viable treatment option. To make this drug a reality, NCI scientists needed the backing of a commercial partner to provide expertise on commercial-scale manufacturing and to help finance this expensive process.

Although pharmaceutical companies showed interest in licensing the technology after Drs. Kochenderfer and Rosenberg published the results of their first clinical trial,[12] these companies were dissuaded by the

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[5] Steven A. Rosenberg. "A journey in science: immersion in the search for effective cancer immunotherapies." *Molecular Medicine* 27, no 63 (2021). https://doi.org/10.1186/s10020-021-00321-3

[6] Zelig Eshhar. "From the Mouse Cage to Human Therapy: A Personal Perspective of the Emergence of T-Bodies/Chimeric Antigen Receptor T Cells." *Human Gene Therapy* 25, no 9 (2014): 773–778. https://doi.org/10.1089/hum.2014.2532

[7] P. Hwu et al. "In Vivo Antitumor Activity of T Cells Redirected with Chimeric Antibody/T-Cell Receptor Genes." *Cancer Research* 55, no 15 (August 1,1995): 3369-3373. Retrieved from https://pubmed.ncbi.nlm.nih.gov/7614473/

[8] James N. Kochenderfer et al. "Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor." *Journal of Immunotherapy* 32, no 7 (September 2009): 689–702. https://doi.org/10.1097/CJI.0b013e3181ac6138

[9] Steven A. Rosenberg. A Journey in Science: Immersion in the Search for Effective Cancer Immunotherapies. *Molecular Medicine* 27, no 63 (2021). https://doi.org/10.1186/s10020-021-00321-3

[10] James N. Kochenderfer et al. "Eradication of B-Lineage Cells and Regression of Lymphoma in a Patient Treated with Autologous T Cells Genetically Engineered to Recognize CD19." *Blood* 116, no 20 (2010): 4099–4102. https://doi.org/10.1182/blood-2010-04-281931

[11] James N. Kochenderfer et al. "B-Cell Depletion and Remissions of Malignancy Along with Cytokine-Associated Toxicity in a Clinical Trial of Anti-CD19 chimeric-Antigen-Receptor-Transduced T Cells." *Blood* 119, no 12 (2012): 2709–2720. https://doi.org/10.1182/blood-2011-10-384388

[12] James N. Kochenderfer et al. "Eradication of B-Lineage Cells and Regression of Lymphoma in a Patient Treated with Autologous T Cells Genetically Engineered to Recognize CD19." *Blood* 116, no 20 (November 18, 2010):4099–4102. https://doi.org/10.1182/blood-2010-04-281931

laborious, time intensive, and costly process to manufacture CAR T cells. The team, although frustrated, remained confident in the potential of their discovery.

Dr. Arie Belldegrun, who served as a research fellow for Dr. Rosenberg at NCI in the 1980s, visited Dr. Rosenberg's lab in 2010 and saw the same type of scan of the first patient treated with what would later become Yescarta.[13] Dr. Belldegrun, who cofounded Kite Pharma in 2009 to pursue cancer immunotherapy, was intrigued. He knew that this treatment had the potential to redefine cancer treatment.

> *"I had no doubt that this is going to be a drug and, more than that, it will become a platform for multiple products."* [14]
> *—Dr. Arie Belldegrun, Founder, Kite Pharma*

Dr. Belldegrun's time at NCI under Dr. Rosenberg's mentorship ultimately helped secure his belief in the drug. Over the next 2 years, NCI's Technology Transfer Center (TTC) worked out a deal with Kite Pharma that was signed in 2012. Kite Pharma licensed patented inventions related to CAR-T, which are owned, in part, by NIH. The TTC also created a contractual framework of collaboration between NCI scientists and Kite Pharma through two CRADAs. The first CRADA was signed in 2012 and focused on the development of novel engineered peripheral blood autologous T-cell therapeutics (eACT) for the treatment of multiple cancer indications and the optimization of GMP manufacturing processes to enable multi-site clinical trials and eventual commercialization.[15] The second CRADA was signed in 2016 for research and clinical development of a fully human anti-CD19 CAR product candidate for the treatment of B-cell lymphomas and leukemias.[16]

The two CRADAs proved essential for further development and eventual commercialization of axicabtagene ciloleucel. The CRADAs provided a framework for collaboration between the two parties and financing for continued research and development in CAR T cell therapies. Moreover, the CRADAs contributed to three important pieces of intellectual property that underlie axicabtagene ciloleucel: ways to produce T cells to treat B-cell cancers, ways to condition patients so that their bodies can better accept T-cell therapy, and ways to identify potential candidates for treatment.

The symbiotic nature of the relationship between NCI and Kite Pharma enabled the successful commercialization of axicabtagene ciloleucel. Together, they worked within the contractual framework that NCI TTC set up to collaborate on further developing axicabtagene ciloleucel for patients in need, each bringing something to the table. NCI brought the research and

[13] Matt Richtel and Andrew Pollack, "Harnessing the U.S. Taxpayer to Fight Cancer and Make Profits," *New York Times,* December 19, 2016. https://www.nytimes.com/2016/12/19/health/harnessing-the-us-taxpayer-to-fight-cancer-and-make-profits.html

[14] Matt Richtel and Andrew Pollack, "Harnessing the U.S. Taxpayer to Fight Cancer and Make Profits," *New York Times,* December 19, 2016. https://www.nytimes.com/2016/12/19/health/harnessing-the-us-taxpayer-to-fight-cancer-and-make-profits.html

[15] Fierce Biotech, "Kite Pharma Partners with the National Cancer Institute to Develop Novel Cellular Immunotherapy Clinical Products." (October 17, 2012). https://www.fiercebiotech.com/biotech/kite-pharma-partners-national-cancer-institute-to-develop-novel-cellular-immunotherapy

[16] Gilead, "Kite Pharma Expands Its Clinical and Research Partnership with the National Cancer Institute (NCI) for Next-Generation CAR Programs to Treat B-Cell Malignancies." (January 2016). https://www.gilead.com/news-and-press/press-room/press-releases/2016/1/kite-pharma-expands-its-clinical-and-research-partnership-with-the-national-cancer-institute-nci-for-nextgeneration-car-programs-to-treat-bcell-ma

early clinical contributions, whereas Kite contributed to further clinical development, manufacturing improvements along with financing that enabled significant research and testing efforts.

"The CRADA was the basis for NCI to collaborate with Kite Pharma, contributing to three important pieces of IP that ultimately underlie Yescarta."
—Andrew Burke, Technology Transfer Manager for NCI

Role of Licensee (commercialization story)

Although Dr. Rosenberg, Dr. Kochenderfer, and their teams demonstrated in early clinical work the success of this drug, Kite Pharma helped scale it to be a commercially viable treatment option. Without the contributions of both parties, axicabtagene ciloleucel would not have become a second-line treatment option for adults with large B-cell lymphoma or a third-line treatment for follicular lymphoma. In August 2017, Gilead Sciences, Inc., announced its intended acquisition of Kite Pharma. The promise of the NCI technology licensed by Kite Pharma is evidenced by Gilead paying nearly $12 billion to acquire the company.[17] In October 2017, axicabtagene ciloleucel was FDA-approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. In the same month, a deal was finalized for Gilead Sciences to acquire Kite Pharma.

Impact

The contributions from NCI scientists, NCI TTC, and Kite Pharma supported the commercialization of the first FDA-approved CAR T-cell therapy for the treatment of adult patients with relapsed or refractory large B-cell lymphoma.[18] Axicabtagene ciloleucel has provided significant clinical benefits to a vast majority of the patients who receive the therapeutic. It is giving new life to patients with lymphoma who otherwise had no treatment options. In ZUMA-7, a Kite Pharma led and funded study, a global, multicenter, single-arm, open label Phase 2 study that evaluated axicabtagene ciloleucel in patients with relapsed or refractory indolent NHL after at least two prior lines of therapy, it was demonstrated that, of all treated patients, 92% had an overall response rate with a 75% complete response.[19]

Beyond the significant clinical benefits that the therapy has provided, axicabtagene ciloleucel's successes have also had far-reaching impacts for the adoptive cell therapy discipline as a whole. The successful commercialization of axicabtagene ciloleucel substantially decreased the perceived risk of adoptive cell therapy. Transitioning the therapeutic from the lab to Kite Pharma's manufacturing facilities, and ultimately to become a viable treatment option for adult patients with certain types of B-cell lymphomas, demonstrated that adoptive cell therapy works. This has resulted in an explosive growth of research and development within the space as companies continue to multiply and develop adoptive cell therapies for various indications.

[17] Chris Frew, "Three Examples That Show Why NCI is a Goldmine of Blockbuster Technologies for Commercialization," *BioBuzz*, May 7, 2019. https://biobuzz.io/why-nci-is-a-goldmine-of-blockbuster-technologies-for-commercializing/

[18] Amber C. King, and Jennifer S Orozco. "Axicabtagene Ciloleucel: The First FDA-Approved CAR T-Cell Therapy for Relapsed/Refractory Large B-Cell Lymphoma." *Journal of the Advanced Practitioner in Oncology* 10, no. 8, (2019): 878–882. https://doi.org/10.6004/jadpro.2019.10.8.9

[19] Businesswire, "Yescarta® Demonstrates Durable Two-Year Clinical Benefit in Adults with Relapsed or Refractory Indolent Non-Hodgkin Lymphoma Including Follicular Lymphoma." (December 11, 2021). https://www.businesswire.com/news/home/20211211005053/en/Yescarta%C2%AE-Demonstrates-Durable-Two-Year-Clinical-Benefit-in-Adults-With-Relapsed-or-Refractory-Indolent-Non-Hodgkin-Lymphoma-Including-Follicular-Lymphoma

Yescarta Timeline
From Invention to Commercialization

PRE-2000 TIMELINE

Foundational research on using T cells for immunotherapy.

NCI and Zelig Eshhar collaborate, resulting in foundational patents in the chimeric antigen receptor (CAR) T-cell therapy space.

1970 1975 1980 1985 1990 1995

Invention

Technology transfer

Commercialization

Dr. Kochenderfer and Dr. Rosenberg start working together.

Dr. Kochenderfer and Dr. Rosenberg design and construct a novel anti-CD19 CAR T cell.

Dr. Rosenberg and Dr. Kochenderfer conduct the first clinical application of a CD19 CAR in hematology in an intensively pretreated patient with follicular lymphoma.

Dr. Arie Belldegrun, former research fellow in Dr. Rosenberg's lab, co-founds Kite Pharma.

Dr. Belldegrun visits Dr. Rosenberg's lab and was shown the X-ray of the first patient treated using the CD19 CAR.

Kite licenses patented inventions related to CAR T which are owned, in part, by NIH.

TTC negotiates CRADA with Kite Pharma for the development and commercialization of novel engineered peripheral blood autologous T-cell therapeutics for the treatment of multiple cancer indications.

Axicabtagene ciloleucel receives FDA breakthrough therapy designation in relapsed or refractory diffuse large B-cell lymphoma.

TTC negotiates CRADA with Kite Pharma for the research and clinical development of a fully human anti-CD19 CAR product candidate for the treatment of B-cell lymphomas and leukemias.

Gilead Sciences announces they will acquire Kite Pharma.

Gilead completes acquisition of Kite Pharma.

Yescarta becomes the first CAR T-cell therapy approved by FDA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

FDA approves axicabtagene ciloleucel for relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

FDA approves axicabtagene ciloleucel as first CAR T-cell therapy for initial treatment of relapsed or refractory large B-cell lymphoma.

2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

PRIMARY TIMELINE

NCI and Kite Pharma collaborate under two CRADAs to advance a pipeline of proprietary eACT product candidates, both CAR and T-cell receptor products, directed to a wide range of cancer indications. The CRADAs contributed to three important pieces of IP that underlie Yescarta, which were jointly filed by NCI's TTC and Kite Pharma:

Methods for Producing Autologous T-Cells Useful to Treat B-Cell Malignancies and Other Cancers and Compositions (US Application 61/935,833)

Methods of Conditioning Patients for T-Cell Therapy (US Application 62/167,750)

Diagnostic Methods for T-Cell Therapy (US Applications 62/167,738)