

Case Histories of Significant Medical Advances: Chimeric Antigen Receptor (CAR) T-Cell Therapy

Amar Bhidé
Srikant Datar

Working Paper 21-034



Case Histories of Significant Medical Advances: Chimeric Antigen Receptor (CAR) T-Cell Therapy

Amar Bhidé
Harvard Business School

Srikant Datar
Harvard Business School

Working Paper 21-034

Copyright © 2020 by Amar Bhidé and Srikant Datar

Working papers are in draft form. This working paper is distributed for purposes of comment and discussion only. It may not be reproduced without permission of the copyright holder. Copies of working papers are available from the author.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Amar Bhidé, Harvard Business School

Srikant Datar, Harvard Business School

Abstract: In 2017, the US Food and Drug Administration (FDA) approved an immunotherapeutic treatment, called CAR-T therapy, for two kinds of blood cancers—acute leukemia (ALL) and a lymphoma. We describe 1) how CAR-T works; 2) the foundational advances and discoveries; 3) development of CAR-T therapy; and 4) the situation in 2019.

Acknowledgments: We would like to thank Sarah Gulick for her research, writing and editorial assistance.

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Using and helping the body's natural ability to fight disease was a basic principle of ancient Hippocratic medicine. In recent decades, this approach, called 'immunotherapy' or 'immune-oncology,' has emerged as a new way to treat cancers. Unlike most traditional drugs synthesized from chemicals, immunotherapy uses products bio-engineered from living cells, substances derived from cells, or laboratory-produced versions of such substances.¹

In 2017, the US Food and Drug Administration (FDA) approved an immunotherapeutic treatment, called CAR-T therapy, for two kinds of blood cancers—acute leukemia (ALL) and a lymphoma.² The therapy genetically modified the T cells of patients to create cells with "chimeric antigen receptors" capable of attacking cancer cells that normal T cells cannot kill.

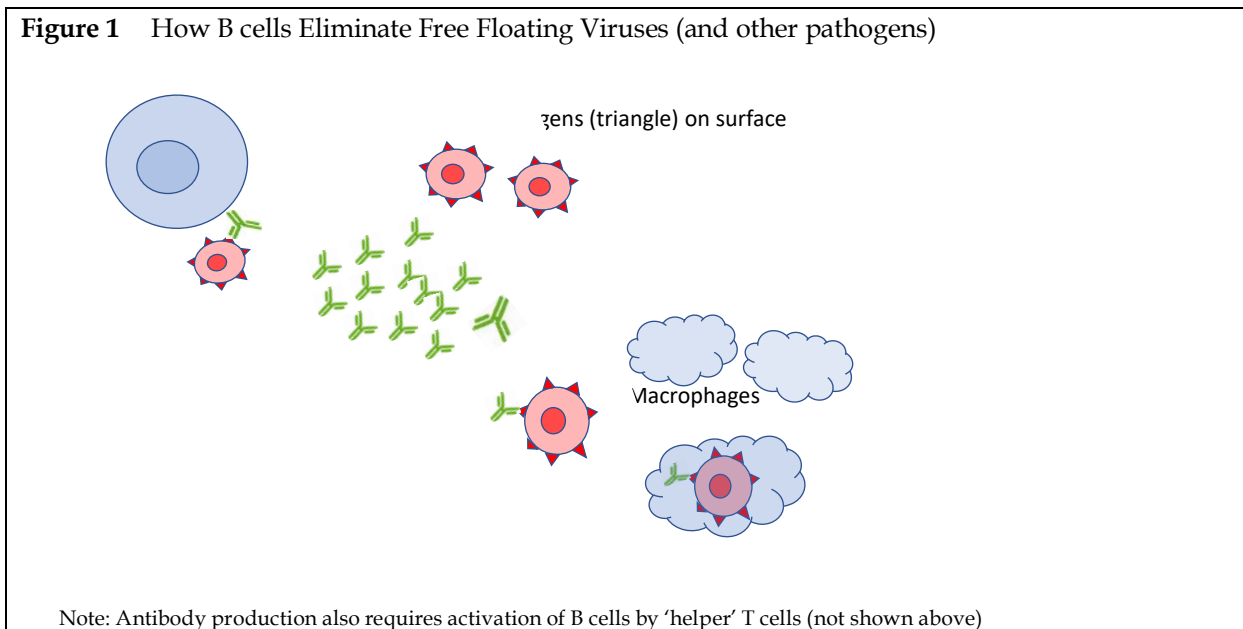
We summarize, 1) how CAR-T works; 2) the foundational advances and discoveries; 3) development of CAR-T therapy; and 4) the situation in 2019.

1. How CAR-T Therapy Works

Innate and Adaptive Immunity. Cells that can attack any intruding virus, bacteria, or other pathogen provide 'innate' immunity. If this innate, general purpose immunity fails, an 'adaptive' response emerges to eliminate specific pathogens such as viruses or bacteria.

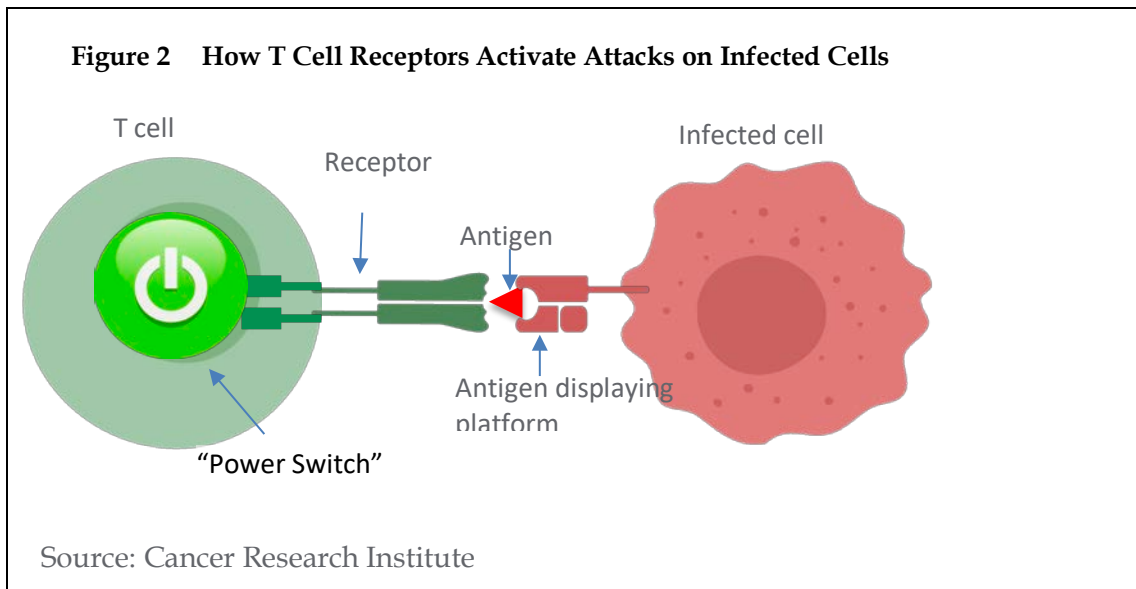
B- and T cells provide adaptive immunity. Simplifying greatly, B cells help attack 'free-floating' pathogens, whereas 'killer' T-cells eliminate cells infected by pathogens.

B cells produce 'antibodies' after they recognize a pathogen. Antibodies have Y-shaped arms that can attach to targets ("antigens") present on the surfaces of the pathogens the B cell had recognized. When antibodies attach to a targeted antigen, this 'tags' the pathogens for elimination by other immune system cells, such as macrophages.^{3*}



* 'Neutralizing' antibodies can also directly disable pathogens

T cells that eliminate infected cells have 'receptors' that allow them to target antigens on infected cells. Infections cause cells to display (or "present") these antigens on molecular platforms on their surfaces, as if to tag themselves for elimination. When a T cell receptor connects to a suitably displayed antigen, it activates a "power switch" that causes the T cell to fire chemicals (cytotoxins) to kill the infected cell (See Figure 2). Activating the power switch also instructs T cells to reproduce quickly and get help from other kinds of immune cells.⁴

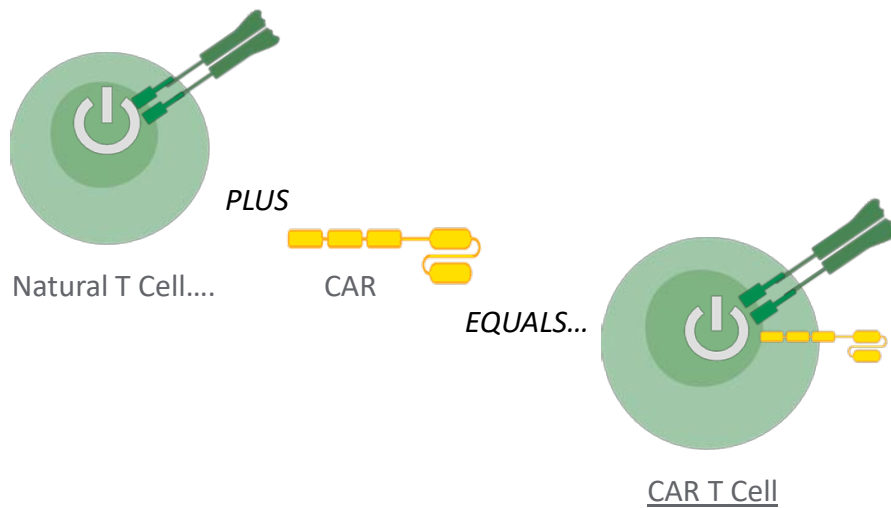


The adaptive immunity provided by B and killer T cells is highly specific: A particular B cell can only 'recognize' its matched pathogen and the arms of the antibodies it produces can only attach to the pathogen's distinctive antigens. Similarly, T cells are specialized killers: their receptors activate attacks only after attaching to the distinctive antigens produced by particular infections.

Limitations against cancer cells. T cells can eliminate cells that develop abnormalities for a wide range of reasons including random mutations or exposure to radiation, not just infections. However, T-cell attacks on abnormal cells, require the cells to "present" distinctive antigens on their "display platforms." But many cancer cells do not present distinctive antigen targets on their display platforms. Moreover, even if T cells can identify targets they may not respond quickly enough or strongly enough to stop the rapid growth of cancer cells.⁵

Advantages of 'chimeric' receptors. Inserting an artificial gene into the genetic code of natural T cells can help the T cells overcome these limitations in the following way: the inserted genes cause T cells to produce (or "express") an unnatural, composite (and thus 'chimeric') receptor, in addition to their natural receptors. The chimeric receptor has, like a natural T cell receptor, a prong protruding from its surface that can recognize and attach to a distinctive target on the surface of a cancer cell.⁶ (See **Figure 3**.)

Figure 3 Genetically Engineered CAR-T Cells



Source: Cancer Research Institute

Crucially, chimeric receptors can target molecules that cancer cells do not put on adequate display. For instance, CAR-Ts now used to treat blood cancers target CD19 molecules on the surface of the cancer cells. The immune system would not naturally develop T-cells that target these molecules because the molecules are not “presented” on the right “display platforms.” Moreover, healthy B-cells also have CD19 molecules. This would also prevent the adaptive immune system from naturally selecting CD19 as targets for eliminating cancer cells.

Genetically engineered CAR-T cells can however attach to the CD19 molecules. And as it happens, killing healthy B-cells along with cancer cells is worthwhile for patients with otherwise incurable blood cancers (whereas natural immune systems would not make this calculated sacrifice.)

Genetic modification has another advantage because it is done outside the body: the modified cells can then be reproduced in large numbers before they are reintroduced into patients’ bodies. This is vital in treating leukemias which have already damaged the body’s immune cell ‘factories.’

Furthermore, genetically modified T cells continue to multiply after they are infused into patients. One infused cell can multiply into a thousand cancer killing cells. CAR-T cells are therefore considered “living drugs” that can become more potent after they are administered (unlike inanimate pharmaceutical chemicals that immediately start getting consumed.)⁷

As the CAR-T cell attacks kill cancer cells, the CAR-T cells stop multiplying and their numbers decline. However, some CAR-T cells remain (‘persist’) in the body, ready to respond should the cancer (with CD19 targets) recur.⁸

Side Effects. Patients’ immune systems can overreact to infused CAR-T cells. Notably, when the infused CAR-T cells connect with CD19 molecules on blood cancer cells, they trigger the release of cytokine molecules. The cytokine molecules instruct other immune system cells to attack the cancer cells. But the immune response activated by the cytokines can itself trigger the release of more cytokines. In its mild form, experienced by about 70% of patients, this cytokine release syndrome (CRS) produces flu-like symptoms like nausea, fatigue, headaches, chills and fevers.⁹ Between 7% and 25% of patients experience more severe “cytokine storms” with life-threatening effects including sharp drops in blood pressure, heart attacks and failure of vital organs such as the kidney¹⁰.

CAR-T treatments may also produce (for reasons that are not yet well understood) neurological problems such as confusion, delirium, involuntary muscle twitching, hallucinations, or seizures. These problems, which occur in about 40% of patients, can be severe in 10% to 30% of patients.¹¹

And, as mentioned, CAR-T cells kill normal B-cells along with cancer cells. When the CAR-T cells themselves decline, B-cells usually return. However, some patients suffer from prolonged B cell depletion, and thus a reduced capacity to resist infections.¹²

Steps in the Process. CAR-T treatments **approved and regulated by the US FDA** typically proceed through the following sequence:¹³

- *Prescreening* Patients have to ‘fit’ the conditions (‘indications’) for which the treatment has been approved. Additionally, the cancer centers providing the treatment often perform additional radiology studies, EKG/echocardiograms, bone marrow biopsies, and blood work and have patients meet physicians and other members of their treatment teams.

- *Collecting T-cells* Blood is taken from the patient’s body through a catheter in a large chest vein and processed in a blood collection machine to remove T-cells. The remaining blood is then infused back into the patient, while the T-cells are concentrated (see **Exhibit 1**).

- *Producing CAR-T cells* The DNAs of the collected T-cells are modified by inserting a gene that will make the T-cells produce chimeric receptors. The modified T-cells are then multiplied¹⁴ (although in practice, the modification and multiplication is often done at the same time in a bioreactor). After enough CAR-T cells have been produced, the CAR-T cells are frozen, and kept ready for infusion into patients (see **Exhibit 2**).

- *Infusing CAR-T cells* Patients are first administered chemotherapy to prepare them for CAR-T cell infusion. The CAR-T cells are then infused after thawing into patients’ veins. To prevent possible reactions, patients receive pre-infusion medications.¹⁵

Treatment Teams and Centers. Treatments are provided in certified centers by specialized professionals who may include dialysis nurses to draw the patient’s blood, oncology nurses to infuse CAR-T cells, pharmacists for pre-treatment drugs and control of post-treatment side effects, critical care teams standing by during CAR-T infusions, ready to step in if side effects are severe, and neurologists, to treat neurological side effects.¹⁶

Some large cancer centers with active research programs who provide CAR-T treatments make their own CAR-T cells.¹⁷ Other treatment centers send their patients’ T cells to specialized commercial facilities who produce and send back frozen CAR-T cells. In either case, the FDA tightly regulates the facilities and procedures for producing CAR-T cells.¹⁸

2. Foundational Developments

Coley’s Toxins

In the early 1890s, Dr. William Coley, attending surgeon at New York’s Memorial Hospital (later Memorial Sloan Kettering) had noticed that some cancer patients who contracted acute bacterial infections experienced spontaneous remissions. Acting on a hunch, Dr. Coley injected bacteria into a patient with an inoperable tumor to induce a “virulent infection.” When the patient recovered completely, Dr. Coley developed a bacterial mixture, known as “Coley’s mixed bacterial toxins,” for treating cancer patients.¹⁹

But because of inconsistent, difficult to reproduce results, the toxins were dismissed as snake oil and eventually included in the American Cancer Society’s list of ‘Unproven Methods of Cancer Management.’ Coley’s contributions to establishing the first cancer research fund in the U.S. and in shaping the mission of the Memorial Sloan-Kettering Cancer Center were forgotten. And through the mid-1950s, researchers and practicing physicians favored radiology and chemotherapy for cancer treatment although immunology, including vaccine development, continued for other diseases such as polio.²⁰

After Coley's death, his daughter, Helen Coley Nauts, found records of her father's "toxin treatment." Nauts, a housewife with no medical training, then taught herself oncology, immunology, and record keeping, tracked down patients who had been treated with Coley toxins, and published findings showing the beneficial effects. Nauts also secured a \$2,000 grant from Nelson Rockefeller to start the Cancer Research Institute (CRI) in 1953. In 1971, the CRI recruited Dr. Lloyd Old, a physician/researcher, as its medical director.²¹

Dr. Old, who was also chair of the Department of Immunology at Memorial Sloan Kettering, started an immunology fellowship program. According to a CRI board member the fellowships stimulated "basic research that provides the foundation of today's immunotherapies."²²

Bone Marrow Transplants

Bone marrow transplants became the first treatments to successfully treat leukemia with the help of new immune cells (and are now also used for several other diseases). Treatments start with intense chemotherapy to eliminate the patient's existing, and often diseased, bone marrow cells. The chemotherapy also helps kill any other diseased cells in the patient's body. New bone marrow cells, often from a well-matched donor, are then transfused to rebuild the patient's bone marrow.²³ If successful, the rebuilt bone marrow helps produce healthy immune cells. T cells that were part of the donated bone marrow cells can also help eliminate some cancer cells that might survive initial chemotherapy.²⁴

The development of the treatment, which started in the 1950s, was long and difficult (see **Exhibit 3**) and treatment itself continues to have severe side effects.²⁵ These may arise for instance from the chemotherapy given before the transplant, from the rejection of donated marrow cells, or conversely from graft-versus-host attacks by new immune cells (that treat the patient's existing cells as intruders). Effectiveness of the treatment remains hit or miss. Bone marrow transplants for cancer patients therefore typically follow other failed treatments.²⁶

T Cell Discoveries

In 1960 Eva and George Klein, working at the Karolinska Institute in Stockholm, showed that immune cells could kill cancer in mice.²⁷ Which specific cells did the killing and how was not known, however. In fact, little was then known about immune cells. In 1890, Emil von Behring and Shibasaburo Kitasato had discovered that antibodies, which they called antitoxins, helped provide immunity to diphtheria and tetanus.²⁸ Then, in the late 1940s and 1950s researchers identified cells produced in the bone marrow (hence 'B'-cells) as the source of antibodies.²⁹

In 1961, Jacques Miller, a PhD student at the University of London, found that cells developed in the thymus gland – 'T' cells – played a vital role in protecting animals against some diseases.³⁰ Two years later Miller and Graham Mitchell specified an important feature of this role, namely that T cells helped B-cells produce effective antibodies. Miller and his colleagues then launched a new field of biomedical research: T cell biology. This research then identified several types of T cells that performed a variety of functions in the immune system.³¹

In 1983, Tak Mak, a young Hong Kong-born post-doctoral researcher at a small Canadian laboratory, the Ontario Cancer Institute in Canada, identified a crucial genetic building block of T cell receptors. The discovery, made with the help of recently developed genetic technologies, was based on Mak's hypothesis that T cell and B-cell receptors had completely different structures. Much was already known about B-cell receptors and most other scientists were using that as a template for researching T cell receptors. Mak proceeded instead on the assumption that T cell receptors had completely different structures. Mak's discovery provided a foundation for cloning the genes of T cell receptors – and thus synthesizing chimeric T cell receptors.³²

A lucky experiment, done by a physician-researcher around the time of Mak's investigations, would also later play an important role. Carl June, then working on bone marrow transplants at the Fred Hutchinson Cancer Research Center in Seattle, made the chance discovery that the CD28 molecule was an important

activating switch for T cells. A T cell receptor-antigen connection alone did not effectively sustain the killing of unwanted cell. In fact, later research showed that without the 'co-stimulatory' signal provided by CD28 molecules, a T cell receptor-antigen connection could make T cells 'anergic' (unresponsive).³³

Gene Modification

Methods for modifying DNA molecules that carried the genetic blueprints of T cells (that Mak and other scientists were discovering) advanced through considerable trial and error. Many of the methods developed used deactivated viruses that caused AIDS ('HIV' viruses) and whose own genetic structures were progressively better mapped in the 1980s. Although deactivation made the AIDS viruses harmless, they could still enter cells to insert new genes.³⁴ The new genes would in turn change the structures and behavior of the genetically modified cells. Many of these modifications did not however directly produce effective treatments and using the methods required considerable skill. Complementary methods developed to multiply modified and unmodified T cells in laboratory cultures also required skills acquired through experience.³⁵

3. Development of CAR-T Treatments

T-bodies

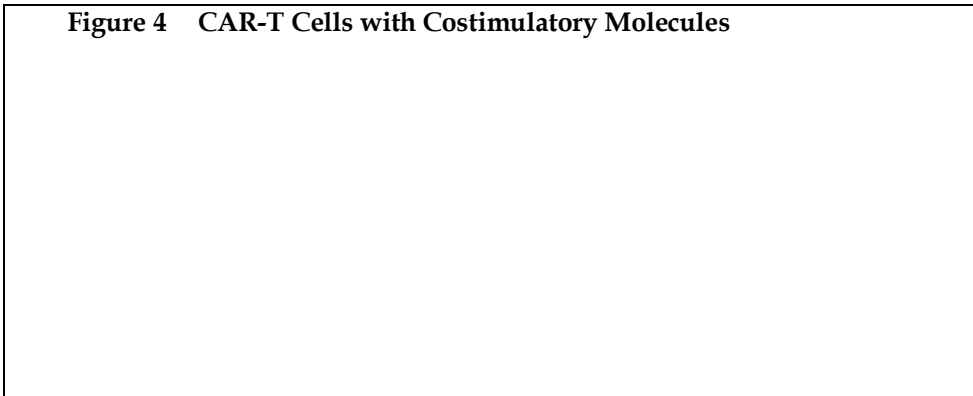
In the late 1980s, immunologist Zelig Eshhar and his colleagues at the Weizmann Institute in Israel used genetic manipulation to create what Eshhar called a 'T-body.' The T-body had molecules from antibodies mounted on the receptors of T cells.³⁶ In principle, the antibody part would help the receptor recognize and attach to the antigen of a cancer cell. The attachment would, in the usual course, stimulate the killing of the cancer cells.

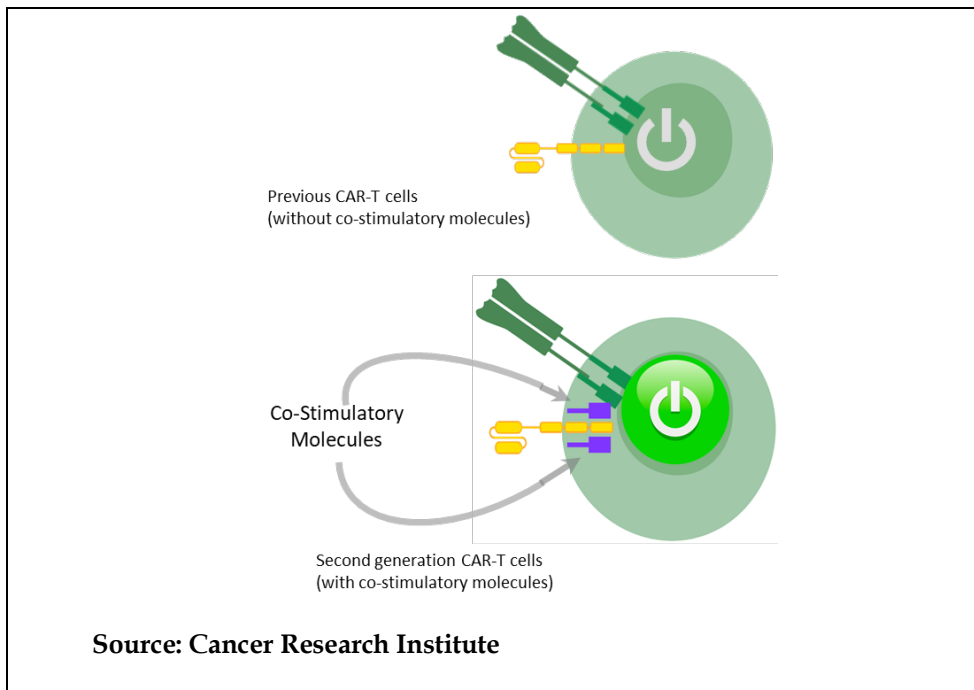
Laboratory experiments showed that the T-bodies could attach themselves to cancer cells, but they could not sustain an effective attack. Further development produced T cells, now called 'first generation' CAR-T cells, with more streamlined and better integrated receptors. They too could not sustain effective attacks on cancer cells.³⁷

Co-stimulatory Molecules

In the 1990s, Michel Sadelain, a physician researcher at Memorial Sloan-Kettering designed and produced chimeric T cell receptors that could execute effective attacks. Sadelain, whose prior post-doctoral work at the Massachusetts Institute had included improved ways of inserting genes to modify the genetic blueprints of T cells, created chimeric receptors with CD28 molecules.³⁸ As mentioned, CD28 molecules, help turn on the activity of natural T cells. In Sadelain's genetically modified receptors the molecules served a "co-stimulatory" function. (See Figure 4)

Figure 4 CAR-T Cells with Costimulatory Molecules





Now, the signal produced when the CAR's external prongs connected with an antigen on the surface of a cancer cell would not only trigger the release of chemicals to kill the cancer cell; the signal would also instruct the CAR-T cell to multiply and get help from other immune system cells.³⁹

Selecting Target Antigens

Whereas natural T cells select their target antigens through a blind Darwinian process of trial and error, developers of CAR-T cells choose targets for their receptors. By 1997, Sadelain's team had chosen the CD19 molecule as their target. CD19 was found on many blood cancer cells which would be easier for CAR-Ts to reach than cancer cells in solid tumors. And, although (as mentioned) it was also found on normal B-cells – which would then become targets for CAR-T attack – the B-cells were temporarily expendable and would eventually return.⁴⁰

Other researchers developing CAR-T cells (and also using Sadelain's co-stimulatory molecule design) then chose the same CD19 target. These included teams at the Children's Hospital of Philadelphia (CHOP), at the Seattle 'Hutch,' and, at the National Cancer Institute (N.C.I) in Bethesda, Maryland.

Carl June who led the CHOP team had worked on AIDS treatments that used genetically modified T cells (after, performing the "lucky accident" mentioned earlier that had identified the role of CD28 molecules in activating T cells).⁴¹

Leadership of the Hutch team included Stanley Riddell who had previously isolated and grown T cells that would protect patients receiving bone marrow transplants from viral infections.

And, a surgeon-oncologist, Steven Rosenberg, led the NCI team.⁴² Rosenberg had earlier extracted T cells that had somehow entered solid tumors, grown them with the help of a drug (Interleukin 2), and reinfused them into patients. The treatment had not initially yielded reliable results. However, Rosenberg then

administered the drug, Interleukin 2, with lab-grown T cells to produce a pathbreaking treatment for melanomas.^{43*}

Human Trials

It would take about ten years after Sadelain had chosen the CD19 target to start human trials. Researchers had to learn how to reliably insert genes and multiply cells on a scale that would support the treatment of patients and build a dedicated facility for the therapy.

Skepticism about CAR-T limited funding,⁴⁴ forcing many researchers to quit. Even June and Sadelain, who had become the leading experts in CAR-T, could not “squeeze another dime out of the NCI.”⁴⁵ June was however able to raise funds from a philanthropic Penn alum and his team applied to start human trials in 2006.⁴⁶ The trial was approved in 2009 and enrolled three patients in 2010. In 2011, no patients were treated because of the lack of funds.⁴⁷

A few other centers were also able to start trials by 2010. All the trials had enrolled leukemia patients who had failed to respond to traditional treatments, such as chemotherapy.⁴⁸ Traditional treatments for such cancers are usually effective. But patients who don’t respond or who have relapses have low life expectancy. With these nearly hopeless cases researchers didn’t know what to expect: Earlier CAR-T treatments had neither been particularly effective nor toxic.

Cytokine Syndrome Control

Treatment of the June team’s first enrolled patient in 2010, expected to die in a week, produced surprising results. The patient, 65-year-old Bill Ludwig, became “terrifyingly ill” after receiving three doses of his genetically modified CAR-T cells. His lungs, kidney, and heart were failing, and his temperature rose to a hundred and five degrees. Doctors who suspected an acute infection – although they could find no signs of a virus or bacteria – put Ludwig in the hospital’s Intensive Care Unit.⁴⁹

After a week in the ICU Ludwig’s condition dramatically improved on its own. His tumor masses had disappeared during his illness and a biopsy done twenty-eight days after his treatment had started found no cancer cells.⁵⁰

A subsequent analysis of the tests that had been performed during his mysterious illness suggested it was the first recorded instance of a ‘cytokine storm’: the attack of CAR-Ts on Ludwig’s cancer cells had triggered a new syndrome, CRS, which had produced the symptoms of an acute infection. Subsequent experience showed this to be a common side effect among patients when CAR-Ts attacked cancer cells.⁵¹

The near death of the seventh patient treated at the CHOP produced an important advance in controlling cytokine storms. Six-year-old Emily’s condition was dire when she started CAR-T therapy in 2012. She had already received intense chemotherapy for her leukemia but had relapsed after two brief remissions. Most of her organs were filled with cancer cells. Then, two days after her first CAR-T infusion, Emily suddenly became severely ill. Her temperature jumped, her lungs and kidneys began to fail, and she was drifting in and out of consciousness. She was quickly placed on a ventilator in an intensive care unit and put into an induced coma.⁵²

Earlier experience prompted physicians to look for elevated cytokines. They found one cytokine, IL-6, was nearly a thousand times its normal level. Coincidentally, June’s own daughter had juvenile arthritis and June knew of a recently approved drug to treat that disease that blocks IL-6. June got permission from experimental ‘off-label’ use of the drug which a nurse immediately administered to Emily. Days later, on her seventh birthday, the girl regained consciousness. Her tumors soon melted away and a biopsy done days later showed

* Rosenberg’s pioneering approach of extracting, growing, and reinfusing T cells that had somehow entered solid cancer tumors provide the basis for Tumor Infiltrating Leukocyte, or ‘TIL,’ treatments.

complete remission of Emily's cancer.⁵³ The IL-6 blocking drug then became a standard of care for severe CRS.⁵⁴

Exciting Results

Rosenberg's NCI team was the first to publish the results of its human trials in July 2010. June's team was second in August 2011 and in November of that year Sadelain's team published its results. Although, number of patients enrolled in the trials was small the treatment had apparently worked "beyond anyone's expectations."⁵⁵

Enthusiasm now overcame skepticism. Until the founding of Kite Pharma in 2009, no specialized biotech had been started to develop CAR-T therapy and established pharma and bio-pharma companies had also shown little interest. In 2012, however Novartis announced a collaboration with Carl June's team (which had by then treated just the three patients it had enrolled in its trial in 2010).⁵⁶

"With that deal, the field exploded" according to *Drug Discovery World*.⁵⁷ In 2012, for example Kite Pharma entered into a Cooperative Research and Development Agreement with the NCI. In 2013, Juno Therapeutics was founded through a collaboration of the Fred Hutchinson Cancer Research Center, Memorial Sloan-Kettering Cancer Center and Seattle Children's Research Institute. Several large pharma companies, including Merck, Pfizer, Celgene and Amgen, "also joined the CAR-T partnering arms race."⁵⁸

Approved CAR-T treatments

Kymriah was the first treatment approved by the FDA. It was based on CAR-Ts initially developed by June's team and which Novartis had joined as a co-developer in 2012, as mentioned.⁵⁹ Novartis applied for FDA approval to market its product in the US in March 2017. The next month the FDA announced that it would expedite its review under its 'breakthrough therapy' designation and in August 2017 approved Kymriah as a treatment for under-25 ALL patients.

The agency based its approval on trials conducted on 88 patients treated with Kymriah in the US, EU, Canada, Australia and Japan. 83% of the patients had complete remissions within three months and 63 of the 88 (71.5%) had survived without a relapse after six months.⁶⁰ A member of the FDA panel that had unanimously voted to approve the Novartis application praised its "high-quality data" and "thorough analyses" that showed "substantial and robust" benefit.⁶¹ He did point out however that the absence of a control group made it impossible to judge the contribution of the treatment to overall survival.

The FDA's approval letter required Novartis to follow the outcomes of at least 1,000 ALL patients for 15 years after their Kymriah treatments and report the results to the FDA by December 31, 2038. Clinics dispensing Kymriah would be specially certified. Certification would require training staff to recognize and manage cytokine storms and protocols to ensure immediate treatment. The FDA also concurrently expanded approved uses of IL-6 blocking anti-arthritis drugs to include treatment of CRS.⁶²

In October 2017, the FDA approved the marketing of a second CAR-T product, Yescarta, to treat diffuse large B-cell lymphoma (DLBCL) for adult patients who had relapsed or had not responded to existing treatments. It had been developed by Kite Pharma, which, as mentioned, had a collaboration agreement with the NCI. Yescarta's application to the FDA had been made in March 2017—the same month as Kymriah's application—and had also received a breakthrough therapy designation. Like Kymriah, Yescarta targeted CD19 molecules on cancer cells.⁶³

Yescarta's application reported the results of a two-year study in which the treatment had produced complete remissions in 51% of 111 patients. As in the Kymriah study, the Yescarta trial did not include a control group.⁶⁴

The FDA did not approve any new CAR-T products in 2018 and 2019, although, as in previous years, the agency continued to quickly approve clinical trials of such products. The FDA did however expand Kymriah's approved indications, authorizing Novartis to offer this treatment to adults with certain types of non-

Hodgkin lymphomas in May 2018. And in August 2018, the European Medicine Agency gave Novartis and Kite approvals for the leukemia and lymphoma treatments they had secured from the FDA.⁶⁵

Markets and Pricing. The FDA-approved indications covered an estimated 600 leukemia patients⁶⁶ and 7,500 lymphoma patients each year. Novartis would produce Kymriah (from patients' T cells) at a facility in New Jersey, charging cancer treatment centers \$475,000 for each patient—but would forgo payment for patients who did not respond after a month.⁶⁷ Kite would produce Yescarta in a California facility and charge \$373,000 per treatment (whether or not patients responded).⁶⁸

Clinical Refinements. As physicians gained experience in treating patients with CAR-T they became better at:

- 'Preparing' patients with chemotherapy. Physicians learned to improve the efficacy of treatments by administering chemotherapy to reduce the number of existing T cells. But this depletion did not have to be as extreme as in bone marrow transplants where the patient's existing immune system was entirely replaced. And less severe, more controlled depletion reduced the unpleasant side effects chemotherapy produces.⁶⁹
- Treatment with single doses, administered during one hospital stay. Initially CAR-Ts had been administered through a series of transfusions given over several days.
- Managing CAR-T cell peaks and persistence. As mentioned, CAR-T cells grow after they are infused, reach a peak, and then decline. Some persist after the decline to protect against relapses. Researchers discovered that persistence was very important in treating leukemia (ALL) but less so in non-Hodgkin lymphomas. In treating lymphoma, a high peak—a "bigger sledgehammer to put the cancer away" as one Canadian researcher, Kevin Hay put it—was more important. Physicians then experimented with ways to control peaks and persistence by, for instance, adjusting CAR-T doses and the pretreatment chemotherapy given to patients.⁷⁰
- Forestalling severe cytokine storms. Experience showed that severe CRS developed gradually—the sudden onset that occurred in the cases of Bill Ludwig and Emily Whitehead were unusual. And, intervention in a 'window' of mild CRS could prevent severe subsequent attacks. Experience also showed that the early use of steroids to prevent severe CRS did not reduce the efficacy of CAR-T treatments as had been initially feared.⁷¹

4. The Situation in 2019

Efficacy and Side Effects. Kymriah and Yescarta treatments had continued to produce the remission rates found in the trials that had secured them FDA approvals. Experience had further shown that leukemias did not recur in patients who showed complete remission and survived for a year. They could therefore be provisionally considered cured.⁷² However, survival rates of leukemia patients who did not respond to treatments, did not have complete remissions, or relapsed in less than a year, were found to be low. And remission rates in lymphoma patients were higher than in leukemia patients.⁷³

Research had further suggested that high rates of initial multiplication and the subsequent persistence of CAR-T cells alone did not prevent relapses. CAR-T cells could persist yet become exhausted and thus unable to effectively attack cancer cells.⁷⁴

Early intervention protocols had reduced but not eliminated cytokine storms and neurological problems. And patient-to-patient variations in their T cells and the extent of their cancers made predicting the timing and intensity of the side-effects difficult. Moreover, the mechanisms that triggered the side effects were not well understood. Experiments in laboratory mice for instance had suggested that CRS wasn't the simple result of CAR-T cell interactions with cancer cells producing a cascading release of cytokines.

CAR-T cell treatments continued to kill healthy B-cells along with cancer cells, reducing the production of antibodies that help prevent other diseases. In severe cases, patients were given transfusions of donated antibodies.

Researchers were experimenting with a variety of ways to increase efficacy and reduce side effects including:

- Standardization of T cell inputs to improve control of dosages and side-effects. As mentioned, the immune system includes many kinds of T cells, some with different functions. Making CAR-T cells from a better defined “cocktail” of natural T cells could help standardize treatments with more uniform efficacy and improved control of side effects.⁷⁵
- Administering drugs to prevent the onset of toxicities (rather than just early treatment of CRS symptoms.)⁷⁶
- Combinations with other cancer treatments. For instance, some trials had suggested that following CAR-T treatments with stem cell transplants could improve outcomes. But other studies had not shown much benefit from the follow-on treatments, and the transplantation procedure was itself a risky, complicated procedure.⁷⁷ Other experimental CAR-T combinations included immunotherapy drugs such as the mono-clonal antibody pembrolizumab.⁷⁸ (In 2018 the FDA had approved pembrolizumab to treat a wide range of cancers including B-cell lymphomas).⁷⁹
- Multiple Targets. Identifying more than one “target” molecule (instead of just CD19) could provide a more precise way to mark malignant cells and avoid damaging healthy cells.⁸⁰ Multiple targets could also reduce the problem of resistance— for instance, cancer cells escaping CD19 targeted attacks by not displaying the molecule on their surfaces.
- Safer and more effective CAR-T cells. Researchers were experimenting with different co-stimulatory molecules and sophisticated genetic modifications of natural T cells. When CAR-T cells had been first developed, introducing just one gene had been extremely challenging. New technologies had made inserting two or three genes straightforward and gene editing tools were widening the possibilities. Researchers were using these techniques to try to develop CAR-T cells that would be more persistent and less prone to “exhaustion.”⁸¹ They were also attempting to include suicide switches that could be activated by drugs to instruct the CAR-T cells to self-destruct if their toxicity seemed to be spiraling out of control.⁸²

Quality and Efficiency of Production

The FDA required, as with other prescription drugs, testing the purity and potency of every batch of CAR-T cells produced. But the distinctive nature of CAR-T cells made testing “challenging at best and perhaps impossible.”⁸³ Unlike traditional drugs (comprising small molecules or biomolecules) that can be chemically defined, CAR-T products included “thousands of proteins, lipids, nucleic acids, and other organic compounds” and “hundreds of millions or billions of cells” whose chemical compositions varied greatly from cell to cell.⁸⁴ This complexity made ‘purity’ difficult to define, let alone test.

Tests for potency—how effectively CAR-T cells produced would kill cancer when administered to patients—were also difficult to specify. The result of lab tests of batches produced appeared to have little correlation with their potency in patients. One possible reason was that the ‘descendants’ of infused CAR-T cells that had multiplied in the body did much of the killing of cancer cells.⁸⁵ Moreover, the descendants of only a few cells (or even just one cell) of the millions of cells in a dose given to a patient might provide most of the therapeutic effect of the treatment.⁸⁶

Consistent production of CAR-T cells even in sophisticated, highly controlled facilities was difficult: in June 2018 Novartis reported “variability” problems with Kymriah.⁸⁷ And high production costs could make CAR-T products unaffordable. Other new antibody drugs for cancer (see **Exhibit 4**) also required low-volume,

high-cost bioengineering. What made CAR-T production especially expensive was personalization – making doses for individual patients from their own blood.⁸⁸

Personalization also was slow. In 2017 Kite’s “state of the art” manufacturing and logistics for Yescarta took 17 days “vein-to-vein,” from the time blood was first taken from a patient to the time the CAR-T cells produced from the blood were reinfused. (Novartis reported 22 day vein-to-vein time for Kymriah that year).⁸⁹ But sick patients could die before their CAR-T cells reached them and the “time sensitive” manufacturing was encouraging investment in Information Technology to ensure “product efficacy and on-time manufacturing.”⁹⁰

Some researchers were attempting a radically different approach of developing treatments that used “off-the-shelf” rather than personalized CAR-T cells: this alternative would modify T cells from donors that could then be infused into any patient. Or the CAR-T cells could be directly grown out of stem cells in laboratory cultures. In either case, CAR-T cells could be produced in higher volumes and stored for the immediate treatment of many patients.

Off-the-shelf CAR-T cell treatments however posed the same kind of rejection and graft-versus-host problems that arise in bone marrow transplants: a CAR-T cell made from a donor’s T cells rather than the patient’s own T cells could be attacked by the patient’s immune system as a foreign intruder. Conversely, a CAR-T cell put into an ‘alien’ body could attack its host. Researchers were accordingly trying to genetically engineer ways to prevent 1) the CAR-T cells from recognizing anything besides its intended cancer target and 2) the host’s immune system from recognizing the “foreign” origins of infused CAR-T cells.⁹¹

In principle, this could be done through genetic modifications that produced CAR-T cells that 1) only had chimeric receptors designed to target cancer cells, whereas current CAR-T cells retained natural receptors that could potentially target healthy host cells and 2) didn’t have surface molecules that would reveal the CAR-T cell’s “foreign” origins. But, genetic manipulation that simultaneously produced chimeric receptors but blocked natural receptors and origin disclosing surface molecules had not been successfully done so far.⁹²

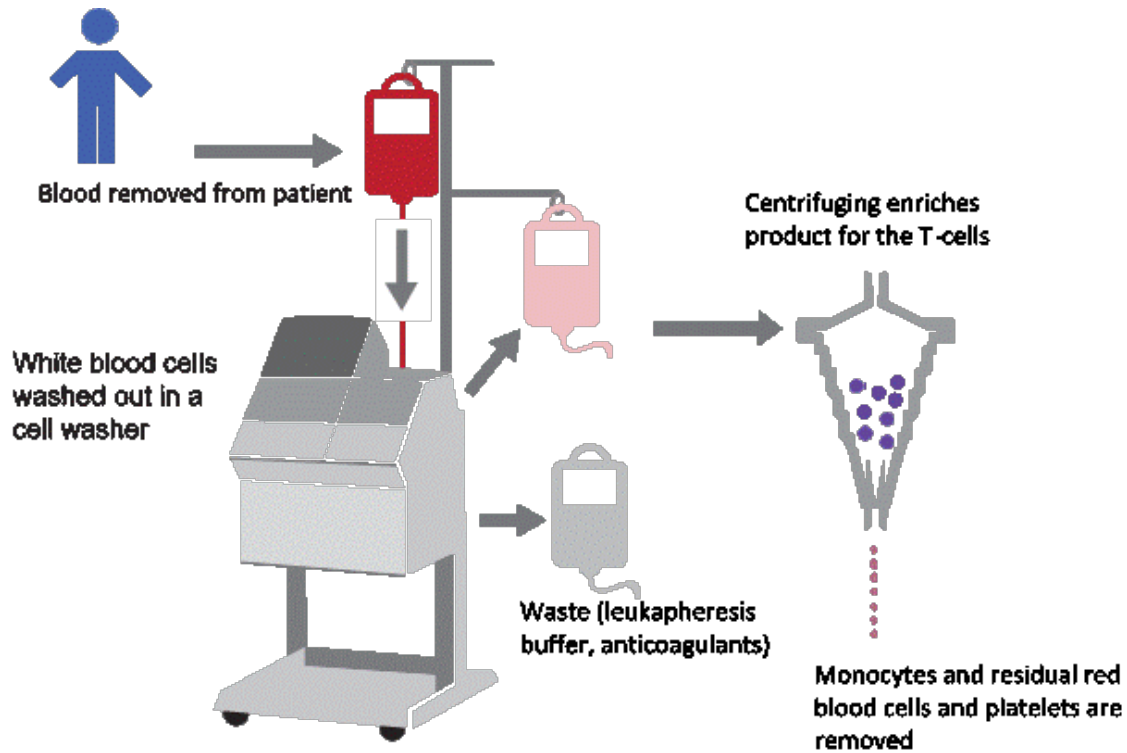
Treating Other Cancers. Identifying targets that did not produce “off-target” toxicity was a major barrier: a good target not only had to be recognizably present on the surface of a cancer cell; it also had to be absent from surfaces of normal cells that performed essential functions. And even the presence of even a few targets on essential cells could do great harm. For instance, an experimental CAR-T treatment for colon cancer had killed a patient because the colon cancer target chosen is also found in cells of the lung. But it was difficult to anticipate all possible off-target toxicities. Therefore ‘dose low, go slow’ had become the motto for trials done to screen for safety of new drugs.⁹³

Nonetheless by 2019, CAR-T treatments had been found to be effective (to varying degrees) for several blood cancers. Like Kymriah and Yescarta the treatments could also harm normal tissue (see **Exhibit 5**), but to an extent their developers hoped was acceptable.⁹⁴

Solid tumors (e.g. solid malignant masses forming in breast, colon, kidneys, liver and so on) had however resisted effective treatment. Solid tumors posed several problems. One was that their cancer cells were heterogenous making it difficult to identify a single effective target. Another problem was that tumors did not consist of just cancer cells but were surrounded by a “tumor environment” that included blood vessels and other cells. This tumor environment helped the cancer cells resist immune system attacks (by, for instance, activating “off switches” on T cells).⁹⁵

Sadelain and other pioneers were hopeful however that good targets could be found to attack solid tumors and that combining CAR-T with other immunotherapies could produce effective treatments.⁹⁶

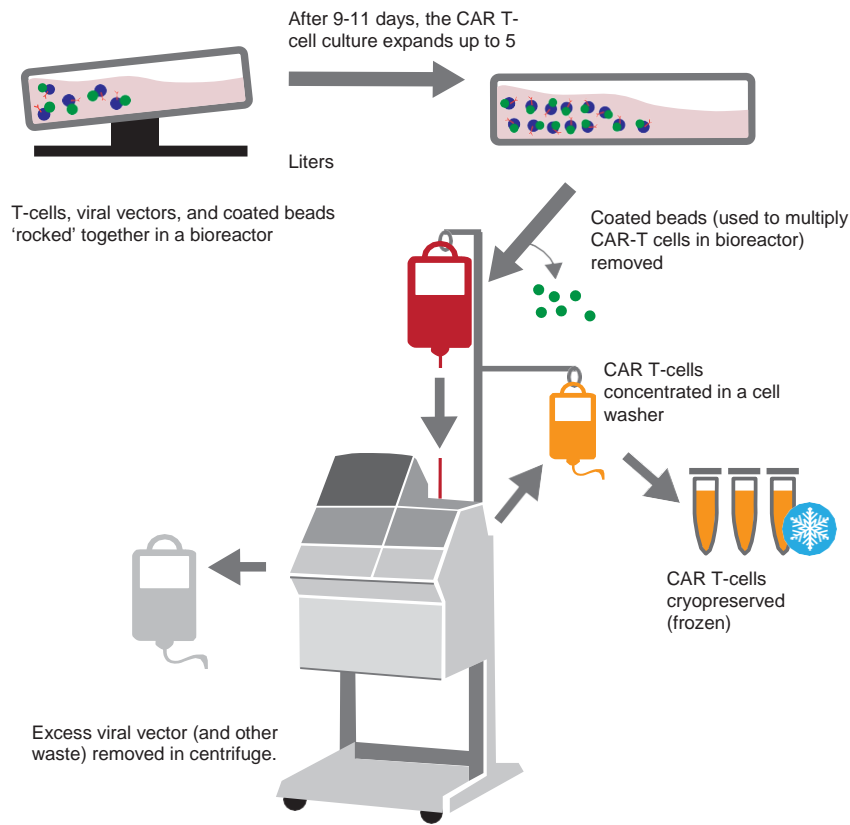
Exhibit 1 Leukapheresis to Isolate T Cells



Leukocytes (colloquially called white blood cells) are removed from the patient's blood via leukapheresis, using anticoagulants to prevent clotting. The anticoagulants are then washed out in a cell washer and the cells are concentrated and enriched in a centrifuge, which separates cells by size and density.

Source: Adapted from Bruce L. Levine, James Miskin, Keith Wonnacott, and Christopher Keir, "Global Manufacturing of CAR T Cell Therapy," *Molecular Therapy—Methods & Clinical Development*, Vol. 4, March 17, 2017, <http://dx.doi.org/10.1016/j.omtm.2016.12.006>, accessed June 2020, pp. 92-101.

Exhibit 2 Manufacturing CAR-T cells (by modification and multiplication of natural cells T cells secured through leukapheresis)



Source: Adapted from Bruce L. Levine, James Miskin, Keith Wonnacott, and Christopher Keir, "Global Manufacturing of CAR T Cell Therapy," *Molecular Therapy—Methods & Clinical Development*, Vol. 4, March 17, 2017, <http://dx.doi.org/10.1016/j.omtm.2016.12.006>, accessed June 2020, pp. 92-101.

Exhibit 3 The Development of Bone Marrow Transplants

Georges Mathé (1922 – 2010), a French oncologist and immunologist, performed the first successful bone marrow transplants on unrelated human beings in 1958: four out of five subjects who had accidentally been exposed to high radiation, survived. His group then used bone marrow transplants to treat leukemia patients. The transplants produced complete remissions for 5 to 9 months before all the patients died of infections or what would now be called ‘graft-versus-host disease’ (GVHD).

Around that time, E. Donnall Thomas, a physician scientist then based in Cooperstown, New York also transplanted bone marrow into leukemia patients with terminal malignancies. Again, none of the patients survived. Thomas then devoted the rest of his career to bone marrow transplantation at the ‘Hutch’ in Seattle and shared the 1990 Nobel Prize in Medicine for that work.

Progress was however difficult. Eighty-three of the first hundred leukemia patients given transplants by Thomas’s team at the Hutch died within the first several months. A review of 203 recorded transplants (including at the Hutch) attempted between 1939 and 1969 on patients with leukemia, genetic immunodeficiencies, anemia from radiation exposures, and other diseases showed that Thomas’s experience was usual.

During the 1970s Thomas and other researchers developed drugs and better donor matching to reduce graft rejections. They also refined chemotherapy and radiation treatments to eliminate existing cancer cells and immune cells that might resist grafts and supportive care to protect against infections while transplanted bone marrow cells were building new immune systems. They also learned that T cells that came along with donated bone marrow cells could kill cancer cells that that survived the patient’s ‘pretreatment’ with radiation and chemotherapy.

The number of transplants increased rapidly as bone marrow registries were created in the 1980s and 1990s and new methods were introduced to prevent GVHD by depleting the patient’s T cells. (The new methods turned out to have complications and limited effectiveness however).

The range of ‘indications’ for transplants continued to widen and by 2012, the year of Thomas’s death, about 65,000 of the procedures were performed world-wide and their cumulative number had exceeded a million transplants.

Source: Adapted from Michael C. Milone and Vijay G Bhoj. “The Pharmacology of T Cell Therapies.” *Molecular Therapy – Methods & Clinical Development*, vol. 8 210-221. January 31, 2018, <https://dx.doi.org/10.1016%2Fj.omtm.2018.01.010>; Siddhartha Mukherjee, “The Promise and Price of Cellular Therapies,” *The New Yorker*, Vol. XCV, Issue 20, July 15, 2019, ed. July 22, 2019, <https://www.newyorker.com/magazine/2019/07/22/the-promise-and-price-of-cellular-therapies>; Frederick R. Appelbaum, “E. Donnall Thomas (1920–2012),” *Science*, Vol. 338, Iss. 6111, November 30, 2012, <https://science.sciencemag.org/content/338/6111/1163.full?rss=1>; all accessed June 2020.

Exhibit 4 Monoclonal Antibody Treatments for Cancer

Besides CAR-T, several other immunotherapies, many based on ‘monoclonal’ antibodies, were being developed for cancer treatment. Some had already received FDA approvals. Others were in clinical or pre-clinical trials.

Like CAR-T cells, the monoclonal antibody drugs were bio-engineered “living cells”: they were typically made using recombinant techniques in cell cultures (unlike the natural antibodies produced inside the body by B-cells). However, unlike CAR-Ts, the monoclonal antibodies discussed below typically used “off-the-shelf” rather than “patient specific” cells. (The ‘Tumor Infiltrating Leukocyte’ treatments that the NCI’s Steven Rosenberg pioneered, also grow selected T cells of individual patients outside their bodies.)

Checkpoint Inhibitors

Antibody drugs called ‘check point inhibitors’ are based on Jim Allison’s 1995 discovery of a molecule called CTLA-4 that helped “brake” the activity of T cells. These and other such “checkpoint” molecules are present on the surface of T cells. When these molecules encounter matching counterparts on other cells, this activates a “brake” that stops T cells from attacking those cells (carrying the matching counterpart).

The braking can prevent accidental attacks on healthy cells. But activating the checkpoint brakes also protects cancer cells.

Allison’s laboratory experiments also showed that blocking CTLA-4 molecules released the checkpoint brakes, allowing T cells to continue their attacks on cancer cells.

This research led to the development of antibody drugs to release T cell brakes. The FDA approved the first such drug, ipilimumab, in 2011 as a treatment for advanced melanoma. The drug, made using recombinant techniques in Chinese hamster ovarian cell cultures, blocks the CTLA-4 molecule that Allison had discovered in 1995.

Two new antibody drugs (also made in ovarian cell cultures) followed the discovery of a second immune checkpoint molecule, PD-1, in 2000. The two drugs, pembrolizumab and nivolumab are used to treat several cancers, including melanoma, kidney cancer, bladder cancer, head and neck cancers, and non-Hodgkin’s lymphoma.

Bispecific T cell engagers (BiTEs)

BiTE antibodies help T cells find cancer-cells that don’t have distinguishing, well displayed surface molecules. BiTEs have two arms, like many natural antibodies. However unlike natural antibodies, BiTEs use only one of their arms to connect to a targeted surface molecule (that is not displayed well enough for a natural attack); the other arm of the BiTE connects to a T cell (that cannot recognize the targeted surface molecule on its own.) When both arms connect, this activates the T cell to start its attack.

The FDA approved the first BiTE antibody drug, Blincyto, in 2015 to treat ALL – two years before it approved the CAR-T drug, Kymriah, for this cancer. Blincyto, like Kymriah, targets CD19 molecules on cancer cells but through an arm of a bioengineered antibody, not the chimeric receptors’ genetically modified T cells. Additionally, unlike Kymriah, the BiTE antibody is an off-the-shelf drug; it has been shown to prolong the survival of ALL patients but not produce many sustained remissions of their cancers.

Other Therapeutic antibodies

Several other antibodies that interact with or block specific molecules have been developed to treat cancers. They can work in several different ways such as:

- Interfering with the growth of the cancer and alerting the immune system to destroy cancer cells to which the antibody is attached. Trastuzumab (Herceptin), which binds to HER2 (from 'human epidermal growth factor receptor 2') molecules which promote the development of certain aggressive types of breast cancer, is an example.

- Inducing cancer cells to commit suicide. Examples are rituximab (Rituxan®) and ofatumumab (Arzerra®), which target CD20 molecules on the surface of B cells.

- Delivering a toxic substance (such as a bacterial poison, a traditional drug molecule, or a radioactive compound) that kills cancer cells to which the antibody binds. Examples are Kadcyła® which is taken up by and kills cancer cells with HER2 on their surface, and Adcetris® which kills lymphoma cells with CD30 on their surface.

Source: "Immune Checkpoint Inhibitors," MD Anderson Cancer Center, 2020, <https://www.mdanderson.org/treatment-options/immune-checkpoint-inhibitors.html>; National Cancer Institute, "Biological Therapies for Cancer," April 26, 2018, <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet>; and C. H. Weaver, "BiTE – The Next Innovative Treatment in Lymphoma and Myeloma?," CancerConnect, September 13, 2019, updated December 2019, https://news.cancerconnect.com/treatment-care/bite-the-next-innovative-treatment-in-lymphoma-and-myeloma-l-Z3_QLXl06OkKo8xa_7rg; all accessed June 2020.

Exhibit 5 Antigen targeted in approved blood cancer treatments and trials and the normal cells and tissue they could potentially harm (“off-tumor targets”)

Antigen Targeted	Blood Cancer	Potential Normal Tissue Impacted
CD19	ALL, CLL, NHL, HL	Normal B cells
CD20	CLL, NHL	Normal B cells
CD22	ALL, NHL	Normal B cells
Ig _κ	CLL, NHL, myeloma	Normal B cells
ROR1	CLL, NHL	Pancreas, parathyroid, adipose cells
CD30	NHL, HL	Resting CD8 T cells
CD138	Myeloma	Precursor and plasma B cells, epithelia
CD123	AML	Bone marrow myeloid progenitors, B cells, mast cells, monocytes, macrophages, endothelial cells
NKG2D-L	AML, myeloma	Gastrointestinal lining, endothelial cells
BCMA	Myeloma	B cells
Lewis-Y carbohydrate antigen (CD174)	AML, myeloma	Early myeloid progenitor cells

Key: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen [also known as “tumor necrosis factor receptor”]; CAR, chimeric antigen receptor; CD, cluster designation; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; Ig_κ, immunoglobulin kappa light chain; NHL, non-Hodgkin’s lymphoma; NKG2D-L, natural killer group 2D-ligands; ROR 1, receptor tyrosine kinase-like orphan receptor 1

Source: Adapted from Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” 2019, https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS27_CART_Facts_2019_FINAL_Rev.1219.pdf, accessed June 2020, p. 3.

Endnotes

- ¹ National Cancer Institute, "Biological Therapies for Cancer," April 26, 2018, <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet>, accessed June 2020.
- ² Dana Farber, "Frequently Asked Questions About CAR T cell Therapy," Dana-Farber website, 2020, <https://www.dana-farber.org/cellular-therapies-program/car-T-cell-therapy/faq-about-car-T-cell-therapy/>, accessed March 2020.
- ³ "Ask a Biologist; B-Cells," Arizona State University School of Life Sciences, <https://askbiologist.asu.edu/b-cell>, accessed February 2020.
- ⁴ "Ask a Biologist; T cells," Arizona State University School of Life Sciences.
- ⁵ Gabriella Beer, "Science Surgery: 'Why doesn't the immune system attack cancer cells?'," Cancer Research UK website, February 28, 2019, <https://scienceblog.cancerresearchuk.org/2019/02/28/science-surgery-why-doesnt-the-immune-system-attack-cancer-cells/>, accessed February 2020.
- ⁶ Siddhartha Mukherjee, "The Promise and Price of Cellular Therapies," *The New Yorker*, Vol. XCV, Issue 20, July 15, 2019, ed. July 22, 2019, <https://www.newyorker.com/magazine/2019/07/22/the-promise-and-price-of-cellular-therapies>, accessed January 2020.
- ⁷ Cancer Research Institute, "What's Next in CAR T Cell Therapy with Dr. Michel Sadelain."
- ⁸ Kevin Hay, The Leukemia & Lymphoma Society of Canada, "New treatment horizon: Chimeric Antigen Receptor CAR T Cell Therapy," October 3, 2019, <https://www.youtube.com/watch?v=gmlLSeAXAmw&t=358s>, accessed June 2020.
- ⁹ Kevin Hay, The Leukemia & Lymphoma Society of Canada, "New treatment horizon."
- ¹⁰ Fewer antibodies may increase infections but this risk has not been recorded to any significant degree yet. Kevin Hay, The Leukemia & Lymphoma Society of Canada, "New treatment horizon."
- ¹¹ Kevin Hay, The Leukemia & Lymphoma Society of Canada, "New treatment horizon."
- ¹² Kevin Hay, The Leukemia & Lymphoma Society of Canada, "New treatment horizon."
- ¹³ The description is based on The Blood and Marrow Transplant Group of Georgia's webpage, "How Does CAR T-Cell Therapy Work?"
- ¹⁴ The Blood and Marrow Transplant Group of Georgia, "How Does CAR T-Cell Therapy Work?"
- ¹⁵ The Blood and Marrow Transplant Group of Georgia, "How Does CAR T-Cell Therapy Work?"
- ¹⁶ The Blood and Marrow Transplant Group of Georgia, "How Does CAR T-Cell Therapy Work?"
- ¹⁷ In the U.S., these include Memorial Sloan-Kettering Hospital in New York, the Fred Hutchinson Cancer Research Center in Seattle (the 'Hutch'), and, The Children's Hospital of Philadelphia (affiliated with University of Pennsylvania and often called the CHOP).
- ¹⁸ Cancer Research Institute, "What's Next in CAR T Cell Therapy with Dr. Michel Sadelain."
- ¹⁹ Amar Bhidé (2017): "Constraining Knowledge: Traditions and Rules that Limit Medical Innovation," *Critical Review* vol. 29, iss. 1, 2017, <http://dx.doi.org/10.1080/08913811.2017.1288464>, accessed June 2020, p. 14.
- ²⁰ Kelly Church, Bupe Mazimba, and Arkady Ho, "Helen Coley Nauts," (unpublished final paper by students at the Fletcher School submitted to Professor Bhidé), December 27, 2018.
- ²¹ Bhidé, "Constraining Knowledge," p. 14.
- ²² Bhidé, "Constraining Knowledge," p. 14.
- ²³ Editors of the Encyclopedia Britannica, "Bone marrow transplant," *Encyclopedia Britannica*, February 4, 2009, <https://www.britannica.com/science/bone-marrow-transplant>, accessed June 2020.
- ²⁴ Mukherjee, "The Promise and Price of Cellular Therapies."
- ²⁵ Mukherjee, "The Promise and Price of Cellular Therapies."
- ²⁶ American Cancer Society, "Stem Cell or Bone Marrow Transplant Side Effects," March 20, 2020, <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/stem-cell-transplant/transplant-side-effects.html>, accessed June 2020.
- ²⁷ Memorial Sloan Kettering Cancer Center, "CAR T Cells: Timeline of Progress," <https://www.mskcc.org/timeline/car-t-timeline-progress>, accessed June 2020.

-
- ²⁸ Bio-Rad Laboratories, "An Overview of B Cells – from Discovery to Therapy," 2016, <https://www.bio-rad-antibodies.com/static/2016/b-cell/minireview/an-overview-of-b-cells--from-discovery-to-therapy-mini-review.pdf>, accessed June 2020.
- ²⁹ Bio-Rad Laboratories, "An Overview of B Cells – from Discovery to Therapy."
- ³⁰ Memorial Sloan Kettering Cancer Center, "CAR T Cells: Timeline of Progress."
- ³¹ Jacques Miller, "The early work on the discovery of the function of the thymus, an interview with Jacques Miller," *Cell Death and Differentiation* 27, 396–401 (2020), <https://doi.org/10.1038/s41418-019-0462-y>, accessed June 2020.
- ³² Neil Canavan, *A Cure Within; Scientists Unleashing the Immune System to Kill Cancer*. New York: Cold Spring Harbor Laboratory Press, 2017.
- ³³ Canavan, *A Cure Within*.
- ³⁴ Canavan, *A Cure Within*.
- ³⁵ Canavan, *A Cure Within*, pp. 109-116.
- ³⁶ Memorial Sloan Kettering Cancer Center, "CAR T Cells: Timeline of Progress."
- ³⁷ Memorial Sloan Kettering Cancer Center, "CAR T Cells: Timeline of Progress."
- ³⁸ Canavan, *A Cure Within*.
- ³⁹ Memorial Sloan Kettering Cancer Center, "CAR T Cells: Timeline of Progress."
- ⁴⁰ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁴¹ Canavan, *A Cure Within*.
- ⁴² Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁴³ Canavan, *A Cure Within*, pp. 134-135.
- ⁴⁴ Canavan, *A Cure Within*.
- ⁴⁵ Canavan, *A Cure Within*.
- ⁴⁶ Canavan, *A Cure Within*.
- ⁴⁷ Jakub Svoboda, "The Early Chimeric Antigen Receptor (CAR) T-cell Experience From An Academic Perspective," PowerPoint presentation, February 28, 2018, Cancer Drug Development Forum, Innsbruck, Austria.
- ⁴⁸ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁴⁹ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁵⁰ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁵¹ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁵² Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁵³ Mukherjee, "The Promise and Price of Cellular Therapies."
- ⁵⁴ Canavan, *A Cure Within*, p. 169.
- ⁵⁵ Canavan, *A Cure Within*, p. 166.
- ⁵⁶ Christoph Oldenburg, Markus Thunecke, and John Herrmann, "CAR-T; Looking beyond the hype," *Drug Discovery World* (Winter 2015/2016), p. 10.
- ⁵⁷ Oldenburg, Thunecke, and Herrmann, "CAR-T; Looking beyond the hype," p. 11.
- ⁵⁸ Oldenburg, Thunecke, and Herrmann, "CAR-T; Looking beyond the hype," p. 11.
- ⁵⁹ Oldenburg, Thunecke, and Herrmann, "CAR-T; Looking beyond the hype," p. 10.
- ⁶⁰ Verdict Media Ltd., "Kymriah (tisagenlecleucel) for the Treatment of Acute Lymphoblastic Leukaemia," Clinical Trials Arena, <https://www.clinicaltrialsarena.com/projects/kymriah-tisagenlecleucel-for-the-treatment-of-acute-lymphoblastic-leukaemia/>, accessed June 2020.
- ⁶¹ "FDA Approves First CAR-T Gene Therapy Treatment," September 1, 2017, FDA Week, Vol. 23, No. 35, via Factiva, accessed June 2020.

-
- ⁶² “FDA Approves First CAR-T Gene Therapy Treatment,” September 1, 2017, FDA Week, Vol. 23, No. 35, via Factiva, accessed June 2020.
- ⁶³ Gilead, “Kite’s Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA for the Treatment of Adult Patients With Relapsed or Refractory Large B-Cell Lymphoma After Two or More Lines of Systemic Therapy,” (press release), October 18, 2017, <https://www.gilead.com/news-and-press/press-room/press-releases/2017/10/kites-yescarta-axicabtagene-ciloleucel-becomes-first-car-t-therapy-approved-by-the-fda-for-the-treatment-of-adult-patients-with-relapsed-or-refrac>, accessed June 2020.
- ⁶⁴ Gilead, “Kite’s Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA.”
- ⁶⁵ Gilead, “Kite’s Yescarta™. (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA”
- ⁶⁶ John Wilkerson, “CMS May Test Drug-Pay Schemes Similar To Kymriah’s Outcomes-Based Arrangement,” August 30, 2017, <https://insidehealthpolicy.com/inside-cms/cms-may-test-drug-pay-schemes-similar-kymriahs-outcomes-based-arrangement>, accessed June 2020.
- ⁶⁷ Wilkerson, “CMS May Test Drug-Pay Schemes Similar To Kymriah’s Outcomes-Based Arrangement.”
- ⁶⁸ Gilead, “Kite’s Yescarta™ (Axicabtagene Ciloleucel) Becomes First CAR T Therapy Approved by the FDA.”
- ⁶⁹ Kevin Hay, The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷⁰ Kevin Hay, The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷¹ Kevin Hay, The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷² Kevin Hay, The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷³ Kevin Hay, The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷⁴ Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain.”
- ⁷⁵ Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” 2019, https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS27_CART_Facts_2019_FINAL_Rev.1219.pdf, accessed June 2020, p. 7.
- ⁷⁶ Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” p. 7.
- ⁷⁷ The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”
- ⁷⁸ Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” p. 7.
- ⁷⁹ U.S. Food and Drug Administration, “FDA approves pembrolizumab for treatment of relapsed or refractory PMBCL,” June 13, 2018, <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-treatment-relapsed-or-refractory-pmbcl>, accessed June 2020.
- ⁸⁰ Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” p. 7.
- ⁸¹ Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain.”
- ⁸² Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” p. 7.
- ⁸³ Michael C. Milone and Vijay G. Bhoj. “The Pharmacology of T Cell Therapies.” *Molecular Therapy – Methods & Clinical Development*, vol. 8 210-221. January 31, 2018, <https://dx.doi.org/10.1016%2Fj.omtm.2018.01.010>, accessed June 2020.
- ⁸⁴ Milone and Bhoj, “The Pharmacology of T Cell Therapies.”
- ⁸⁵ Milone and Bhoj, “The Pharmacology of T Cell Therapies.”
- ⁸⁶ Milone and Bhoj, “The Pharmacology of T Cell Therapies.”
- ⁸⁷ Flora Southey, “CAR-T concerns for Novartis as Kymriah identified out of spec,” BioPharma-Reporter.com, July 25, 2018, <https://www.biopharma-reporter.com/Article/2018/07/25/CAR-T-concerns-for-Novartis-as-Kymriah-identified-out-of-spec>, accessed June 2020.
- ⁸⁸ Mukherjee, “The Promise and Price of Cellular Therapies.”
- ⁸⁹ Richard Staines, “Gilead gains CAR-T approval, undercuts rival’s headline price,” pharmaphorum, October 19, 2017, <https://pharmaphorum.com/news/fda-approves-gilead-car-t-cancer-therapy/>, accessed June 2020.
- ⁹⁰ Global Transformational Health Research Team at Frost & Sullivan, “Growth Opportunities in the Global Cell Therapy Market, Forecast to 2025,” Frost & Sullivan, October 2018.
- ⁹¹ Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain.”

⁹² Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain,” and The Leukemia & Lymphoma Society of Canada, “New treatment horizon.”

⁹³ Oldenburg, Thunecke, and Herrmann, “CAR-T; Looking beyond the hype,” p. 12.

⁹⁴ Leukemia & Lymphoma Society, “Chimeric Antigen Receptor (CAR) T-Cell Therapy,” p. 3.

⁹⁵ Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain.”

⁹⁶ Cancer Research Institute, “What’s Next in CAR T Cell Therapy with Dr. Michel Sadelain.”