

Working Paper 21-035

Case Histories of Transformational Advances

# Chimeric Antigen Receptor T-Cell Therapy – Living Drugs

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*CASE HISTORIES OF TRANSFORMATIONAL ADVANCES*

## **Chimeric Antigen Receptor T-Cell Therapy – Living Drugs**

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**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) the development of CAR-T therapy, and 4) the situation in 2019.

**Acknowledgments:** We thank Sarah Gulick for valuable research, writing, and editorial assistance.

## Chimeric Antigen Receptor T-Cell Therapy – Living Drugs

Using the body's natural ability to fight disease was a basic principle of ancient Hippocratic medicine. In recent decades, this approach, called 'immunotherapy' or 'immuno-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.<sup>1</sup>

In 2017, the US Food and Drug Administration (FDA) approved an immunotherapeutic treatment, , for two kinds of blood cancers – acute lymphoblastic leukemia (ALL) and large B-cell lymphoma.<sup>2</sup> The therapy, often called CAR-T therapy, genetically modifies the T cells of patients to create cells with "chimeric antigen receptors" capable of attacking cancer cells that normal T cells cannot kill.

This case history summarizes 1) how CAR-T therapies (are believed to) work; 2) foundational advances and discoveries (through the 1980s); 3) the development of CAR-T therapy (during and after the 1990s); and 4) prospects for the 2020s. (Some readers might prefer to skim the first section and return to it after reading the second section).

### 1. How CAR-T Therapies Work (beliefs and conjectures in 2019)

*Natural 'B' and 'T' cells.* Before describing the role of genetically engineered CAR-T cells, it will be helpful to briefly review the functions – and limitations -- of natural immune system cells.

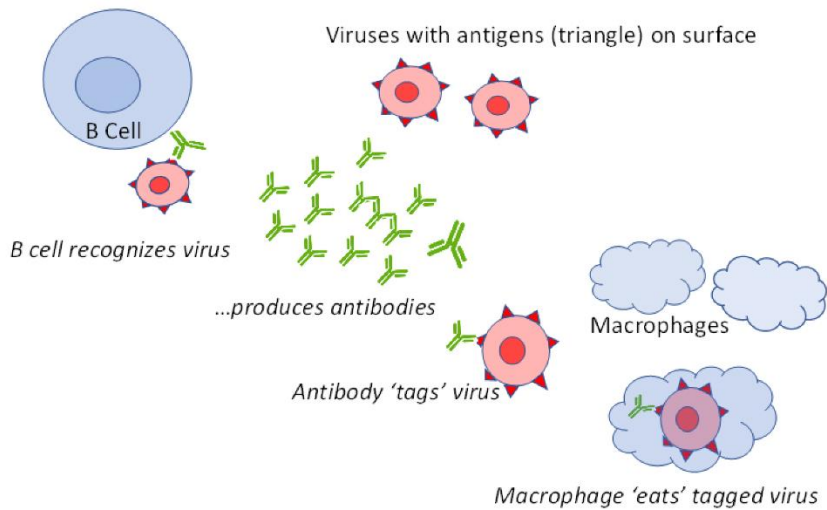
Simplifying greatly, the immune system includes many kinds of cells that provide two types of immunity: 'innate' and 'adaptive.' Cells that can attack any intruding virus, bacteria, or other pathogen provide 'innate' immunity. If this innate, general-purpose immunity fails, an 'adaptive' response emerges to eliminate specific disease-causing viruses, bacteria, and other pathogens. Notably, and again simplifying greatly, the adaptive response includes producing B cells (that help attack 'free-floating' pathogens) and 'killer' T-cells (that eliminate cells already 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.<sup>3</sup> ('Neutralizing' antibodies can also directly disable pathogens).

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This case history does not present original research or new thesis. Instead, it summarizes historical developments and includes questions to stimulate reflection and discussion.

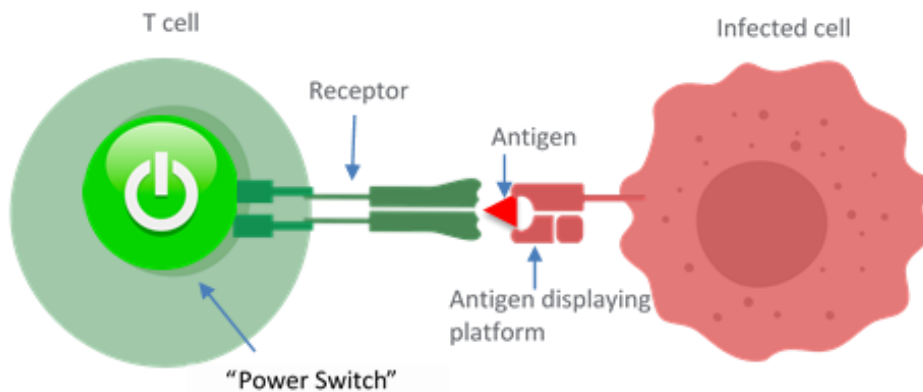
**Figure 1** How B cells Eliminate Free-floating viruses (and other pathogens)



Note: Antibody production also requires activation of B cells by 'helper' T cells (not shown above).

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.<sup>4</sup>

**Figure 2** How T-cell Receptors Activate Attacks on Infected Cells



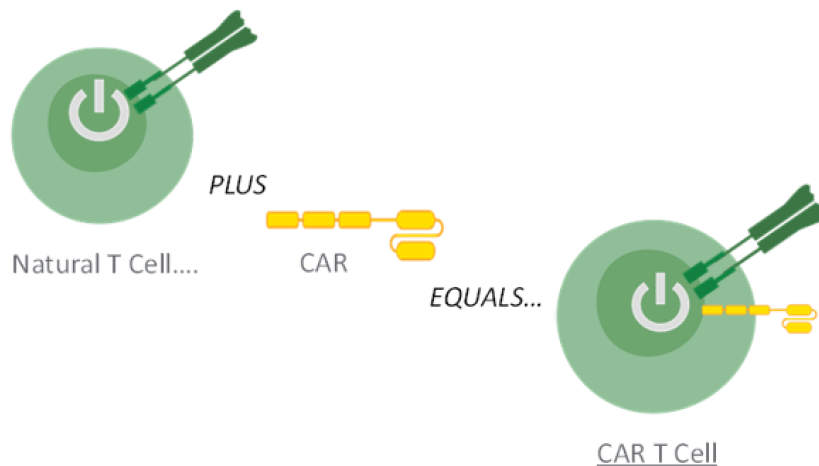
Source: Cancer Research Institute.

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. (This matching of B cells, antibodies, and T-cell receptors to distinctive antigens emerges from a Darwinian, ‘adaptive’ process of trial and error, not through purposeful design.)

**Limitations Against Cancer Cells.** T cells can eliminate cells that develop abnormalities for several 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 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.<sup>5</sup>

**Advantages of ‘Chimeric’ Receptors.** Inserting an artificial gene into the DNA of natural T cells can help 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. Like a natural T cell receptor, the chimeric receptor has a prong protruding from its surface that can recognize and attach to a distinctive target on the surface of a cancer cell.<sup>6</sup> (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 prevent the adaptive immune system from naturally selecting CD19 as targets for eliminating cancer cells even if the molecules were suitably displayed.)

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 or degraded.)<sup>7</sup>

As the CAR-T cell attacks kill cancer cells, the CAR-T cells stop multiplying, and their numbers decline. Some CAR-T cells can remain ('persist') in the body, ready to respond should the cancer (with CD19 targets) recur.<sup>8</sup>

**Side Effects.** Currently approved treatments (as of 2019) modify and multiply the patients' own T cells, as shown in Exhibits 1 and 2. This avoids the rejection problems that arise with transplants of donated organs or tissue when the immune system attacks 'alien' intruders. Nonetheless, immune systems can overreact to CAR-T cells made from the patient's own T cells. Notably, when infused CAR-T cells connect with CD19 molecules on blood cancer cells, they trigger the release of cytokine molecules. The cytokine molecules activate other immune system cells, but the immune response activated by the cytokines can itself trigger the cascading release of more cytokines. Mild forms of this cytokine release syndrome (CRS) produce flu-like symptoms. More severe "cytokine storms" have life-threatening effects.

And as mentioned, CAR-T cells kill normal B cells along with cancer cells. When the CAR-T cells then themselves decline, B cells usually return.<sup>9</sup> However, some patients suffer from prolonged B cell depletion and thus a reduced capacity to resist infections.<sup>10</sup>

**Questions (for reflection and discussion):**

Before reading further, please write down (in fewer than ten words) what (as of 2019) you would expect to most increase or limit the use of CAR-T treatments in the future.

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## 2. Foundational Advances (1890s-1980s)

**Coley's Toxins.** The origins of CAR-T and other kinds of immuno-oncology go back to the early 1890s. Dr. William Coley, then attending surgeon at New York's Memorial Hospital (later Memorial Sloan Kettering), noticed that some cancer patients who contracted acute bacterial infections experienced spontaneous remissions. Acting on a hunch, Dr. Coley first applied bacteria to a patient with an inoperable tumor to induce a "virulent infection." When the patient recovered completely, Dr. Coley developed a mixture, known as "Coley's mixed bacterial toxins," to treat cancer patients.<sup>11</sup>

But because of inconsistent, difficult-to-reproduce results, the toxins were dismissed as bogus and later 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 US 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.<sup>12</sup>

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's 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.<sup>13</sup> Dr. Old, who also chaired 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."<sup>14</sup>

**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, usually from a well-matched donor, are then transfused to rebuild the patient's bone marrow.<sup>15</sup> 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 cancer cells that might have survived the initial pre-transplant chemotherapy.<sup>16</sup>

Developing the treatment, which started in the 1950s, was difficult (see **Exhibit 3**), and the treatment continues to have severe side effects.<sup>17</sup> These may arise from the chemotherapy given before the transplant, from the rejection of donated bone marrow cells, or conversely from graft-versus-host attacks by new immune cells (that treat the patient's existing cells as intruders). The effectiveness of the treatment remains hit or miss. Bone marrow transplants for cancer patients, therefore, typically follow other failed treatments.<sup>18</sup>

**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.<sup>19</sup> 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 discovered that antibodies, which they called antitoxins, helped provide immunity against diphtheria and tetanus.<sup>20</sup> Then, in the late 1940s and 1950s, researchers identified cells produced in the bone marrow (hence 'B'-cells) as the source of antibodies.<sup>21</sup>

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.<sup>22</sup> Two years later, Miller and Graham Mitchell specified an important feature of this role: 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 identified several types of T cells performing different immunological functions.<sup>23</sup>



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. Much was already known about B-cell receptors, and most scientists were using that as a template for researching T-cell receptors. Mak proceeded on the assumption that T-cell receptors had completely different structures. Mak's discovery, made with the help of recently developed genetic technologies, provided a foundation for cloning the genes of T-cell receptors—and thus synthesizing chimeric T-cell receptors.<sup>24</sup>

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 (the 'Hutch') in Seattle, accidentally discovered that the CD28 molecule was an activating switch for T cells. A T cell receptor-antigen connection alone did not effectively kill unwanted cells. 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).<sup>25</sup>

**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 HIV viruses (that caused AIDS) and whose own genetic structures were progressively better mapped in the 1980s. Although deactivated, HIV viruses could still enter cells to insert new genes.<sup>26</sup> 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.<sup>27</sup>

**Questions (for reflection and discussion):**

Before reading further, please write down (in less than ten words) what you found most significant or surprising about CAR-T's foundational advances. (Be prepared to explain how this compares to the foundational advances of other transformational case histories you have read about).

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Also, think about what might limit the use of these advances in cancer treatments.

### 3. Development of CAR-T therapies (during and after the 1990s)

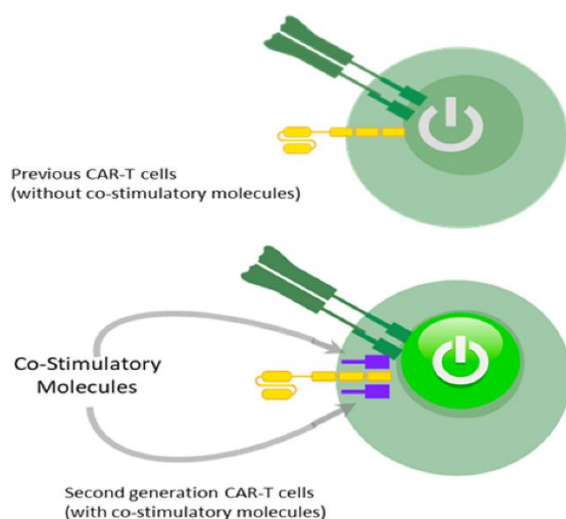
**T-bodies.** In the late 1980s, immunologist Zelig Eshhar and his colleagues at the Weizmann Institute in Israel used genetic manipulation to create what Eshhar called a 'T-body.' The T-body had molecules from antibodies mounted on the receptors of T cells.<sup>28</sup> In principle, the antibody part would help the receptor recognize and attach to the antigen of a cancer cell. The attachment was then expected, in the usual course, to stimulate the killing of cancer cells.

Laboratory experiments showed that 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.<sup>29</sup>

**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 of Technology had included improved ways of inserting genes to modify the genetic blueprints of T cells, created chimeric receptors with CD28 molecules.<sup>30</sup> 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 Co-stimulatory Molecules



Source: Cancer Research Institute.

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 but also instruct the CAR-T cell to multiply and get help from other immune system cells.<sup>31</sup>

**Selecting Target Antigens.** Whereas natural T-cell receptors for target antigens emerge through a blind Darwinian process of trial and error, developers of CAR-T cells chose 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.<sup>32</sup>

Other researchers developing CAR-T cells (using Sadelain’s co-stimulatory molecule design) chose the same CD19 target. These included teams at the Children’s Hospital of Philadelphia (CHOP), the Seattle ‘Hutch,’ and the National Cancer Institute (NCI) 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).<sup>33</sup>

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.

A surgeon-oncologist, Steven Rosenberg, led the NCI team.<sup>34</sup> 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 treat melanomas.<sup>35</sup> (Rosenberg’s pathbreaking approach of extracting, growing, and reinfusing T cells that had somehow entered solid cancer tumors would provide the basis for Tumor Infiltrating Leukocyte, or ‘TIL,’ treatments.)

**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 to build a dedicated facility for the therapy.

Skepticism about CAR-T limited funding,<sup>36</sup> 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.”<sup>37</sup> June was however able to raise funds from a philanthropic Penn alum, and his team applied to start human trials in 2006.<sup>38</sup> The trial was approved in 2009 and enrolled three patients in 2010. In 2011, no patients were treated because of the lack of funds.<sup>39</sup>

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.<sup>40</sup> Although traditional treatments for such cancers are usually effective, patients who do not respond or relapse have low life expectancy. With these nearly hopeless cases researchers did not 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 infection—although they could find no signs of a virus or bacteria—put Ludwig in the hospital’s Intensive Care Unit.<sup>41</sup>

After a week, Ludwig’s condition dramatically improved on its own. His tumor masses had disappeared during that week, and a biopsy done after another twenty days found no cancer cells.<sup>42</sup>

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 the syndrome was a common side effect of CAR-T treatments (as mentioned in the first section of this Note).<sup>43</sup>

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 and put into an induced coma.<sup>44</sup>

Previous 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 for 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 complete remission of Emily's cancer.<sup>45</sup> The IL-6-blocking drug then became a standard of care for severe CRS.<sup>46</sup>

**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 the number of patients enrolled in the trials was small, the treatment had worked "beyond anyone's expectations."<sup>47</sup>

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).<sup>48</sup>

"With that deal, the field exploded," according to *Drug Discovery World*.<sup>49</sup> In 2012, 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."<sup>50</sup>

**Approved Treatments.** Kymriah was the first CAR-T treatment approved by the FDA. It was based on CAR-Ts initially developed by June's team, which Novartis had joined as a co-developer in 2012, as mentioned.<sup>51</sup> Novartis applied for FDA approval to market the product in the US in March 2017. The next month, the FDA announced that it would expedite its review under its 'breakthrough therapy' designation. In August 2017, it approved Kymriah as a treatment for young (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.<sup>52</sup> 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" benefits.<sup>53</sup> 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.<sup>54</sup>

In October 2017, the FDA approved 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.<sup>55</sup>

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.<sup>56</sup>

The FDA did not approve any new CAR-T products in 2018 and 2019, although, as in previous years, the agency quickly approved 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. In August 2018, the European Medicine Agency gave Novartis and Kite Pharma approvals for the leukemia and lymphoma treatments they had secured from the FDA.<sup>57</sup>

**Specialized Treatments Centers.** The FDA approvals of Novartis's Kymriah and Kite's Yescarta did not significantly affect treatments offered by major cancer centers (such as Bethesda's NCI, New York's Memorial Sloan-Kettering, Philadelphia's CHOP, and Seattle's 'Hutch') that had undertaken CAR-T trials and research. These centers had already invested in CAR-T cell production facilities that the FDA already regulated and monitored. The FDA approvals of Kymriah and Yescarta did, however, allow smaller centers to outsource CAR-T cell production to (FDA-certified and supervised) facilities operated by Novartis and Kite. Now, the smaller centers could focus on:<sup>58</sup>

- *Screening patients for 'fit' with the conditions ('indications') for which the treatment had been approved by the FDA.*
- *Collecting T-cells.* Blood was taken from the patient's body and processed to remove T-cells. (See **Exhibit 1**). Centers would then send the T-cells to Novartis's facility in New Jersey or Kite Pharma's facility in California, where they would be genetically modified and multiplied.<sup>59</sup> (After enough CAR-T cells had been produced, frozen CAR-T cells were returned to their originating treatment centers.)
- *Infusing CAR-T cells.* Patients were first administered chemotherapy and other medications to prepare them for CAR-T cell infusion. The CAR-T cells were then infused after thawing into patients' veins.<sup>60</sup>

The FDA regulated the administration of CAR-T treatments (in integrated or specialized centers) and not just the production of CAR-T cells. As mentioned, the FDA was particularly concerned about the

safety and side effects of administration, and FDA-certified treatment centers typically included several specialized professionals such as dialysis nurses to draw the patient’s blood, oncology nurses to infuse CAR-T cells, pharmacists for pretreatment drugs and control of post-treatment side effects, critical care teams standing by during CAR-T infusions, ready to step in if side effects were severe, and neurologists, to treat neurological side effects.<sup>61</sup>

**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 of pretreatment chemotherapy.<sup>62</sup>
- Treatment with single doses, administered during one hospital stay. Initially, CAR-Ts were administered through a series of transfusions 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 pretreatment chemotherapy.<sup>63</sup>
- Forestalling severe cytokine storms. Experience showed that severe CRS developed gradually – the sudden onset in the cases of Bill Ludwig and Emily Whitehead was 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.<sup>64</sup>

**Questions (for reflection and discussion):**

Please write (in less than ten words) what you found most similar or different in the development of CAR-T treatments (compared to other transformational advances you have read about.)

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## Prospects for the 2020s

***Efficacy and Side Effects.*** Kymriah and Yescarta treatments continued to produce the remission rates found in the trials that had secured their FDA approvals. Experience further showed that leukemias did not recur in patients who showed complete remission and survived for a year. They could, therefore, be provisionally considered cured.<sup>65</sup> 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 lower than in leukemia patients.<sup>66</sup>

Research 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 attack cancer cells effectively.<sup>67</sup>

Early intervention protocols had reduced but not eliminated the side effects. About 70% of patients continued to experience flu-like symptoms (such as nausea, fatigue, headaches, chills, and fevers<sup>68</sup>) from mild forms of the cytokine release syndrome.<sup>69</sup> Between 7% to 25% experienced more severe cytokine storms (that could produce sharp drops in blood pressure, heart attacks, and the failure of vital organs such as the kidneys.). Similarly, about 40% of patients experienced neurological problems (such as confusion, delirium, involuntary muscle twitching, hallucinations, or seizures), which could be severe in 10% to 30% of patients.<sup>70</sup>

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 CRS and neurological problems 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 several ways to increase efficacy and reduce side effects, including:

- Standardization of T cell inputs. 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 better controlled side effects.<sup>71</sup>
- Administering drugs to prevent toxicities (rather than just early treatment of CRS symptoms.)<sup>72</sup>
- Combinations with other cancer treatments. Some trials suggested that following CAR-T treatments with stem cell transplants could improve outcomes. But other studies had not shown much benefit, and transplanting stem cells was risky and complicated.<sup>73</sup> Other experimental CAR-T combinations included immunotherapy drugs such as the monoclonal antibody

pembrolizumab.<sup>74</sup> (In 2018, the FDA approved pembrolizumab to treat several cancers, including B cell lymphomas).<sup>75</sup>

- **Multiple Targets.** Identifying more than one “target” molecule (instead of just CD19) could provide a more precise way to attack malignant cells and avoid damaging healthy cells.<sup>76</sup> 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 genetic modifications of natural T cells. When CAR-T cells had been first developed, introducing just one gene was 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.”<sup>77</sup> 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.<sup>78</sup>

**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.”<sup>79</sup> 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.<sup>80</sup> 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 results 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.<sup>81</sup> 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.<sup>82</sup>

Consistent production of CAR-T cells, even in sophisticated, highly controlled facilities, was difficult: in June 2018, Novartis reported “variability” problems with Kymriah.<sup>83</sup> And, high production costs made CAR-T treatments expensive. 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.<sup>84</sup>

(Novartis charged cancer treatment centers \$475,000 per patient –but would forgo payment for patients who did not respond after a month.<sup>85</sup> Kite charged \$373,000 for each Yescarta treatment -- whether or not patients responded.<sup>86</sup>)

Personalization also was slow. In 2017, Kite’s “state of the art” manufacturing and logistics for Yescarta took 17 days “vein-to-vein,” from when blood was first taken from a patient to when the CAR-T cells produced from the blood were reinfused. (Novartis reported a 22-day vein-to-vein time for Kymriah that year).<sup>87</sup> 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.”<sup>88</sup>

Some researchers were taking a radically different approach. They were attempting 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 grown directly 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.

CAR-T cells (made from donated T-cells) could, however, attack patients’ healthy cells as if they were ‘alien’ cells. Conversely, patient’s immune systems could reject CAR-T cells made from a donor’s ‘alien’ T cells. Researchers were accordingly trying to genetically engineer ways to 1) limit CAR-T cell attacks to their intended cancer targets and 2) prevent patients’ immune systems from treating infused CAR-T cells as ‘aliens.’<sup>89</sup>

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) did not have surface molecules that would reveal the CAR-T cell’s ‘alien’ origins. But, such genetic modifications had not been successful (as of 2019).<sup>90</sup>

***Treating Other Cancers.*** FDA-approved indications (as of 2019) covered an estimated 600 leukemia patients<sup>91</sup> and 7,500 lymphoma patients each year. Treating other cancers would increase the use of CAR-T therapies, but identifying targets that did not produce “off-target” toxicity was a major barrier: a 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 the presence of even a few targets on essential cells could do great harm. For instance, an experimental CAR-T treatment for colon cancer killed a patient because the colon cancer target chosen was 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 experimental treatments.<sup>92</sup>

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.<sup>93</sup>

Solid tumors (in breasts, colons, kidneys, livers, and so on), however, resisted effective treatment. Cancer cells in solid tumors are heterogeneous, making it difficult to identify a single effective target. Tumors are also surrounded by a “tumor environment” that includes blood vessels and other cells. This environment helps the cancer cells resist immune system attacks (by, for instance, activating “off switches” on T cells).<sup>94</sup>

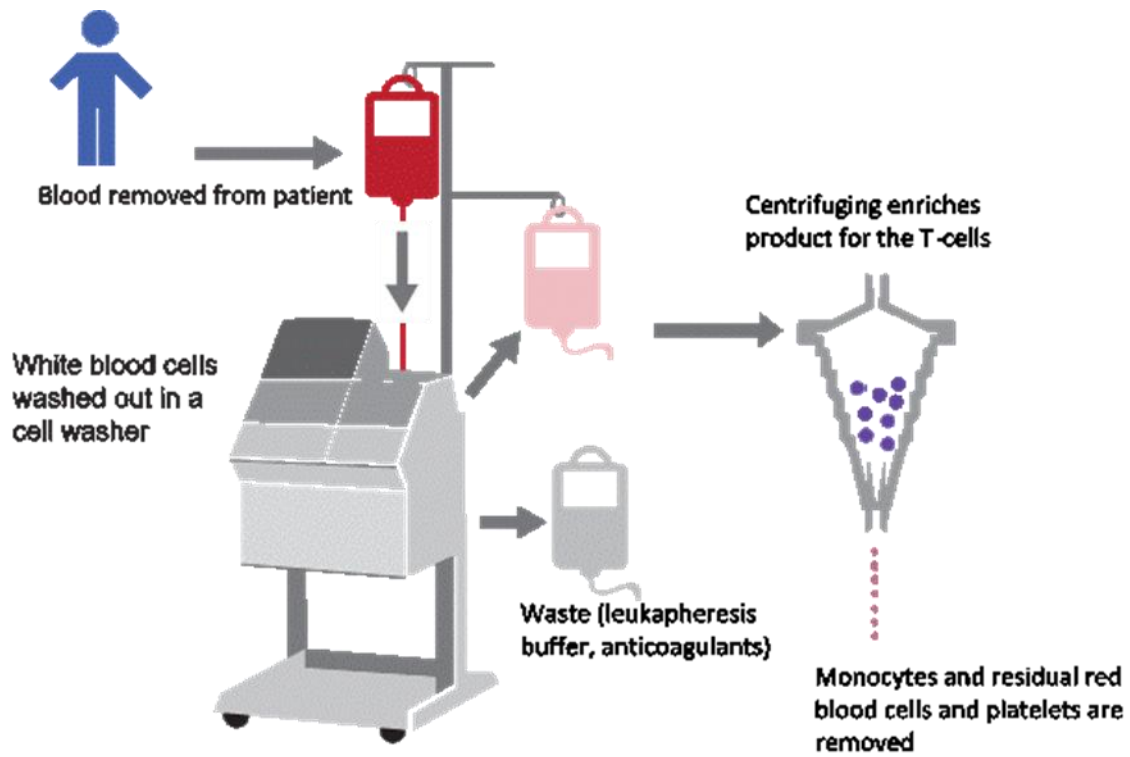
Sadelain and other pioneers were hopeful, however, that good targets could be found to attack solid tumors and that combining CAR-T with other immunotherapies could produce effective treatments.<sup>95</sup>

**Questions (for Reflection and Discussion):**

Based on this history (and its exhibits) and other histories you previously read, what initiatives undertaken in 2019- if any - could make CAR-T a more commonly used treatment by 2029? (in 10 words or less)

- \_\_\_\_\_

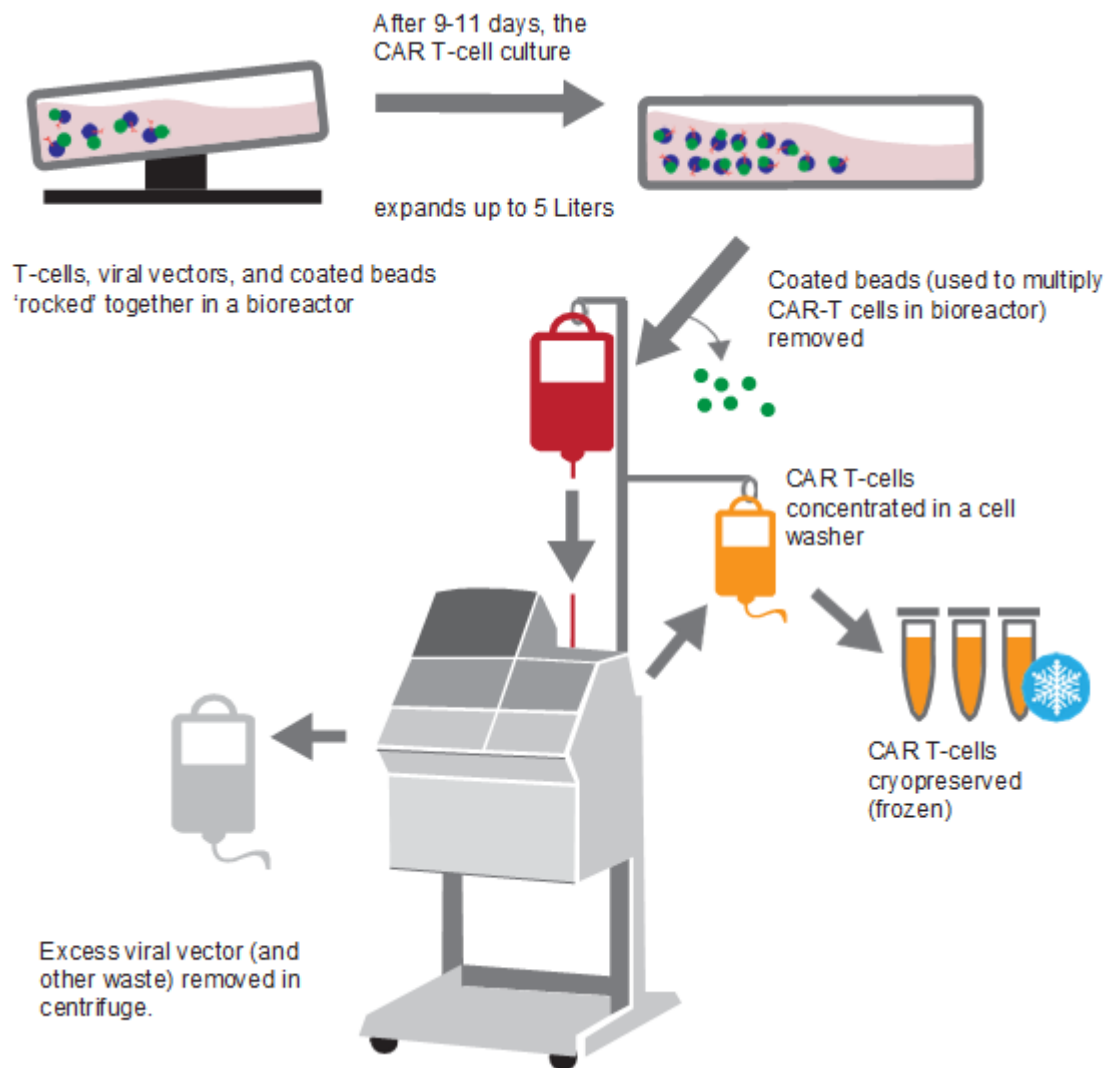
**Exhibit 1** Leukapheresis to Isolate T Cells



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: 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 (from natural cells T cells secured through leukapheresis)



Source: 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-researcher 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 transplants 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 had 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 worldwide, and their cumulative number had exceeded a million transplants.

Sources: 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>; accessed June 2020.

#### **Exhibit 4** 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, 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 grew selected T cells of individual patients outside their bodies.)

#### **Checkpoint Inhibitors**

Antibody drugs called ‘checkpoint inhibitors’ were 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 encountered matching counterparts on other cells, this activated a “brake” that stopped 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, blocked 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, were 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 helped T cells find cancer cells that did not have distinguishing, well-displayed surface molecules. BiTEs had two arms, like many natural antibodies. However, unlike natural antibodies, BiTEs used only one of their arms to connect to a targeted surface molecule (that was not displayed well enough for a natural attack); the other arm of the BiTE connected to a T cell (that could not recognize the targeted surface molecule on its own.) When both arms connect, this activates the T cell to 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, targeted 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 was an off-the-shelf drug; it had 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 interacted with or blocked specific molecules had been developed to treat cancers. They could 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 was attached. Trastuzumab (Herceptin), which binds to HER2 (from 'human epidermal growth factor receptor 2') molecules that promote the development of certain aggressive types of breast cancer, was an example.
- Inducing cancer cells to commit suicide. Examples were rituximab (Rituxan®) and ofatumumab (Arzerra®), which targeted 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 bound itself. Examples were Kadcyla®, which killed cancer cells with HER2 on their surface, and Adcetris®, which killed lymphoma cells with CD30 on their surface.

Sources: "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-I-Z3\\_QLXl06OkKo8xa\\_7rg](https://news.cancerconnect.com/treatment-care/bite-the-next-innovative-treatment-in-lymphoma-and-myeloma-I-Z3_QLXl06OkKo8xa_7rg); accessed June 2020.

**Exhibit 5** Antigens 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  |
| Igκ                                  | 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; Igκ, 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: 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](https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FS27_CART_Facts_2019_FINAL_Rev.1219.pdf), accessed June 2020, p. 3.



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