How Scientists Built a ‘Living Drug’ to Beat Cancer

In 2010, Emily Whitehead was diagnosed with Acute Lymphoblastic Leukemia, a cancer of certain cells in the immune system. This is the most common form of childhood cancer, her parents were told, and Emily had a good chance to beat it with chemotherapy. Remission rates for the most common variety were around 85 percent. It would be 20 months before they’d understand the shadow behind that sunny statistic, and the chilling prospect of volunteering their daughter as patient zero for the world’s first living drug.

*From the book* The Breakthrough: Immunotherapy and the Race to Cure Cancer, *Copyright (c) 2018 by Charles Graeber.* [*Buy on Amazon*](https://www.amazon.com/Breakthrough-Immunotherapy-Race-Cure-Cancer/dp/1455568503)*.*

Emily started on the 26-month chemotherapy regimen. She lost her hair and most of her kid energy, and the curative poison seemed to be doing its job, sickening her body as it killed the disease. But her cancer, like all cancers, was alive, a constellation of mutant cells that continued to mutate into new variations. Some of these new mutants were immune to the chemotherapy and continued to thrive.

By October 2011, Emily had relapsed; in the language of immunotherapists, her cancer had “escaped.” Her physicians at Pennsylvania’s Hershey Medical Center could only offer more chemo, more aggressively. In February 2012 she relapsed again. Now it was painfully obvious that Emily was one of the 15 percent of kids with leukemia for whom chemotherapy did not work. The cancer was doubling daily in her bloodstream, and it was too late for a bone marrow transplant—she was too sick. Oncologists now referred to Emily’s cancer as “terminal.” She was 6 years old.

Cancer is shitty and unfair, but that shitty unfairness reaches a whole other level when it happens to a kid. Tom and Kari Whitehead were told that they needed to consider hospice for their daughter. Or, if they wanted, she could die at home. Traditional medicine had nothing else to offer her. But a researcher at the Children’s Hospital of Philadelphia might, if Emily’s parents were willing to take the risk.

The Whiteheads learned of this possibility on a Sunday. By Monday, they were in Philadelphia. Emily Whitehead would be the world’s first kid to try an experimental cancer therapy, called CAR-T. Researchers were offering to reprogram her immune cells into a clone army of cancer-targeting serial killers.

A CAR-T cell is a reengineered T cell that has been removed from the cancer patient, tweaked in the lab to recognize that patient’s cancer, and then injected back into the patient. Because each of these reengineered cells is a monstrous robocop-like assemblage of immune cell parts, researchers had given their invention the equally monstrous name of “Chimeric Antigen Receptor T cell” (in Greek mythology, the chimera is a patchwork monster combining aspects of a lion, goat, and serpent), but “CAR-T” sounds much better.

CAR-T is often called the “most complex drug ever created,” but it is not really a drug in the traditional sense. Unlike an inert molecule introduced to the body for some temporary effect, CAR-T is alive. If it worked as designed, this “living drug” would go on living in Emily’s bloodstream like a cancer-killing superpower, providing her with a sort of immunity against her disease. And in the process, it would give humanity a revolutionary new weapon in the war on cancer.

And if it didn’t work? If the unleashed cellular serial killers turned on the girl’s healthy cells instead of the cancer? Well, the Whiteheads decided, best not to think about that. At this point, their only daughter had nothing to lose. The hundreds of millions of T cells that patrol our bloodstreams and lymph nodes are expert at recognizing sick body cells and killing them. And, although the idea was [dismissed by most scientists](https://www.amazon.com/Emperor-All-Maladies-Biography-Cancer/dp/1439170916?tag=w050b-20) for the past 100 years, a handful of these T cells are predisposed to recognizing and killing cancer, too.

So, why doesn’t our immune system do that job? You always know when you have a cold or the flu, but cancer arrives without so much as a sniffle. Why does it usually require a test to know that we have this deadly disease? The answer to that question came in a series of breakthrough discoveries of how cancer uses tricks to turn off, hide from, and overwhelm our immune response. Cancer shuts down T cells before they get a chance to call for reinforcements, reproduce into an overwhelming clone army, and do their job. But what if there was a way to overwhelm cancer instead, barraging it with huge numbers of immune cells capable of recognizing and killing it?

The group of researchers considering this possibility were called cancer immunotherapists, and by the time Emily Whitehead showed up at the hospital, they had already spent decades on the problem. But before they could hope to make that clone army, they needed to comb through the hundreds of millions of cells in a patient’s immune system and identify the one or two T cells that happened to be perfectly tuned to recognizing that patient’s personal cancer. Not surprisingly, Mr. Perfect was hard to find. In fact, until the 1980s, even cancer immunotherapists weren’t entirely certain that Mr. Perfect existed.

Identifying, extracting, fertilizing, growing, cloning, and then activating the perfect T cell against cancer—this was largely trial and error work, done with little funding and little grasp of the overwhelming biological complexities of cancer or the immune system. The science was all impossibly new; T cells had only been discovered in the late 1960s.

Cancer immunotherapists floundered for decades, the laughing stock of the research community, unable to prove their theory that the immune system could be helped recognize and kill cancer cells, and largely unable to help real cancer patients. Meanwhile, another group of cancer immunotherapists had started to consider a different approach: Rather than hoping to somehow locate the perfect cancer killing T cells in a patient’s body, they’d make their own Mr. Perfect, engineering a Frankenstein T cell stitched together from various parts in the lab. The Weird Science T cell would be designed specifically to seek and destroy a patient’s specific cancer.

The engineering is complex, but the concept is simple. An individual T cell recognizes only the distinct sick cell protein (called an antigen) that they are born to “see,” as determined by a random assignment process. The business end of that “seeing” is called the T cell receptor, or TCR.

Change the TCR, and you might be able to change what that T cell targets. Change it to the right one, and you might even be able to get it to target a specific disease. That was exactly what occurred to a charismatic Israeli researcher named Zelig Eshhar.

In the early ’80s this beekeeping PhD started thinking about the business end of the TCR—the part that extends out through the surface of the T cell like a grabby protein antenna and “sees” specific antigen targets. To Eshhar, that looked a lot like the grabby protein claws of an antibody. It seemed to work the same way too. These Y-shaped immune structures come in lots of flavors (hundreds of millions), each sticky to a different disease-specific protein. Each was a key in search of its lock.

Eshhar could imagine popping off the end of the TCR and popping on a new antibody like a vacuum attachment; change the antibody, and you might change what the T cell targets. In theory, you could have a near infinite number of new attachments, each specific to recognize and bind with a different antigen, and thus target a different disease. Such a technology would create a whole new class of medicines.

Turning Eshhar’s theory to reality required a fancy bit of bioengineering, but somehow, in 1985, he managed to produce a simple proof of concept. He called his primitive CAR a T-body. It was a T cell retooled to recognize a relatively obvious antigen target that he had selected, a telltale protein worn by the fungus *Trichophyton mentagrophytes*, better known as athlete’s foot. This humble experiment cloaked mind-blowing possibilities.

And it caught the attention of those who’d spent their lives laboring in the trenches of cancer immunotherapy, including a pioneering immunotherapist Steve Rosenberg. Rosenberg had first become convinced of the immune system’s potential to kill cancer in the 1960s, after examining a former stage IV cancer patient whose immune system had spontaneously cured his own disease. Rosenberg had wondered whether the man’s supercharged immune cells could help other cancer patients, too.

In experiments unthinkable today, Rosenberg had tried just that, transfusing the cured man’s blood into the veins of a terminal cancer patient in the next bed. It didn’t work, but the promise of cellular transfer therapy stuck with him. For the next five decades, Rosenbergs’s National Institutes of Health laboratory (and that of Philip Greenberg at the Fred Hutchinson Cancer Research Center in Seattle) would serve as a sort of hive and haven for immunotherapy talent.

In 1989 Eshhar was persuaded to spend a sabbatical there, joining another brilliant young NIH researcher named Patrick Hwu to create an updated take on what would eventually be known as “adoptive cell therapy.”

Examining a patient’s tumors under the microscope revealed that, even when the larger immune attack had failed, a few T cells still managed to successfully recognize the tumor antigens and nose their way in. These robust infiltrators would be their Mr. Perfect T cells and, hopefully, seeds for their clone army of targeted cancer killers.

Hwu’s focus was to try to weaponize this subset of successful “tumor-infiltrating lymphocytes,” or TILs, by packing them with an additional payload of powerful tumor-killing hormones. “Zelig had shown that an antibody and a T cell could be combined to target something,” says Hwu, who serves as the head of the division of cancer medicine at Anderson Cancer Center in Houston, Texas. “Now the question was, could we get it to target cancer cells?”

In order to work as little guided missiles, they needed a guidance system, one that researchers could choose and customize to target various types of cancers. Starting with a batch of T cells they’d found to be Mr. Perfect TILs active against melanoma, Hwu and Eshhar Frankensteined them with new TCRs to instead target ovarian, colon, and breast cancers. “Zelig made the receptor, I put it into T cells,” Hwu remembers. “It was really hard to do that in the 1990s.”

Without the benefit of retroviral vectors or Crispr, the task required sticking a little needle into a T cell and micro injecting the new TCR genes one cell at a time. “We spent a lot of time together,” Hwe says with a laugh. “A lot of all-nighters in the lab.”

None of the results was perfect, but the TILs they had retargeted to ovarian cancer worked best of the three, and the team was able to publish on the result, heralding the new CAR-T name and the enticing implications of the technology. They hadn’t cured any cancer, but they’d advanced the science. They had successfully replaced the T cell steering wheel and that knew how to find a specific cancer. “The first time I got that to work I was so elated,” Hwu remembers. But it would take more than retargeting to engineer a cancer-killing machine.

To be effective, these new cells also needed to thrive and replicate themselves, like normal T cells do. Their first-generation cars didn’t do that. It was as if some vital essence had been lost during the retrofit, resulting in lemon CARs that didn’t run long enough to replicate or kill. Their Frankenstein would rise from the table, only to keel over.

It would be up to researcher Michel Sadelain to provide the clever workaround for this and several other engineering problems, creating a truly “living drug,” as Sadelain called it, a second generation CAR that could recognize a target, expand clonally, and retain its other T cell functionality, with a life span as long as that of the patient’s. Working in his lab, Sadelain (a laconic scientific intellectual who is the founding director of the Memorial Sloan Kettering Cancer Center of Cell Engineering, among other things) also gave his new CAR an important new target—a protein called CD19 found uniquely on the surface of certain blood cancer cells.

CD-19 seemed like a good CAR choice. It was found in abundance on the surface of certain cancers. It was also expressed by some normal B cells, but that was acceptable. If the CAR attacked healthy cells as well the cancer, the collateral damage was survivable. In a healthy human, B cells are essential aspects of the normal immune system. But in patients like Emily, those B cells had mutated and become cancerous. To survive, she would need to lose them. Luckily, physicians had long ago learned to keep patients alive without B cells. “If you’re facing terminal cancer,” Sadelain says, “losing your B cells isn’t so bad.”

Sadelain now had a sleek, stylish, and self-replicating second-generation CAR with plenty of fuel and a realistic cancer target. His group shared the sequence of their new CAR with Rosenberg’s group at the National Cancer Institute, as well as the lab of University of Pennsylvania researcher and physician Carl June. (June in turn also based aspects of his CAR design on a sample borrowed from Dario Campagna of St. Jude’s Children’s Research Hospital.)

These three groups—all pushing for human trials of this complex and powerful new cancer therapy—were now competitors. At the same time, they worked together, borrowing and improving upon each other’s ideas. Sadelain’s group had been first to start CAR-19 T cell clinical trials, Rosenberg’s first to publish; their successful CAR-T trial shrank tumors in a lymphoma patient. But it would be Carl June’s trial with Emily Whitehead that would take the spotlight and determine whether there was a future for CAR-T.

June was well aware of the stakes. If his CAR was too aggressive for a pediatric patient, if his powerful Franken-drug proved to be a killer too powerful to control, Emily would die. And any hope of saving hundreds of other children with this technology would likely die with her.

Though June is trained as an oncologist specializing in leukemia, his work on the AIDS crisis had convinced him of the cancer-killing potential of the immune system. Several cancer immunologists had gained their faith that way. Witnessing the prevalence of previously rare cancers in immune compromised patients seemed proof of a connection between the immune system and cancer, even if the scientific concensus was that no such connection existed.

But if the little girl died from the experiment, if his powerful Franken-drug attacked her body instead of the cancer, he was equally certain that the result would be horrifying and tragic. And that any possibility of CAR-T ever curing cancer in the hundreds of other children dying from ALL would likely die with her.

In the 1990s June was working off his Naval medical school debt at the National Institutes of Health, helping in the development of an experimental CAR-like treatment that redirected killer T cells to hunt down infected T cells in AIDS patients. Early data looked good, but before the work was complete it had become unnecessary, due to the 1997 development of drugs that blocked the HIV virus from replicating.

Overnight, these first protease inhibitors changed the prognosis for millions of people, and the direction of June’s career. Finally, June could move his work and practice to a laboratory at UPenn and the Children’s Hospital of Philadelphia and return to focusing on cancer. Unfortunately, fighting the disease had recently become excruciatingly personal.

In 1996 June’s wife, Cynthia, had been diagnosed with ovarian cancer. When Cindy June didn’t respond to traditional therapies, June had turned to immunotherapy approaches still in their infancy, customizing a version of another lab’s promising immunotherapy vaccine.

It was called GVAX, a personalized approach that took a piece of a patient’s tumor, fitted it with extra genes coding for cytokines that would alert the immune system, and reinjected the result into the patient. June thought GVAX had tremendous potential. He quickly learned how difficult it was to turn a laboratory experiement into a clinical trial.

June eventually started his wife on the treatment. She seemed to be having a good response to her personalized vaccine. But, as with all cancer vaccines of the era, that response did not last. June correctly suspected that the tumors were somehow turning that immune response off.

This suspicion was fueled in part by the pioneering work of [Jim Allison, a harmonica-playing Texas immunology researcher](https://www.wired.com/story/meet-jim-allison-the-texan-who-just-won-a-nobel-cancer-breakthrough/). In 1987, Allison had found one of the tricks cancer used to shut down immune response and developed an antibody to block that trick in mice, unleashing their immune systems to kill cancer. Thirty-one years later that discovery would be recognized as a breakthrough in our war with cancer and win Allison the Nobel Prize. But in 1999, Allison’s work still hadn’t been turned into a medicine. It hadn’t even been tested in humans.

Combining Allison’s antibody discovery with GVAX “was a no-brainer,” June says. To try to save his wife, June had no option but to push ahead blindly. “I knew in mice, his antibody made immunotherapies work better,” June told me. Combining Allison’s antibody discovery with GVAX “was a no-brainer,” June says. He tried repeatedly to get a sample of the precious anti-CTLA-4 antibody—Allison's creation—from the pharmaceutical manufacturer, and was repeatedly denied. Loaning desparate doctors untested experimental antibodies just wasn’t done. It was too risky.

“It was very frustrating,” June says. He couldn’t imagine how the outcome of a hail Mary attempt with an experimental drug could be more dangerous than the certain results of untreatable cancer. When Cindy June died in 2001 at the age of 46, June funneled his grief for the mother of their three children into his work and, he says, moved his focus on cancer “to the front burner.”

It took nine years, but finally, his CAR was waiting. The essential CAR concept hadn’t much changed, but the technology of placing genes into cells had come a long way since Hwu had started injecting them by hand. In June’s UPenn lab, the foreman in this modernized CAR assembly line was the repurposed shell of the virus that causes AIDS.

Viruses are essentially just genes with legs in a protein shell, and they exist at the edge of our definition of life. These stripped-down DNA carriers also lack the tools to reproduce on their own.

To make more copies of themselves, viruses outsource the work to the cellular machinery of the larger, more complex cells they infect, injecting their own viral genetic blueprints into their host’s cellular manufacturing plants. In the case of the human Immunodeficiency virus, that host cell is a T cell. HIV is devastatingly effective at targeting T cells. Usually, that results in the virus infecting that T cell with instructions to make more HIV, rendering it useless at defending against disease and a shutdown of adaptive immunity in the body, what we know as acquired immune deficiency syndrome, or AIDS.

But that aptitude for changing the DNA of T cells is also exactly what made HIV attractive as a delivery system for a CAR-T’s genetic blueprints. In theory, this killer could be turned into a life-saving technology.

In June’s lab at UPenn, an HIV virus was emptied and fitted with new genetic instructions. It was then introduced to Emily’s T cells, which had been carefully centrifuged from Emily's drawn blood. Instead of delivering disease, June’s repurposed virus “infected” T cells with new genetic instructions, reprogramming them to target only the CD19 protein on the surface of her cancerous B cells.

Finally an IV bag full of virus-reprogrammed CAR-19 T cells was brought to the wards of Children’s Hospital. Emily Whitehead was propped on a hospital bed, a little girl, bald and browless in a sparkly purple dress. A line was inserted. Her reprogrammed T cells were slowly reintroduced into their native veins. It wasn’t until the third bag that the side effects started.

At the time, physicians were not familiar with the power and toxicity of the new T cell therapy. Now they know it by several names; most scientifically “cytokine release syndrome” (or CRS), most notably “cytokine storm,” most casually “shake and bake.”

As the names suggest, these are a whirlwind of exhausting and dangerous symptoms, like a a monstrously amplified version of the debilitating side effects of an immune battle with the flu, caused by the torrent of immune signaling hormones released during the T cell feeding frenzy. Such side effects are essentially the sound and fury of immune battle..

The research team were well aware that children have more powerful immune systems than adults, but the intensity of Emily’s reaction to the therapy was more extreme than they could have anticipated. Emily’s CRS was, in the language of her medical reports, “severe.” A Powerful cytokines whipsawed through Emily’s system, leaving her sweating and shaking. Her breathing became labored, her blood pressure dropped perilously, and her temperature spiked to 105 degrees.

When it reached 106, Emily was rushed to the intensive care unit. She stayed there, a tube down her throat, another in her nose, comatose and breathing by machine. Days passed. She was not improving.

On the fifth day she was given steroids. Emily’s symptoms calmed for a moment, only to gain force like an offshore cyclone and come raging back. On day seven the little girl rising to the pump of a ventilator motor was unrecognizable, swollen as a hot water bottle. She had multiple organ failure. It seemed the cure, rather than the disease, would kill her. Desperate, her oncologist and clinical trial lead investigator, Stephan Grupp, ordered battery of blood tests covering every immune-related molecule he could think of.

The bloods came back two hours later. Two numbers stood out. Both her interferon gamma (INFγ) and interleukin-6 levels were remarkably high. Grupp carried the readout into his 3 pm lab meeting, a group gathered to work the problem and brainstorm possible options. Nobody saw any.

What was clear that her interleukin-6 level had spiked a thousand times above normal. Whether that was disease or symptom, a source of the problem or an aspect of the body’s attempt to ameliorate it, they weren’t sure.

Interpreting the notes and melodies within the chemical symphony of immune response was still an art in its infancy, and interleukin-6 was known to be a cytokine with a host of roles in normal immune function, both inflammatory and anti-inflammatory, push and pull. It was also known to be partly responsible for the inflammation of rheumatoid arthritis. And this was where Emily Whitehead got very lucky.

As it happened, June was intimately familiar with the debilitating effects of rheumatoid arthritis in children. His own daughter suffered from it, and he had been following the literature for years. June had been watching a promising new antibody that seemed to block the interleukin-6 receptors and turn down the cytokine call for inflammation and swelling “No one working in cancer would have had a reason to know about it,” June said. “It was just pure luck that I did.” He’d even presented an award to the Japanese professor who had discovered this antibody.

Only a few months earlier it had cleared clinical trials and was finally FDA approved as a drug called tocilizumab. June had stocked up on the stuff, just in case his daughter experienced a flareup. Now, June wondered, would this new arthritis drug help a kid with cancer too?

There were no experts to consult—they were the experts. Emily’s fever had hit 107. Tom and Kari Whitehead had been told to consider a do-not-resuscitate order for their unconscious daughter.

Grupp wrote a prescription for tocilizumab. He ran it down to where Emily was languishing in the ICU and told the doctors what he planned to do. Grupp believed the drug would help Emily. It might do nothing, or worse.

The drug was new, it had never been tried on CRS patients; nobody had ever treated the side effects of CAR-T therapy before. “(The ICU doctors) called him a cowboy,” June remembers. This was Wild West stuff, uncharted territory. But without a map, without precedent, an untested, unproven answer was the only answer possible.

Grupp readied a syringe and injected the tocilizumab directly into Emily’s IV port. And gradually, the anti-interleukin-6 antibodies blocked their receptors and calmed Emily’s cytokine storm. Over the next days Emily was weaned off the ventilator and the blood pressure medications but remained in a coma.

The waiting was hard for everyone, especially her parents. A week later, Emily opened her eyes to the tune of “Happy Birthday” sung by the hospital staff. She was exactly 7 years old. And she was alive. A single CAR-T cell can take out as many as a hundred thousand cancer cells and produce freakishly rapid remissions that take even the most ardent immunotherapist by surprise. Sadelain calls them “a living drug.” June sometimes refers to them as “serial killers” of cancer.

Only four weeks after her first CAR infusion Emily’s lab results showed no incidence of cancer—a lab error, obviously, so June ordered a second biopsy. But there was no error. The procedure had been a success—as a drug for Emily and as a proof of concept. That was good, but not the end. Emily wasn’t the only childhood leukemia patient to receive the experimental treatment.

June had also treated another juvenile ALL patient at Children’s Hospital, a 10-year-old girl. Her leukemia had responded to the CAR-T therapy, and she had gone into remission, only to relapse two months later.

Biopsies showed that this girl’s leukemia had mutated and escaped on B cells that did not carry the CD19 target protein. The cancer had changed uniforms, but they didn’t have another CAR to give her.

And so in September 2012, Emily Whitehead returned to school with a sick note signed by President Obama, a cute national success story celebrated on Good Morning America as proof our progress against cancer. The other girl died of her disease, a sad and humbling reminder of the work yet to be done. Emily Whitehead’s complete remission made the headlines and energized the entire field, propelling CAR-T funding and development into overdrive.

Each of the research teams—once collaborators, now competitors—quickly coupled up with a pharmaceutical partner to turn the technology into medicine. The National Cancer Institute went with Kite Pharma (which gained approval for its CAR-T, called Yescarta for large B-cell lymphoma); Memorial Sloan Kettering Cancer Center, together with the Fred Hutchinson Cancer Research Center and the Seattle Children’s Research Group, partnered with Juno Therapeutics.

The drug giant Novartis licensed the CAR-T technology from the University of Pennsylvania. It received FDA approval for the therapy used on Emily Whitehead, which it now sells under the brand name Kymriah. That approval came in 2017, but CD-19 CAR-T therapy has already helped thousands of people, including hundreds of children with cancer.

Even the 85 percent of children for whom ALL is treatable with chemotherapy are candidates for the new therapy. For children, such a cure comes with a hidden cost; two years of chemo takes a toll on developing bodies and minds.

The experimental treatment now known as Kymriah is both a medicine and a product. It is dispensed from a handsome translucent package with a blood-orange luminosity. Each is customized for the patient, engineered from the patient’s own T cells.

At the moment each of these bespoke one-time infusions cost $475,000. When hospital charges are added, the total cost approaches $1 million per patient. The next best treatment for acute B-lymphoma is a bone marrow transplant costing over $100,000 more. This “economic toxicity” is currently another serious side effect of cutting-edge cancer cures like cancer immunotherapy, yet to be treated.

For a CAR-T patient, the process of receiving the treatment goes something like this: An eligible patient travels to an affiliated medical center. There, blood is drawn and centrifuged for at least 15 minutes at 2,200 to 2,500 rpm to separate the T cells from the plasma, platelets, and the rest.

The T cells are then cryogenically frozen, packed in a special cryovac container, and shipped off to the 180,000-square-foot Novartis mothership facility in Morris Plains, New Jersey, where they are thawed and reengineered to recognize a protein specific to the patient’s cancer.

This proceeds in steps. First the T cells are activated. Then they are transduced with a virus containing new genetic instructions. Then they are grown and multiplied until they number in the hundreds of millions. The clone army of supersoldier T cells is then re-cryopreserved, shipped back to the certified medical center, and rethawed to be dripped back into the patient.

Cryopreservation allows patients from all over the world to use the treatment. The turnaround time, from walk-in center to finished customized T cell treatment, is 22 days. Preliminary data suggests that therapies using these bespoke T cells deliver durable response rates for formerly hopeless cases.



Emily and her mother, Kari Whitehead.

Jeff Swensen/The New York Times/Getty Images

Emily is part of that happy statistic. As of July 2019 she remains in remission. The bright-eyed little sick girl is now a tween. She plays ukulele and runs road races. But mostly, she’s a kid again. There is great danger, of course, in any engineered fiddling with the hair triggers, feedback loops, and checks and balances of an immune system evolved over millennia, and great trepidation in using experimental therapies on any patient, especially a child. At the same time, the worst possible side effect of these treatments is death; untreatable leukemia ends the same way.

Those first experimental treatments, and the new approach to treating cytokine storm, quickly demonstrated that for these patients, the rewards far outweighed the risks. For such patients, CAR-T has changed the numbers seemingly overnight.

Before CAR, kids like Emily had a zero percent survival rate. Currently, that estimated survival rates now stand at 83 percent or higher, and combination therapies—combining a CAR with another immunotherapy drug that blocks the tricks cancer uses to shut down immune response—are driving that rate even higher. The goal, of course, is a cure.

Developing this cancer-killing technology is one thing, getting access to it is another. For cancer patients, delays and bureaucracy can be deadly. It’s understandable that extra caution is still exercised when considering the ethics of giving experimental therapies to kids. June understands that, but he’s also seen first hand the price paid when potentially lifesaving but experimental drugs are denied. That almost happened to Emily. She couldn’t start her CAR treatment until a lengthy ethical review. By the time it was finished, it was nearly too late.

This highlights one of the other challenges of such rapid discovery and technology: how to properly regulate it, while getting it into the hands and bodies of patients as quickly as possible. In this breakthrough age, clinical trials are more important than ever—and more relevant. Thousands of new cancer immunotherapy drugs are now in the pipeline. And yet many patients don’t fully realize it. Remarkably, not all doctors do either.

Researchers increasingly understand cytokine storm and how to control it, making CAR-T therapies far less of a rough ride, and a safer one. An additional safeguard now comes standard in the new experimental CARs as well, in the form of built-in cellular “kill switches”; if Frankenstein goes crazy, researchers can just pull the plug.

It has only been two years since CARs were FDA approved as a medicine, but already the technology is blossoming with new permutations on the original design. Some base their new CARS on donated T cells (rather than a patient’s own), in hopes of creating off-the-shelf solutions that are cheaper and more readily available than the current bespoke CAR models. Other labs are tricking out their CARs with add-on customizations and combining them with other forms of cancer immunotherapy, multiplying their effectiveness.

Researchers at Massachusetts General Hospital, [publishing in Nature Biotechnology](https://www.nature.com/articles/s41587-019-0192-1.epdf), recently announced the results of just such a creative combo approach to getting CAR to target glioblastoma, the most common and deadly form of brain cancer.

Further progress can’t come soon enough. The median survival time from a diagnosis of glioblastoma is only 15 months. Gliobastomas is especially difficult to treat because not all of the cancerous cells express the same antigen.

In the new approach, their compact CAR is ferried across the blood brain barrier, then deploys a tethered secondary antibody guidance system, like a dragster popping a parachute. The CAR now has two separate guidance systems and two different means to “see” the cancer target. In preclinical models of human glioblastoma, this additional "bi-specific T-cell engager" (or BiTE) helped the CAR clear 80 percent of the tumors.

In theory, you could attach other guidance systems as well or other cancer-killing payloads or continue to refine and customize and soup up ad infinitum, an evolving design guided by both imagination and biology. CAR-T is really a gateway technology, and there’s no reason to imagine that those of the near future will bear any more resemblance to these first designs than a Tesla Model X does to a Ford Model T.

Customizable variations, collaboration, and creative combinations are a logical response to a this confounding disease; a mutating answer to a mutating problem. What’s clear is that as we increasingly come to understand how complex and personal both our cancers and our immune systems truly are, what we now think of as “personalized’ medicine will one day just be called medicine. So far, CAR-T has been proven effective in some “liquid” cancers, like lymphomas and leukemias. The next challenge is to move that success to treat solid tumors as well—liver masses, lung cancers, brain lesions, and many more.

To do that, researchers have needed to identify antigens unique to such cancers, and create CARs that can recognize them. One of the antigens showing promise is a protein called mesothelin, recently found to be commonly and uniquely expressed by the cancers of an estimated 2 million cancer patients in the US alone.

Results from a phase I study targeting this antigen with CAR-T, unveiled at the end of April, suggested promise; Michel Sadelain was lead author of the study supported by the Parker Institute of Cancer Immunotherapy, founded by Napster legend Sean Parker. The technology has since been licensed to Atara Biotherapeutics for development and, hopefully, a new breakthrough drug that widens the circle of cancer immunotherapy responders.

Other new targets include other (non-CD19) antigens expressed by various leukemias and non-Hodgkin lymphoma, as well as solid tumor targets such as metastaic melanoma, neuroblastoma and synovia cell sarcoma, recurrent glioblastoma, advanced ovarian cancer, colorectal cancer and mesothelioma.

And clinical trials are ongoing for cancers including lung, cervical, esophageal, liver, breast stomach, prostate pancreatic—with nearly 500 such studies presently running, any list is incomplete, and growing quickly, up 84 percent in the last two years. We’re still a long way from what anyone might consider a “cure” for cancer, but the expert consensus is that hope is warranted, especially regarding cancers (such as pancreatic cancer and triple negative breast cancer) against which we’ve not seen progress in generations.

For 100 years most scientists were dead certain that the immune system couldn’t target cancer. And they were dead wrong. The immunotherapy breakthrough against cancer is bigger than just CAR-T or any single cancer therapy or drug; the real breakthrough is in our scientific understanding of the disease and ourselves and the validation of cancer immunotherapy as the most likely road to progress—and perhaps a cure.

The discovery that cancer uses tricks to shut down or hide from the immune system has made sense of generations of failed attempts to get immunotherapy to work. And now that we can block those tricks, some of those cellular therapies are getting a second look. For example last August, Steve Rosenberg’s National Institutes of Health lab announced the results of their TIL therapy trial for a group of women with late stage metastatic breast cancer and no other options.

Most were not helped by the therapy, but one went into complete remission. Judy Perkins knows she was one of the lucky ones. Now the race is on to figure out how to reproduce what happened to Perkins in everyone else. These are early days, and CAR-T and other adoptive cell therapies are only one small arm of an immunotherapy breakthrough researchers refer to as our “penicillin moment” against cancer. Whatever happens, there’s reason to hope that more patients like Emily Whitehead will be around to see it.