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A decade of success: CAR-T pioneers reflect on past, look toward future

Ten years ago, researchers at NCI reported use of CD19-directed chimeric antigen receptor T-cell therapy that successfully induced remission in a patient with follicular lymphoma.

Despite the case study's potentially practice-changing implications, the findings intrigued only a core group of niche researchers.



Michel Sadelain, MD, recounts the role that his lab and others at Memorial Sloan Kettering Cancer Center played in the development of CD19 CAR T-cell therapy.

A decade later, with three commercially available products on the market and hundreds more in development, CAR T-cell therapy has evolved into one of the most promising treatments for poor-prognosis patients with hematologic malignancies.

The rapid progress is hard to fathom even for those directly involved in the field's early success.

“Back in 2009, what we were doing was kind of unheard of outside of a very small group of researchers,” James N. Kochenderfer, MD, senior investigator in the surgery branch of NCI and co-author of the case study published in 2010, told *Cell Therapy Next*. “We definitely did not think it would blow up to become as big as it did.”

Cell Therapy Next asked leaders in the field to reflect on the early developments that laid the groundwork for CAR T-cell therapy, the research advances made over the past 10 years, and the most formidable challenges that must be overcome to increase treatment efficacy, improve safety, reduce costs and expand patient access.

Laying a Foundation

Steven A. Rosenberg, MD, PhD, chief of the surgery branch and head of the tumor immunology section of NCI's Center for Cancer Research, had a "light-bulb moment" in 1984 when he was conducting research into the role of interleukin-2 for treating tumors.

A report by his team, published in 1985 in *The New England Journal of Medicine*, documented the first tumor regressions using what he called "an immunologic maneuver."

"[The finding] demonstrated that it was indeed possible to use the immune system to cause tumor regression," Rosenberg told *Cell Therapy Next*.

Twenty-five years later, Rosenberg served as leader of the CAR-T case study published by the NCI group.

The clinical findings were the first of a series that proved anti-CD19 CAR T cells could be effective for treatment of certain advanced hematologic malignancies.

However, the report generated little fanfare among the broader medical community or pharmaceutical industry.

"It was just a blip," **Michel Sadelain, MD, PhD**, director of Center for Cell Engineering at Memorial Sloan Kettering Cancer Center, told *Cell Therapy Next*. "It was only of interest to a handful of people at a few centers that were conducting trials."

As the volume of evidence grew, so did the interest.

A University of Pennsylvania research group was working on another CD19-directed CAR T-cell therapy that used a different CAR construct.

The findings published by the NCI proved to be "an exciting advancement," according to **David L. Porter, MD**, director of cell therapy and transplantation at University of Pennsylvania's Abramson Cancer Center and a *Cell Therapy Next* Peer Perspective Board Member.

"In this field, when using therapies in patients for the first time, you can learn tremendous amounts from even a single patient," Porter told *Cell Therapy Next*. "It really led us and many others to believe this approach really could work."

The group at University of Pennsylvania published their results in 2011 in *Science Translational Medicine* and *The New England Journal of Medicine* reporting on the first three patients with advanced, treatment-refractory chronic lymphocytic leukemia they treated with anti-CD19 CAR T-cell therapy. Their approach led to "dramatic responses" in all three patients — and complete responses in two patients that are still ongoing — according to Porter, who led the clinical trial at University of Pennsylvania.

In 2013, Sadelain's group published a report in *Science Translational Medicine* that established the safety and efficacy of anti-CD19 CAR T-cell therapy for adults with acute lymphoblastic leukemia.

"The fact that all three of our centers rolled out our data on CD19 CAR-T at about the same time convinced the world that the findings were valid," Sadelain said.



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He also acknowledged that all CD19 CARs were made possible by the preclinical research of Brentjens and colleagues, who showed in 2003 that CD19 could be used as a target for B-cell malignancies.

'Paradigm-Changing' Research

Tanya Siddiqi, MD, associate professor and director of the CLL program at City of Hope, was peripherally aware of the early series of clinical papers when they were published.

At that time, Siddiqi — a new junior faculty member — was learning about immunotherapy and cellular therapy research being conducted at the institution under the leadership of another CAR-T pioneer, **Stephen J. Forman, MD**, director of the T Cell Therapeutics Research Laboratory in the Cellular Immunotherapy Center.

Siddiqi — who also is a member of the *Cell Therapy Next* Peer Perspective Board — said the publications were discussed in Forman's lab meetings, and she pulled data from them for one of her junior investigator proposals to ASH.

"I was struck by the beauty of this type of engineering and the promise it held as a way to harness the body's own immune system to fight cancer," Siddiqi told *Cell Therapy Next*.

These early research efforts proved to be "paradigm changing," according to **Elizabeth J. Shpall, MD**, professor and chair ad interim of the department of stem cell transplantation and cellular therapy and director of the cell therapy laboratory and cord blood bank at The University of Texas MD Anderson Cancer Center.

"It's a new day in terms of options for our patients," Shpall told *Cell Therapy Next*. "CD19 CAR T-cell therapies have been extremely effective and have produced long-term remissions in many patients who likely would not have been rendered disease-free for extended periods in the past."

Challenges for the Next Decade

In 10 years, cellular therapy has established itself as a "fourth arm" of cancer treatment, Shpall said, complementing traditional pharmaceutical treatments, surgery and radiation.

The FDA approved three CAR T-cell therapies between August 2017 and August of this year: tisagenlecleucel (Kymriah, Novartis) for treatment of certain patients with diffuse large B-cell lymphoma or B-cell acute lymphoblastic leukemia; axicabtagene ciloleucel (Yescarta, Kite Pharma/Gilead) for treatment of adults with relapsed or refractory large B-cell lymphoma; and brexucabtagene autoleucel (Tecartus, Kite Pharma/Gilead) for treatment of adults with relapsed or refractory mantle cell lymphoma.

An FDA decision on approval of lisocabtagene maraleucel (Bristol Myers Squibb) — in development for treatment of patients with relapsed or refractory large B-cell lymphoma — was expected in mid-November.

Many of the researchers who contributed to the development and advancement of CAR T-cell therapy during the past 10 years believe the next decade could yield even better results.

Still, they acknowledge several challenges must be overcome in order to build on the modality's success.

The most formidable may be determining how to effectively adopt cellular therapy beyond blood cancers, Rosenberg said.

“Solid tumors result in 90% of cancer deaths ... so that’s a great challenge now for all of oncology,” he said.

Rosenberg’s current research focuses on how to apply immunotherapies to patients with solid tumors whose disease does not respond to surgery, radiation or chemotherapy.

“We’re doing that by identifying the exact antigens that are recognized on cancers and developing T-cell immunotherapy that we can use as a drug to treat those patients,” he said.

The most significant challenge of the next decade will be to reduce the cost, Shpall said.

The list prices for the first three FDA-approved CAR T-cell therapies range from \$373,000 to \$475,000. A study by Lyman and colleagues, published earlier this year in *JAMA Network Open*, showed additional post-infusion costs — such as hospitalization and office visits — typically range from another \$23,500 to \$53,000 depending on treatment setting.

“Autologous CAR T-cell therapy is cost-prohibitive, and the cost makes it unsustainable over the long term,” Shpall said.

The average patient who would benefit from CAR T-cell therapy is aged 65 years or older, Shpall added, and Medicare cannot absorb the costs of the product plus inpatient care required for current therapies.

“Many of the people who would benefit from this therapy will be unable to have it,” Shpall told *Cell Therapy Next*.

The development of scalable, allogeneic — or “off-the-shelf” — CAR-T or CAR-natural killer (NK) cell products would help reduce costs, she said.

Shpall said the field will achieve the goal of reducing costs over the next decade with the help of allogeneic options.

“For example, from one cord blood unit we can make 100 allogeneic CAR-NK cell doses,” she said. “The ability to scale the process to make thousands of doses at a dramatically lower cost will be possible compared with making a single autologous product for each patient.”

Siddiqi emphasized the importance of increased access and the development of next-generation therapies that allow reengineered cells to persist in the body for a longer period of time and with fewer adverse effects.

The ability to make CAR T-cell therapy safer is especially important, she added, as it would allow for outpatient administration and help reduce treatment costs.

That may also allow for earlier use of CAR T cells, according to **Sattva S. Neelapu, MD**, professor and deputy chair of the department of lymphoma/myeloma in the division of cancer medicine at The University of Texas MD Anderson Cancer Center.

“Standard chemotherapy is typically successful at treating B-cell malignancies at first, so it’s hard to justify the current cost of CAR-T as an earlier line of therapy,” Neelapu told *Cell Therapy Next*. “I would like to see CAR T cells go toward the direction of earlier therapy because, if we can change the current 6-month course of therapy for B-cell malignancies into a one-time infusion of cells that allows the patient to resume normal life activities after a month, it would be a huge advance.”

Neelapu said, within 10 years, CAR T-cell therapy is likely to be used as a first-line therapy for at least some B-cell lymphomas.

“Lowering the cost of therapy and showing comparable or better efficacy than the current standard of chemoimmunotherapy could make that possible,” he added.

Sadelain agreed that improving treatment durability is a major challenge.

“Although most patients with lymphoma or ALL will benefit from this treatment, about half of them will relapse,” he said.

One of the keys to overcoming the challenge, according to Sadelain, is to better understand the mechanisms behind antigen escape, which could lead to more durable therapies and actual cures.

“The promise of cell therapy is to go beyond inducing responses and ultimately be curative,” Sadelain said. “The potential is there in some patients, but we need to better understand what it takes to get curative responses in all patients.”

Sadelain predicted that several new CAR therapies will be approved over the next decade, including those for cancer and beyond – from those treating intractable infections to autoimmune disease.



Tanya Siddiqi

“Some CAR therapies will use T cells and others NK cells,” he said. “Other cell types will be harnessed, including naturally developed cells and others born in a bioreactor starting from pluripotent cells or other progenitors.”

Kochenderfer said he thinks the next decade will be “very promising” for the development of cellular therapies, but he agreed with Sadelain that achieving durable responses in a higher proportion of patients remains the primary challenge.

“Even though CD19 CAR T-cell therapy is very effective, especially for lymphoma, we are seeing long-term remissions in approximately 40% of patients with B-cell lymphoma,” he said. “I would like to increase that number to over 90%.”

Best Chance for a Cure?

Cellular therapy may not offer a cure for all patients, but it might be the best option for many patients with relapsed or refractory cancers who lack viable alternatives, Rosenberg said.

“I believe we are curing patients who could not be cured by standard modalities, and I think the future of immunotherapy is bright because there’s so much enthusiasm now about using the body’s own immune defenses to treat cancer,” he said. “I see immunotherapy as the highest likelihood for progress in the next decade when it comes to developing effective cancer treatments.”

Siddiqi said she expects use of immunotherapies — especially cellular therapies — to increase over the next decade, with chemotherapy continuing to play a role in certain situations.

Challenges facing cellular therapies over the next decade



Affordability



Treating solid tumors



More durable responses

Healio 

“We are already curing cancer,” she said. “As far as relapsed aggressive lymphoma specifically is concerned, we were curing some with transplants in the past, but we are definitely curing more of these patients with CAR T-cell therapy now.”

Siddiqi said the future of cancer therapy definitely will include cellular therapies — including both CAR T cells and transplants — for patients with aggressive relapsed or refractory lymphoma.

Cell therapy will be part of a combinational strategy with other modalities to eradicate cancer in patients with relapsed or refractory disease, Shpall said.

“We are already seeing cellular therapies providing the types of responses that were not possible with other therapies, so I think they will be a critical piece of a new strategy — including chemotherapy and radiation,” she said. “In the end, we will probably need all modalities to achieve a cure for some patients.”

At University of Pennsylvania, cellular therapies have induced long-term remissions among patients with CD19-positive malignancies such as ALL and non-Hodgkin lymphoma, and some patients with CLL remain in remission more than 10 years after treatment.

“I strongly believe we are curing some of these patients,” Porter said. “There is no doubt cellular therapy will continue to be an important part of curing these patients with previously incurable diseases. As the technology gets better and safer, I am confident these immunotherapies will be applied earlier in the course of these diseases.”

Kochenderfer was more reserved when discussing the possibility of cellular therapies leading to cures for cancer.

“It is likely, but not definitively proven, that patients have been cured with anti-CD19 CAR T cells,” he said. “My goal is to find definitively curative CAR T-cell therapies for many patients with hematologic malignancies.”

Even so, the importance of developing treatments that provide many years of DFS with a high quality of life cannot be underestimated.

The fact that CAR T-cell therapy is complex or presents major short-term toxicities is an acceptable trade-off until future improvements to the therapy are achieved, he said.

Sadelain described the story of CAR T-cell therapy's development over the past decade as "wonderful" and "positive" for the many patients who have benefited from this rapidly advancing treatment option.

"One of the great values of the CD19 CAR story is that it convinced almost all of Big Pharma to enter a territory that they had until then avoided: using cells as drugs," he said.

Like Kochenderfer, Sadelain said he believes the promise of CAR-T is in providing patients with long-term remissions and years of high-quality life after a single infusion.

"Hopefully the pharma companies will follow-up on what we academics have started by making the manufacturing of engineered cells cheaper," he said.

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