Living medicine:
The story of CAR T cell therapy

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Abstract
The advent of chimeric antigen receptor (CAR) T cell therapies follows a decades-long quest to personalise the treatment of disease. This article highlights the early research that paved the way for the field today, touching on early pioneers in the field and the biotechnological methods used to engineer CARs. With six CAR T cell therapies approved by US and EU regulatory bodies, and many more to come over the next decade, the field is challenged by slow manufacturing times and limited accessibility. Future CAR-based treatments will include additional cell types and indications, as well as automated and continuous manufacturing protocols that will help reduce the cost of goods.

Introduction
Cure is a strong word, used hesitantly and infrequently when describing any kind of cancer treatment. Cancer of any kind is a devastating diagnosis, and overpromising yet underdelivering is all too common.

In the same vein, hope is exactly what cancer patients need, to comfort them during one of the most challenging parts of their lives. And hope is what a new type of cancer immunotherapy called chimeric antigen receptor (CAR) T cell therapy, a type of cell and gene therapy (CGT), promises to patients who have gone through multiple lines of treatment to no avail.

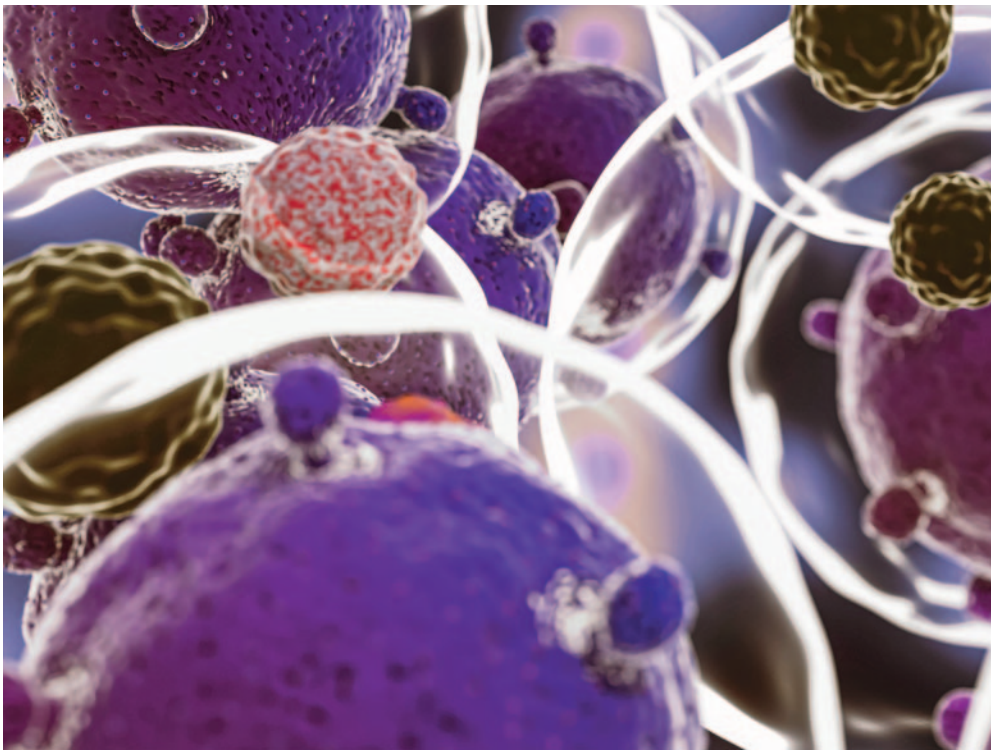
But cure too, is a real possibility. In contrast to complete remission, which is defined as a lack of any signs or symptoms of cancer at any given time point, the term "cure" suggests the cancer will never return. For Doug Olson and Bill Ludwig, some of the first patients to receive CAR T cell therapies, cure is a daily part of life. Both have been cancer-free for over a decade, and the infused CAR T cells they were administered continue to live on with them, a positive sign that they may continue to protect against relapses.[1]

What is CAR T cell therapy?
CAR T cells are genetically engineered T cells that kill cancer cells directly by targeting specific surface antigens.[2] They harness the intrinsic "seek and destroy" capabilities of T cells but can be customized by using viral vectors and non-viral methods to insert genes that redirect the T cell for a more targeted effect.[3,4]

As of today, there are six CAR T therapies available for treatment, approved by both US and EU authorities (Table 1). Each of them requires only one dose to work, after which the cells continue to proliferate in the patient's body after treatment, conferring, in theory, long-term protection against the disease. Clinical trials showed high rates of response to treatment, with many patients seeing their cancer disappear completely.[5] However, some patients still relapse and the majority of patients experience side effects. Understanding why some patients achieve remission and others don't is a daunting task, and factors such as prior medication use, the timing of treatment, how the CAR T cells were grown, and the cellular structure of the CAR T cell are some factors explaining varied treatment effects.[6]

Due to the immunosuppressive tumour microenvironment and the varied nature of solid tumour cells, current generation CAR T cells have a harder time selectively targeting solid cancers. Currently approved therapies are indicated exclusively for blood cancers, which tend to express antigens more uniformly.[7]

The role of biotechnology in CAR T cell therapy
Biotechnology may be defined as the innovative and creative application of biological substances and processes to develop industrial-scale solutions to complex problems. Biotechnological



advancements drive the pharmaceutical industry forward through its constant striving for safer and more effective therapies. They also benefit the food, energy, and healthcare industries.

Biopharmaceutical companies are often developed around specific biotechnological methods. One prominent example is CRISPR Therapeutics, a company co-founded by Nobel laureate Emmanuelle Charpentier, one of the two researchers who discovered CRISPR-Cas9 technology for gene editing. This tool has been adopted widely due to the ease by which genome editing can be customized. Many major players in the CAR T cell therapy space use it to improve the potency and safety of CAR T cell therapies.[8]

This process often begins in research laboratories, where manufacturing processes are developed through trial and error and subsequently refined. Once a consistent approach is discovered, a therapy can make its way to the clinic. Here, a multidisciplinary effort is required to make the process more reproducible, so that a consistent product can be produced in preparation for later-stage clinical trials and commercial manufacture, where adherence to current Good Manufacturing Practice (cGMP) guidelines is required.

Since the first regulatory approvals of CAR T cell therapies in 2017, there has been an explosion of interest in this field. Every aspect of this treatment is evolving at a rapid pace, including regulatory, manufacturing, supply chain and logistics, pricing and access, and the possible indications. Despite their popularity today, CAR T cell therapy was no overnight success story.

How CAR T cell therapy came to be

The first chimeric T cell receptors were engineered in the late 1980s and demonstrated for the first time that T cells can be supercharged with chimeric genes, allowing them to target specific cells.[9–10] The possibilities were now endless. In 1993, one of these researchers, Zelig Eshhar, from the Weizmann Institute of Science in Israel, proposed a method to use CAR T cells to target tumours, creating the first generation of CARs.[11]

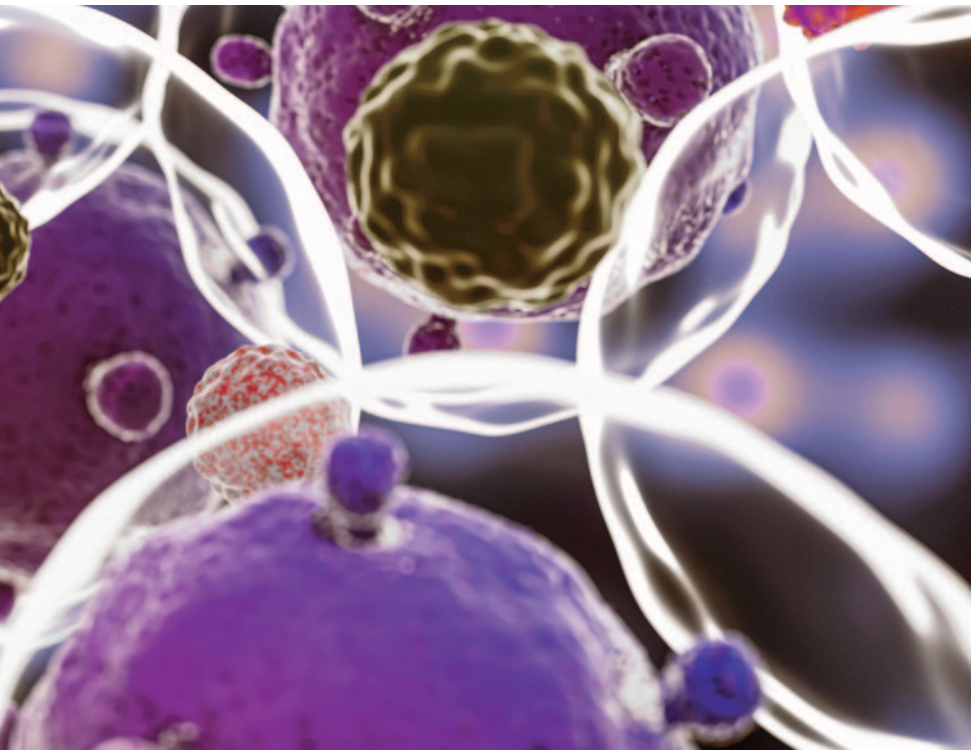
Chimeric T cell receptors do not only target specific antigens, they can activate other CAR T cells to help fight cancer.[12] When CAR-T cells encounter cancer cells displaying the target antigen, the CAR's extracellular domain binds to the antigen. This binding triggers a signalling cascade within the CAR T cell, leading to T cell activation and proliferation. The activated CAR T cells proliferate and lead to a robust immune response, consisting of cytokine release, helping to eliminate the target tumour cells.

One of the pioneers in CAR T cell therapy, Carl June at Penn Medicine, did not expect the treatment to apply to cancer when he first began researching it. In the mid-1990s, June was working to treat human immunodeficiency virus patients with genetically engineered T cells. Although this treatment was not effective against the virus, June and his colleagues made one important discovery: the activated T cells were found in the blood circulation of almost all the patients months after treatment, indicating the potential for long-term protection.[13] This phenomenon is called persistence and is an important element of how CAR-based therapies work.

CAR T cell therapies entered their first clinical trials in the early 2000s, to target kidney and ovarian cancers, two types of solid tumors.[14–15] Not only were the cells ineffective, they had "on target, off cancer" effects, destroying healthy tissue. These findings spoke to the importance of target specificity, and the need to engineer T cells that were more precise.

A breakthrough occurred only a few years later, when preclinical research conducted by three independent research teams and led by Michel Sadelain, Carl June, and Steven Rosenberg, demonstrated that CAR T cells targeting the cluster of differentiation 19 (CD19) antigen, a common marker found on B cells, had significant anti-leukemic activity.[16–18] Clinical trials on anti-CD19 CAR T cells were underway in the early 2010s, for acute lymphoblastic leukaemia and chronic lymphocytic leukaemia, two malignancies that mostly involve B cells. For the first time, patients achieved partial or complete remission with this treatment.[19–20] Emily Whitehead was one of those patients. When she was enrolled in the clinical trial when she was just a child, she was given only a few weeks to live and no other treatment had worked previously. Today, she has been cancer-free for ten years.

Now, other patients like her, such as Doug Olsen and Bill Ludwig, who were refractory to previous lines of treatment and had relapsed, have another lifeline. Unfortunately, most of the patients who hope to receive this treatment face unacceptable wait times. Bringing cell and gene therapies to patients at scale is not yet possible with current methods, but that is a major factor driving the industry forward.



Bringing CAR T cell treatments to more patients

One of the greatest challenges facing CAR T cell therapy, as well as cell therapy more broadly, is the complicated manufacturing process. The six approved therapies are manufactured using autologous T cells, which means that they are collected from and delivered to the same patient. This vein-to-vein workflow typically takes two to three weeks. The patient's T cells are isolated from peripheral blood mononuclear cells, enriched, grown to the desired dosage, and preserved until administration in the autologous CAR T cell therapy.[21]

In contrast, allogeneic CAR T cells would come from any healthy donor and would be processed otherwise in the same way. The race is on to develop effective allogeneic, or "off the shelf", CAR T celltherapy treatments because they would make this therapy more accessible to patients. Autologous therapies, on the other hand, are often transported across continents multiple times before they are given to the patient. The major disadvantage of allogeneic CAR T cell therapy is a higher risk of graft versus host disease and that the innate immune system will attack the CAR T cells.

Instead of a one-size-fits-all approach to cancer treatment, cell and gene therapies are individualised therapies. Each treatment is manufactured one at a time, resulting in long wait times. According to one physician survey, about 25% of patients eligible for CAR T cell therapy died in the process of waiting for treatment.[22] About a third of patients receive the treatments too late, which lowers their effectiveness and increases mortality risk.[23–24] Bringing more CAR T therapies to patients will involve further testing of their effects as first- and second-line treatments and building a faster manufacturing process.

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The process is the product

One unique aspect of the manufacturing of CAR T cell therapies is that "the process is the product." This adage is a subject of debate; however, it continues to guide the industry. Because of the variable nature of cellular products, not as much is known about the therapy itself and its mechanisms of action compared to small molecules and biologics.

Because of this, regulatory authorities require that manufacturers of CGT products use the same manufacturing process every time they release a new

Table 1. Approved CAR T cell therapies available in the United States and the European Union

BCMA denotes B-cell maturation antigen. CD19 is a protein expressed on the surface of B cells. Both are common targets for CAR-T cell therapies.

Brand Name	Scientific name	Manufacturer	Disease treated	Target antigen
Abecma	idecabtagene vicleucel	Bristol-Myers Squibb	Multiple myeloma	BCMA
Carvykti	ciltacabtagene autoleucel	Janssen Biotech, Inc.	Multiple myeloma	BCMA
Breyanzi	lisocabtagene maraleucel	Kite Pharma, Inc.	DLBCL, HGBCL, PMBCL, FL3B	CD19
Kymriah	tisagenlecleucel	Novartis Pharmaceuticals Corporation	ALL, DLBCL, FL	CD19
Tecartus	brexucabtagene autoleucel	Kite Pharma, Inc.	ALL, MCL	CD19
Yescarta	axicabtagene ciloleucel	Kite Pharma, Inc.	HCBL, DLBCL, FL	CD19

The indications for each CAR T cell therapy listed in this table include marketing authorisations from both the EU and the US, but differ based on the region. ALL: acute lymphoblastic leukaemia. BCMA: B-cell maturation antigen. DLBCL: diffuse large B-cell lymphoma. FL: follicular lymphoma. FL3B: follicular lymphoma grade 3B. HGBCL: high-grade B-cell lymphoma. MCL: mantle cell lymphoma. PMBCL: primary mediastinal large B-cell lymphoma.

batch of product. This even applies to the choice of equipment used to process the cells. Any changes to the manufacturing process require submitting evidence that the product has not changed in any meaningful capacity, as evidenced by comparability studies.[25]

Manufacturing changes are inevitable as more knowledge of the product and process develop together. But ideally, it is recommended to start with the best process and have all the expertise built in the company from the beginning, a difficult feat for any organisation. In contrast to running a marathon where you know where the finish line is and can always see the road in front of you, successfully commercialising a cell and gene therapy product is akin to a marathon on a road under construction.

The role of quality writing in this field

Medical communications play a vital role in keeping professionals informed of the latest developments in the CGT space. Writers should stay abreast of regulatory and manufacturing news, as well as be aware of macroeconomic forces. With cell and gene therapies set to be the fastest-growing type of pharmaceutical product over the coming decade, as measured by the number of clinical trials,[26] the US FDA is preparing to approve therapies faster. This has led to, for example, changing the name of the Office of Tissues and Advanced Therapies to the Office of Therapeutic Products, a "super office" as they describe it.[27]

Anticipating the future needs of biotech companies is important in understanding how to position a new innovation or product in the best way possible for success. Communicating strategically cannot occur alone here; collaboration within company departments as well as external partners is essential for acquiring key insights that might benefit a company's stakeholders.

This type of writing could be exciting for those who enjoy working in a dynamic environment, and intimidating for those more accustomed to working alone, and less so in a journalistic fashion. What excites me is knowing that what I create depends on data and ideas that are unique, context-dependent, and do not exist yet in the public domain. Effective scientific communication is the bridge between innovation and transformation in this field and provides the opportunity to be both creative and acutely aware of the scientific issues at hand.

What the future holds

Bringing down the costs of CAR T cell therapies is a top priority. [28] The treatments that are on the market today cost £450,000 for the treatment alone, but the total cost of care in the US healthcare system has been found to exceed $1M for some patients.[28-29] Discussions of lowering the cost of goods cite Pharma 4.0 as a necessary step in this endeavour and involves digitisation, automation, and the continuous manufacturing of biomedical products.[30] Another way to reduce costs is to enable allogeneic CAR T cell therapies and manufacturing them more centrally to the patient, eliminating overseas shipping and vastly improving patient reach.[31]

Autoimmune and cardiometabolic diseases may also be one day treated through CAR-based therapies, and a variety of cell types could be used as starting material.[32] Clinical trials are underway for CAR natural killer cell therapy, CAR macrophage therapy, tumour infiltrating lymphocyte therapies, T-cell receptor-based therapy, and extracellular vesicle therapy. Central to all of this innovation are people, and industry is working rapidly to train scientists to expand manufacturing capacities in the rush to get products to the clinic.

What we know today about cell and gene therapies will undoubtedly change in five to ten years. However, considering the scientific hurdles CAR T cell therapy has overcome in order to be as effective as it is today, and the hope that this treatment could ward off cancer, forever, and after just one dose, guarantees that study of CAR T cells will continue.

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Disclosures and conflicts of interest

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