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# Immuno-oncology cell therapy branches out

**Optimization of CAR-T cell technology and application of other immune cell types such as NK cells are tackling the efficacy, cost and logistical challenges of cell therapies for cancer.**

Nick Taylor

In 2017, a new modality for cancer therapy reached the market, when the US Food and Drug Administration (FDA) approved anti-CD19 chimeric antigen receptor (CAR)-T cell therapies developed for some types of blood cancer by Novartis and Kite. Although neither Kymriah (Novartis) nor Yescarta (Kite) has yet lived up to commercial expectations, in 2019 analysts still forecasted consensus peak revenues for each product of $1.7 billion, and the field is booming. More than 1,000 cell therapy agents are now in clinical development for cancer (*Nat. Rev. Drug Discov.* https://doi.org/10.1038/d41573-020-00099-9; 2020), and dealmaking has been highly active, led by Gilead's $11.9 billion purchase of Kite in 2017.

Gilead, Novartis and Bristol-Myers Squibb—which gained Juno Therapeutics' CAR-T cell therapies through its $74 billion takeover of Celgene in 2019—are seeking to build on their status as the leaders of the first generation of cancer cell therapies. The incumbents are facing growing competition from a sea of startups and other, deal-hungry biopharma companies in the race to better the efficacy of Yescarta and Kymriah in blood cancers, expand the use of cell therapies to new indications, including solid tumors, and simplify logistics and manufacturing.

## Simplifying logistics

Yescarta and Kymriah are made by taking blood from each patient, isolating, genetically engineering and expanding their T cells, and then reinfusing them—a long and costly process. Although neither Gilead nor Novartis has shared the cost of making their cell therapies, one independent analysis (*Cell Gene Ther. Insights* **4**, 1105–1116; 2018) estimated Yescarta costs at between $48,000 and $106,000 per dose to make. At the top end of that range, manufacturing would account for 28% of Yescarta's list price. Reducing the cost of making cell therapies could lower prices, enabling more patients to access the treatments.

As well as its cost, the personalized aspect of the manufacturing process used to make Kymriah and Yescarta requires patients to wait for treatment. In the USA, for example, Novartis aims to manufacture Kymriah in 22 days, meaning weeks pass in which a patient with a progressive disease is unable to receive treatment.

Off-the-shelf cell therapies (*Nat. Rev. Drug Discov.* **19**, 185–199; 2020) based on engineering cells from healthy donors could eliminate these logistical challenges (Fig. 1). Allogene Therapeutics, a startup in San Francisco founded in 2017 by ex-Kite executives, typically doses patients with its off-the-shelf anti-CD19 CAR-T therapy ALLO-501 five days after they enrol in its ongoing phase 1 trial in patients with lymphoma.

One potential risk with off-the-shelf CAR-Ts, also known as allogeneic products, is that the immune system will reject them and cause potentially serious graft-versus-host disease (GvHD). Allogene aims to mitigate that risk by using transcription activator-like effector nuclease (TALEN) gene-editing technology from Cellectis to knock out the α-chain of the T cell receptor (TCR) in products such as ALLO-501, which is being developed in partnership with Servier. In an early clinical assessment of ALLO-501 reported at ASCO (*J. Clin. Oncol.* https://10.1200/JCO.2020.38.15_suppl.8002; 2020), no cases of GvHD were observed, and the regimen showed signs of comparable efficacy to Kymriah and Yescarta.

Allogene's rivals are exploring other cell types that may be innately free of the GvHD risk. Biotechs such as Nkarta Therapeutics and Fate Therapeutics are pushing CAR-enhanced natural killer (NK) cells (*Nat. Rev. Drug Discov.* **19**, 200–218; 2020)—which lack TCRs—in light of evidence that their ability to use major histocompatibility complex (MHC) class I molecules to discriminate between normal cells and cancer cells will lower the risk of GvHD. Johnson & Johnson (J&J) bought into the idea in April 2020 by paying Fate $50 million to work on CAR-NK and CAR-T cell therapies, and Takeda signed a deal with undisclosed terms in November 2019 to access CAR-NK cell candidates from the MD Anderson Cancer Center.

Kuur Therapeutics has hitched its future to NKT cells, a rare immune cell subtype that shares some characteristics of T and NK cells, partly in the belief that their unchanging TCR supports an allogeneic approach. Other companies see γδ T cells (*Nat. Rev. Drug Discov.* **19**, 169–184; 2020) as the answer. Michael Koslowski, CMO at GammaDelta Therapeutics, explained why. "They don't recognize antigens in a MHC-dependent manner," he said. "They recognize what we call stress ligands on transformed cells. This is why you can actually use them as an allogeneic cell therapy platform". Takeda signed a $100 million deal with GammaDelta in 2017, which includes an option to purchase the company.

The proliferation of allogeneic approaches is yet to end interest in autologous cell therapies, though. Autolus Therapeutics, for example, has a pipeline of autologous CAR-T therapies that it thinks can succeed even if allogeneic rivals come to market.

Christian Itin, its CEO, expects to see a massive reduction in the time it takes to make autologous therapies in the future. In Itin's vision, production will take a similar time to the processing of prior authorization requests to payers and the other tasks that happen between the prescription and administration of a drug, meaning it will make little difference to patients and physicians whether a cell therapy is autologous or allogeneic. That could tip the balance back in favour of autologous therapies that, as they come from a patient, are free from the risk of immune rejection that lingers even after the TCR is knocked out. "Immune recognition of cells is complex. It's not just a question of MHC and TCR interactions," Itin said.

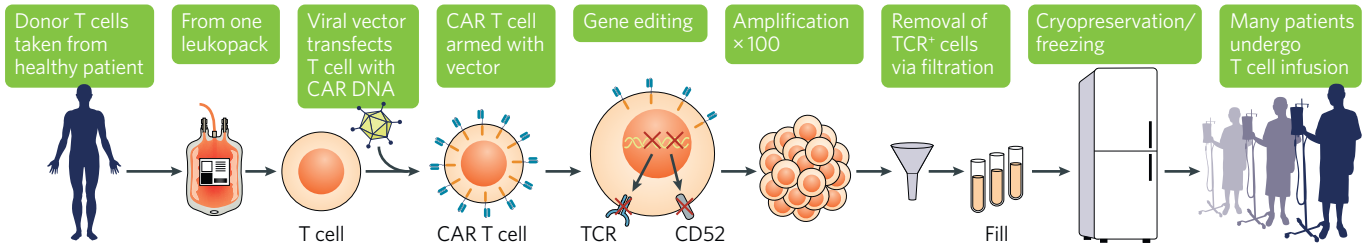


**Fig.1 | The process for manufacturing allogeneic CAR-T cells.** CAR, chimeric antigen receptor; TCR, T cell receptor.

## Enhancing efficacy

The push to simplify the logistics of cell therapy production is advancing alongside efforts to improve on the efficacy of first-generation products. Neither Yescarta nor Kymriah can be controlled after they are administered, creating potential safety issues, and most patients relapse after treatment. One efficacy issue is that anti-CD19 CAR-Ts such as Kymriah and Yescarta effectively select for cancer cells that are invisible to the therapies, as Yvonne Chen, Associate Professor of Microbiology, Immunology and Molecular Genetics at the University of California, Los Angeles, explained at the AACR Annual Meeting, held virtually in April 2020.

"A substantial fraction of [responders to CD19 CAR-Ts] eventually relapse," she said. "Many of them relapse with CD19-negative disease. Tumors escape from therapy by losing the antigen that T cells are targeting. This happens at such high frequency that many researchers have tried to identify additional antigens, aside from CD19, that could be used to target B cell malignancies".

Chen's comments related to the National Cancer Institute (NCI) trial of a bispecific CAR-T cell in B cell malignancies. By targeting CD19 and CD22 simultaneously, the drug is designed to stop antigenic escape. Biotechs including Autolus and Gracell Biotechnologies are developing similar cell therapies.

However, early data from the NCI trial show antigen escape is only part of the problem. Two of the five patients to experience complete responses relapsed with CD19/CD22-positive disease within 4–9 months, indicating an issue other than antigenic escape is at play, with limited persistence of the cells the likely cause of the relapses. The CAR-T cells persisted for 13–87 days in the peripheral blood. Beyond that, the patients appear to have lacked CAR-T cells to counter resurgent cancer cells.

"Persistence is probably a very good thing because you want to be able to nip relapsing cancer cells in the bud," Kurt Gunter, CMO at Kuur Therapeutics said. Kuur is trying to boost the persistence of its NKT cells by engineering IL-15 into them and introducing a short hairpin RNA (shRNA) system to knock down human leukocyte antigen (HLA) molecules that could cause immune rejection. The modifications could enhance endogenous efficacy of NKT cells that stems from their ability to kill tumor cells that are positive for CD1d, a molecule co-expressed with CD19 on B cell lymphomas. The potential for the dual targeting of CD19 and CD1d to improve on the efficacy of first-generation CAR-T cells has spurred work at Kuur and the team of Anastasios Karadimitris, Professor of Hematology at Imperial College London.

Other companies are tackling the persistence problem differently. Autolus' lead asset relies on optimized engagement of CD19 to enhance persistence. Poseida Therapeutics, which received a $75 million investment from Novartis in April 2019, is trying to achieve the same goal by using a high percentage of less-differentiated T cells.

Drug developers are also applying CAR-T technology to targets beyond CD19. In late 2017, for example, J&J paid $350 million upfront to Legend Biotech in Nanjing, China, for rights to an anti-BCMA CAR-T therapy that went on to record a 69% complete response rate in heavily pre-treated multiple myeloma patients. A later update showed deepening responses despite a lack of CAR-T cell persistence in many patients.

## Hitting solid tumors

Researchers still struggle to develop cell therapies that work well in solid tumors, often due to the lack of suitable cell surface targets for agents such as CAR-T cells in comparison to blood cancers; CD19 is expressed only on B cells, whereas low-level expression of a potential solid tumor target on normal tissue could pose a risk of high toxicity. And even if targets for solid tumors with a suitable tumor-selectivity profile can be identified, other factors may limit the activity of cell therapies that target them, including the low oxygen concentrations around such cancers, their expression of certain checkpoint genes and lacklustre T cell penetration.

Harpreet Singh, CEO of Immatics, thinks the failure of CAR-T cells in solid tumors stems from their restriction to cell surface targets. "Most of the relevant targets are actually hidden inside the cell, and the only way to make them accessible to immuno-oncology is through the peptide–HLA presentation pathway," he said. Celgene and GlaxoSmithKline have pursued this approach, paying Immatics $75 million and $50 million, respectively, to develop T cell therapies against intracellular targets.

While Immatics and its partners are betting on intracellular targets, others are trying to grow the list of cell surface targets they can safely hit. GammaDelta's Koslowski, for example, said the T cells his team are developing can differentiate between normal and transformed cells. That ability may enable GammaDelta to chase targets that would typically be considered likely to trigger safety and tolerability problems as they are expressed on healthy and cancerous cells."It definitely broadens the target space," he added.

## Partnering cell therapies

The diversity of challenges posed by different cancer types suggests researchers will need to come up with a similarly broad set of technologies for enhancing the efficacy and safety of cell therapies. With institutional and strategic investors willing to bankroll novel approaches, the stage is set for the industry to advance assets that overcome a variety of the defenses mounted by cancer cells.

As startups advance those projects, many companies will be interested in their assets. Gilead, Novartis and, to a lesser extent, Bristol-Myers Squibb have cell therapy businesses to defend, and their peers, including AbbVie, GSK, J&J, Roche and Takeda, have already bought into parts of cell therapy. Even biotechs are acquisitive, with Allogene buying Notch Therapeutics for a renewable cell source and Bayer-backed Century Therapeutics buying Empirica.

Biotechs that choose to partner or sell up gain the money and external validation that drives deals involving all drug modalities. In addition, the importance of specialized, hard-to-gain capabilities to cell therapy development and commercialization gives biotechs further impetus to strike deals.

Immatics' Singh said it is "very beneficial" for cell therapy biotechs to gain the experience of a partner that has a commercial perspective. Having partnered with Celgene and GSK, Immatics is done with single-target pacts, but the market dynamics look set to support more deals across the wider sector.

Improving the efficacy, pricing and safety of emerging cell therapies continue to be priorities, and increased partnering and investment is fueling efforts to address these challenges.

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