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Financing and Reimbursement of Cures in the US

RESEARCH BRIEF

By MIT NEWDIGS FoCUS Project

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Clinical trials and investment trends for novel CAR-T and TCR therapies

KEY TAKEAWAYS

Compared to small-molecule therapies, the nature of CAR-T/TCR therapies is such that they can be diversified with lower probability of failure in the clinic.

Many companies and academic entities are running clinical trials with different CAR-T/TCR products that often target the same disease.

A second wave of financial investments in CAR-T/TCR products has emerged alongside two early product approvals. Payers must be cognizant of future products emerging from the pipeline, expansion of indications, and the expected toll on their budgets.

Chimeric antigen receptor and T cell receptor (CAR-T/TCR) therapies have in the recent decade become one of the biggest breakthroughs in the history of medicine. This therapy is a result of over a century of scientific research aimed to understand the molecular and cellular biology related to human immunology and disease. The most successful use of CAR-T therapy was achieved with patients suffering from refractory B-cell lymphoma and leukemia, resulting in the launch of two FDA approved products: Kymriah (Novartis) and Yescarta (Kite Pharma). These companies used a similar CAR-T approach in which they eradicated all patient B cells, including both leukemic and healthy. For many patients, these therapies proved to be curative and they set the stage for the use of CAR-T cells in other oncology settings.

CAR-T/TCR therapies are complex. They are composed of cytotoxic cells that contain modular receptors. A diagram and a short scientific outline of a typical CAR-T/TCR design is presented in Box 1 and Figure 1. Receptor modules are rationally designed and each module has a unique therapeutic role. For example, there is a module that specifically targets the cytotoxic cell to recognize a cancer cell. A different module signals to the cytotoxic cell that a cancer cell is recognized so that the cytotoxic activity is activated only when the cancer cell is recognized. Much like Legos, these modules do not have to be fixed, as they can function independently of each other, and still be put together into a functional receptor. Therefore, when researchers want to build a new product by changing the specificity or other functional properties of CAR-T/TCR therapy, they can change and test each module independently with low probability of functional failure for the entire receptor. This is different compared to a small-molecule approach where small changes in the active molecule can have gross and unpredictable effects on many of its pharmacodynamic and therapeutic properties. For this reason, there is a higher barrier for diversifying a small-molecule therapy compared to a CAR-T/TCR therapy. Therefore, it would be expected that many different CAR-T/TCR products be developed for the same disease.

Our analysis of all available CAR-T/TCR clinical trials conducted under FDA guidelines confirms this expectation. Most notably, there have been at least 35 different therapies targeting CD19 B-cell leukemias and lymphomas that have

Box 1. The Basics of Chimeric Antigen Receptor

The *chimeric* in Chimeric Antigen Receptor (CAR) comes from the fact that this is an artificial gene assembled from parts of several other naturally occurring genes. The receptor is composed of several modules as outlined in the Figure 1:

- A module used to specifically recognize a target antigen is called scFv.
- The transmembrane domain is a module that keeps the CAR on the surface of the cytotoxic cell.
- Co-stimulatory and CD3ζ stimulatory domains are modules that send an activating intracellular signal to the cytoxic cell, resulting in the killing of the target cell.

Each of these modules can be changed, replaced, or other domains can be added without adversely affecting the ability of the cytotoxic cell to specifically kill a cancer cell. Other modifications are also possible with CAR-T cells, such as genetically engineering them to be more resistant to immunosuppressive signals that are often encountered in the tumor microenvironment.

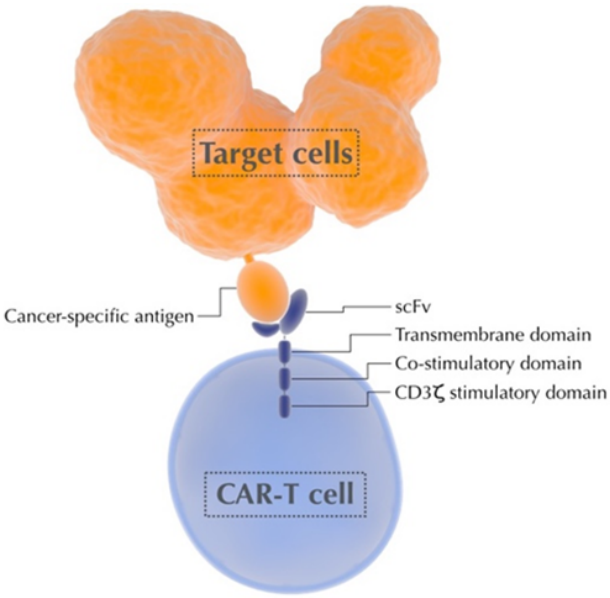

Figure 1. Structural Overview of Chimeric Antigen Receptor T-Cell (CAR-T) and Target Cell.

undergone FDA trials, for which two products have already been approved. In fact, there have been 201 initiated clinical trials that involve targeting CD19, which represent approximately 50% of all trials. The number of CAR-T/TCR clinical trials initiated each year continues to grow, and has risen exponentially since 2013 as seen in Figure 2. The reports of the first successful trials in the space were around this time.

In our analysis, we also compiled a list of CAR-T/TCR developers, for which we sourced venture capital, public offering, corporate deal, and grant money. From this analysis, we noticed the presence of several interesting properties. In contrast with the small-molecule landscape, which is typically dominated by a single agent such as one large pharmaceutical company, the CAR-T financial landscape is distinguished by a rather extensive network that contains many players who are connected financially, academically, and via technology licensing. In addition, financial flows into the CAR-T arena can be broadly characterized by two distinct waves as can be seen in Figure 3. The first wave is exhibited by an upward spike in investment starting in 2013, around the time clinical trials had risen exponentially. This wave was then followed by an abrupt dip in the latter half of 2016, a period which was marked by 5 deaths in Juno's CAR-T clinical trials due to off-target effects and toxicities related to cytokine release syndrome, as well as Novartis' decision to close its Cell and Gene Therapies Unit (Chen et al., 2016; Lash 2016, Ellis et al., 2016). Since the latter half of 2017, we have observed a sharp spike up in CAR-T investment and have entered what we designate as the second wave of investment.

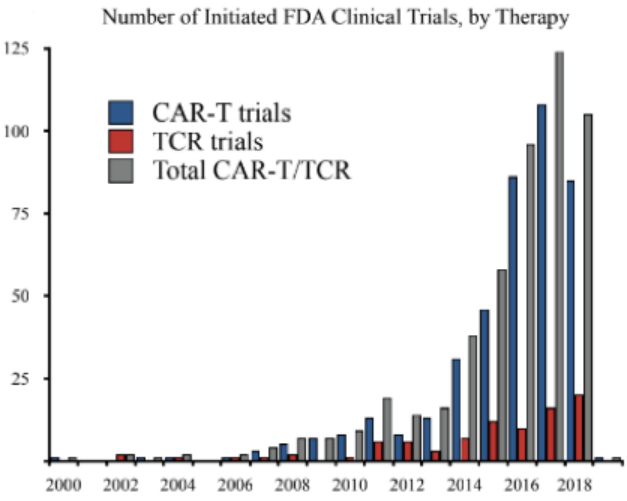

Figure 2. Number of Initiated FDA Clinical Trials per Year.

Our ultimate goal is to understand how this complicated network of different CAR-T/TCR developers with their numerous (yet similar) offerings will affect the landscape of the United States drug market. We also seek to comprehend the potential budget impact to payers moving forward, as the approvals of these early CAR-T products have officially set the stage for future product approvals and expansion of indications. Lastly, our work may serve useful to public policymakers overlooking public investment in the CAR-T/TCR market. Since there are many financial players investing in CD19 CAR-T therapies, it may make sense for the government to invest into a less saturated area, such as CAR-T therapies for head and neck cancer.

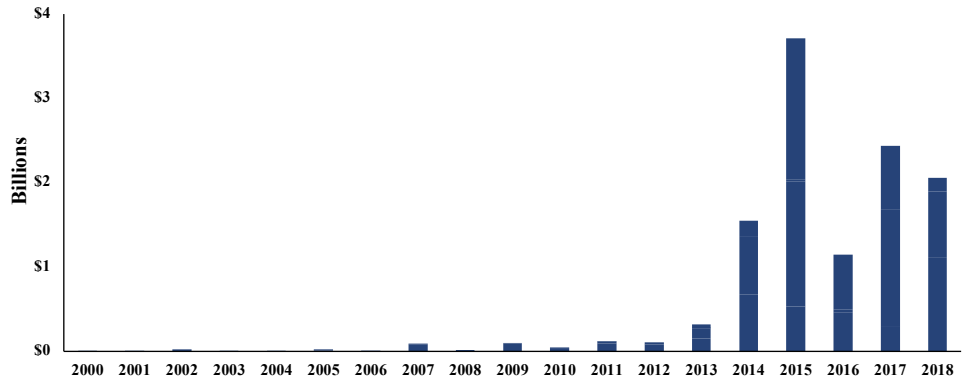

Figure 3. Annual Investment in the CAR-T Space from 2000 to Present.

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ABOUT FOCUS

The MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by durable therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement.

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