From fiction to reality: CAR-T therapies

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"Two years ago CAR-T was science fiction
One year ago it could never be a commercial product
Today there are two applications at FDA"
(Brad Loncar)

A patient enters a physician's office and has their cells extracted. These cells are then enhanced in a laboratory to train them to recognize, attack and eliminate a specific type of cancer. The engineered cells are then re-infused back into the patient and the cancer regresses. Imagining this process requires some fantasy and seemed improbable less than five years ago. Implementing this process into clinical practice opened logistic challenges that were deemed impossible to overcome less than two years ago. However, today the FDA is evaluating not just one, but two applications to bring this kind of therapy to patients in real life.

Autologous T-Cell Therapies are personalized approaches aimed at "training" a patient's immune system to fight his or her cancer. In the last year these therapies demonstrated potent and durable responses in several refractory (returning or recurrent) forms of cancer. One of the leading therapies in this family is the CAR-T (Chimeric Antigen Receptor T-cell) approach, targeting an antigen (CD19) found on several types of cancer.

It has been known for decades that humans can produce immune cells (called T-cells) that are able to recognize, fight and ultimately eliminate some tumors. Sadly though, cancer patients are often incapable of using these cells because their activity is blocked by the tumor or because the necessary T-cells are absent or not produced in sufficient quantities to be effective.

In recent years, several drugs termed checkpoint inhibitors, primarily monoclonal antibodies, have been developed to address the inhibitory mechanism that cancer cells use to avoid T-cell attack. Several of these drugs have garnered both clinical and market success, this includes approved treatments such as Yervoy, Opdivo or Keytruda from Bristol-Myers Squibb and Merck respectively.

To address the second problem, absence or lack of production of T-Cells, multiple academic research groups have attempted to isolate tumor infiltrating lymphocytes (the specific T-cells able to attack tumors), induce proliferation outside of the patient's body and then re-infuse a higher number of cells to the patient in order to combat the tumor.

Both these approaches are therapeutic options, but both rely on the capability of the patient's immune system to identify and recognize the tumor without external medical intervention and as a consequence their efficacy is highly variable from patient to patient and tumor type.

More recently, to face this latter aspect, multiple groups have developed methods for engineering anti-tumor T-cell responses by extracting the patient's T-cells, manipulating them to recognize particular antigens found on the relevant type of cancer and then re-infusing the patient with his or her "improved" T-cells.

The complexity of this process requires the perfect harmonization of several steps, but the possibilities are limited only by the identification of antigens specific to a disease (not only tumors) and the isolation and engineering of a receptor specific for the identified antigens.

The multiple challenges of the process span from the availability of functional T-cells in the patient that can be isolated and improved, to the organization and logistic of patient appointments, clinical staff, company

manufacturing processes and shipments of cryopreserved T-cells. The possibility of cryopreserving the modified T-cells gives the opportunity to re-treat patients without the need to repeat the full process from the beginning.

This approach to Immune-Oncology or Cancer Immunotherapy, that seemed very far from becoming a reality just a couple of years ago, is currently awaiting approval to treat liquid tumors, with applications in solid tumors coming in the next few years.

There are two companies that are recognized as the pioneers in CAR-T: Novartis and Kite Pharma, and they are in a race to bring this treatment to market.

Novartis has recently received its second breakthrough therapy designation by the FDA (a label that warrants a speedier review process by the agency) for CTL019 (tisagenlecleucel-T) for which a Biologic License Application has been accepted by the agency and applications in the EU are ongoing. Responses from the FDA are expected by the end of 2017 or the beginning of 2018. The CTL019 submission is based on the results of the ELIANA study in pediatric patients with relapsed and refractory B-cell Acute Lymphoblastic Leukemia that showed an 82% remission rate and of the JULIET study in adult patients with relapsed and refractory Diffuse Large B-cell Lymphoma. The results of the study will be disclosed later this year.

Kite Pharma is developing its KTE-C19, axicaptagene ciloleucel, to treat a form of Non-Hodgkin lymphoma. Late stage studies demonstrated positive results after a single infusion. The company has submitted a Biologic License Application, has a breakthrough therapy designation with the FDA and will submit a Marketing Authorization Application with the European Medicines Agency later this year. Responses from the agencies are expected by the end of 2017 or the beginning of 2018. Kite's submission is based on results from the ZUMA-1 study in patients with aggressive relapsed and refractory forms of Non-Hodgkin Lymphoma with 82% remissions of which 49% are complete remissions.

Both Novartis and Kite are approaching CAR-T with an autologous process, meaning that the T-cells that are "trained" to fight cancer come from the patient's body to minimize the risk of rejection.

Cellectis, a French based company, is developing UCART19, an allogeneic CAR-T therapy, which means that the engineered T-cells come from healthy donors. With this approach the treatment will be not be prepared patient-by-patient but is an "off the shelf" treatment tailored to a specific disease, making it easier to store, administer and also reducing the costs associated with this potentially life-saving procedure.

Cellectis is currently in phase I clinical trials, examining UCART19's safety, tolerability and antileukemic activity in patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia. Based on previous *in vitro* and *in vivo* studies the company is confident it will be able to provide a potent and viable treatment for hematological malignancies in the coming years.

The commonality shared by Novartis, Kite and Cellectis is that they are all targeting forms of liquid tumors; this is mainly because in order to induce a favorable clinical outcome in solid tumors, CAR-T cells have to surmount a series of increasingly arduous hurdles. First they have to be made specific for an antigen whose expression clearly demarcate tumors from normal tissues. Then they must be able to locate and penetrate the desmoplastic stroma that surrounds the tumor. Once within the tumor they must expand and do their job in an extremely hostile immunosuppressive microenvironment that is harsher as compared to liquid tumors.

One of the first companies trying to attack solid tumors with CAR-T is Celyad, an R&D company specialized in cell therapy that is developing technologies using both autologous and allogeneic approaches. Its lead asset is CAR-T NKR-2 that is currently being evaluated in the phase I THINK trial in 7 different indications,

both hematological (Acute Myeloid Leukemia and Multiple Myeloma) and solid tumors (bladder, ovarian, breast, pancreas and colorectal).

Tremendous progress has been made in the CAR-T approach to fight cancer. Promising therapies will soon be adopted by oncologists worldwide and scientists are constantly researching to further develop new and effective weapons against this disease.

The companies mentioned in this article represent an investment opportunity that can provide outstanding return to investors, but choosing the right investment needs expertise and know-how that only specialists can provide. The evaluation of early stage biotech companies involves the knowledge of economics, basic science, clinical execution, the competitive landscape of the sector and its regulatory framework. This is why all investors without in-depth knowledge of the industry should be careful and use professionals to drive their investment decisions.

Sources: Bristol-Myers Squibb Company, CAR-T cells for solid tumors by Sunitha Kakarla and Stephen Gottschalk, Cellectis SA, Celyad SA, Cowen and Company, European Cancer Patients Coalition, Kite Pharma Inc, Novartis Institute for Biomedical Research, Us National Cancer Institute, US National Center for Biotechnology Information.

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