MANUFACTURING ADOPTIVE IMMUNOTHERAPIES

ADOPTIVE CELLULAR THERAPIES ARE BASED ON THE ADMINISTRATION OF LIVE CELLS INTO A PATIENT IN ORDER FOR THEM TO SERVE A THERAPEUTIC PURPOSE.

Pharmaceutical products have been historically made of purified small molecules or proteins. Conversely, live human cells are a complex substance made of millions of different molecules, which proportions vary as cells are exposed to different environments and conditions. The composition of a cell-based product is essentially determined by the process, cell culture conditions and environment it went through. The challenges associated with mastering the production and control of cellular products are much higher than for classical drugs. It takes significant resources, special know-how and expertise, and may also require long development times.

ALLOGENEIC ADOPTIVE CELL THERAPIES: THE TRANSITION FROM THE WORLD OF GRAFT TO PHARMACEUTICAL PRODUCTS

Cell-based therapies have grown in the world of individual grafts. A major limitation in that field lies with donor-recipient compatibility. Tissues or cells from a donor may be rejected when infused into another person unless a particular compatibility exists between the two individuals. Moreover, there is another risk, that may lead to the grafted cells attacking the healthy tissues of the grafted patient (known as "graft versus host disease").

As a result, most of cell-based therapies are autologous: the cells infused into the patient originate from that very patient. Each patient requires an individual bespoke product, which is a significant hurdle to the standardization and industrial manufacturing of such therapies.

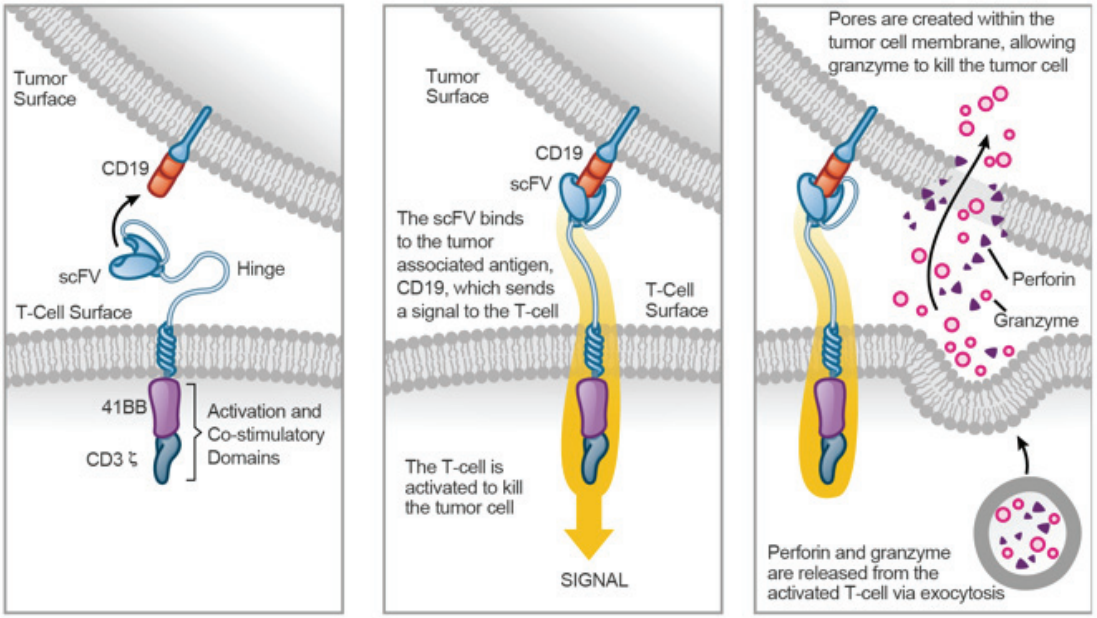
Cellectis is using its gene-editing expertise and capabilities to develop allogeneic cell therapies, meaning they are derived from healthy donors rather than from the patients themselves. With this approach, Cellectis is turning these therapies into industrial pharmaceutical products that could be cost-effective, made readily available - "off-the-shelf" - to broad patient populations in hospitals without need for local cell manufacturing facilities, and easily distributed across all geographies. That paradigm-changing strategy relies on the successful development and deployment of a solid, scalable and industrial manufacturing for these powerful cellular therapeutics.

MANUFACTURING "OFF-THE-SHELF" ADOPTIVE T-CELL IMMUNOTHERAPIES

PROVIDING SOLUTIONS FOR UNMET MEDICAL NEEDS

Cancer immunotherapies consist in harnessing the power of the immune system to fight cancers. The immune system protects the human organism by identifying and destroying foreign bodies, such as infected or abnormal cells, that carry "non-self" antigens (molecular signatures). A key component of the immune system lies in the T-cells, a kind of white blood cells that are specialized both in sensing and killing infected or abnormal cells, as well as in coordinating the activation of other cells and mounting an immune response.
However, cancer cells thrive, in part, because they trick the immune system into treating them as "self" cells, even though they express abnormal antigens. Cellectis' therapeutic programs are focused on developing genetically modified T-cells that express a Chimeric Antigen Receptor (CAR) enabling them to target and kill cancer cells, and that also have additional features, such as compatibility between healthy donor T-cells and numerous patients, or compatibility of the engineered T-cells with drugs that are normally given to cancer patients. Cellectis' gene editing is also used to circumvent tumor defense mechanisms so that T-cells can treat cancer as abnormal cells.

The mechanism by which a CAR T-cell attacks a tumor cell



HOW ARE UCART PRODUCT CANDIDATES MADE?

FROM LABS TO HOSPITALS

Before the actual manufacturing process may be completed, several steps are required in order to design standardized products:

- Cellectis' research & development team draws up and carries out experimental protocols, then analyzes and interprets the results. Researchers showcase their results and present technological developments to the scientific community and file licenses and patents.
- The process development team is in charge of turning R&D methods into production processes that will be implemented in a cGMP environment. These scientists develop and run a broad range of analytical tests, in order to ensure that the production process is reliable and fully controlled.
- Preclinical studies, conducted both *in vitro* and *in vivo*, aim to demonstrate the anti-tumor activity of the UCART product candidates, to study their mechanism of action and to assess their potential toxicity following administration to patients.

Guidelines and regulations pertaining to the manufacturing of pharmaceuticals are established by government agencies such as the Food and Drug Administration (FDA) in the US in order to ensure the safety and efficacy of each batch of medicines a patient receives. Various significant elements must be considered while implementing a manufacturing process:

- The current Good Manufacturing Practices regulations enforced by the FDA provide for specific systems ensuring that design, monitoring, and control of manufacturing processes and facilities are consistent and quality-controlled.
- "Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations." - Facts About the current Good Manufacturing Practices (cGMP), www.fda.org
- A quality system, adapted to each product development phases, guarantees that cGMP are followed. Quality assurance is based on a manual defining policies to be observed, in order to ensure the homogeneity of documentation relating to product development and ensures compliance with standards and regulations in case of technology evolutions.
- The regulatory affairs consist in ensuring that drug candidates' development is carried out according to the applicable rules, regulations and directives. The regulatory affairs team elaborates the drug candidates' development plan and acts as an interface with regulatory agencies.

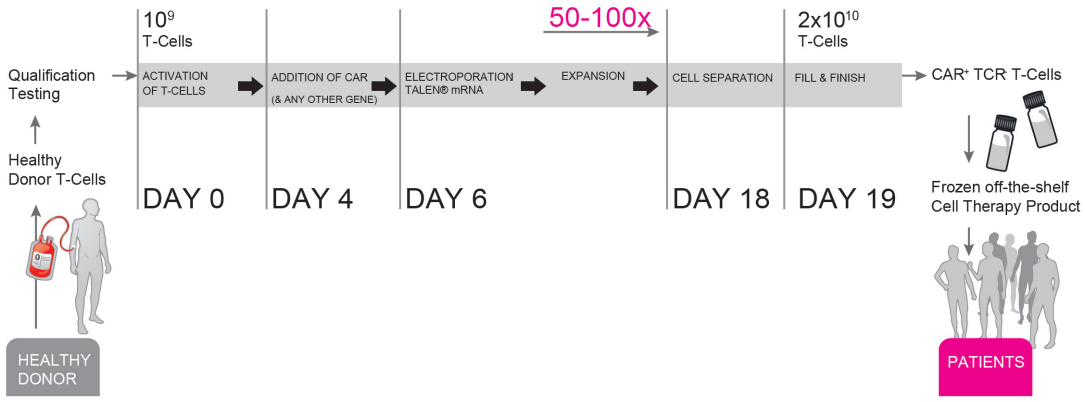
Once the manufacturing procedures have been implemented and validated as safe and consistent, the product developed can be distributed during several stages:

- Clinical studies consist in administrating the product candidate to groups of selected volunteers that can vary according to the stages of product candidate development. These studies usually start with small groups of volunteers and aim to assess the product's safety and efficacy through marketing authorization.
- Commercialization of a new product in the US is subject to the FDA's approval, based on the Biologic License Application (BLA) that is submitted by pharmaceutical companies to gain approval for sale and marketing.

A SOPHISTICATED MANUFACTURING PROCESS

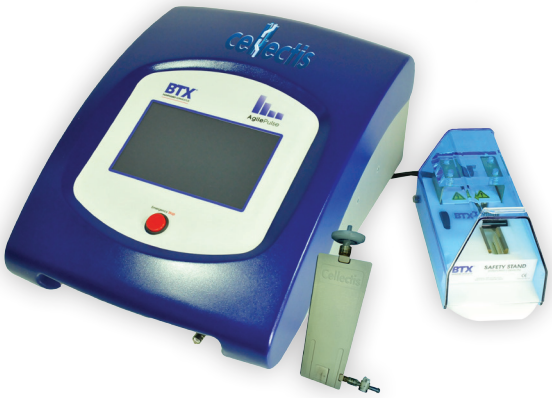
Cellectis has developed a process to systematically and consistently engineer, produce and control allogeneic universal CAR T-cells (UCARTs), in cGMP conditions, abiding by the high pharmaceutical quality standards applicable to the manufacturing of drugs. This process extends over a 19 days period and involves multiple steps of cell handling, activating, engineering, amplification, purification as well as final filling and freezing. It is then followed by extensive quality control on the frozen product candidate.

Manufacturing process platform: designed for cGMP compatibility



HEALTHY DONOR T-CELLS ARE THE STARTING MATERIAL

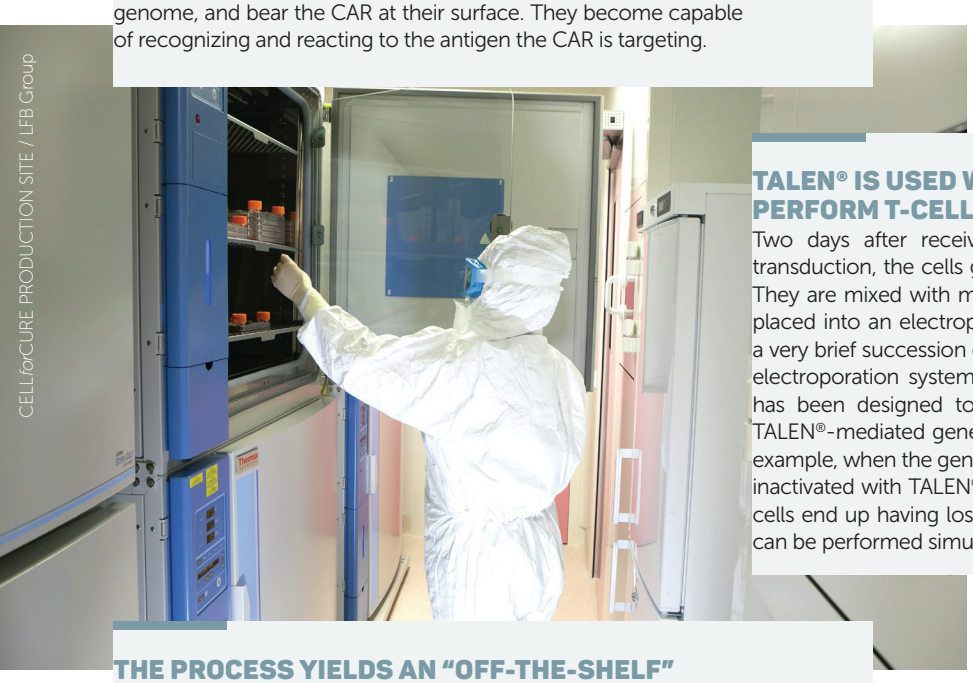
UCARTs are engineered allogeneic cell therapy "off-the-shelf" product candidates. They come from white blood cell collections ("leukapheresis") performed in the US as per guidelines and regulations applicable both in America and Europe. The donors are selected volunteers whose health is being controlled prior to donation. The few billion cells collected ("PBMC") undergo quality control. They are frozen in multiple bags and shipped to the manufacturing facility where they can be stored until UCART production runs start.



PulseAgile is a proprietary system that allows introducing macromolecules, such as mRNA coding for TALEN®, into living cells. This electroporation system achieves both high efficiency and high cell viability, ensuring better products and yields.

GENES INCLUDING THE CAR ARE ADDED, USING AN ENGINEERED VECTOR

A UCART production run starts from a bag of frozen controlled cells coming from a healthy donor. The cells are placed in culture and activated to start multiplying. Then the first engineering step takes place. Genetic material is permanently added to the cells by placing them in close contact with a viral vector carrying the genes to be added to the cells' genome. That vector is basically an inactivated viral vehicle that cannot multiply but can deliver the CAR gene and also additional genes (such as a suicide peptide-coding gene for example) into the cells. Once transduced, the cells start expressing the transgenes they have received and incorporated into their genome, and bear the CAR at their surface. They become capable of recognizing and reacting to the antigen the CAR is targeting.



CELL*for*CURE PRODUCTION SITE / LFB Group

TALEN® IS USED WITH PULSEAGILE TO PERFORM T-CELL GENE EDITING

Two days after receiving new genes through this vector transduction, the cells go through a second engineering step. They are mixed with messenger RNA coding for TALEN® and placed into an electroporation chamber where they undergo a very brief succession of electrical pulses. Cellectis' PulseAgile electroporation system delivers an electrical wave form that has been designed to provide both high efficiency in the TALEN®-mediated gene inactivation and high cell viability. For example, when the gene coding for the T-cell receptor (TCR) is inactivated with TALEN® in that system, more than 80% of the cells end up having lost their TCR. Multiple gene inactivations can be performed simultaneously in a single pulse.

THE PROCESS YIELDS AN "OFF-THE-SHELF" PHARMACEUTICAL PRODUCT

After these engineering steps, the cells are cultured for about 11 days during which they multiply. They are then purified to get rid of remaining TCR bearing T-cells, and aliquoted in vials prior to being frozen. Extensive quality control takes place during the entire process, and also for weeks after on the frozen product. Starting from about 1.5 billion PBMCs, the process yields dozens of billions of frozen cells, enough for hundreds of patient doses. Cellectis' UCART manufacturing process delivers an "off-the-shelf" pharmaceutical product with all associated controls, allowing systematic and reproducible uses of the product and ensuring its quality.

CELLECTIS, AT THE FOREFRONT OF THIS REVOLUTION

CELLECTIS' PIPELINE

Cellectis' current solid therapeutic pipeline is focused on UCARTs targeting liquid (i.e. blood) cancers. All the product candidates are "off-the-shelf" engineered CAR T-cell-based. Cellectis' wholly owned products include product candidates aimed at up to 12 targets. Four product candidates have been disclosed at this day.

UCART123 is the lead engineered allogeneic T-cell product candidate in Cellectis' wholly owned portfolio. UCART123 targets CD123, an antigen expressed on the surface of cancer cells in malignancies, such as acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cells neoplasm (BPDCN). This product candidate is being developed in these two indications in collaboration with renowned clinical centers at Weill Cornell Medical College (New York City, NY) and the M.D. Anderson Cancer Center (Houston, TX).

UCARTCS1 and **UCART38** are engineered allogeneic T-cell products designed for the treatment of CS1-expressing or CD38-expressing hematologic malignancies that develop in multiple myeloma (MM). In addition, CD38 is also a target in T-cell leukemias. These product candidates are being developed in these two indications in collaboration with the M.D. Anderson Cancer Center.

UCART22 could be used in acute lymphoblastic leukemia (ALL) and B-cell malignancies. CD22 is a cell surface antigen expressed from the pre B-cell stage of development through mature B-cells. CD22 expression can be maintained in CD19-negative blast cells in ALL.

MANUFACTURING CAPACITIES

In 2015, Cellectis developed its UCART manufacturing process and deployed it into a cGMP industrial environment. This capacity to produce clinical supplies of its product candidates is transformative and key in establishing Cellectis as a biopharmaceutical company.

Our lead immuno-oncology product candidates

Product name Targeted Indication	Product development	*In Vitro* Studies	*In Vivo* Studies	Manufacturing	CTA/IND filing	Alliance
UCART123 Acute Myeloid Leukemia (AML) / Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)						Wholly-Owned
UCARTCS1 Multiple Myeloma (MM)						Wholly-Owned
UCART38 Multiple Myeloma (MM) / T-cell Acute Lymphoblastic Leukemia (T-ALL)						Wholly-Owned
UCART22 Acute Lymphoblastic Leukemia (ALL)						Wholly-Owned

COLLABORATION WITH CELL*FOR*CURE

In order to build on highly-efficient and reliable manufacturing processes, Cellectis has been working since 2014 in partnership with CELL*for*CURE, the largest commercial industrial facility for the production of innovative therapeutic cell therapies in Europe, and a subsidiary of the biopharmaceutical group LFB. Pursuant to their agreement, Cellectis entrusts CELL*for*CURE with the manufacturing of cGMP clinical batches of Cellectis UCART product family.

In January 2016, following the recent successful production of UCART19, Cellectis announced that it entrusted CELL*for*CURE with the cGMP manufacturing of UCART123 clinical batches, Cellectis' lead product candidate. CELL*for*CURE is in charge of implementing cGMP manufacturing processes designed and developed by Cellectis.

CELL*for*CURE PRODUCTION SITE / LFB Group

GLOSSARY

cGMP (OR GMP IN EUROPE)
Current Good Manufacturing Practices, or cGMP, are a set of regulations applicable to the manufacturing of health products, especially medicines intended for human use, such as UCART products.

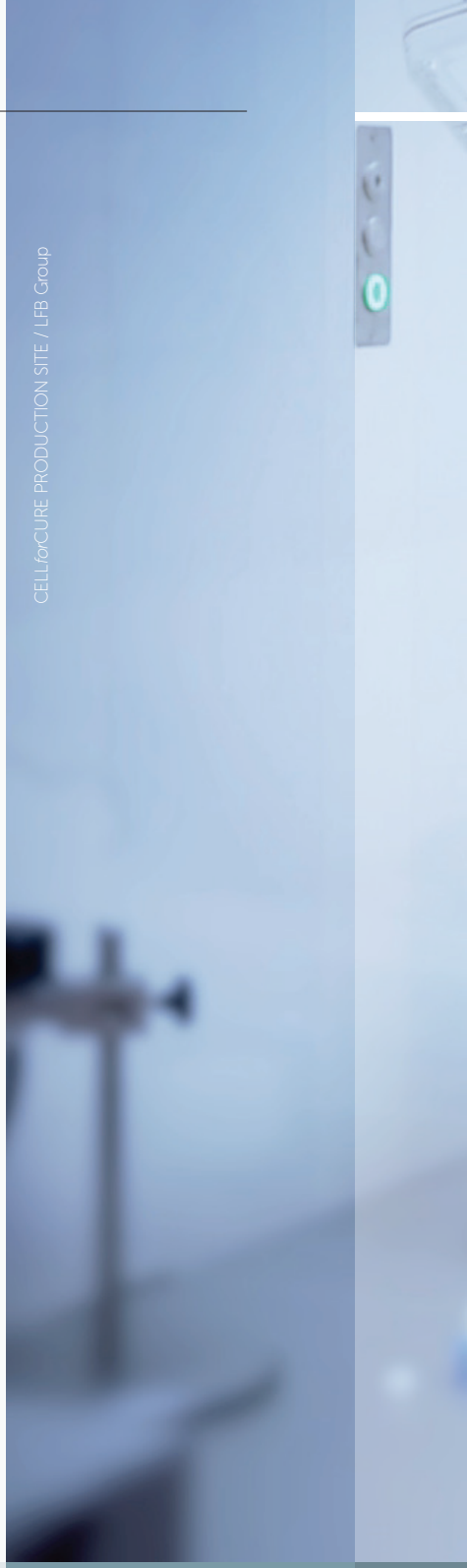
T-CELLS
T-cells can be considered as the immune system's soldiers. They are a type of white blood cells that play a key role in the immune system, by searching for and destroying infected or abnormal cells; however, cancer cells often develop mechanisms to evade the immune system.

UCART
UCARTs (Universal Chimeric Antigen Receptor T-cells) are "off-the-shelf" allogeneic CAR T-cells engineered to be used for treating any patient with a particular cancer type.

TALEN®
TALEN® are engineered sequence-specific highly potent nucleases used as "DNA scissors" that bind and cleave pre-selected DNA sequences.

CAR
Chimeric Antigen Receptors, or CARs, are engineered molecules that, when present at the surface of T-cells, enable them to recognize specific proteins or antigens that are present on the surface of other cells.

PBMC
Peripheral Blood Mononuclear Cells, or PBMC, are white blood cells. They include multiple cell types such as lymphocytes (T-cells, B-cells, NK-cells) and monocytes, that are components of the immune system.



CELLECTIS IN BRIEF
Cellectis is a biopharmaceutical company focused on developing immunotherapies based on gene edited engineered CAR T-cells (UCART). The company's mission is to develop a new generation of cancer therapies based on engineered T-cells. Cellectis capitalizes on its 16 years of expertise in genome engineering - based on its flagship TALEN® products and meganucleases and pioneering electroporation PulseAgile technology - to create a new generation of immunotherapies. CAR technologies are designed to target surface antigens expressed on cells. Using its life-science-focused, pioneering genome-engineering technologies, Cellectis' goal is to create innovative products in multiple fields and with various target markets. Cellectis S.A. is listed on the Nasdaq Global Market and on the NYSE Alternext market.

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