SOMATIC-CELL THERAPY INTRODUCTION

PR. NATHALIE CHAPUT - INSTITUT GUSTAVE ROUSSY_CELL THERAPY UNIT_ ADULT HEMATOLOGY DEPARTMENT - UNIVERSITE PARIS-SCALAY_M1 INTERNATIONAL

COURSE OUTLINE

- What is somatic-cell therapy
- Regulations for somatic-cell therapy products : Somatic-cell therapy products or Advanced Therapy Medicinal Products ?
- Global vision of the production process for a somatic-cell therapy
- Somatic-cell therapy products
- ATMPs validated for clinical use in humans

SOMATIC-CELL THERAPY

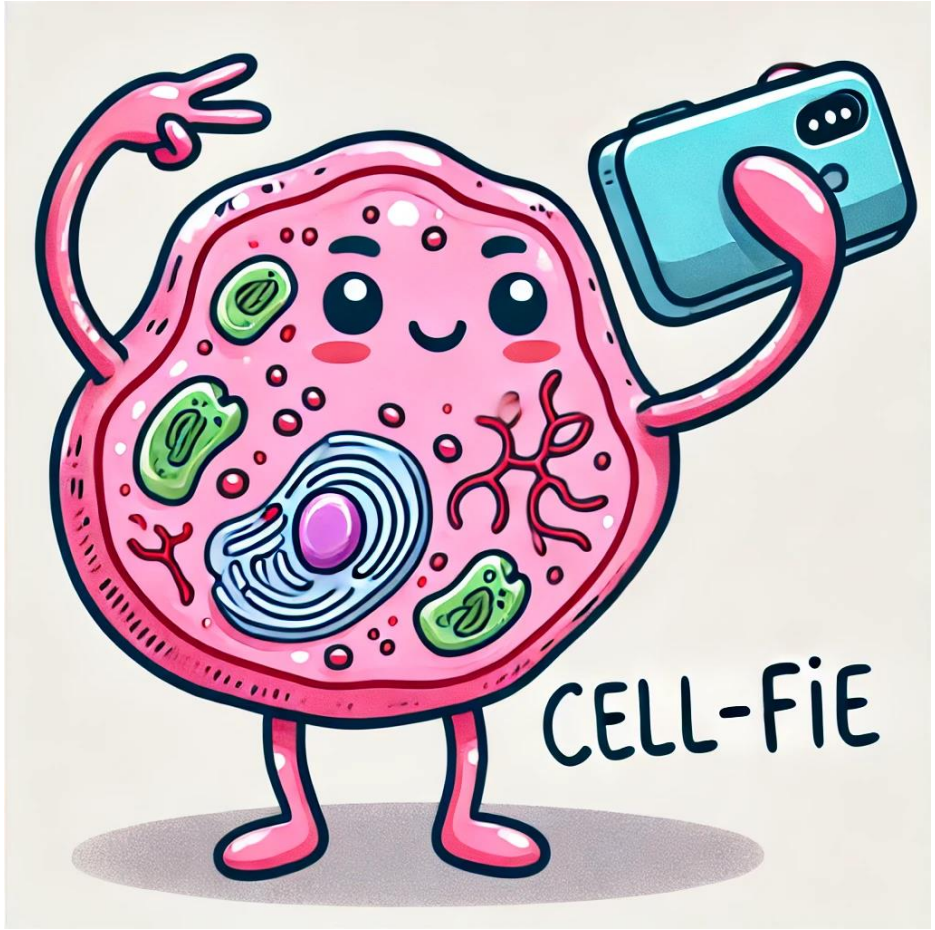
SOMATIC-CELL = ANY CELL OF THE BODY EXCEPT GERM LINE CELLS

SOMATIC-CELL THERAPY VERSUS TISSUE ENGINEERED THERAPY

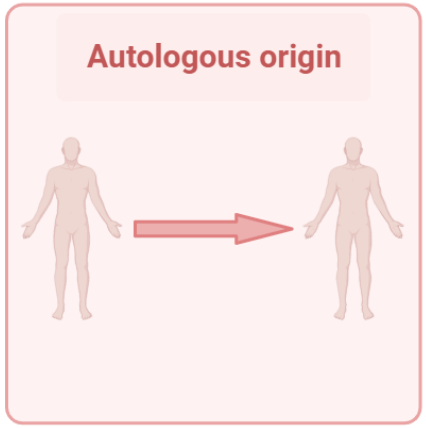
- Somatic cell therapy **contains cells or tissues** that have been manipulated before being reintroduced into patients.
- These cells or tissues may be of **autologous** (from the same individual), **allogeneic** (from a donor of the same species), or **xenogeneic origin** (from a donor of a different species).
- The goal of **somatic cell therapy** is to **treat, diagnose, or prevent diseases**.
- The goal of **tissue engineered therapy** is to **repair, regenerate, replace**

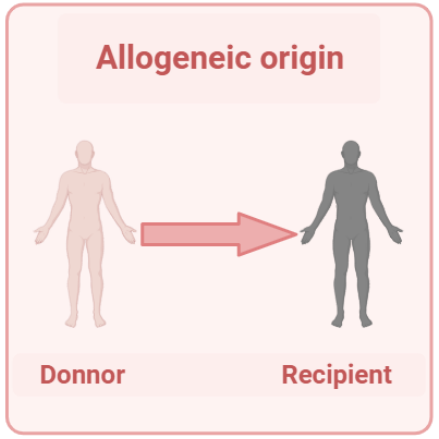
SOMATIC-CELL THERAPY

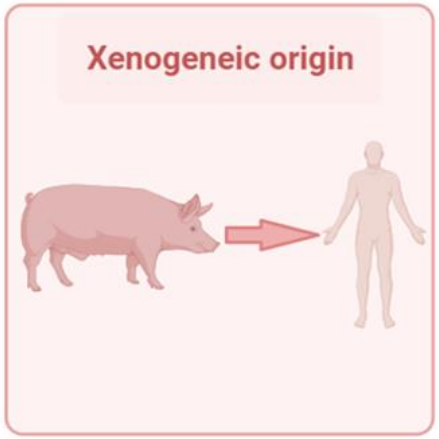
- To perform cell therapy, **living cells** are required.



SOMATIC-CELL THERAPY







SOMATIC-CELL THERAPY
AUTOLOGOUS VERSUS ALLOGENEIC

Autologous Somatic-cell therapy medicine

+	-
Well tolerated	Supply remains limited
Can be amplified in vitro	Process standardization remains difficult
Raise fewer ethical issues	

Allogeneic Somatic-cell therapy medicine

+	-
Available in greater numbers than autologous cells	Raise ethical issues if they are derived from embryos
Possibility of process standardization	Frequent immune reactions
Can be amplified in vitro	

Off-the-Shelf treatment

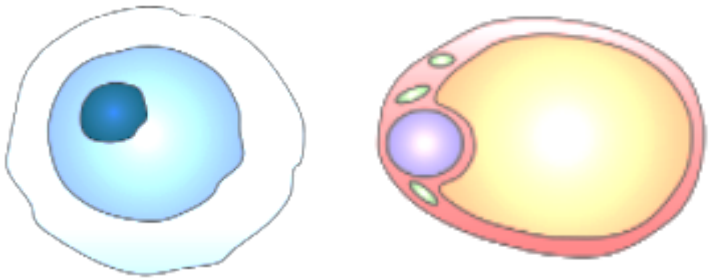
CELLS THAT ARE USED FOR CELL THERAPY

- In cell therapy, various cell types are used, each with specific characteristics and applications.
- Today, in clinically validated cell therapy, the primary cells used are **stem cells**

CELLS THAT ARE USED FOR CELL THERAPY

Cells used are categorized according

- to their origin
- and their level of differentiation

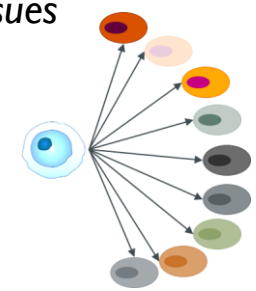


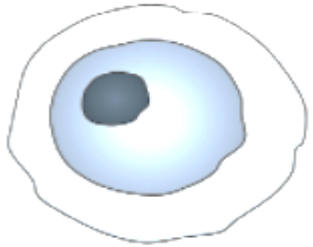
Stem cell Specialized cell

CELLS THAT ARE USED FOR CELL THERAPY

Pluripotent embryonic stem cells

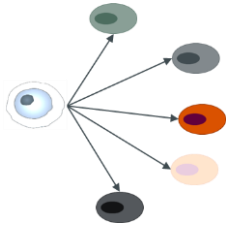
- *Stem cells capable of **producing all types of cells** in an organism except extra-embryonic tissues*

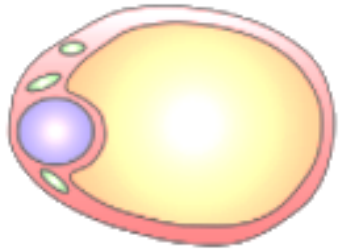




Adult multipotent stem cells

- *Stem cells capable of producing a **large number** of cell types **but not all** of them. Ex : hematopoietic stem cells*





Differentiated / specialized cells

- *Functional ("mature") differentiated cells can produce active substances as soon as they are implanted*

REGULATION FOR CELL THERAPY PRODUCTS

- Regulation distinguishing somatic cell therapy as a **Cell Therapy Preparation (**not considered as a medicine!) and **Advanced Therapy Medicinal Products** (ATMP, considered as a medicine)
- … 2 different regulations …

REGULATION FOR CELL THERAPY PRODUCTS

Cell or tissue-engineered therapy products

A therapeutic product that contains or consists of cells to treat, prevent, or diagnose a disease (cell), or to repair, regenerate, or replace human tissue (tissue), but is not considered a medicinal product ≠ ATMP.

- These are cells or tissues that have not undergone any substantial modification
- **And** their essential properties remain unaltered, and they are intended to perform the same physiological function.

Example: Hematopoietic stem cell transplantation for hematologic reconstitution

Advanced Therapy Medicinal Products (ATMP)

A therapeutic product that contains or consists of cells to treat, prevent, or diagnose a disease (cell therapy medicines), or to repair, regenerate, or replace human tissue (tissue-engineered medicines), with medicinal product status.

- These products have either undergone substantial modification
- **Or** are intended for different physiological functions than originally performed.

Example : Alofisel (MSC) to treat complex anal fistulas in adults

REGULATIONS : GENERAL RULES

	ATMPs	Cell therapy products
Authorized manufacturer facility	Pharmaceutical company	Cell processing facility Authorized by the French Drug Agency (ANSM) in France
Manufacturing rules	Good Manufacturing Practice for drugs (PART IV)*	Good Manufacturing Practice for Cellular therapy products **
Person in charge	Qualified person : pharm. D. in France or master degree in pharmacy, medicine, pharmaceutical chemistry, biology or veterinary medicine elsewhere in Europe	Processing facility director i.e medical degree or doctoral degree (MD, PharmD, PhD)
Import / Export	Yes	Yes if authorized (ANSM in France)

** December 29, 2015 version, modified by the decisions of December 30, 2016 and May 6, 2019. Part IV: Specific to ATMPs*

*** Article L. 1245-6 du Code du CSP_ Decision of May 5, 2017 modifies the good practices for the preparation, preservation, transport, distribution and disposal of tissues, cells and cell therapy preparations _transposition into French law of the European Directive (EU) 2015/565*

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

ATMPs (Advanced Therapy Medicinal Products) **are medicines for human use** that are based on genes, tissues, or cells. They offer groundbreaking opportunities for treating disease and injury.

ATMPs are classified into three main types:

- **Somatic-cell therapy medicines**: These contain cells or tissues that have been manipulated to alter their biological characteristics or are used for functions different from their original role in the body. They may be used to treat, diagnose, or prevent diseases.
- **Gene therapy medicines**: These contain genes designed to produce a therapeutic, prophylactic, or diagnostic effect. They work by inserting 'recombinant' genes into the body, typically to address genetic disorders, cancer, or chronic diseases. A recombinant gene is a laboratory-created DNA sequence that combines DNA from different sources.
- **Tissue-engineered medicines**: These products contain cells or tissues modified for use in repairing, regenerating, or replacing human tissue.

For detailed definitions of the different groups of advanced therapy medicinal products, refer to Regulation (EC) No 1394/2007 and Directive 2001/83/EC

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, which are referred to as **combined ATMPs**.

- An example of this is cells embedded in a biodegradable matrix or scaffold.

Gaharwar, A.K., Singh, I., Khademhosseini, A., 2020. Engineered biomaterials for in situ tissue regeneration. Nature Reviews Materials 5, 686–705.. doi:10.1038/s41578-020-0209-x

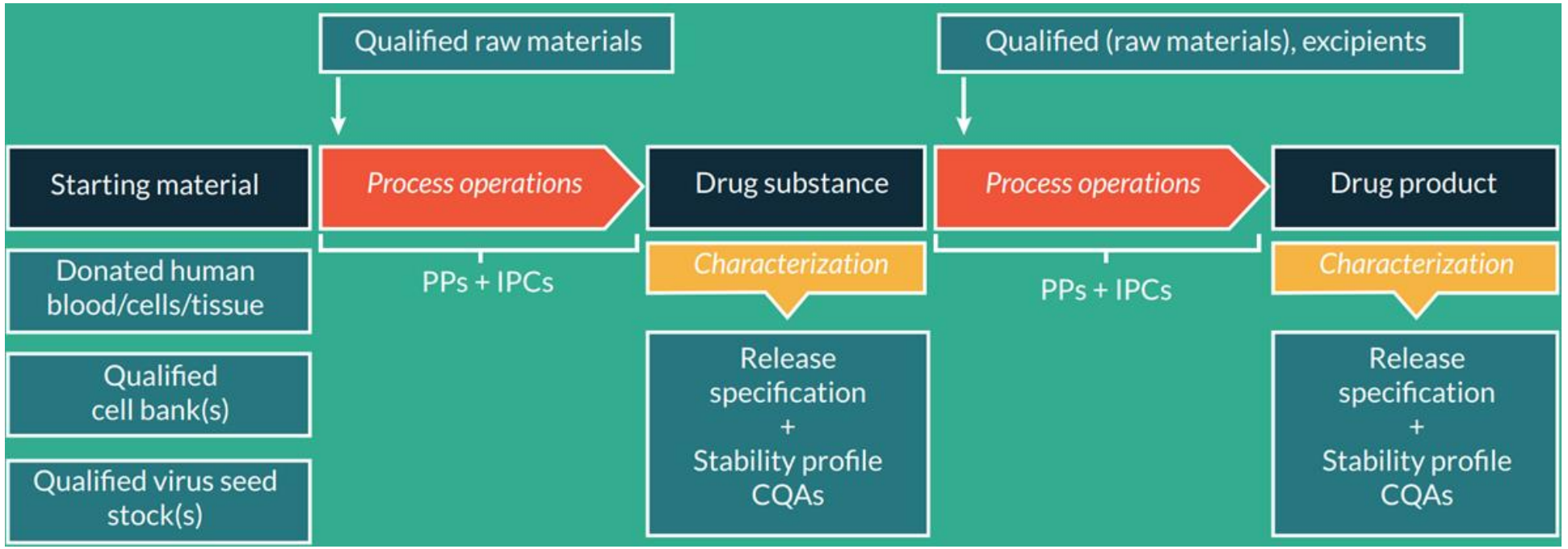
ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPS)

Advanced therapies in the product lifecycle

Research and development	Marketing authorisation	Post-authorisation
Support for advanced therapy developers		
Scientific guidelines		
	Advanced therapy classification	
	Marketing authorisation procedures for advanced therapy medicinal products	
		Pharmacovigilance for advanced therapies

Molecular Therapy: Methods & Clinical Development Vol. 13 June 2019

GLOBAL VISION OF PRODUCTION PROCESSES FOR SOMATIC-CELL THERAPY



in-process controls (IPCs)

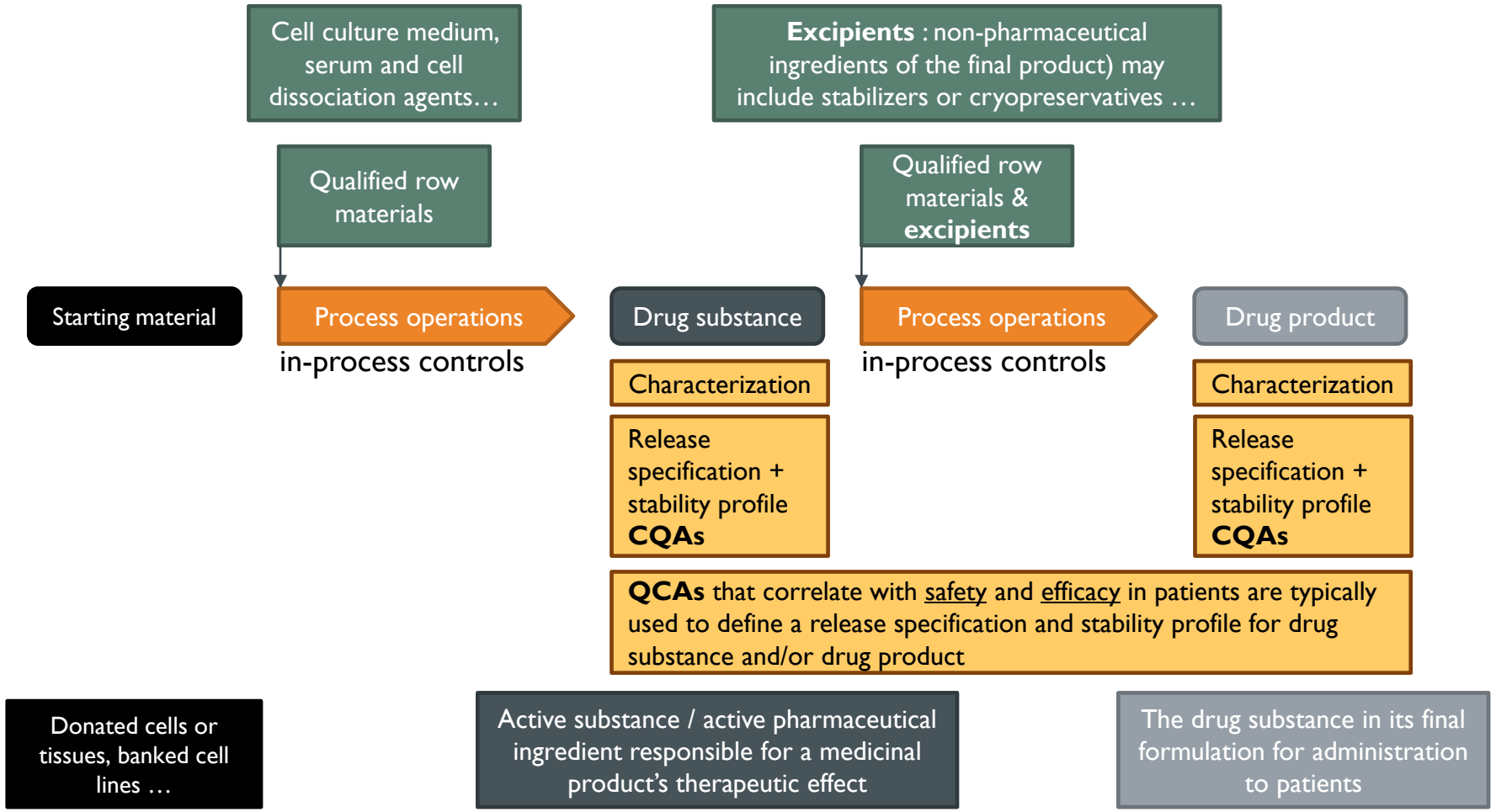
critical quality attributes (CQAs)

DOI: 10.18609/cgti.2016.056

GLOBAL VISION OF PRODUCTION PROCESSES FOR SOMATIC-CELL THERAPY

- **Starting materials** for ATMP manufacture include donated cells or tissues, banked cell lines …
- **Raw materials** may include cell culture medium, serum and cell dissociation agents, while **excipients** (non-pharmaceutical ingredients of the final product) may include stabilizers or cryopreservatives.
- The **drug substance** is the active substance/active pharmaceutical ingredient responsible for a medicinal product's therapeutic effect
- The **drug product** is the drug substance in its final formulation for administration to patients.
- The **drug substance and drug product should be fully characterized** during the development phase using appropriate analytical methods to identify the product-specific quality attributes
- The critical quality attributes that **correlate with safety and efficacy in patients** are typically used to define a **release specification and stability profile for drug substance and/or drug product**.

GLOBAL VISION OF PRODUCTION PROCESSES FOR SOMATIC-CELL THERAPY

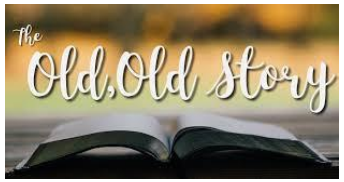


Critical Quality Attributes (CQAs)

CELL THERAPY PRODUCTS

- Some examples

HEMATOPOIETIC STEM CELLS TRANSPLANTATION (HSCT)



- In 1959 first bone marrow from a healthy identical twin restored the blood system of a leukemic child (*Thomas et al. Journal of clinical investigation, 1959)*
- Allogeneic or autologous HSCT is a **cell therapy product** for therapeutic purposes
- Hematopoietic stem cells (HSC) are multipotent : differentiate into all the cells of the hematopoietic tissue
- These properties leads to the development of HSCT protocols for hematopoietic reconstitution

In France, total number of HSCT is about 5000/year

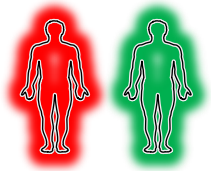
Cell therapy product not ATMP

HEMATOPOIETIC STEM CELLS TRANSPLANTATION (HSCT)

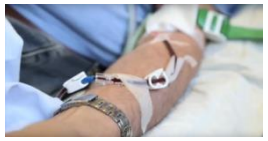
Donor or patients → Collection → Starting cell suspension → Processing → Storage / release / certificate of analysis → Administration to patient

Allogeneic cells

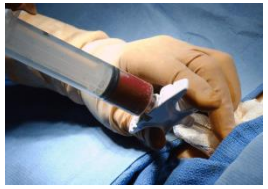
Autologous cells



Blood collection (apheresis)



Blood marrow collection



Cord Blood collection

Hematopoietic stem cells

No substantial modifications
Cell therapy products

Washing

Volume reduction

Ficoll

Increase the volume

No substantial modification of the therapeutic cell i.e CSH

Storage

CQAs

Thawing

Freezing

Administration

CQA :
- Viability
- Number of leukocytes
- Number of HSC (CD34+/kg)
- CFU-GM (clonogenicity)
- Contaminants
- Microbiology
- Others…

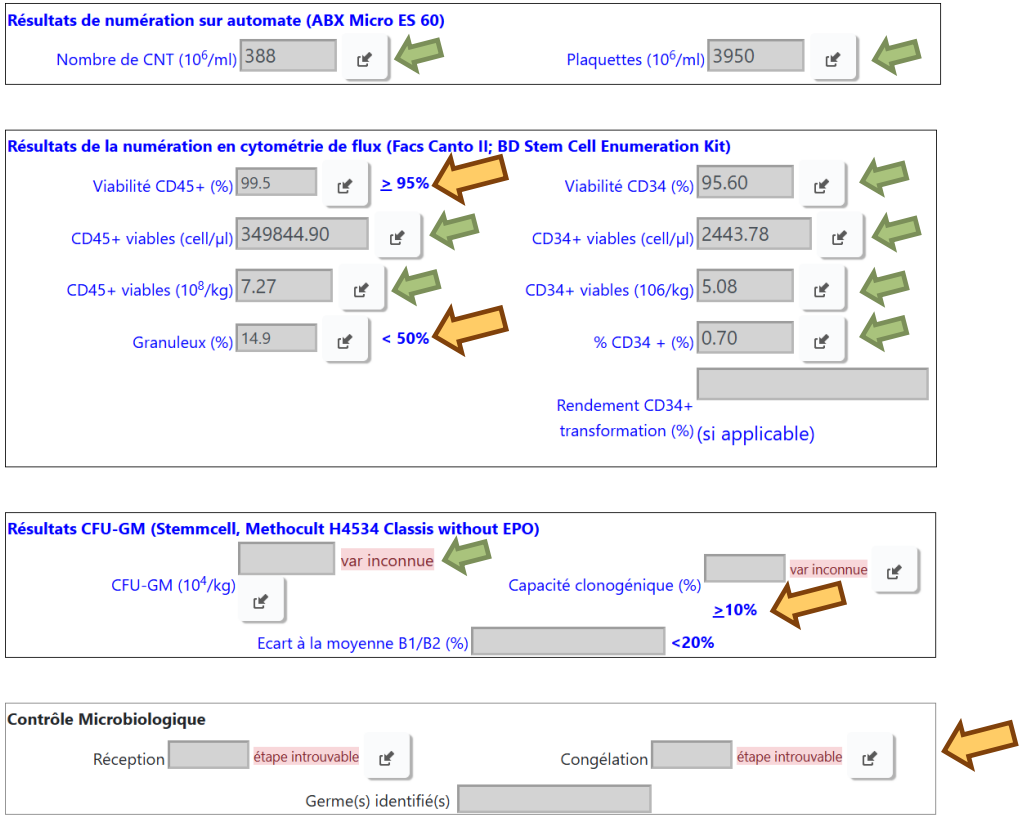
Release specifications :
- Viability
- CFU-GM (clonogenicity)
- Contaminants
- Microbiology
- Others…

Critical Quality Attributes (CQAs)

EXAMPLE OF RELEASE CERTIFICATE FOR AN AUTOLOGOUS FRESH HSC TRANSPLANTATION

CQA :
- Total cells in the product
- Plateletts in the product
- Viability CD45 and CD34+ (HSC)
- Number of leukocytes (CD45/µL and CD45 10e8/kg)
- % and Number of HSC (CD34+/kg)
- CFU-GM 10e4/kg and clonogenicity
- Contaminants (Granuleux)
- Microbiology
- Others…

Release specifications :
- Viability
- CFU-GM (clonogenicity)
- Contaminants (Granuleux)
- Microbiology



HEMATOPOIETIC STEM CELLS TRANSPLANTATION (HSCT)

- Main objective of **autologous HSCT** : Reconstruction of hematopoietic tissue in aplastic patients

After HSCT, infectious, hemorrhagic and hemodynamic risks are theoretically reduced when neutrophils > 0,5 G/L and platelets > 20 G/L

- **Objectives of allogeneic HSCT**
  - Reconstruction of hematopoietic tissue in aplastic patients
  - Curative effect through *graft versus "leukemia"* activity (onco-hematology indications)

- Main clinical indications of autologous and allogeneic HSCT
  - Hematological malignancies (90%)

Cell therapy product not ATMP

ADVANCED THERAPY MEDICINAL PRODUCTS VALIDATED FOR CLINICAL USE IN HUMANS

- Somatic and tissue engineered medicinal products

SOMATIC AND TISSUE ENGINEERED MEDICINAL PRODUCTS (ATMP)

Somatic-cell therapy medicinal products				
Provenge®	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	Other immunostimulants/L03AX17	Prostatic Neoplasms	Neoplasms
Alofisel®	(HSV-TK Mut2) Darvadstrocel	Immunosuppressants/L04	Rectal Fistula	Diseases of the digestive system
Tissue-engineered medicinal products				
	cultured chondrocytes	musculoskeletal system/M09AX02		system and connective tissue
Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Other drugs for disorders of the musculoskeletal system/M09AX02	Cartilage Diseases	Diseases of the musculoskeletal system and connective tissue
Holoclar®	*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells	Ophthalmologicals/S01XA19	Stem Cell Corneal Diseases	Diseases of the eye and adnexa

PROVENGE

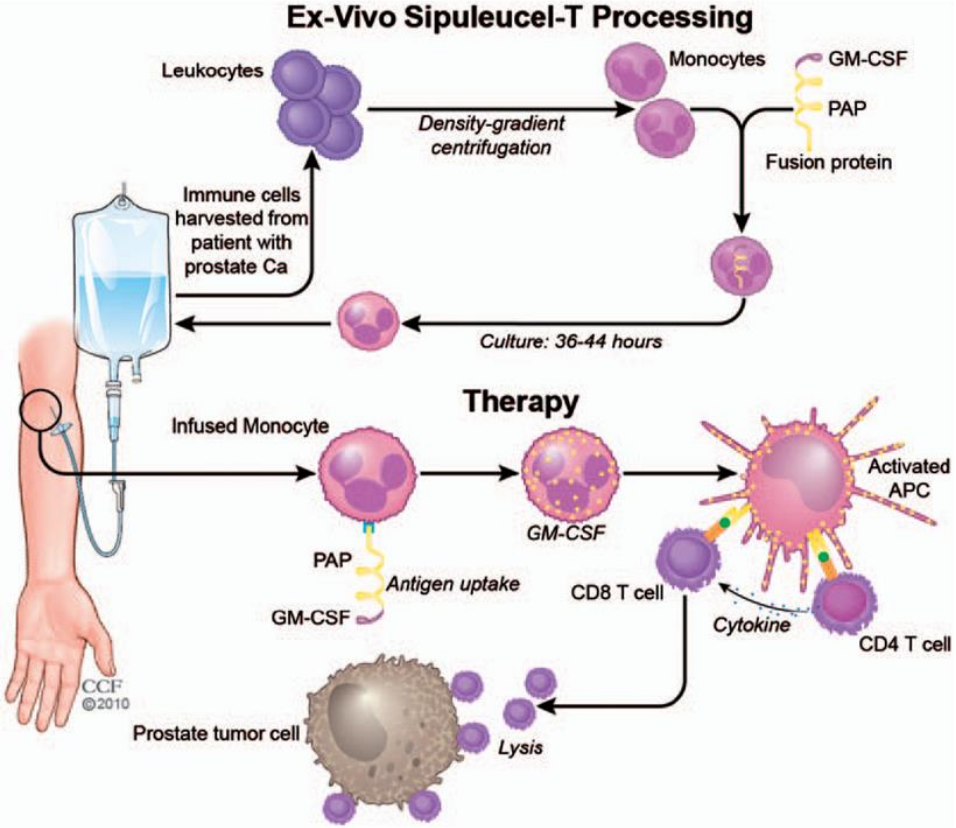
WITHDRAWN
This medicine is now withdrawn from use in the European Union.

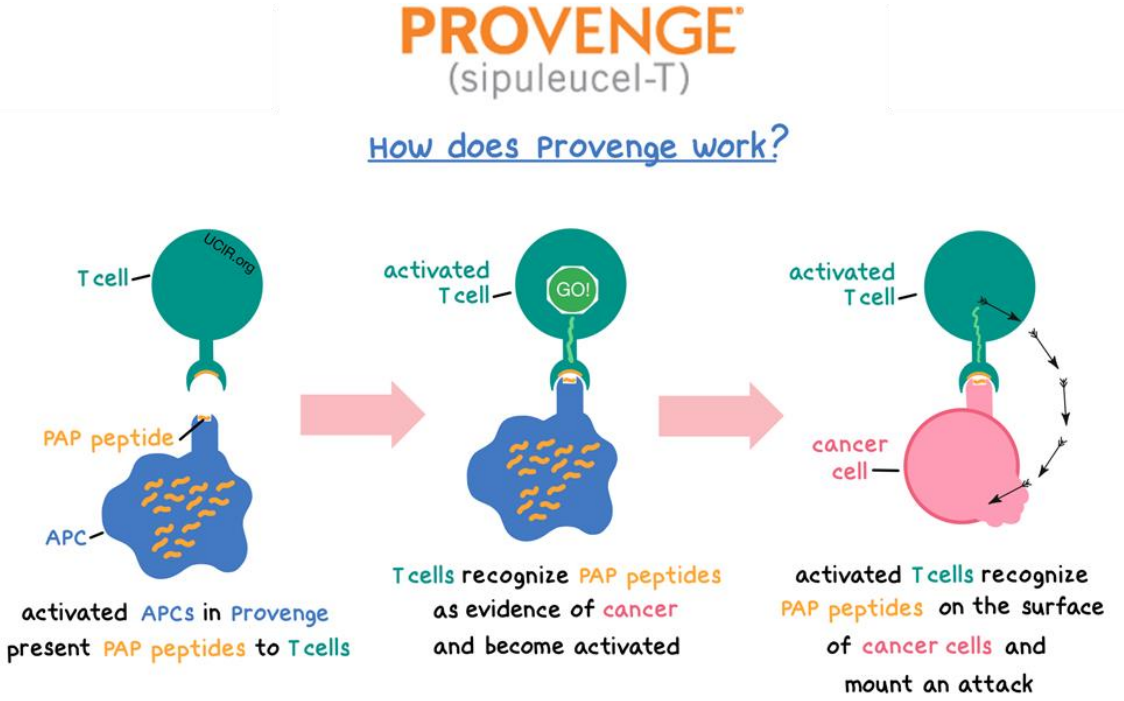
- **Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)**
- Provenge 50 x 10^6 $CD54^+$ cells/250mL dispersion for infusion
- Provenge was indicated for treatment of **asymptomatic or minimally symptomatic metastatic (nonvisceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated**.

Somatic-cell therapy medicinal product

PROVENGE

WITHDRAWN
This medicine is now withdrawn from use in the European Union.



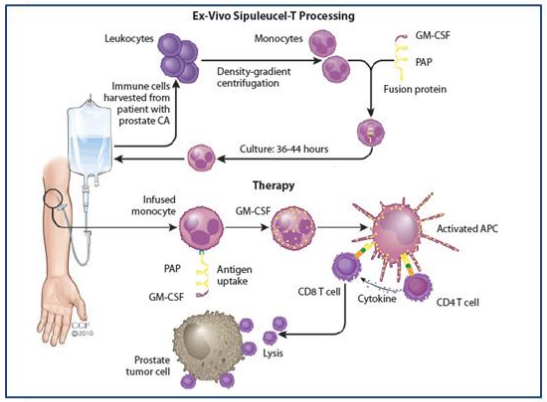


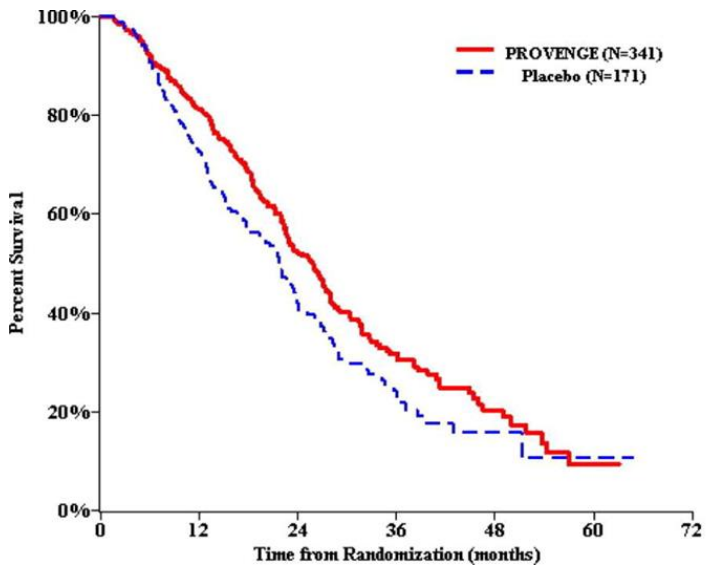
Somatic-cell therapy medicinal product

PROVENGE

WITHDRAWN
This medicine is now withdrawn from use in the European Union.

PROVENGE®
(sipuleucel-T)
Helping you help yourself





PROVENGE®
(sipuleucel-T)

Table 2 Summary of Overall Survival (All Patients as Randomized)

	Study 1		Study 2	
	PROVENGE (N=341)	Control (N=171)	PROVENGE (N=82)	Control (N=45)
Overall Survival				
Median, months (95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)	25.9 (20.0, 32.4)	21.4 (12.3, 25.8)
Hazard Ratio (95% CI)	0.775 [a] (0.614, 0.979)		0.586 [b] (0.388, 0.884)	
p-value	0.032 [a]		0.010 [c]	

[a] Hazard ratio and p-value based on the Cox Model adjusted for PSA (ln) and LDH (ln) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.
[b] Hazard ratio based on the unadjusted Cox Model (not pre-specified).
[c] p-value based on a log-rank test (not pre-specified).
Abbreviations: CI = confidence interval.

PROVENGE

WITHDRAWN
This medicine is now withdrawn from use in the European Union.

- Provenge **was the first cellular therapy** to treat advanced prostate cancers.
- It was the first treatment of its kind to be marketed in the United States in 2010.
- This therapy was using the body's immune system as a vaccine to fight cancer (cellular immunotherapy)
- However, the prohibitive cost of the treatment - $93,000 - marketing errors, and competition have dashed the hopes raised by this drug

➔ Dendreon manufactures the Provenge vaccine against prostate cancer, approved by the US authorities in 2010 but which did not meet expectations, leading the group to bankruptcy in 2014.

Somatic-cell therapy medicinal product

ALOFISEL : DARVADSTROCEL

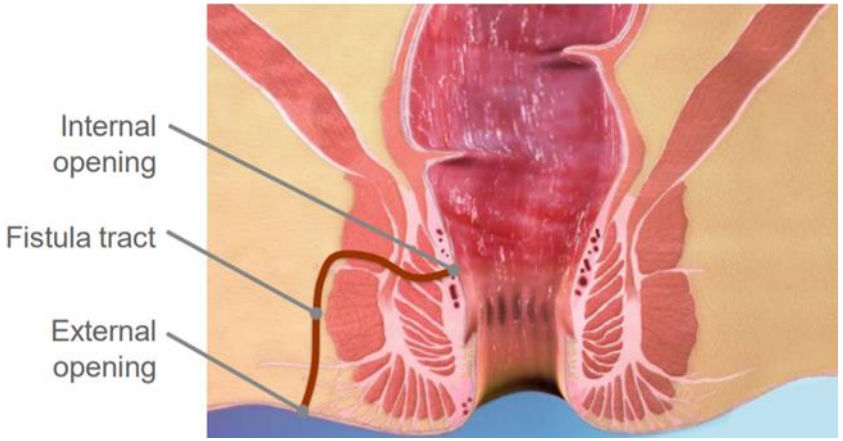
AUTHORISED
This medicine is authorised for use in the European Union.

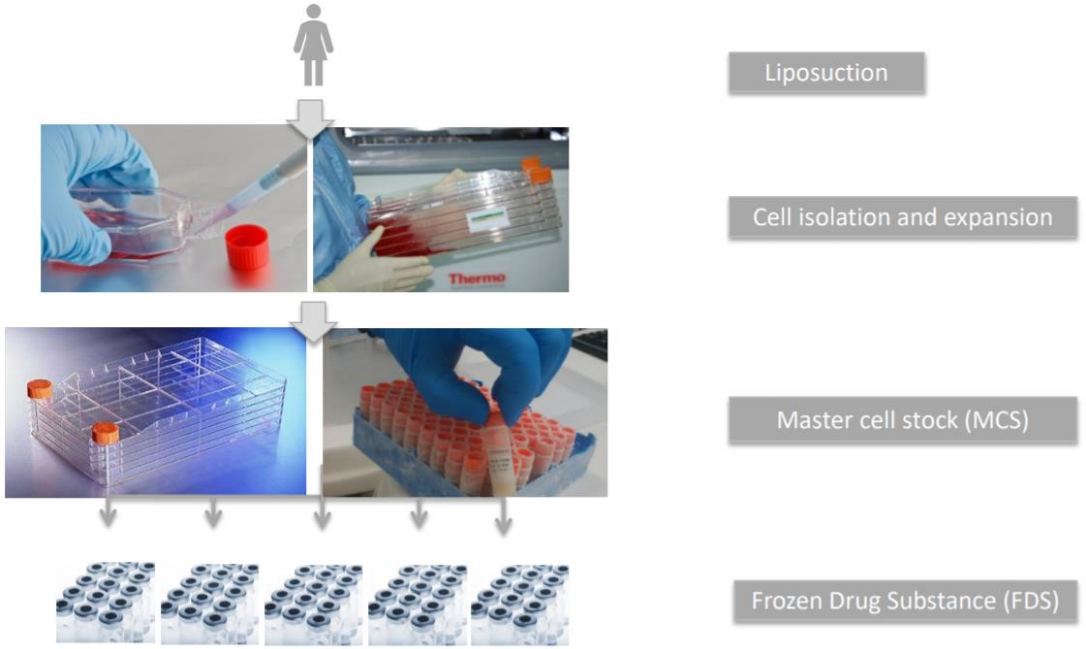
- ALOFISEL : Darvadstrocel is expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells)
- Treatment of **complex perianal fistulas** in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy

Somatic-cell therapy medicinal product

ALOFISEL : DARVADSTROCEL

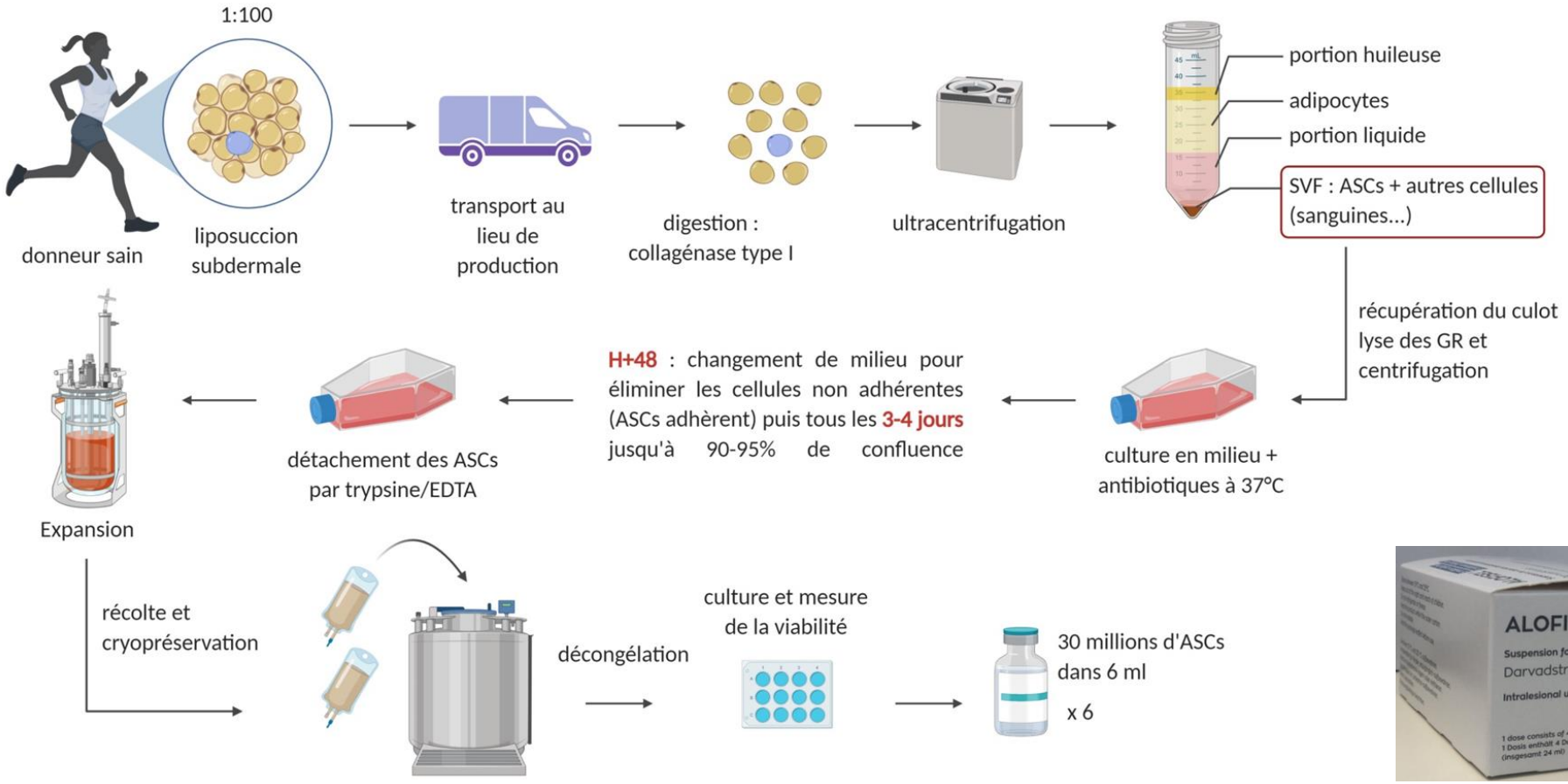
✓ AUTHORISED
This medicine is authorised for use in the European Union.





ALOFISEL : DARVADSTROCEL

AUTHORISED
This medicine is authorised for use in the European Union.



Adipose-derived mesenchymal stem cells (ASCs)

Somatic-cell therapy medicinal product

ALOFISEL : DARVADSTROCEL

AUTHORISED
This medicine is authorised for use in the European Union.

- The study was a **randomised, double-blind**, parallel-group, placebo-controlled, multi-centre clinical trial.
- A total of 212 patients took part in the clinical study, including 205 that were administered a local intralesional injection of either **Alofisel 120 million cells or placebo in a 1:1 ratio**.
- Patients who received Alofisel **showed a 44% greater probability of achieving combined remission compared to those given the placebo.**
- Alofisel contains allogeneic (donor-derived) expanded adipose-derived stem cells (eASCs), which show **immunomodulatory and anti-inflammatory effects at inflammation sites.**
- The drug impairs proliferation of activated lymphocytes, while its immunoregulatory properties reduce the inflammatory cytokines.
- Approved EMA 2018

Price France : 4 vials de 5 millions cells/ml : 51 300 euros.

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

AUTHORISED
This medicine is authorised for use in the European Union.

- Somatic cell therapy medicinal product
- Allogeneic immunotherapy with Epstein-Barr virus (EBV)-specific T lymphocytes
- Treatment for adult and pediatric patients (≥2 years) with relapsed or refractory Epstein-Barr virus-positive post-transplant lymphoproliferative disease (EBV+ PTLD)

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

AUTHORISED
This medicine is authorised for use in the European Union.

- In transplant patients on immunosuppressants, T lymphocyte (T cell) activity is inhibited, and the EBV infection remains undetectable by the immune system.
- Without T cell control, EBV-infected B lymphocytes (B cells) can rapidly proliferate uncontrollably
- ➔ B cell transformation, immortalization, and lymphoproliferative syndrome

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

- Rare transplant complication: 1,000 cases/year in the US
- Can be life-threatening
- Limited treatment options: rituximab +/- chemotherapy
- Patients relapsing or refractory to rituximab:
  - 0.7 months median survival after hematopoietic stem cell transplant
  - 4.1 months median survival after solid organ transplant
  - ➔ Therapeutic urgency

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

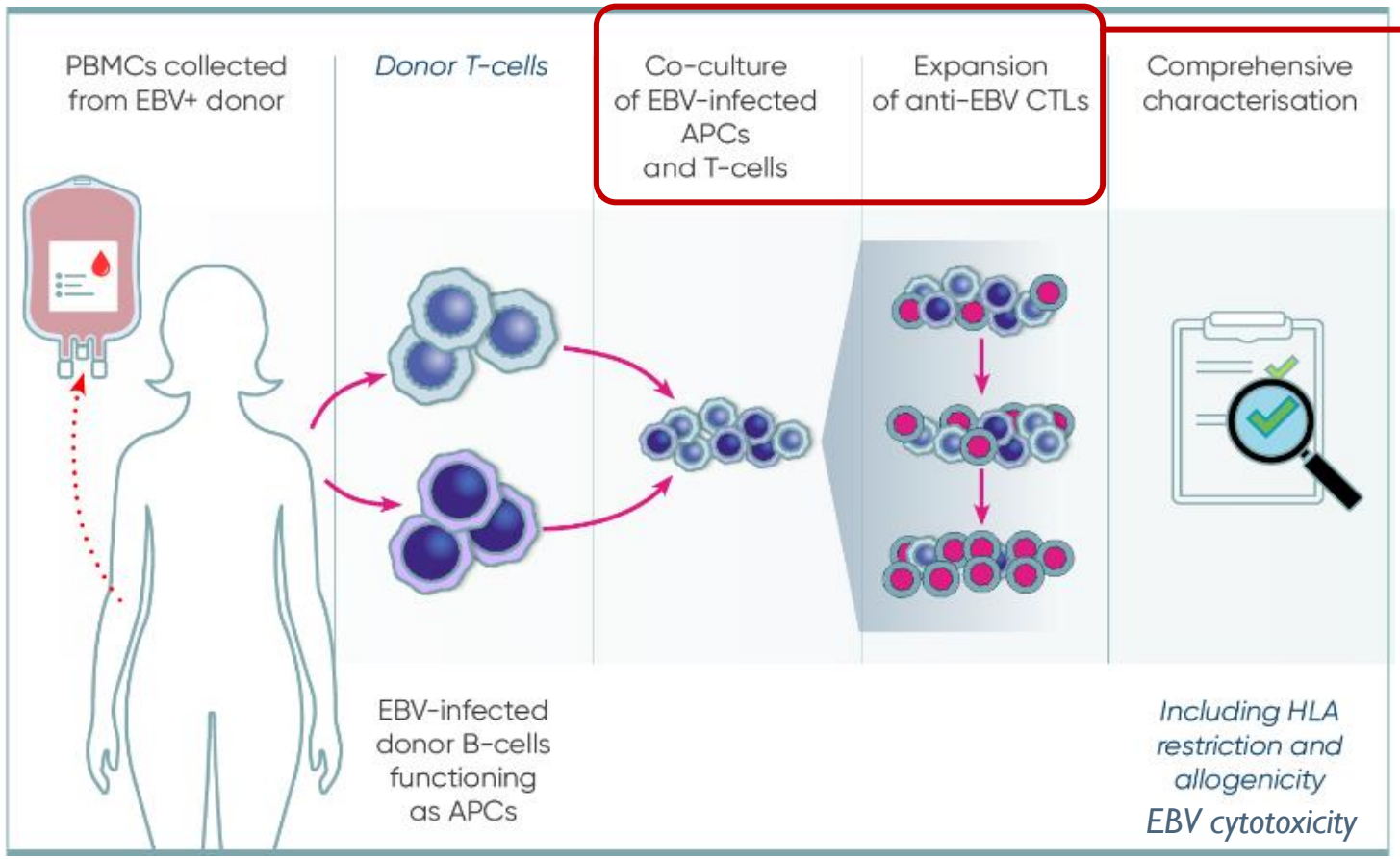
AUTHORISED
This medicine is authorised for use in the European Union.

- Allogeneic immunotherapy available **'on demand'** for this indication

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

✓ AUTHORISED
This medicine is authorised for use in the European Union.



Substantial modifications: ATMP
The cells are not genetically modified = a cell therapy medicinal product

Somatic-cell therapy medicinal product

https://www.ebvallo-ebv.com/about-ebvallo#pid35

EBVALLO : TABELECLEUCEL

AUTHORISED
This medicine is authorised for use in the European Union.

- Phase III ALLELE study, multicenter, single-arm.
- N=30 patients included with EBV+ PTLD following solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) who had not responded to treatment.
- Injection of Ebvallo ($2x10^6$ viable T cells/kg) On Day 1, Day 8, and Day 15
- For each patient, selection based on appropriate HLA restriction
- Response evaluated on Day 28

	EBV+ PTLD post SOT (n=16)	**EBV+ PTLD post HSCT** (n=14)
Objective response rate (CR + PR)	56.3% (n=9)	50% (n=7)
Response duration (median)	2.3 months	15.9 months

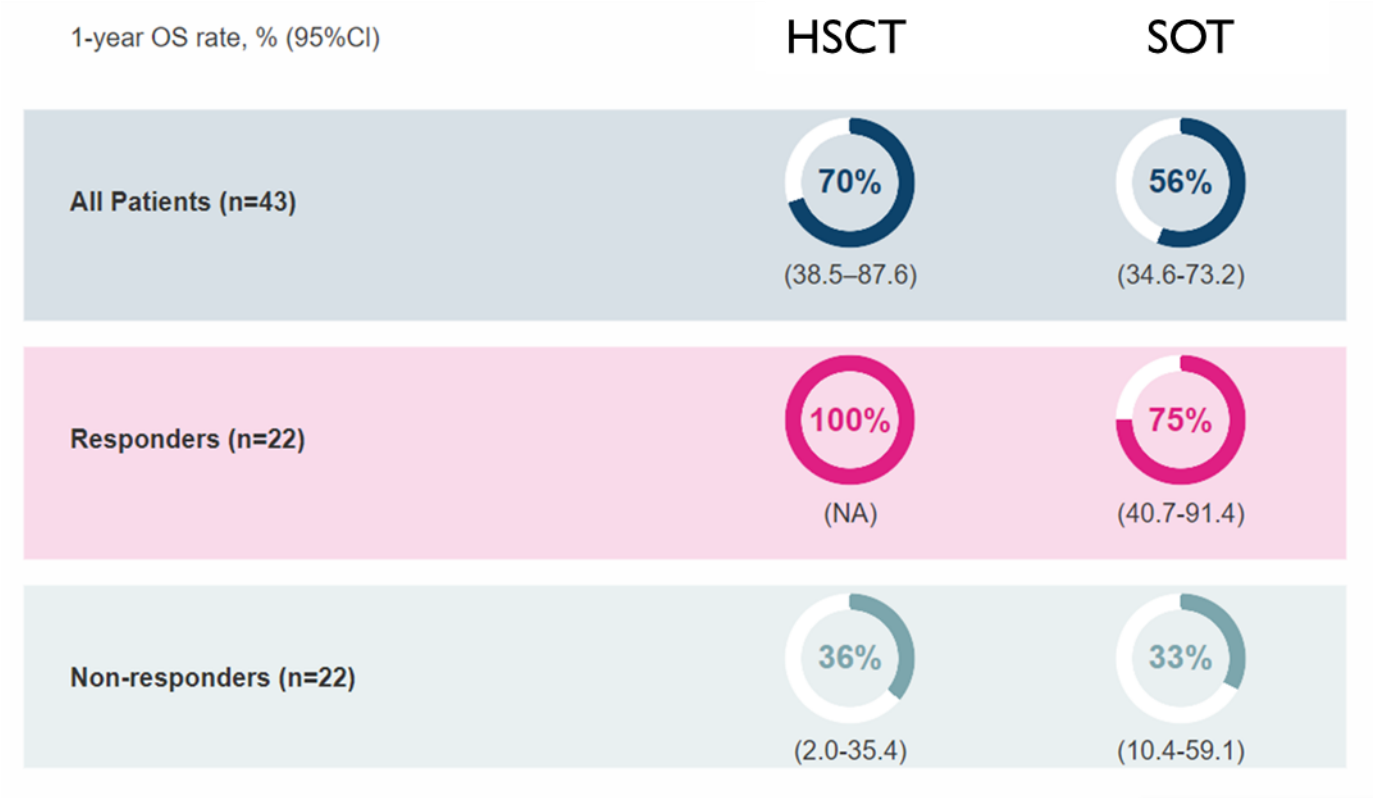
https://ec.europa.eu/health/documents/community-register/2022/20221216157616/anx_157616_fr.pdf

Somatic-cell therapy medicinal product

EBVALLO : TABELECLEUCEL

AUTHORISED
This medicine is authorised for use in the European Union.

- All responding HSCT patients and 75% of responding SOT patients were alive one year after treatment.



Somatic-cell therapy medicinal product

HOLOCLAR

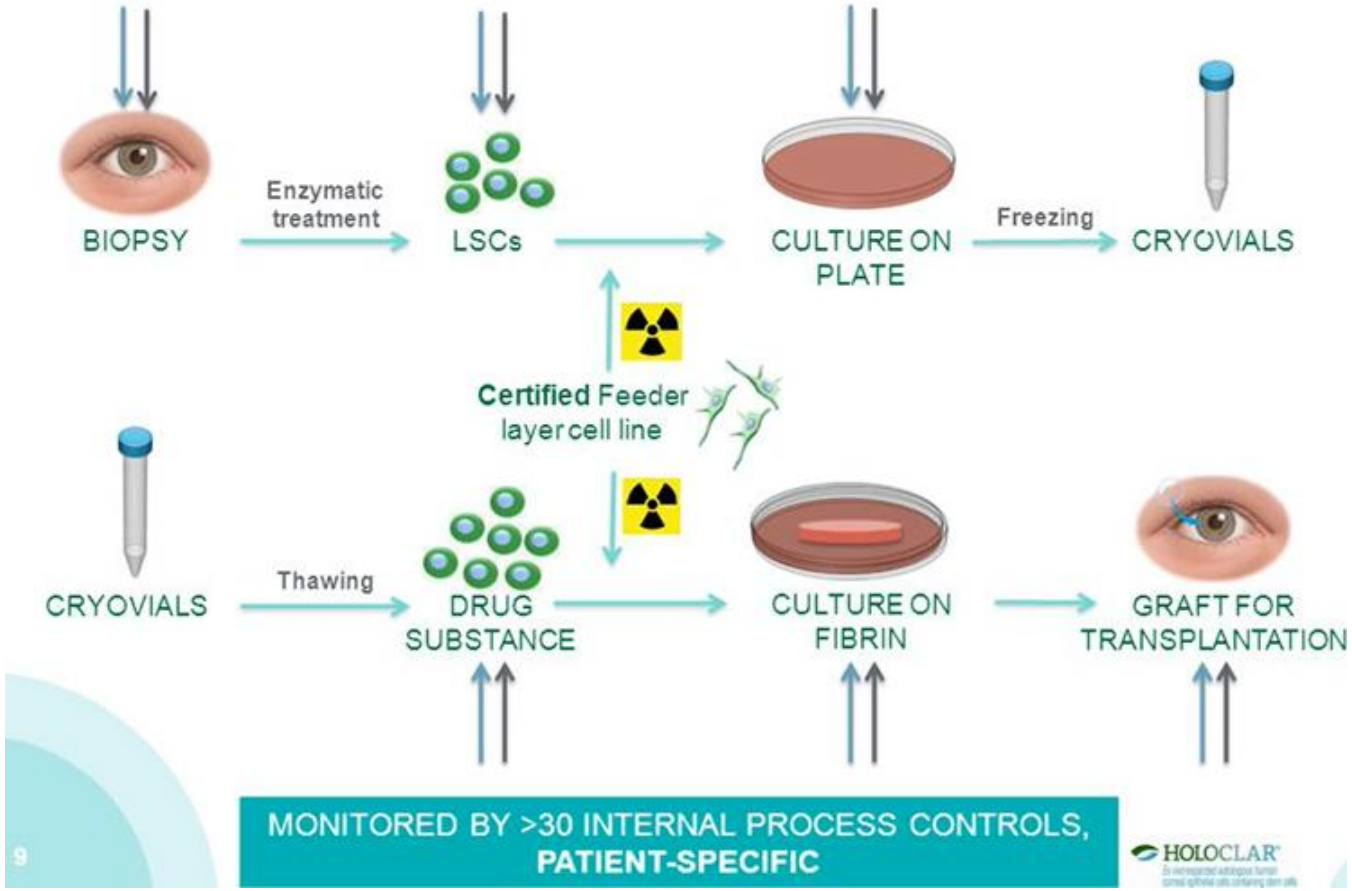
AUTHORISED
This medicine is authorised for use in the European Union.

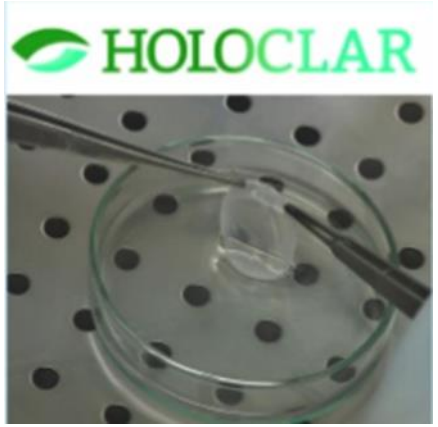
- Ex vivo expanded autologous human corneal epithelial cells containing stem cells
- Treatment of adult patients with moderate to severe limbal stem cell deficiency
- Tissue-engineered medicinal product

Tissue-engineered medicinal product

HOLOCLAR

AUTHORISED
This medicine is authorised for use in the European Union.

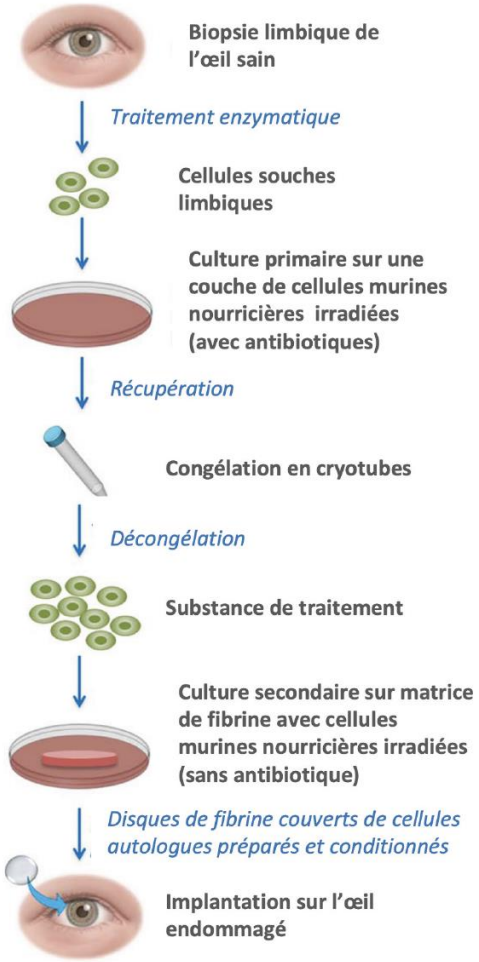




Tissue-engineered medicinal product

HOLOCLAR

AUTHORISED
This medicine is authorised for use in the European Union.

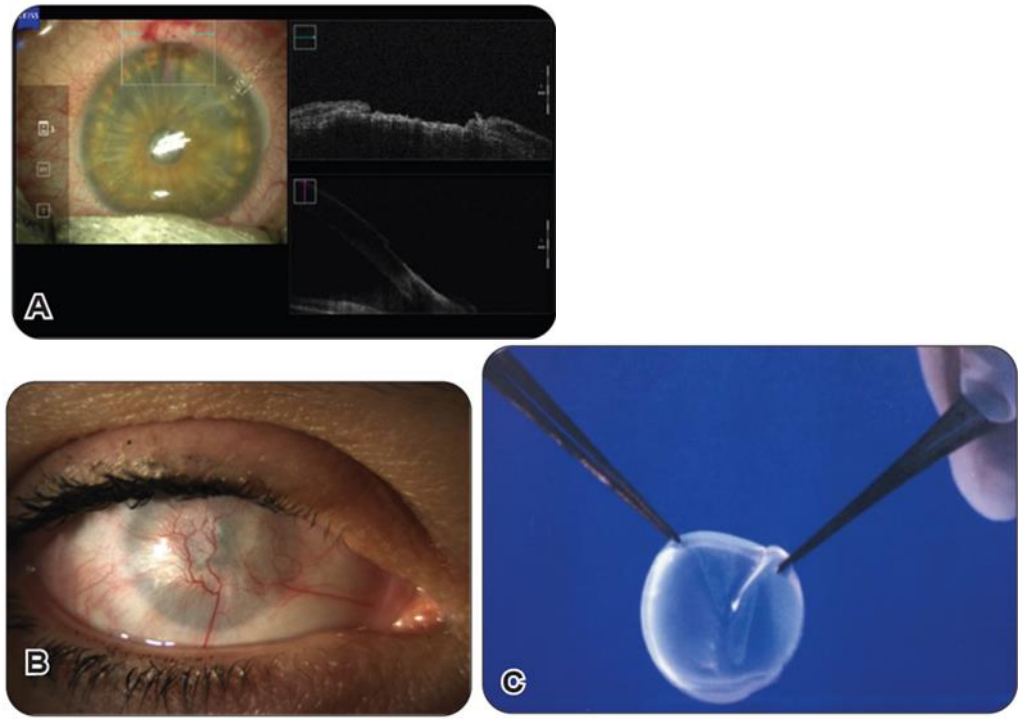


- In 2015, Holoclar finally has been authorized by European Commission for the use in all the partner countries

Tissue-engineered medicinal product

HOLOCLAR

AUTHORISED
This medicine is authorised for use in the European Union.



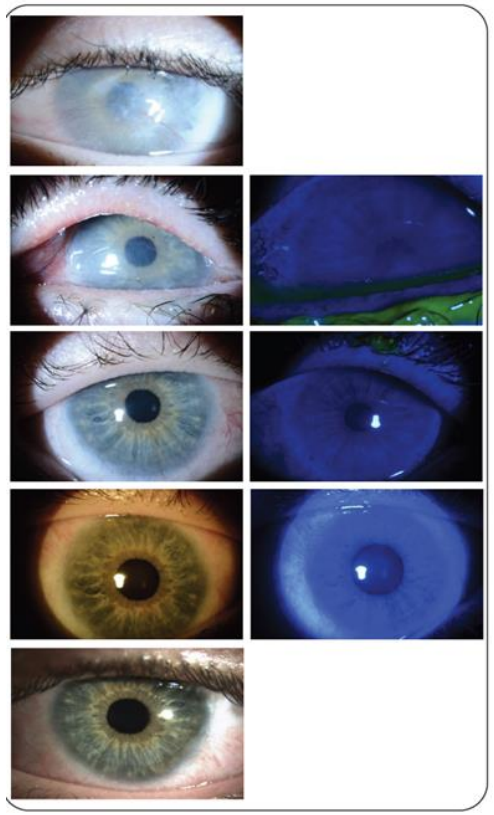
Description of the procedure steps.

- (A) Biopsy of 2 x 2 mm² at a depth of 100-200 microns (the thickness of a normal cornea is about 540 microns).
- (B) In the second surgical step, dissection of the fibrovascular pannus.
- (C) In this second surgical step, placement of the Holoclar® sheet by a Vycril suture

Tissue-engineered medicinal product

HOLOCLAR

AUTHORISED
This medicine is authorised for use in the European Union.



- Evolution of the ocular appearance at different times after Holoclar® implantation.
- The right column shows the surface of the eye with the use of fluorescein and blue light illumination. This technique highlights lesions of the corneal epithelium.
- The treatment is a success for this patients
- Price : USD 105,000 per eye in Europe
- Medication not reimbursed in France because it is not considered to be a major medical need

Tissue-engineered medicinal product

HOLOCLAR : HLSTM01 STUDY

AUTHORISED
This medicine is authorised for use in the European Union.

- Non-comparative, retrospective case study, uncontrolled.
- 104 patients underwent transplantation with Holoclar.
- Procedure success: presence of a stable corneal epithelium with no recurrence of neovascularization.
  - Transplant success in 72.1% of patients after 12 months.
  - 49% experienced an improvement in visual acuity

Tissue-engineered medicinal product

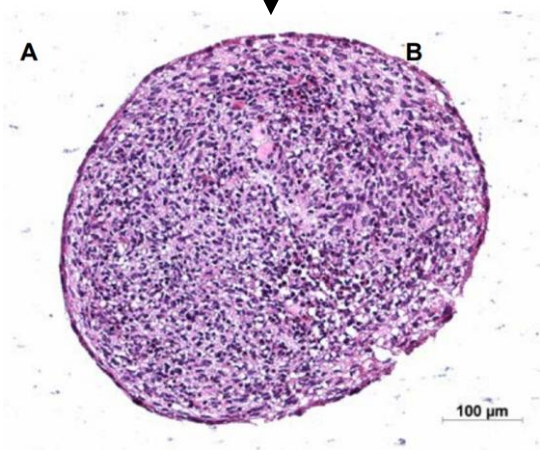
SPHEROX

AUTHORISED
This medicine is authorised for use in the European Union.

- **Repair** of **symptomatic cartilage lesions of the articular cartilage** on the femoral condyle and patella (ICRS stage III or IV) with a surface area ≤ 10 cm^2 in adults and adolescents with closed epiphyseal growth plates in the affected joint
- 10 - 70 spheroids/cm^2

ICRS : International Cartilage Regeneration & Joint Preservation Society

Tissue-engineered medicinal product



SPHEROX

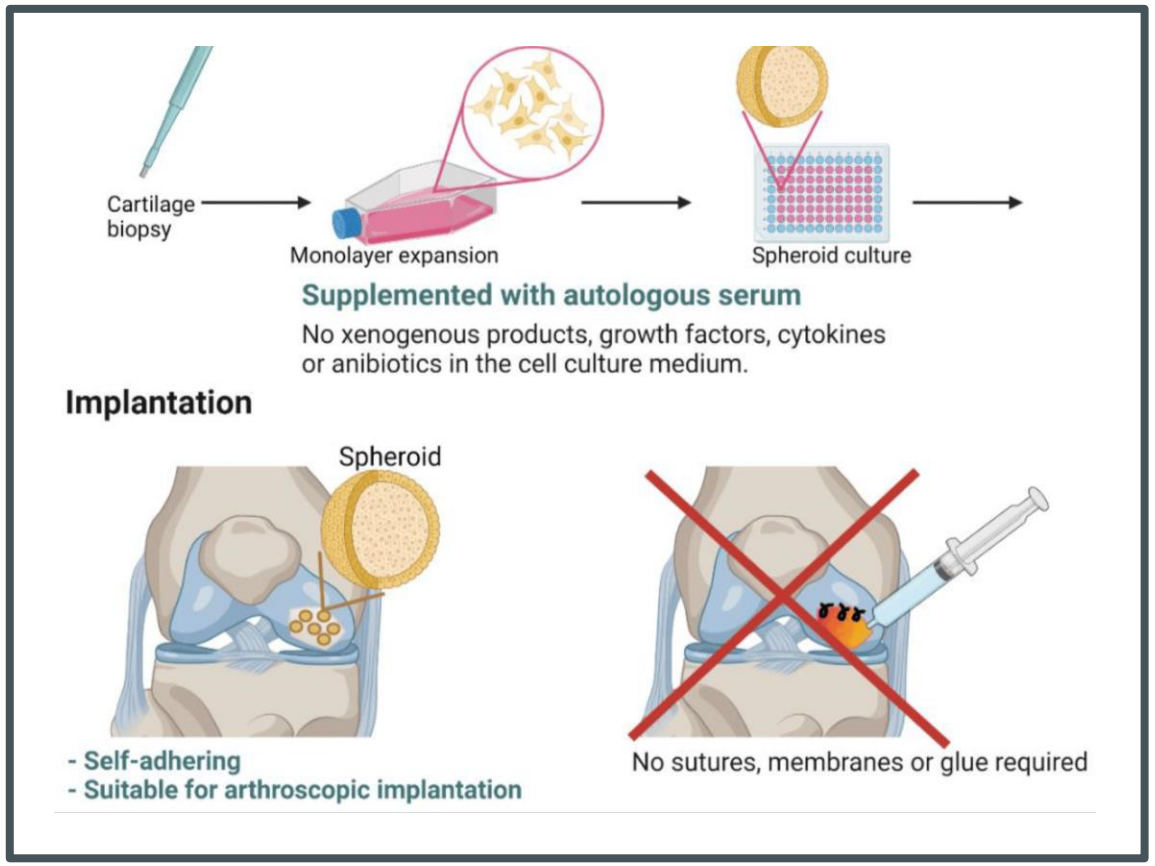
AUTHORISED
This medicine is authorised for use in the European Union.

- Spheroid: spherical aggregates of chondrocytes and self-synthesized extracellular matrix

Tissue-engineered medicinal product

SPHEROX

AUTHORISED
This medicine is authorised for use in the European Union.



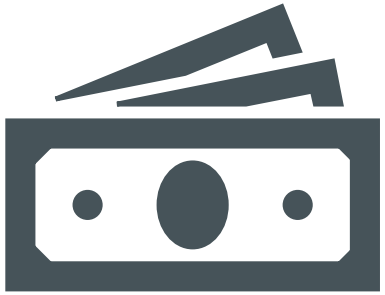
- Autologous chondrocytes are harvested and cultured in a medium containing autologous serum, without antibiotics, growth factors, or cytokines.
- Chondrocyte spheroids form and are self-adherent to the bone, allowing implantation without the need for sutures or glue

https://www.has-sante.fr/upload/docs/evamed/CT-19838_SPHEROX_PIC_INS_AvisDef_CT19838.pdf

Tissue-engineered medicinal product

SPHEROX

AUTHORISED
This medicine is authorised for use in the European Union.

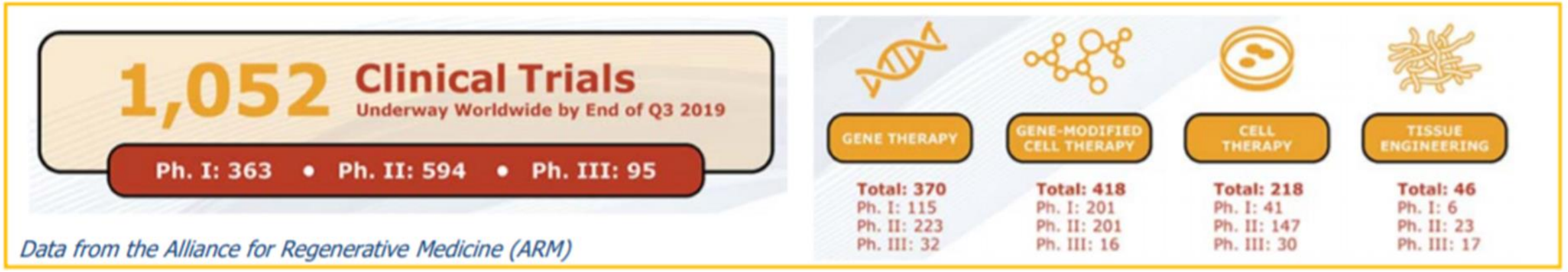


Not reimbursed in France as the data were considered as insufficient. It is not considered to be a major medical need.

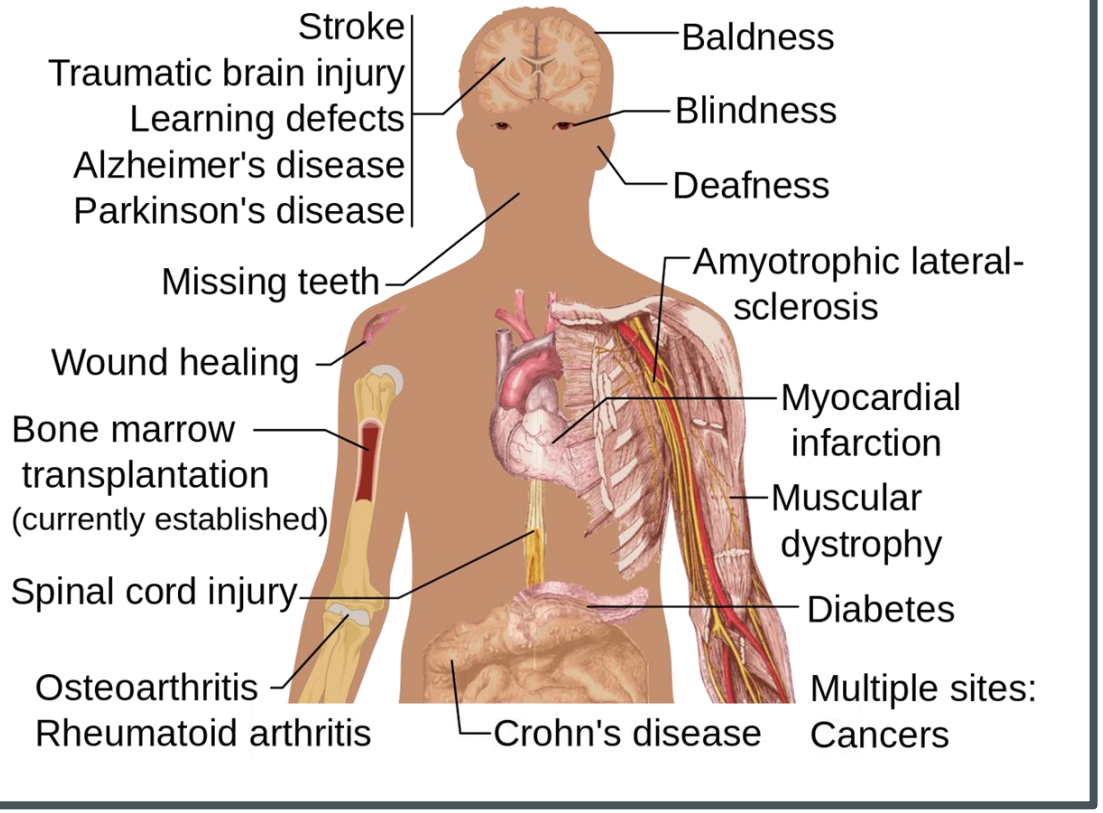
However, it has received marketing authorization in other European countries such as the UK, as well as in the USA.

CLINICAL DEVELOPMENTS

- ATMPs clinical trials



CLINICAL DEVELOPMENTS



- Diseases and conditions where cell therapy treatment is promising or emerging

THANK YOU FOR ATTENTION