DEVELOPMENT AND PRODUCTION OF ADVANCED THERAPY MEDICINAL PRODUCTS

Carla Cardoso

Stemlab SA (Crioestaminal)

PENICHE 2023

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stemlab advanced
ultimate cell therapies

Carla Cardoso, Bárbara Silva, Filipa Monteiro, Carolina Santos, Margarida Vieira, Helena Henriques-Antunes, Irina Simões, Sofia Couceiro, Francisco Santos, Ana Mafalda Quinte

Stemlab, S.A. - Biocant Park, Cantanhede, Portugal
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Introduction

Advanced Therapy Medicinal Products (ATMPs) are a new category of medicines for human use with a wide therapeutic potential for treating different types of diseases, such as autoimmune and cardiovascular diseases, among others. These medicines are based on genes, tissues or cells and can be classified into three main types: gene therapy medicines, somatic-cell therapy medicines and tissue-engineered medicines. Moreover, some ATMPs may contain one or more medical devices as integral part of the medicine, being referred to as combined ATMPs. With the aim of providing access to this kind of medicines, in 2017, Stemlab decided to build an area dedicated to the production of ATMPs. The GMP facility was authorized by Infarmed in January 2020 and currently has the capacity to manufacture autologous (from self) and allogeneic (from a donor) cell therapy products. The GMP activity was initiated with an autologous product for a phase IIa clinical trial in stroke patients, based CD34⁺ cells isolated from the patients' own bone marrow (**Stemlab_CD34BM**). This clinical trial aims to assess the efficacy of intra-arterial administration of CD34⁺ cells 7 and 20 days after acute ischemic stroke. Now Stemlab is also producing allogeneic products, e. g., a cell therapy product based on mesenchymal stem cells (MSCs) from the umbilical cord tissue (**SLCTmsc02**) for a phase II clinical trial in patients with Acute Respiratory Distress Syndrome (ARDS), a life-threatening complication of severe cases of Covid-19 and other conditions. This trial aims to assess the safety and efficacy of a single intravenous infusion of umbilical cord tissue MSCs in patients with ARDS.





PROCESS DEVELOPMENT
- Process gap analysis
- Process design and optimization
- Critical Quality Attributes definition
- Stability testing
- Comparability studies

GMP MANUFACTURING
- Technology transfer
- Process validation
- Clinical Batch Production
- Batch Release
- Cryopreservation

QUALITY
- Batch certification
- Development and validation of analytical methods
- Regulatory support for IMPD submission
- Safety testing (sterility, endotoxins and mycoplasma)
- Quality Control

RESEARCHERS & INDUSTRY → PRE-CLINICAL DEVELOPMENT → CLINICAL DEVELOPMENT → MARKETING AUTHORIZATION

Results

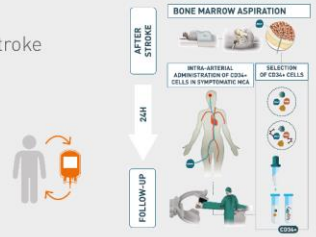
ATMPs – Production

*** Autologous product**

Stemlab_CD34BM (Bone marrow) in stroke

Collection → Processing → Product → Infusion

Autologous bone-marrow (BM) derived CD34⁺ cells for acute ischemic stroke - a Phase IIa clinical trial. A Phase I clinical trial demonstrated that BM-CD34⁺ cells administration in acute ischemic stroke patients is safe and feasible.



*** Allogeneic product (off-the-shelf)**

SLCTmsc02 (Umbilical cord tissue) in ARDS

Collection → Processing → Cell Bank → Thaw → Processing → Product → Infusion

Allogeneic cell therapy product based on Umbilical cord tissue MSCs for ARDS patients - a Phase II clinical trial. MSCs have been applied in patients with severe COVID-19 with favorable results.

ATMPs – Quality Control

Starting Material → Manufacturing Process - IPC → Final Product

QUALITY CONTROL


Umbilical Cord Tissue MSCs

Analytical control
- Number of cells, viability, immunophenotype
- Differentiation, immunosuppression
- Sterility, endotoxins, mycoplasma, karyotype

SCAN ME
WITH YOUR PHONE

Conclusions

The production of cell therapies for clinical use requires adherence to GMP standards to ensure standardization, reproducibility and product safety and quality. To achieve those purposes, qualified personnel, adequate facilities/equipment, raw materials and starting materials management and control, and validated manufacturing processes and quality controls are fundamental. The EMA/CAT considered that **Stemlab_CD34BM** falls within the definition of tissue engineered product and that **SLCTmsc02** is a somatic cell therapy medicinal product, as provided in Article 2 of Regulation (EC) No 1394/2007. At this point, Stemlab has dedicated facilities for the development, manufacture, and quality control of cell-based therapies for clinical trials and hospital exemptions, with three distinct production areas, allowing to safely manufacture different types of ATMPs. With this activity, Stemlab aims to contribute to the treatment of diseases that nowadays have few effective treatment options.

Funding CellTherapy4COVID-19 project (POCI-01-0247-FEDER-046816), RescueCord project (POCI-01-0247-FEDER-063311), MSCellProduction project (POCI-01-0247-FEDER-030836), StrokeTherapy project (POCI-01-0247-FEDER-069386), Crutmorf project (CENTRO-02-0853-FEDER-022844).

References Eudralex Vol4 GMP, PanEV -ATMPs, European Pharmacopeia (Ph. Eur.), PIDS, ICH, ISO standards.

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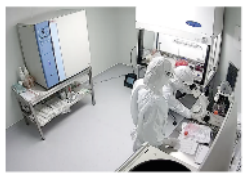


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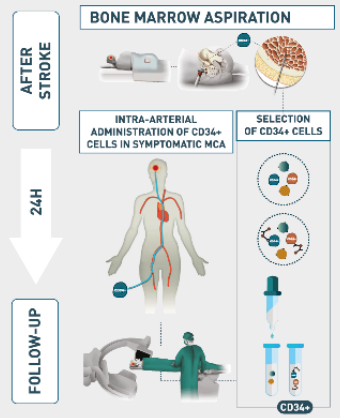
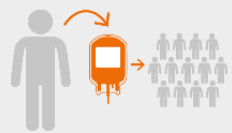


* Allogeneic product (off-the-shelf)

SLCTmsc02 (Umbilical cord tissue) in ARDS

Allogeneic cell therapy product based on Umbilical cord tissue MSCs for ARDS patients - a Phase II clinical trial. MSCs have been applied in patients with severe COVID-19 with favorable results.



ATMPs – Quality Control

Umbilical Cord Tissue MSCs

Analytical control
-Number of cells, viability, immunophenotype
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The production of cell therapies for clinical use requires adherence to GMP standards to ensure standardization, reproducibility and product safety and quality. To achieve those purposes, qualified personnel, adequate facilities/equipment, raw materials and starting materials management and control, and validated manufacturing processes and quality controls are fundamental. The EMA/CAT considered that **Stemlab_CD34BM** falls within the definition of tissue engineered product and that **SLCTmsc02** is a somatic cell therapy medicinal product, as provided in Article 2 of Regulation (EC) No 1394/2007. At this point, Stemlab has dedicated facilities for the development, manufacture, and quality control of cell-based therapies for clinical trials and hospital exemptions, with three distinct production areas, allowing to safely manufacture different types of ATMPs. With this activity, Stemlab aims to contribute to the treatment of diseases that nowadays have few effective treatment options.

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References Eudralex Vol4 GMP; PartIV –ATMPs; European Pharmacopeia (Ph. Eur.); PIC/S; ICH; ISO standards.

Advanced Therapy Medicinal Products (ATMPs)

Advanced Therapy Medicinal Products (ATMPs) are a new category of medicines for human use with a wide therapeutic potential for treating different types of diseases

Medicines based on **genes, tissues** or **cells**

Classified into three main types:

- **gene therapy medicines (GTMP)** – contain genes that lead to a therapeutic, prophylactic or diagnostic effect; work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases
- **somatic-cell therapy medicines (CTMP)** – contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body
- **tissue-engineered medicines (TEP)** – intended to regenerate, repair or replace a human tissue

Some ATMPs may contain one or more **medical devices** as integral part of the medicine, being referred to as **combined ATMPs (cATMPs).**

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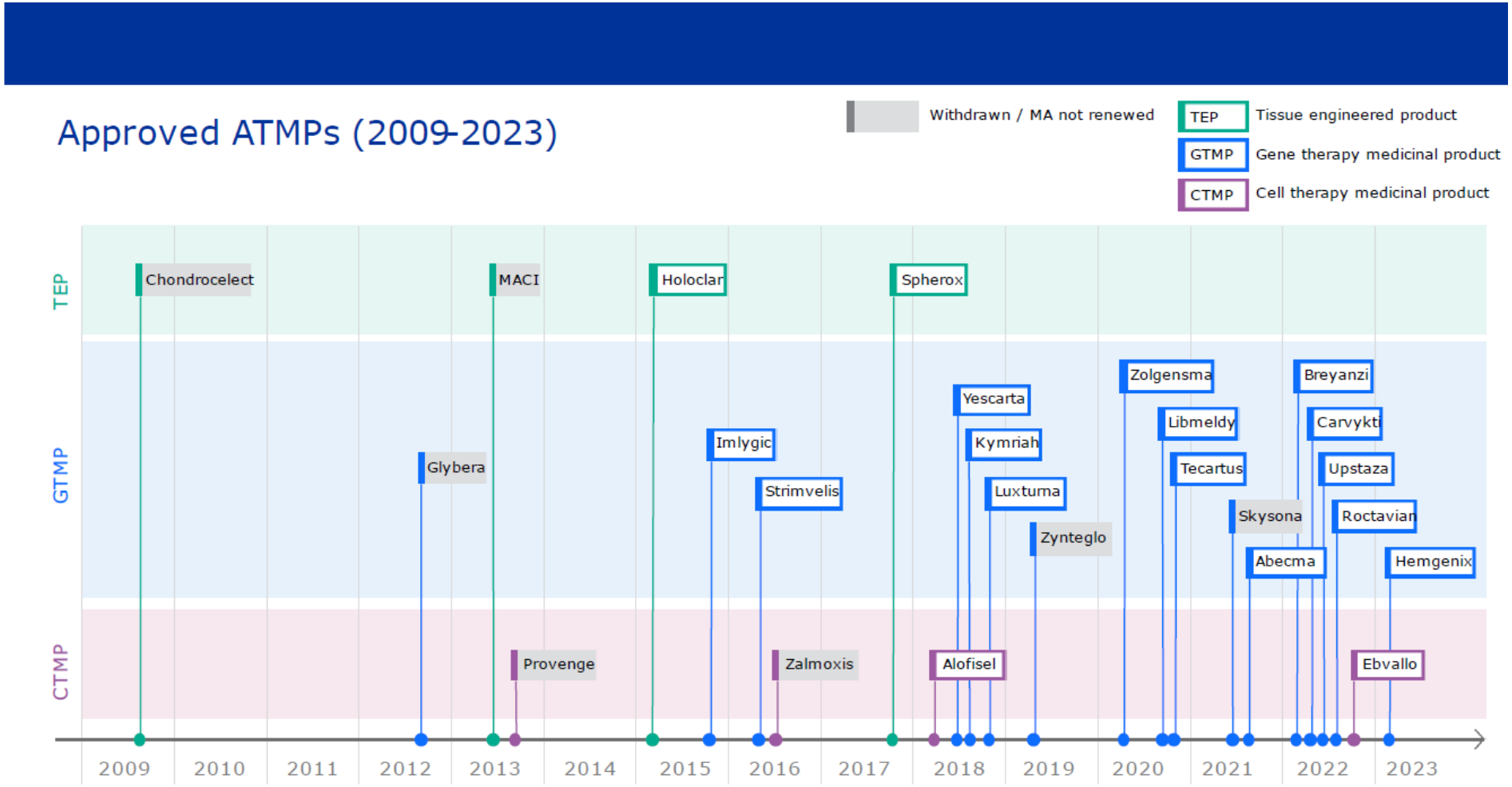
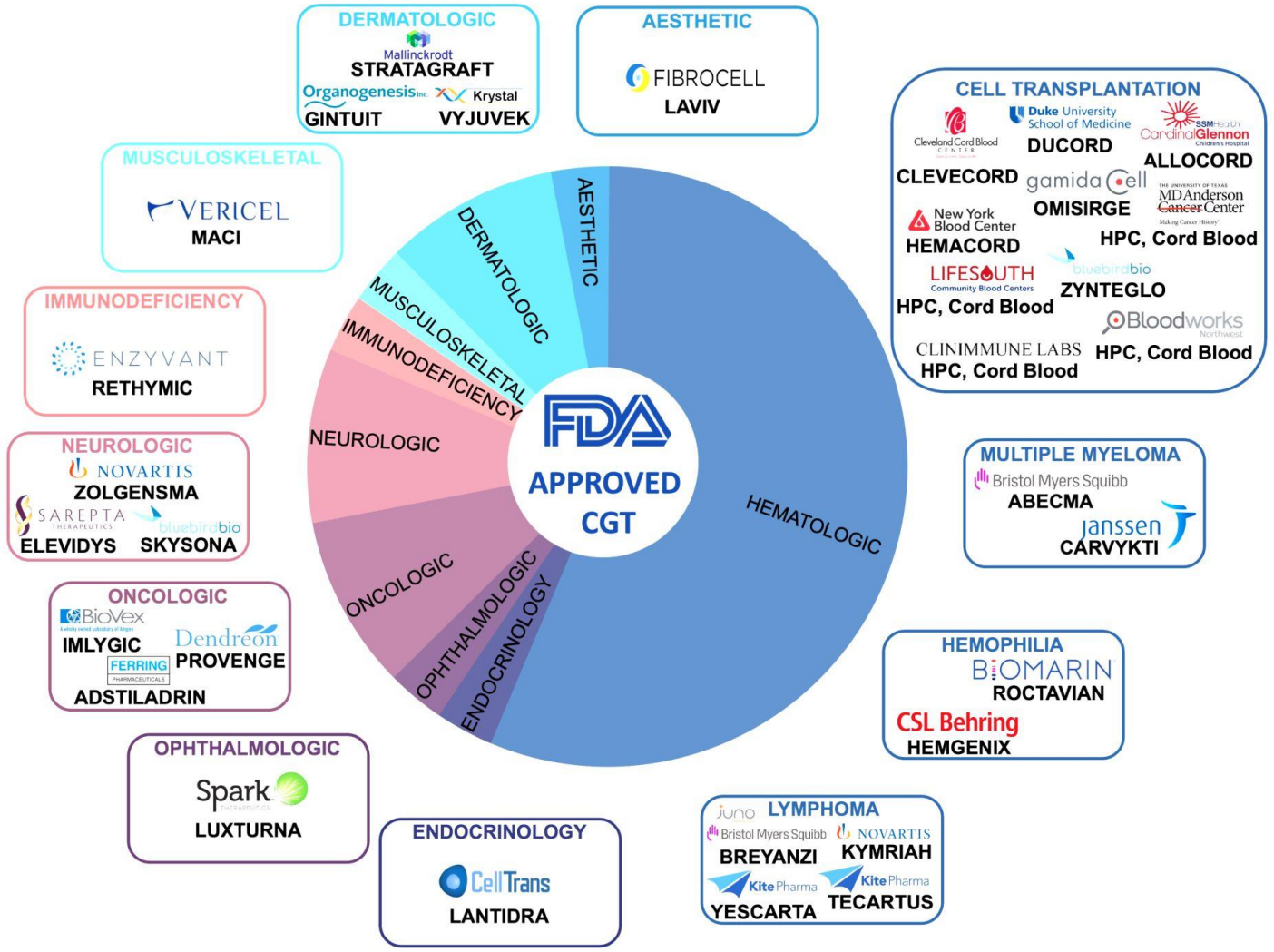
Advanced Therapy Medicinal Products (ATMPs)



EMA/CAT report July 2023

Advanced Therapy Medicinal Products (ATMPs)



Source: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

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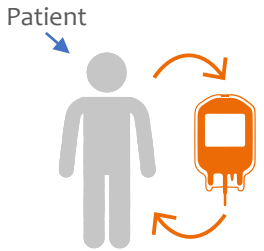
Advanced Therapy Medicinal Products (ATMPs)

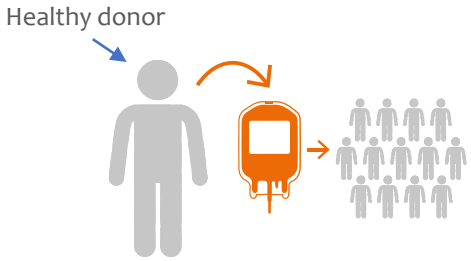
With the aim of providing access to this kind of medicines, in 2017, **Stemlab** decided to build an area dedicated to the production of ATMPs.

The **GMP facility** authorized (**Infarmed)** in **January 2020** and currently has the capacity to manufacture:

- **Autologous** (from self) cell therapy products



- **Allogeneic** (from a donor) cell therapy products



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Advanced Therapy Medicinal Products (ATMPs)

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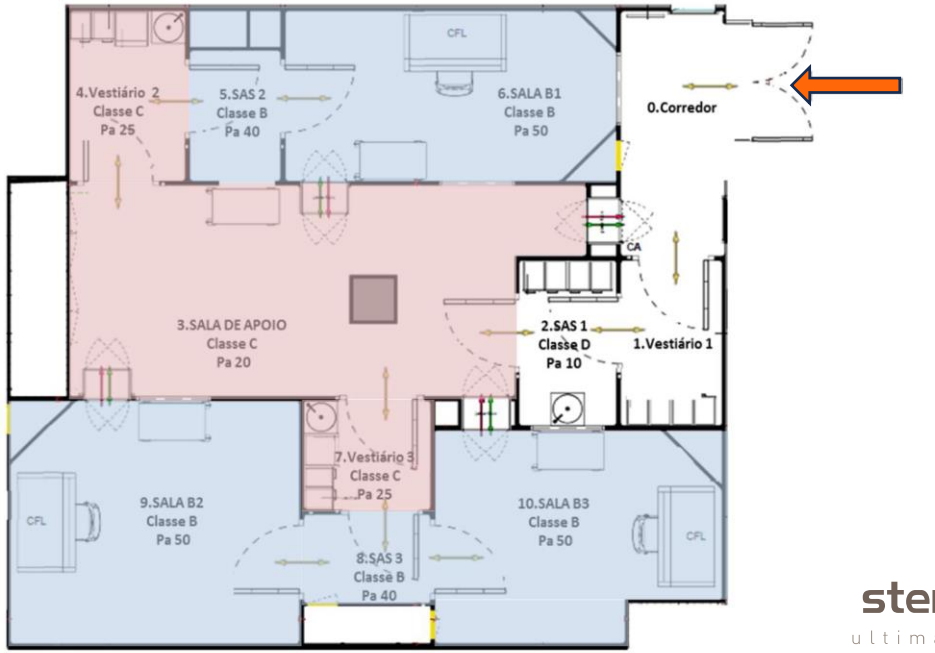
Our facilities



TOTAL AREA: ~100 M²

CLASS B: 2 X 10 M² + 1 X 12.5 M²

CLASS C: 20.6 M²

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Advanced Therapy Medicinal Products (ATMPs)

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Our facilities

- Dedicated GMP facilities
- Distinct production areas
- Concurrent manufacturing of different ATMPs

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Advanced Therapy Medicinal Products (ATMPs)

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Our facilities

- Storage area

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Advanced Therapy Medicinal Products (ATMPs)

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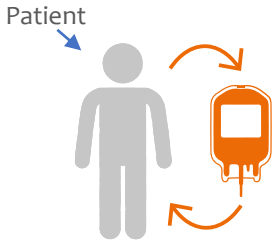
GMP activity initiated

- an **autologous product** for a **phase IIa clinical trial in stroke patients,** based on CD34+ cells isolated from the patients' own Bone Marrow (**Stemlab_CD34BM**).

AIM: Assess efficacy of intra-arterial administration of CD34+ cells 7 and 20 days after **acute ischemic stroke.**



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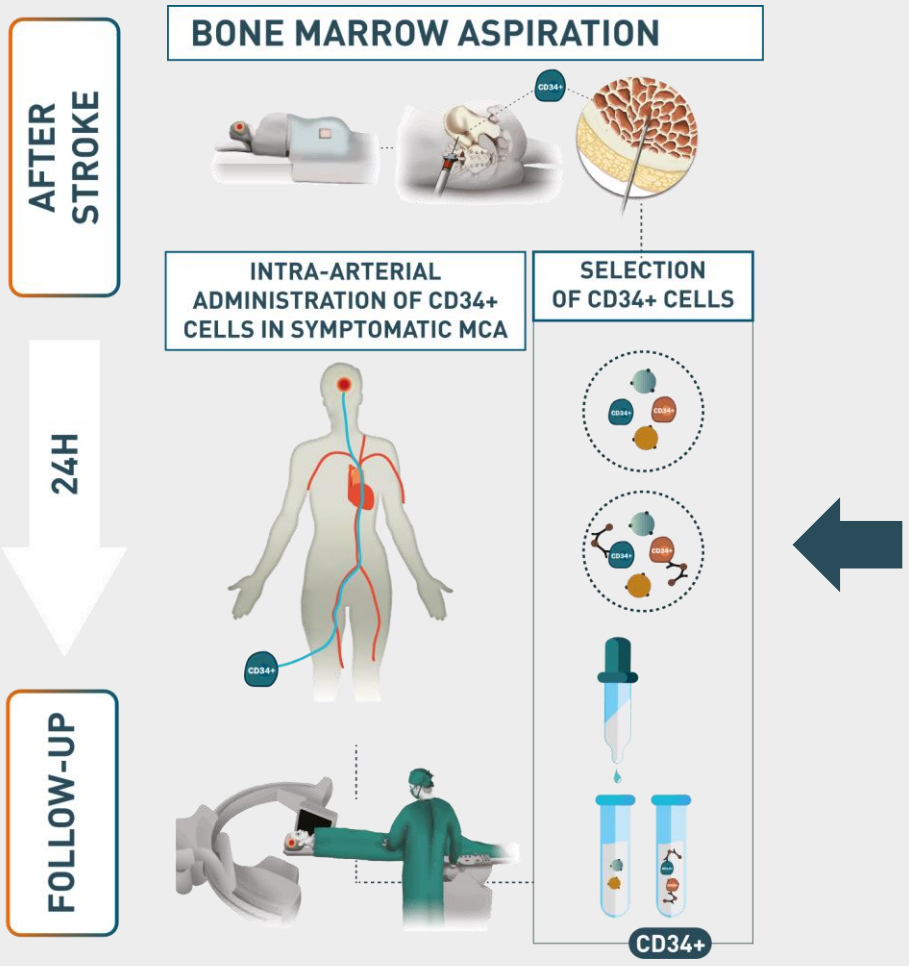
Stemlab_CD34BM



CliniMACS Plus - CD34+ cells selection

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ATMPs – Production

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* AUTOLOGOUS PRODUCT

- **STEMLAB_CD34BM (BONE MARROW) IN STROKE**

Autologous bone-marrow (BM) derived CD34+ cells for acute ischemic stroke - a Phase IIa clinical trial.
A Phase I clinical trial demonstrated that BM-CD34+ cells administration in acute ischemic stroke patients is safe and feasible.

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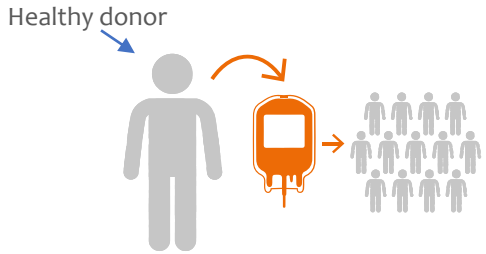
Created with BioRender.com

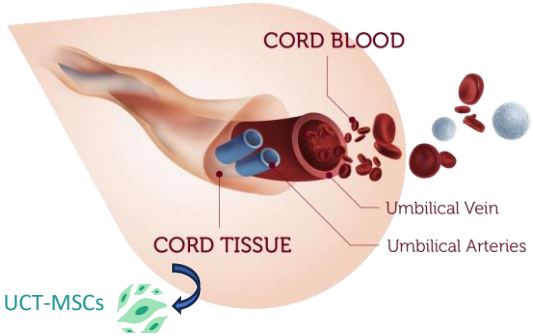
ATMPs – Production

Now **Stemlab** is also producing **allogeneic cell therapy products**



A cell therapy product based on **mesenchymal stem cells (MSCs)** from the **umbilical cord tissue** (SLCTmsc02) for a **phase II clinical trial in patients with Acute Respiratory Distress Syndrome (ARDS)**, a life-threatening complication of severe cases of COVID-19 and other conditions.

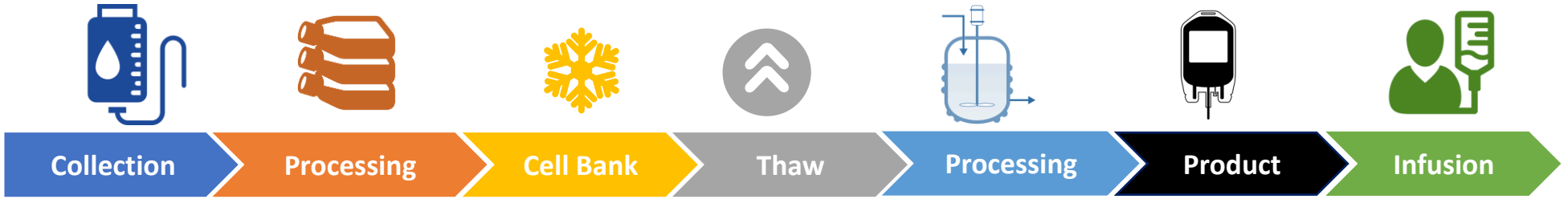
AIM: Assess safety and efficacy of a single intravenous infusion of **umbilical cord tissue MSCs** in patients with ARDS.



ATMPs – Production

* ALLOGENEIC PRODUCT (OFF-THE-SHELF)

➢ SLCTMSC02 (UMBILICAL CORD TISSUE) IN ARDS



Allogeneic cell therapy product based on Umbilical cord tissue MSCs for ARDS patients - a Phase II clinical trial.
MSCs have been applied in patients with severe COVID-19 with favorable results.

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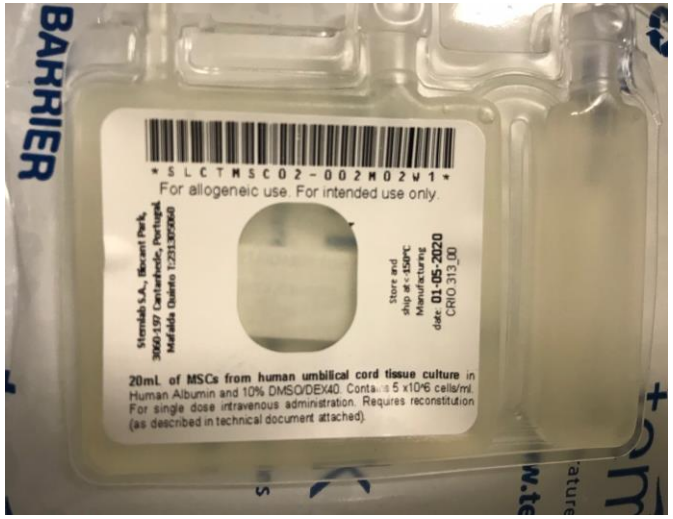
Project: ARDS Clinical Trial

Status: Preparing Application for Clinical trial authorization

On-going

Description: Clinical trial for the treatment of ARDS using allogeneic umbilical cord tissue MSCs

Centro Hospitalar e Universitário de Coimbra (CHUC)



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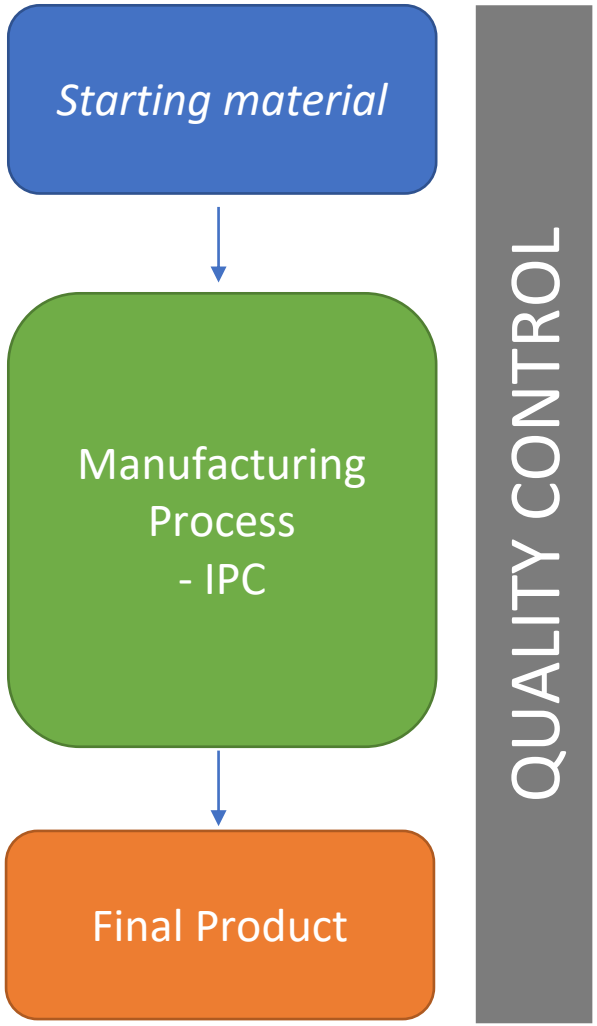
EMA's Committee for Advanced Therapies (CAT)

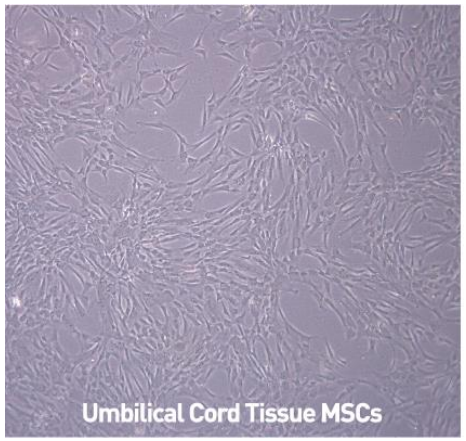
The **EMA/CAT** – Article 2 of Regulation (EC) No 1394/2007 – considered:

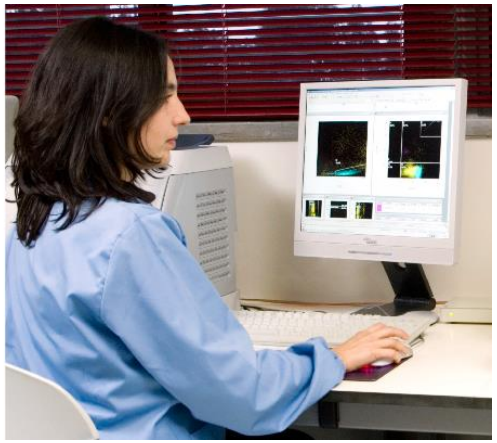
- **Stemlab_CD34BM** is a **Tissue Engineered Product** (intended to **regenerate, repair** or **replace a human tissue**) – **TEP**

- **SLCTmsc02** is a **Somatic Cell Therapy Medicinal Product** (contain cells or tissues that have been manipulated to change their biological characteristics or **cells** or tissues **not intended to be used for the same essential functions in the body**) – **CTMP**

ATMPs – Quality Control







Analytical control

- Number of cells, viability, immunophenotype
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References

- ✓ Eudralex Vol4; GMP Part IV – ATMPs
- ✓ European Pharmacopeia (Ph. Eur.)
- ✓ PIC/S; ICH; ISO standards

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ATMPs Pipeline

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PRODUCT	INDICATION	PRE-CLINICAL	CLINICAL DEVELOPMENT
Allo UCT MSCs	aGvHD		Hospital Exemption
	ARDS		Phase II clinical trial (Part 1 submission CTIS in preparation)
	Lupus	*In vitro*	
	Scleroderma	*In vitro*	
	Multiple sclerosis	*In vitro*	
	Spinal cord injury		Hospital Exemption (to be submitted)
Auto BM CD34+	Acute ischemic stroke		Phase IIa clinical trial (approved)
Auto UCB TNC	Neonatal Hypoxic Ischemic Encephalopathy		Hospital Exemption

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Publications

RACI
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StrokeTherapy

frontiers in Neurology

CLINICAL STUDY PROTOCOL
published: 07 May 2018
doi: 10.3389/fneur.2018.00302

STROKE34 Study Protocol: A Randomized Controlled Phase IIa Trial of Intra-Arterial CD34+ Cells in Acute Ischemic Stroke

João Sargento-Freitas[1,2], Anabela Pereira[3], André Gomes[4], Paula Amorim[3], Teresa Matos[4], Carla M. P. Cardoso[4], Fernando Silva[1], Gustavo Cordeiro Santo[1], César Nunes[1], Orlando Galego[1], José Carda[1], João Branco[3], Víctor Lourenço[3], Luís Cunha[1,2] and Lino Ferreira[2,5]*

[1]Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, [2]Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal, [3]Centro de Medicina de Reabilitação do Centro – Rovisco Pais, Tocha, Portugal, [4]Crioestaminal, Cantanhede, Portugal, [5]Centro de Neurociências e Biologia Celular, Coimbra, Portugal

Rationale/aim: Despite the increasing efficacy of recanalization therapies for acute ischemic stroke, a large number of patients are left with long-term functional impairment, devoid of efficacious treatments. CD34+ cells comprise a subset of bone marrow-derived mononuclear cells with the capacity to promote angiogenesis in ischemic lesions and have shown promising results in observational and *in vitro* studies. In this study, we aim to assess the efficacy of an autotransplant of CD34+ cells in acute ischemic stroke.

Sample size estimates: 30 patients will be randomized for a power of 90% and alpha of 0.05 to detect a difference in 3 months infarct volume.

Methods and design: We will screen 18–80 years old patients with acute ischemic stroke due to occlusion of a middle cerebral artery (MCA) for randomization. Persistent arterial occlusions, contra-indications to magnetic resonance imaging (MRI), premorbid dependency, or other severe diseases will be excluded. Treatment will involve bone marrow aspiration, selection of CD34+ cells, and their administration intra-arterially in the symptomatic MCA by angiography. Patients will be randomized for treatment at 7 (±2) days, 20 (±5 days) or sham procedure, 10 in each group.

Study outcomes: The primary outcome will be infarct volume in MRI performed at 3 months. Secondary outcomes will include adverse events and multidimensional functional and neurological measures.

Discussion/conclusion: STROKE34 is a PROBE design phase IIa clinical trial to assess the efficacy of intra-arterial administration of CD34+ cells 7 and 20 days after acute ischemic stroke.

OPEN ACCESS

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MSCellProduction

Bucar *et al. Stem Cell Research & Therapy* (2021) 12:399
https://doi.org/10.1186/s13287-021-02474-8

Stem Cell Research & Therapy

RESEARCH Open Access

Influence of the mesenchymal stromal cell source on the hematopoietic supportive capacity of umbilical cord blood-derived CD34$^+$-enriched cells

Sara Bucar[1,2], André Dargen de Matos Branco[1,2], Márcia F. Mata[1], João Coutinho Milhano[3], Íris Caramalho[4], Joaquim M. S. Cabral[1,2], Ana Fernandes-Platzgummer[1,2] and Cláudia L. da Silva[1,2]*

Abstract

Background: Umbi
progenitor cells (HS
culture with mesen
standard choice, bu
translation of an exp
(UCM)-, and adipose
UCB CD34$^+$-enriche

Methods: UCB CD3
over an established
serum (FBS) or fibrir
serum-free medium
as immunophenoty
the expanded hema

Results: MSC from
factors (in TNC) sup
Specifically, AT-deriv
derived MSC, but re
(CD34$^+$CD90$^+$) was
and expand a subp
establishment did n

biomedicines

MDPI

Article

Umbilical-Cord-Derived Mesenchymal Stromal Cells Modulate 26 Out of 41 T Cell Subsets from Systemic Sclerosis Patients

Paula Laranjeira [1,2,3,4], Francisco dos Santos [5], Maria João Salvador [6], Irina N. Simões [5], Carla M. P. Cardoso [5], Bárbara M. Silva [7,8,9], Helena Henriques-Antunes [5], Luísa Corte-Real [5], Sofia Couceiro [5], Filipa Monteiro [5], Carolina Santos [5], Tânia Santiago [6], José A. P. da Silva [2,6] and Artur Paiva [1,2,3,10,*]

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Abstract: Systemic sclerosis (SSc) is an immune-mediated disease wherein T cells are particularly implicated, presenting a poor prognosis and limited therapeutic options. Thus, mesenchymal-stem/stromal-cell (MSC)-based therapies can be of great benefit to SSc patients given their immunomodulatory, anti-fibrotic, and pro-angiogenic potential, which is associated with low toxicity. In this study, peripheral blood mononuclear cells from healthy individuals (HC, n = 6) and SSc patients (n = 9) were co-cultured with MSCs in order to assess how MSCs affected the activation

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Review

Stem Cell Therapy for Neonatal Hypoxic-Ischemic Encephalopathy: A Systematic Review of Preclinical Studies

Inês Serrenho [1], Miguel Rosado [2], Alexandra Dinis [3], Carla M. Cardoso [4], Mário Grãos [2,5,6], Bruno Manadas [2,*,†] and Graça Baltazar [1,*,†]

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Abstract: Neonatal hypoxic-ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in the perinatal period. This condition results from a period of ischemia and hypoxia to the brain of neonates, leading to several disorders that profoundly affect the daily life of patients and their families. Currently, therapeutic hypothermia (TH) is the standard of care in developing countries; however, TH is not always effective, especially in severe cases of HIE. Addressing this concern, several preclinical studies assessed the potential of stem cell therapy (SCT) for HIE. With this systematic review, we gathered information included in 58 preclinical studies from the last decade, focusing on the ones using stem cells isolated from the umbilical cord blood, umbilical cord tissue, placenta, and bone marrow. Outstandingly, about 80% of these studies reported a significant improvement of cognitive and/or sensorimotor function, as well as decreased brain damage. These results show the potential of SCT for HIE and the possibility of this therapy, in combination with TH, becoming the next therapeutic approach for HIE. Nonetheless, few preclinical studies assessed the combination of TH and SCT for HIE, and the existent studies show some contradictory results, revealing the need to further explore this line of research.

Keywords: hypoxic-ischemic encephalopathy; stem cell therapy; umbilical cord blood cells; umbilical cord tissue; mesenchymal stem/stromal cells; therapeutic hypothermia

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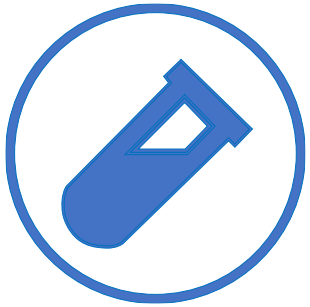

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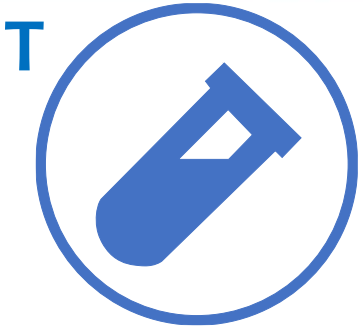

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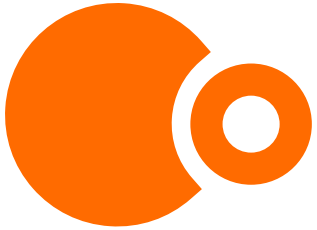

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