ADULT STEM CELLS AS A THERAPEUTIC TOOL

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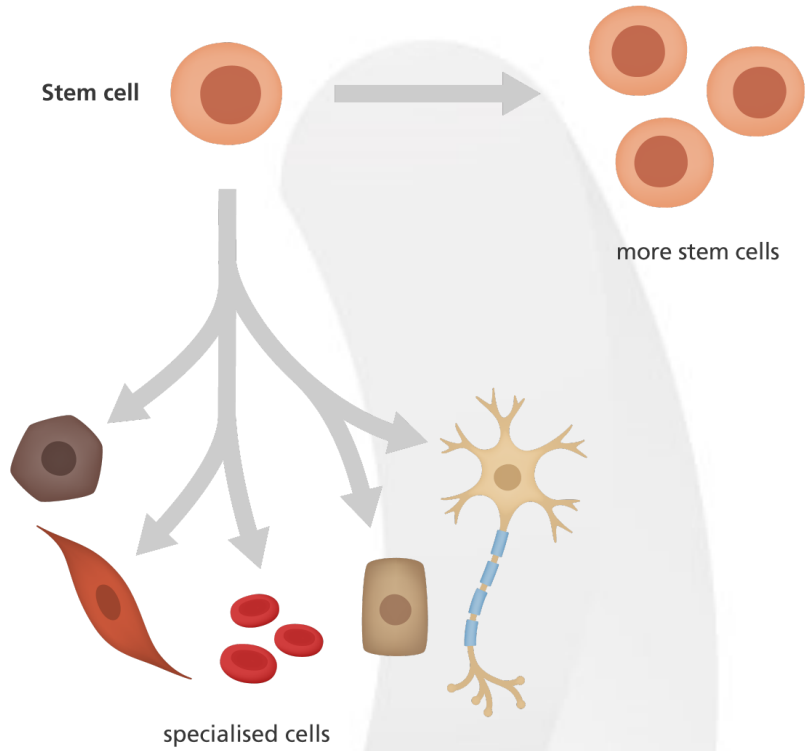
WHAT ARE STEM CELLS?

They are cells with the capacity to multiply, which can also develop functional and structural characteristics of specialized tissues, including cartilage, tendons, muscles and ligaments.



WHY ARE STEM CELLS USED AS A THERAPEUTIC TOOL?

Given their ability to multiply and differentiate, it was inferred that they could replace cells lost due to disease or degenerative conditions.

Clinical and preclinical experiments have shown that these cells also have an important capacity to modulate inflammatory activity, induce neovascularization, modify the extracellular matrix and modulate the immune response.

CAN ALL TYPES OF STEM CELLS BE USED FOR THERAPEUTIC PURPOSES?

No. Only adult or multipotent stem cells (hematopoietic or mesenchymal) are safe as a therapeutic tool, as long as they are properly prepared and tested.

ARE STEM CELLS A SAFE THERAPEUTIC ALTERNATIVE?

Yes, as long as they are produced under suitable conditions, by trained personnel and following strict procedures in terms of quality and safety.

Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials

Manoj M. Lalu[1,5], Lauralyn McIntyre[2,5]*, Christina Pugliese[5], Dean Fergusson[5], Brent W. Winston[6], John C. Marshall[7], John Granton[8], Duncan J. Stewart[3,4], for the Canadian Critical Care Trials Group

- *Thirty-six clinical trials were included, recruiting 1012 patients for the treatment of conditions such as: stroke, Crohn's disease, cardiomyopathy, AMI, GvHD, and healthy volunteers.*
- *There was no association found with toxicity, complications or organ failure, infection, death or cancer.*
- *A direct relationship was found with the development of early and transient febrile peaks.*

Lalu MM, et al. 2012. PLoS ONE.

DO HUMAN ADULT STEM CELLS HAVE ANY TUMOR-FORMING CAPACITY?

NO. Tumor formation has been reported only when cells obtained from rodent tissue samples are used.

The rodent´s stem cells apoptosis system, is activated by increasing oxygen concentration; what occurs during in vitro culture. Only cells that have inactivated the P53 protein, the guardian of the genome, survive the increase in oxygen concentration during in vitro culture and can be used in experiments. The P53 inactivation, make them so prone to the accumulation of mutations and therefore to malignization.

In conclusion, in almost all the stem cells experiments with rodent stem cells, uses malignan cells.

ADULT STEM CELLS SHOULD ONLY BE USED AUTOLOGOUSLY (FROM THE SAME PATIENT)?

No. ***Adult hematopoietic or mesenchymal stem cells can be used autologously (produced from a tissue sample from the same patient) or allogeneically (produced from a tissue sample from another person).***

Mesenchymal stem cells do not express major histocompatibility complex type II (HLA-DR) and although they do express type I (HLA-ABC), they do not express co-stimulatory molecules such as CD80 or CD86. Therefore, they are not subject to immune rejection.

WHAT ARE MESENCHYMAL STEM CELLS (MSCs)?

They are located in the vascularized stroma of tissues of more than nine weeks of gestation. Their name is due to the fact that when they were described, it was inferred they were remnant cells of the mesenchyme, embryonic supporting tissue.

These cells can be obtained from tissues as varied as bone marrow, adipose tissue, dental pulp and umbilical cord.

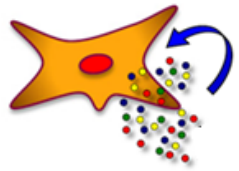
HOW IS THE USE OF MSC PRODUCED FROM UMBILICAL CORD SAMPLES SUPPORTED?

The umbilical cord is perhaps the most widely used tissue source for the procurement and production of mesenchymal stem cells, as the genomic stability and metabolic well-being of cultured cells from these tissue samples have been demonstrated. In addition, the donor can be adequately evaluated to rule out infectious-contagious diseases, and an adequate personal and family history review can be performed.

WHY ARE MSCs USED FOR THE TREATEMENT OF DEGENERATIVE DISEASES SUCH AS OSTEOARTHRITIS, DIABETES AND ALZHEIMER'S DISEASE?

Because they could lead to a significant and long-lasting decrease in symptoms through different mechanisms, including inflammation control, new blood vessels formation, local cells activation, modulation of the immune response and replacement of lost cells in the tissue; these cells induce regeneration of a wide group of diseased tissues, as well as decreasing their inflammation and restore adjacent structures.

Figure 1.



Autocrine stimuli

Soluble Factors Release

Endothelial/Smooth muscle Differentiation or Fusion

PARACRINE EFFECT

Differentiation into tissue lineage cells of the recipient tissue
Fusion with recipient tissue cells

Proliferation of local SCs

Activation of local SCs

Extracellular Matrix modification

Vasculogenesis

Angiogenesis

Arteriogenesis

Cytoprotection and metabolic modulation

Immunomodulation

VASCULAR REGENERATION

Tissue Regeneration

DIRECT RECOVERY OF LOST CELLS

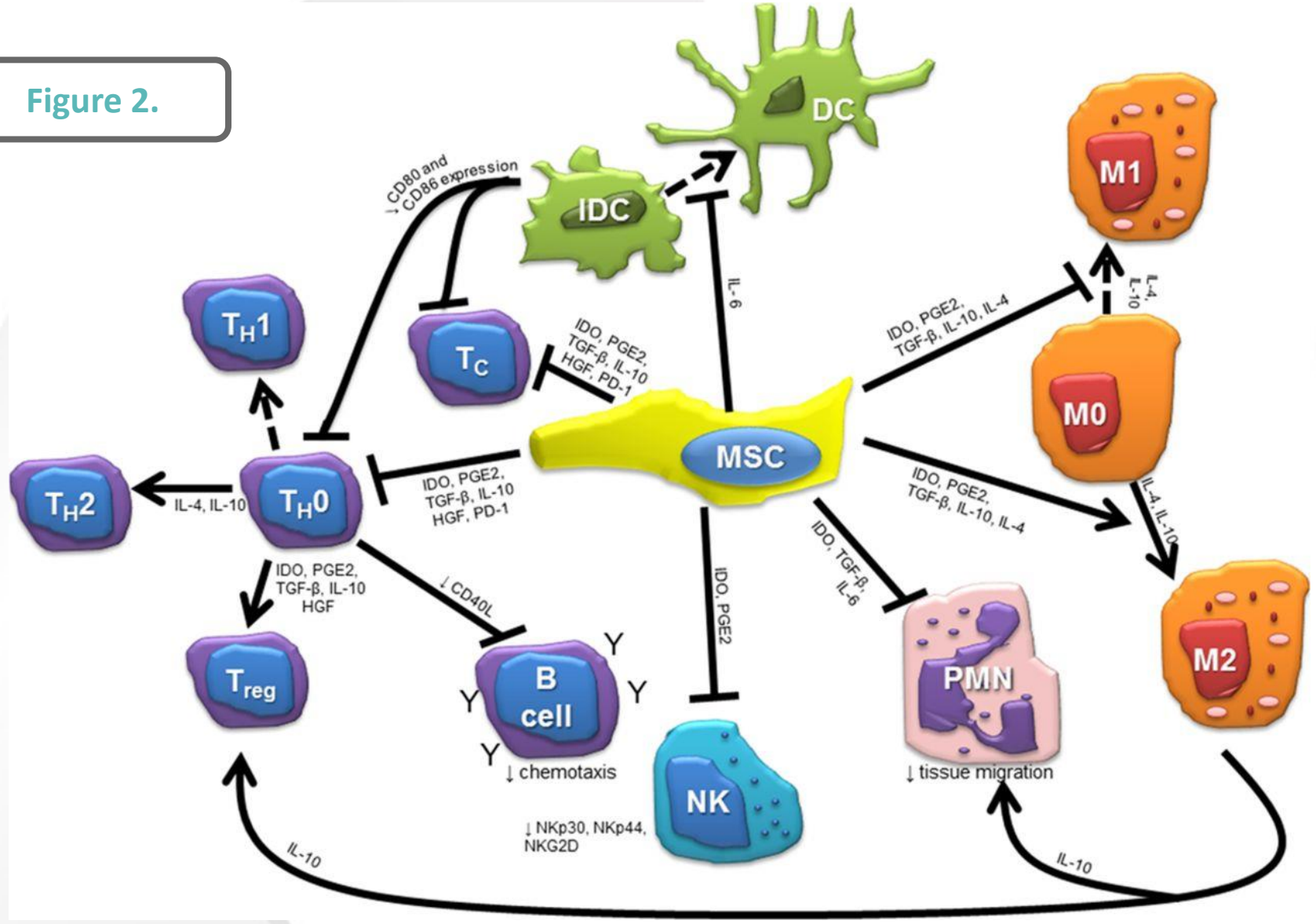
MSCs THERAPEUTIC ACTION MECHANISMS

The therapeutic capacity of MSCs is related to three groups of biological processes, which can be dependent on the differentiation capacity of MSCs and therefore, the direct replacement of lost cells; or on the paracrine trophic capacity of molecules produced by MSCs, which can be inside secretory vesicles (exosomes and microvesicles) or free.
Neovascularization is the result of vasculogenesis, angiogenesis and arteriogenesis. The differentiation capacity of MSCs is directly related to their capacity to favor vasculogenesis. While their capacity to produce trophic molecules with a paracrine effect (within secretory vesicles or not) is directly related to their capacity to induce angiogenesis and arteriogenesis.
The direct replacement of the cell population in the diseased tissue, can naturally be favored by MSCs due to their differentiation capacity, acquiring phenotypic characteristics particular to the cell species of the tissue, or it can also be encouraged by the induction of associated biological processes, leading to the activation of resident cells in the diseased tissue, thus causing their multiplication and migration.
Another large group of biological functions, including metabolic modulation, cytoprotection and immunomodulation, depend exclusively on the paracrine effect of the trophic capacity molecules produced by the cells, not on their differentiation capacity.

Modificado de: Gnecchi M, et al. Vascul Pharmacol. 2012

IMMUNOMODULATORY CAPACITY OF MSCs

Figure 2.

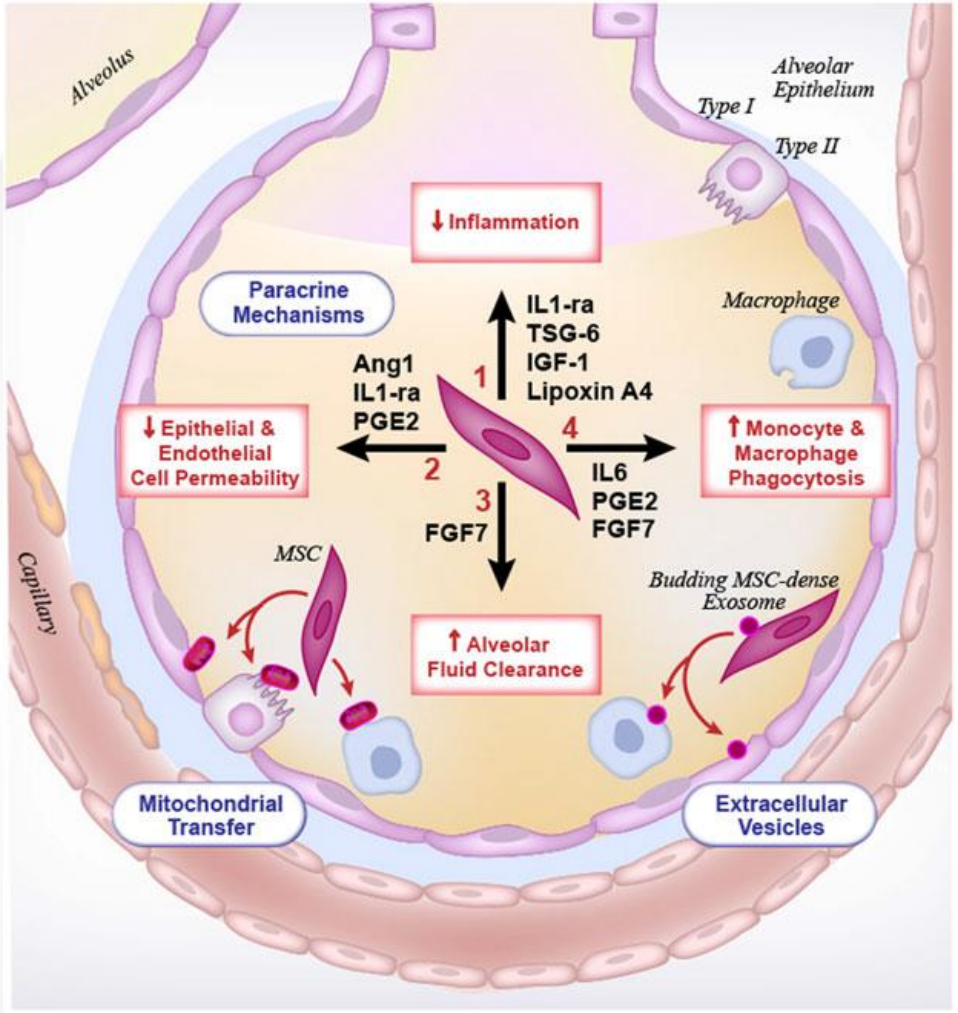


MSCs modulate the functioning of the innate and adaptive immune system, due to the trophic capacity of molecules with paracrine activity, released by them.
IDO: Indolamine-pyrrol2,3-dioxygenase.
PGE2: Prostaglandin E2.
TGF-β: Transforming growth factor β.
IL-10, IL-6 and IL-4: Interleukins 10, 6 and 4.
HGF: Hepatocyte growth factor.

Vasileios Karantalis, and Joshua M. Hare Circ Res. 2015;116:1413-1430

ACUTE RESPIRATORY DISTRESS SYNDROME

Figura 3.



MSCs favor the correction of pulmonary tissue disorders, characteristic of acute respiratory distress syndrome, such as that presented by people who develop severe forms of COVID-19.

PGE2: Prostaglandin E2.

IL-6: Interleukin 6.

FGF7: Keratinocyte growth factor.

IL1-ra: IL-1 receptor antagonist.

TSG-6: Tumor necrosis factor-induced gene 6 protein.

Ang1: Angiopoietin 1.

Lipoxin A4: Lipoxin A4.

IGF-1: Insulin-like growth factor 1.

Huperd L, et al. (2019) TRASNFUSION.

IT IS ACCEPTED THAT MSCs DO NOT REPLACE LOST CELLS, AT LEAST NOT TO A LARGE EXTENT. THEY MODULATE THE TISSUE NICHE, FOSTERING TISSUE REGENERATION.

MSCs do not replace the orchestra musician. They actually replace the orchestra conductor.

WHAT DISEASES OR CONDITIONS OF THE JOINTS, BONES OR MUSCLES COULD BE TREATED WITH MSCs?

The list is broad and varied. It includes sports injuries and general trauma, as well as long-term diseases affecting large joints such as knee, hip and shoulder, long bones such as those of the legs and arms, muscles, tendons and ligaments.

WHAT OTHER TYPES OF DISEASES OR HEALTH CONDITIONS CAN BE TREATED WITH MSCs?

Autoimmune diseases, respiratory and renal problems and all those due to age-related deterioration.

The clinical efficacy and safety of mesenchymal stromal cells for patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials

- ***Significantly lower mortality (at 28 days) in the interventional group (7.6% vs. 21.5%).***
- ***Significantly superior clinical improvement in the intervention group.***
- ***There was no difference in the risk of adverse events between the groups.***

Chen C-Y, et al. 2022. J Infect Public health.

Efficacy and safety of mesenchymal stem cells in the treatment of systemic sclerosis: a systematic review and meta-analysis

Jiehan Cui[1], Lu Jin[1], Meng Ding[1], Jingjing He[2], Lin Yang[1], Shaoxin Cui[1], Xiaoping Wang[1], Jun Ma[3,4] and Aijing Liu[1,3,5*]

- ***Significant improvement in skin thickness in the intervened group.***
- ***Improvement in the hands:***
  - ***Significant reduction in the number of digital ulcers in the interventional group.***
  - ***Significant improvement in hand dysfunction, measured with the visual analog scale of hand pain.***
- ***Significant improvement in oral functionality scales in the intervention group.***
- ***Significant improvement in lung capacity: Carbon dioxide diffusion capacity and forced vital capacity.***

Cui J, et al. 2022. Stem Cel Res Ther.

Expanded Mesenchymal Stromal Cells in knee osteoarthritis: A systematic literature review☆

Paloma Álvarez Hernández, José de la Mata Llord*

- *Significant clinical improvement in 60% of patients and structural improvement in 50% of patients.*
- *Better results when combined with hyaluronic acid or PRP.*
- *Clinical improvement was observed around the third month and structural improvement was observed around the sixth month.*
- *Maximum benefit around 12 months, sustaining benefit for at least 24 months.*
- *Optimal dose of around 40 million cells.*
- *No major adverse events were found.*
- *There was no difference in the use of autologous vs. allogeneic cells.*

Lee B-C, et al. 2021. J Clin Med.

HOW ARE THE MSCs APPLIED TO THE PATIENT?

It depends on the characteristics of each patient, and is influenced by different factors including, of course, their disease and its severity.

They are usually applied directly to the affected area, although intravenous use is also frequent considering the benefit they can generate in the whole body.

CAN ALL PATIENTS BE TREATED WITH MSCs?

No. It must be understood that stem cells (and their exosomes) have an enormous capacity to stimulate the growth of other cells in different tissues.

Therefore, a patient with an active cancerous process could become worse, since MSCs exosomes could stimulate the tumor cells and make the cancerous mass grow.

WHAT CHARACTERISTICS MUST AN MSCs PRODUCTION PROTOCOL HAVE TO COMPLY WITH GOOD MANUFACTURING PRACTICES (GPM)?

For a protocol to be executed within GMP parameters, verification and control mechanisms must be established for all raw materials, materials and reagents used during the production process to ensure the absence of external contaminants that cause cross-contamination and therefore constitute a risk of rejection of the product by the patient (user).

The production process must be carried out in suitable facilities, equipped with appropriate equipment for manufacturing advanced medical therapy products.

The final product must be analyzed, prior to its release for clinical use, in order to verify its quality, suitability and safety for the patient.

HOW CAN THE SAFETY AND SUITABILITY OF MSCs AS A THERAPEUTIC TOOL BE DEMONSTRATED?

The expansion of MSCs is an in-vitro process in which conditions are established that favor cell growth and, consequently, the growth of other undesirable biological agents, such as microorganisms.

Therefore, in order to demonstrate the safety and suitability of MSCs, microbiological, cytogenetic and phenotypic requirements must be defined, which must be evaluated by means of laboratory techniques to demonstrate their compliance.

WHAT POLLUTANTS ARE ALLOWED IN OUR PRODUCTS?

No microbiological agent is allowed either in the raw material or in the final product. For this purpose, in the human tissues used as raw material, the presence of viral, bacterial and fungal agents is ruled out.

The same applies to the ready-to-use cells (final product), which are evaluated by different laboratory techniques to demonstrate the absence of bacteria, fungi, yeasts, Mycoplasma sp. and the absence of toxic substances produced by bacteria, such as endotoxins.

HOW ARE THE SAFETY AND SUITABILITY OF THE CELLS DEMONSTRATED?

The safety of the cells is demonstrated through the analysis of the karyotype of the cells, by which their genomic normality is demonstrated.

The suitability of the cells is demonstrated by the expression of the markers normally recognized for MSCs by the International Society for Cellular Therapy. At least 95% of theses cells must express positive markers (CD73, CD90 and CD105) and no more than 5% should express the negative ones (CD34 and CD45).

IS THERE ANY ALTERNATIVE TO IMPROVE THE OUTCOME OF MSCs TREATMENT?

Yes, sometimes we use growth factors from the patient himself, which are purified under the strictest sterile conditions, in order to make the best use of their therapeutic capabilities and enhance the effect of the cells.

WHAT ARE THE POSSIBLE ADVERSE EFFECTS OF THE USE OF THESE CELLS?

Actually they are scarce and insignificant.

Fever, redness and spasms on the application site may be experienced, which disappear in a couple of days with simple treatment.

WHAT IS TRUSTEM?

Trustem is a biotechnological laboratory focused on the development of advanced medical therapy alternatives for regenerative medicine, implementing the technology and knowledge developed over 10 years of work, with the scientific and academic support of the Fundacion Universitaria de Ciencias de la Salud-FUCS.

WHAT DOES THE MULTIPLICATION THAT WE DO OF THE CELLS CONSIST OF?

In culturing the cells under ideal conditions, through the execution of protocols developed and validated internationally by us and in a specialized laboratory, designed and adapted for this purpose, with the objective of potentiating the therapeutic capacity of the stem cells.

WHAT EXPERIENCE DO WE HAVE IN THE USE OF THESE CELLS?

Trustem was created with the objective of enabling access to advanced medical therapy alternatives.

Our team is made up of professionals in the health sciences, with master's and doctoral degrees. We count on a combined experience of more than 30 years in the development and implementation of advanced medical therapy alternatives for regenerative medicine. Our knowledge and experience allows us to provide you with technical and clinical support in the standardization and implementation of therapeutic protocols with these therapeutic tools.

We have experience in the management of different diseases, conditions and lesions, affecting the nervous, cardiovascular, pulmonary and neuromusculoskeletal systems, in people of different characteristics, including high performance athletes.

trustem

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