

APPLIED HUMAN BIOTECHNOLOGY "BIOTECNOLOGIA HUMANA APLICADA, S.A." (BIOHUMAN S.A.)

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BIOHUMAN, S.A. STAFF

I. INTRODUCTION

A Guatemalan endeavour, our staff consists of professionals with experience in microbiology, clinical biochemistry, biotechnology, cellular immunology/physiology, quality management in clinical laboratories and healthcare companies.

BioHuman prepares Adult Stem Cells, also known as Autologous Cells. This means that they are harvested from the patient's body.

II. AUTOLOGOUS STEM CELLS

This type of cells can be obtained from several tissues in an adult human body, and in enough quantity that, they can be used as an excellent therapeutic option in the treatment of different diseases, generally chronic diseases, and those diseases that have not responded to other treatments.

The stem cell therapy is not new, they have been known and used since the early 1920's. These are some examples:

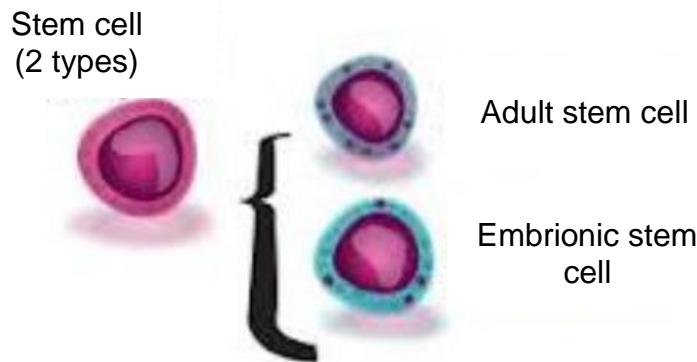
- ▶ In 1924, *Alexander A. Maximow*, a Russian scientist, identified a type of precursor cell in the interior of the mesenchyme that differentiated itself into different types of blood cells.
- ▶ In the 60's, the scientists *Ernest A. McCulloch* and *James E. Till*, demonstrated the clonal nature of the cells in the bone marrow, perpetuating themselves as they divide into their offspring.
- ▶ In the 70's, *Friedenstein & Col*, defined the stroma as a tissue composed of cells able to form colonies of fibroblast cells (CFU-f). They harvested mesenchymal stem cells under osteogenic stimuli, such as ascorbic acid, inorganic phosphate and dexamethasone to develop osteoblast cells. Then they identified other growth factors such as the TGF-beta that induced the cells to convert themselves into chondrocytes.

Stem cells have the capacity of divide themselves asymmetrically into two cells, one with the same properties of the original stem cell, and the other differentiated from the original. This asymmetrical cell division can be charted as a plant with different branches (picture 1), with the less differentiated cells in the stem of the plant, and the more differentiated ones in the branches (picture 2). The cells that have no

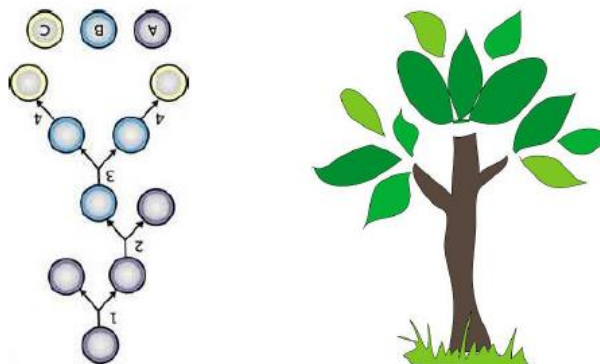
potential to differentiate themselves (that have reached their maximum maturity) are located at the leaves of the tree. Hence the name: "stem cells". They would be located at the beginning of the stem of the plant, giving birth to all varieties of cells. This means that stem cells have been known for a considerable amount of time, although at the beginning the scientific interest was merely academic, and in recent times their therapeutical potential was studied.

Picture 1: Clasification

STEM CELLS AS AISLATED FROM EMBRIONIC OR NOT EMBRIONIC TISSUE



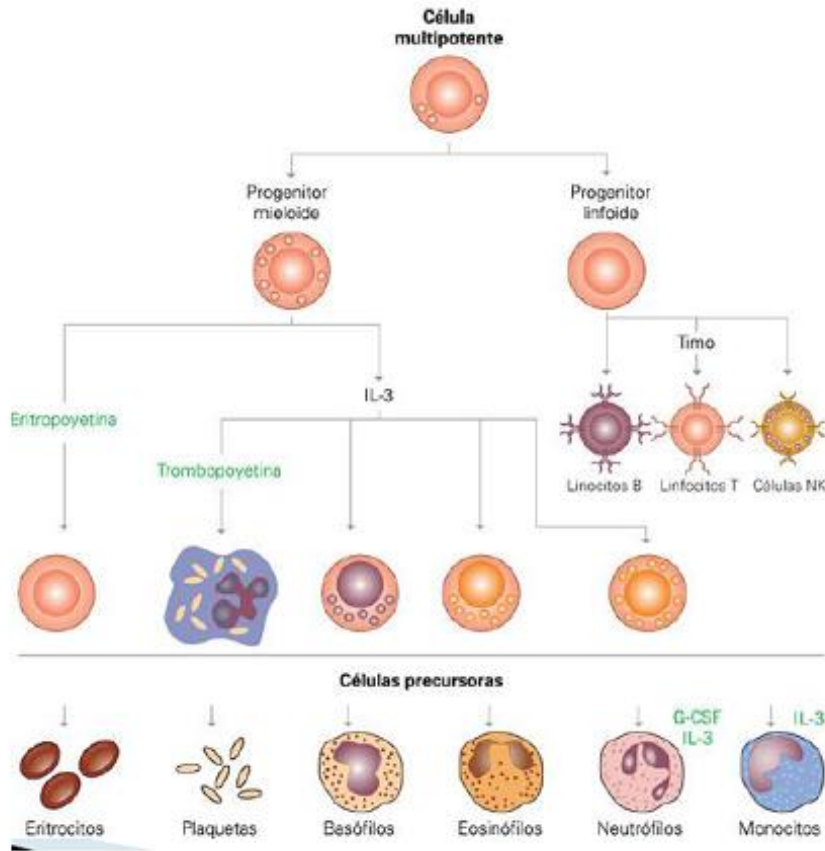
Picture 2: Sketch of how stem cells are represented on their location at the stem plant, and differentiated cells are located at the leaves of the plant



Adult stem cells are catalogued as multipotent in their majority, and they are located in adult tissues such as: bone marrow, peripheral blood, body fat, etc. Adult stem cells are responsible of periodic tissue renewal on tissues subject to continuous wear, or those tissues that have suffered damage, such as the skin, blood and liver. A good example of a multipotent adult stem cell, are the hematopoietic stem cells that are located in the bone marrow and are responsible of the formation of all blood cells. Another example are the adult mesenchymal stem cells, that can differentiate

themselves into muscular, vascular, nervous and osseous cells. Other adult stem cells are direct precursors of the tissues where they are located, such as skin, muscles, or germinal stem cells.

Picture 3: Hematopoietic stem cells give birth to multiple types of blood cells.



When adult stem cells are used in cellular therapies, a specialized medic obtains the initial tissue with standardized methodologies in controlled aseptic conditions. The obtained tissue is later processed in various stages to purify the stem cells of the desired type, and to perform quality validation tests. After this procedure is complete, the cells are delivered to the specialist who will perform the treatment according to the inoculation scheme selected by the patient. Stem cells are capable to migrate to damaged tissues, en a proportional quantity to the gravity and geometry of the lesion. The direction of the migration follows a gradient of the density of certain substances liberated by the damaged tissue.

Stem cell treatments aide in the diminishing of pain and inflammation and improve noticeably the state of diverse pathologies such as diabetes, spinal cord lesions,

muscle damage, infarcts and other conditions as well. The principal use is the treatment on severe refractory autoimmune diseases on approved therapies such as multiple sclerosis (MS), systemic scleroderma, rheumatoid arthritis, systemic lupus erythematosus (SLE), juvenile arthritis and others. In the majority of the patients, there is a observable improvement according to standardized scales for symptoms (EDSS, SCORAD, KWOMAC), due to the fact that stem cells have a powerful immunoregulatory function, and they promote the repair of tissues. Such treatments are autologous (they are made with the patients own cells) and because of this, these treatments can be repeated in multiple occasions without risk of an adverse autoimmune reaction. Other advantages are that these cells don't represent an ethical controversy, and it is not necessary to perform a compatibility test. Therefore, these are an excellent alternative to traditional treatments. Among other possible treatments, the metabolic syndrome, lipodystrophy and aging are result of the wear of the stem cells in the patients body, a treatment with mesenchymal stem cells can be advisable.

III. RELATED STUDIES

Nowadays these therapies are common and ongoing. For this purpose, other developed countries have performed studies such as:

a) The therapeutical potential of stem cells.

Philosophical Transactions of Royal Society 365:155-164, 2010

- Therapy with SC's with applications in: aging, cancer, diabetes, blindness, neurodegeneration.
- There are several cellular lines of embryonic SC's fully characterized, out of which it is known the exact histocompatibility haplotype.
- There is possibility of expansion and differentiation of SC's *in vitro*.
- There are culture matrixes that liberate peptides, growth factors or molecules to differentiate the stem cells in a specific manner.

b) Autologous hematopoietic stem cell transplant for autoimmune diseases: longitudinal study of 12 years by the European Blood and Bone Marrow Transplant in Autoimmune Diseases Group.

Farge, D., Labopin, M. et al.

Haematologica 95(2):284-292, 2010

- Therapy with hematopoietic cells has been used for a long time - can be obtained of bone marrow, peripheral blood or umbilical cord.
- Since 1996 the transplant of hematopoietic cells has been used successfully for the treatment of severe refractory autoimmune diseases on approved therapies.
- In this study, 900 patients with autoimmune diseases were controlled:
345 Multiple sclerosis

| | |
|-----|----------------------------------|
| 175 | Systemic scleroderma |
| 89 | Rheumatoid arthritis |
| 85 | Systemic lupus erythematosus |
| 65 | Juvenile arthritis |
| 37 | Hematologic autoimmune cytopenia |
| 104 | Others |

- It is concluded that the autologous H-SC's induce the remission for over 5 years in patients with severe refractory autoimmune diseases over conventional therapies.
- There is confirmed improvement in all cases, indicating that the bone marrow SC's are better, due that they contain fewer T-Cells than peripheral blood.

c) Treatment of SC's in patients with autoimmune diseases by systemic infusion of autologous stem cells (AD-MSC's) (MSC derived from adipose tissue).

Journal of Translational Medicine 9(181): 1-11, 2011.

- 10 patients were transplanted with AD-MSC's using repetitive injections of expanded cells.
- All patients presented improvement in standardized symptom scales (EDSS, SCORAD, KWOMAC).
- A patient with 3 year-long deafness regained hearing.
- A patient with severe polymyositis could not walk. Regained walking and was able to go up in stairs after the treatment.
- Three patients with rheumatoid arthritis could not walk and were able to walk and reduce the use of steroids.

d) Rheumatoid arthritis therapy with the autologous vascular fraction of stroma: rationalization and clinical security

Paz et al.

International Archives of Medicine 5:5, 1-9, 2012

- The article shows results for 13 patients treated with Autologous Vascular Stroma (SVF) over 1, 3, 6 and 13 months after treatment.
- In their follow-up, it is mentioned that none of the 13 patients experienced any secondary effect in the 13 months apart from one that experienced myalgia and redness of the face on the third injection.
- For the treatment of myocardial heart attacks, it is shown that the mesenchyme stem cells obtained from the adipose tissue are superior over the cells obtained from the bone marrow.
- Presence of regulatory T-Cells in adipose tissue, responsible of anti-inflammatory properties and MSC's with regenerative properties.



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IV. COMMENTS

In Guatemala, this therapeutic option is available to the general public. BioHuman provides assessment service and the preparation and expansion of the stem cells obtained from adipose or bone marrow tissues. BioHuman has the goal to improve the therapeutic options for patients that need it while respecting the Hippocratic Principles (to benefit and not to harm) and to improve your quality of life.