

Mesenchymal stem cells from bone marrow and umbilical cord for treating cardiovascular diseases

Células madre mesenquimales de médula ósea y de cordón umbilical en el tratamiento de enfermedades cardiovasculares

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Stem cells (SC) are internationally divided into fetal or embryonic and somatic, depending on their origin¹.

The embryonic SC are pluripotent cells that generate all types of body cells and they are not used due to ethical problems and existing legislations that prohibit their use, besides the opposition of the church. Somatic cells (**Figure 1**), on the other hand, are the ones employed and they are multipotential, but theoretically, they only generate a specific type of tissue².

Already in the '70s of the last century, studies on these interesting multipotential somatic cells started, in this case, the mesenchymal stem cells, and their

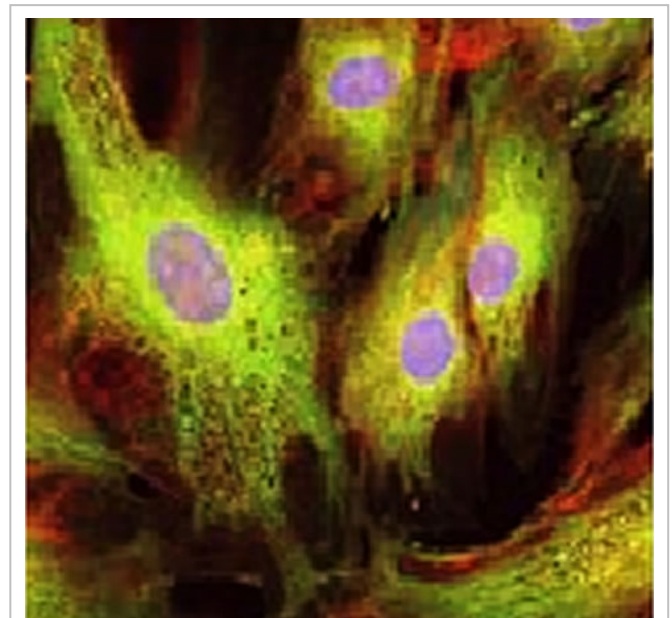


Figure 1. Somatic cells.
Source: microphotography owned by the author.

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wide potential of transdifferentiation to neuronal and muscle tissues³. In addition, it was later proved that they could originate chondrocytes, reticular cells (connective system), bone marrow fibroblasts that produce muscle tissue, adipocytes and osteoblasts⁴.

Also, later, they were used in cardiac surgery because apparently, they can differentiate in cardiomyocytes⁵.

For this reason, these mesenchymal cells are a therapeutic option for multiple diseases, but there is not a standardized technique to obtain them, and even nowadays there is not also a universally accepted nomenclature for classifying them.

It has not been identified a molecule for this cell type which allows identifying and selectively distinguishing these mesenchymal cells⁶.

It has been recently demonstrated that these mesenchymal cells have a great plasticity, which is the power of transdifferentiation they have, thus, they can differentiate into several tissues different from the ones of origin, hence, it could be considered, in part, to include them as pluripotent, but not as strongly as the embryonic or fetal cells⁷. Their main source is the bone marrow, but they are also found, to a lesser extent, in the mobilized peripheral blood, and there is evidence that they can also be in the umbilical cord, which is a very rich source of hematopoietic progenitors and, unlike mesenchymal cells of the bone marrow, these present the phenotypic marker CD34 positive lineage, which is not more than a glyco-phosphoprotein with which they can be identified and quantified⁸. At this point, we are not in complete agreement because such a marker CD34 positive lineage can also be found in the cells of the bone marrow through the flow cytometer⁹.

The proliferative capacity of the umbilical cord cells is higher than the ones of the bone marrow¹⁰. All hematopoietic progenitors constantly suffer from different processes such as proliferation, differentiation and apoptosis (biologically programmed cell death). These cells of the umbilical cord are committed to differentiate from blood cell lines that develop as erythrocytes, leukocytes and platelets, but they also have a certain amount of mesenchymal cells—as explained before—and therefore, they also originate cell lines different from the hematopoietic ones.

Every human being at birth should store and have available in banks of cells, the blood of his/her umbilical cord, for when it could be required (**Figure 2**).

The first transplant of umbilical cord cells was performed in October 1988, although the first at-

tempts date from the last century, since 1972. All these transplants were kind of a source of hematopoietic progenitors for the treatment of bone marrow transplantation in patients with malignant haemopathies and bone marrow failure syndromes; that is, their use was exclusive for their clinical application, restricted to the treatment of hematological diseases¹¹. However, many years later it was found that both, umbilical cord and bone marrow cells represented a great potential in the therapy of other extramedullary diseases, where cardiovascular diseases are included, among others.

On October 18, 2000 was published a news (in the French Newspaper *Le Figaro*) that a medical team of the country, led by the scientist, Dr. Menasche, implanted autologous myoblasts to a patient with an infarcted heart. The procedure was conducted months before this publication and it represented the first trial worldwide of the employment of regenerative therapy in the treatment of extramedullary diseases.

This type of cells was used for several years, but it quickly fell into disuse because they had no transdifferentiation power and their use in Cardiovascular Surgery brought several complications. The first publication in America related to the use of cells in the cell or regenerative therapy was in the Intercon-

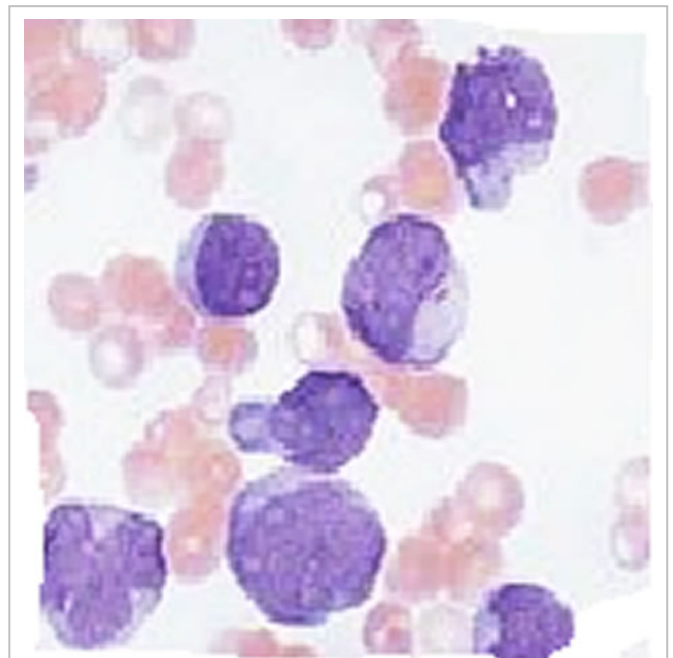


Figure 2. Immature cells of the umbilical cord. Source: microphotography owned by the author.

tinental Cardiology journal, in 2001, by Chachques *et al.*¹¹, from the Department of Cardiovascular Surgery from the Hospitals Broussais and Georges Pompidou of Paris, France.

Rapidly, independent groups from several highly developed countries in their health systems began using bone marrow cells, in this case, mononuclear, where cells marked as CD34 positive lineage were included, with transdifferentiation power¹².

On February 27, 2004, a team of scientists led by the cardiovascular surgeon, Dr. José Hidalgo Díaz, performed the first cardiac transplant of bone marrow SC in Cuba, Central America and the Caribbean, at the *Instituto de Cardiología y Cirugía Cardiovascular* of Havana (**Figure 3**).

Until now, ten cases have been performed such procedure; from them, eight have been surgically (three with the use of cardiopulmonary bypass (CPB)

and anoxic cardiac arrest and five without CPB, on a “beating heart”), and two through direct intracoronary infusion.

The hematological procedure is performed by puncturing the bone marrow stroma of the iliac crest, in order to obtain sufficient material to achieve, in the laboratory, SC in sufficient concentration (2×10^6 cells/ml) and determines the percentage of progenitor cells (CD34+, CD133+, CD6+, CD38+, HLA-DR-, CD90+, CD117+) of the obtained autologous bone marrow samples, as well as their viability. A total of 20 to 30 ml are transplanted by surgery, at the myocardial level, or intracoronary.

It must be noted that, although in all published cases of cell transplantation with different types of ST and by different ways of administration, the procedure has been innocuous, the effectiveness of the method in humans needs to be demonstrated. However, the international scientific community seems optimistic about the future of the cell therapy with SC in the regeneration of the human heart with the use of mononuclear cells and recently, mesenchymal cells¹³.

The members of this group were, in addition to Dr. Hidalgo, who directed the group, the doctors Ángel Paredes, Consuelo Macías, Elvira Dorticós, José Manuel Ballester, Alberto Hernández Cañero and Porfirio Hernández, among others, all members of the Regenerative Therapy Group from the *Instituto de Cardiología y Cirugía Cardiovascular* and the Cuban Institute of Hematology.

The first implant of SC through an intracoronary channel in the Cuban history, Central America and the Caribbean, was also conducted at the Institute of Cardiology on April 2, 2004 by the interventional cardiologist from the Cellular Therapy Group, Dr. Lorenzo D. Llerena Rojas.

Previously, at the Hospital Broussais in Paris, France, experiments were performed on animals, as it is usual in this type of research (*Contrat Commission Européenne* ERB 4001GT957737). It is not internationally acceptable to do these procedures at present without characterizing and accounting for the cells with the use of flow cytometry.

To use peripheral blood and mobilize mononuclear cells with several existent mobilizing factors and only centrifuging it, without employing the Ficoll method or apheresis, is a serious violation of the methods for obtaining

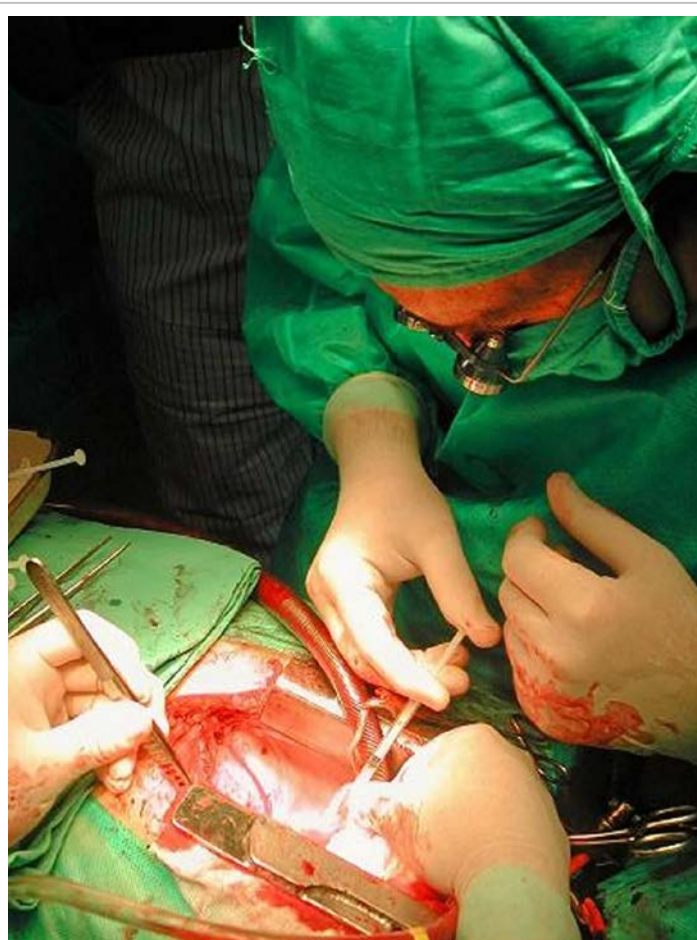


Figure 3. Dr. José R. Hidalgo Díaz implants stem cells directly (surgically) to the heart of a patient who had suffered a myocardial infarction. Source: photo property of the author.

SC for therapeutic purposes that violate the declaration of Helsinki regarding therapeutic procedures in humans. The same happens when peripheral blood from one patient is used to implant it in another. Even more serious is when animal cells are used, whose progeny or lineage is incompatible with that of the human being.

The regenerative therapy is also contraindicated in order to “eliminate significant arterial occlusions” of the coronary arteries (Cardiology and Cardiovascular Surgery) or limbs (Angiology), because these cells do not have that function. The regenerative therapy is associated in these cases to the coronary or peripheral arterial vessels, or to the use of stents (medicated or not), and their complementary use is for treating ischemic cardiac zones or peripheral vascular, not arterial occlusions. The “angiogenic” power of the SC in these cases has never been proved with angiographic studies. Neoformation vessels, observed in a few cases, are totally rudimentary and functionally ineffective. However, the “myogenic” power of these cells has been tested by and echocardiography (color-kinesis) and complementary studies of cardiac nuclear medicine three months after cellular implants. The “antiremodeling” effect of the myocardial tissue that these cells produce when transplanted into fibrous scar sites produced by myocardial infarctions is more than proved¹⁴.

Cell cultures for obtaining SC are internationally accepted methods and they are used, among others, for creating skin disaggregating the cells with trypsin and collagenase. Chondrocytes are grown using the same collagenase.

The INIBIC (*Instituto de Investigaciones Biomédicas de A Coruña*, Spain) separates mesenchymal cells and other types such as the ones of the subcutaneous cellular tissue (fat cells), among others. The tissue engineering advances rapidly and future regenerative therapy with ST remains promising and striking for the treatment of multiple diseases in human beings.

In relation to the use of the product pVEGF (growth factor of the vascular endothelium) in humans, which had long been in use and eventually unused, scientists performing the procedure accompany it with coronary revascularization, which is more realistic in addressing an indication of this kind. This is not performed by all the working groups. There must be assessed other channels to inject the angiogenic product, such as intracoronary, through the coronary sinus, transendocardial or

systemic, which would solve this problem without administrating the pVEGF by surgery; the mere realization of a major surgical procedure to implant a unique angiogenic solution carries more costs than benefits relative to this problem, and ethically, it should neither be warranted the procedure of administration of the product through a surgical channel without performing coronary by-passes or other vascular revascularizations. That is ethically unacceptable, and it violates the reference to the declaration of Helsinki in terms of treatment in humans.

The aforementioned product (pVEGF) is not part of the treatments inherent to the competence of the generative therapy with SC and, despite the long research of which it has been subjected and the innumerable clinical trials to which it has been submitted, it has never met the created expectations.

The cardiac bioassistance with the employment of SC is an ideal and emerging proposal of the scientific community for the treatment of cardiovascular diseases, as in other countless fields of medicine.

CONFLICTS OF INTERESTS

None declared.

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