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Saving 'Stem Cells'

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Content

Clearly, 'stem cells' do not need to be saved; they have been directing the development of animal organisms since the beginning of time and we assume that they will continue to do so indefinitely. From the blastocyst, the umbilical cord, the adipose tissue and the bone marrow, to cite just a few examples, stem cells will continue to carry out with a watchmaker's precision the roles for which they are programmed. It is up to scientists to learn to manage them and appropriately take advantage of their pluripotent nature. What needs to be saved is the meaning of the grammatical term 'stem cells', because its growing inappropriate use is being observed in both the media and the therapeutic setting. Sometimes, the dangerous 'error' ends up infiltrating scientific journals, conferences and even clinical trial database records.

Initially, all this could be attributed to ignorance and dismissed as unimportant. However, the fact is that the term 'stem cells' is obviously in widespread use with fraudulent intent in an attempt to exploit its 'prestige' and the therapeutic expectations it produces.

Such use of the term is 'widespread' in terms of both number of instances and geographic distribution. Even the strictly regulated healthcare environments of the United States and the European Union do not manage to escape the problem.

It is from precisely this 'developed' world that companies that are incorporated and sustained with enormous capital distribute devices with the supposed capacity to achieve a product supposedly made up of 'stem cells' in just a few minutes, through centrifugation of bone marrow aspirate or adipose tissue. It may be administered by local injection; this injection may be, for example, intra-articular, intravenous or both.

In administrative language, these procedures are considered 'non-substantial manipulation'. They are considered something like an 'autotransplantation' performed in a single surgical procedure, and their sponsors assume that they are not obligated to demonstrate its viability, safety or efficacy through regulated clinical trials that undergo monitoring by the healthcare administration.

Therapeutic potential for all manner of disease is ascribed to the product. With respect to our field of action, i.e. the musculoskeletal system, people are assured that such products can regenerate osteoarthritic cartilage, an intervertebral disc, or a femoral head affected by osteonecrosis. Yet, beyond that, people are assured of these products' success against diseases such as autism, multiple sclerosis and Alzheimer's disease. It would seem that the seriousness of these claims should attract the attention of scientists and healthcare authorities, but this does not appear to be the case.

Mesenchymal stem cells are the stem cell type most often used in therapy. They are not a uniform cell population, but rather a heterogeneous mix of populations. There is no single surface marker to positively identify them from among other cell types, and it is difficult to give them a name that precisely defines them.

Over time, they have been called 'bone marrow stromal cells', 'stromal cell precursors' and 'mesenchymal stem cells'. The International Society for Cellular Therapy (ISCT) proposed using the acronym MSC (mesenchymal stem/stromal cell) and established the requirements that isolated human bone marrow cells should meet to be called thus [1]:

– Capacity to adhere to the plastic of the culture material.

– Expression of certain surface markers: more than 95% of the cells in culture should show the molecules CD90, CD105, CD73 (SH2 and SH3) on their surface, and less than 2% of them should be positive in the detection of CD34 (marker of precursor cells for haematopoietic cells), CD45 (leukocyte common antigen), CD14 or CD11b, CD79 or CD19 and HLA-DR.

– Multipotentiality for differentiation to osteoblasts, adipocytes and chondrocytes.

The MSC content of products derived from bone marrow or adipose tissue that have not followed a process of selection and

culture is infinitesimal; only a few MSCs may be found in the quiescent G_0 phase. Taking bone marrow as a source, every 10,000 to 100,000 mononucleated cells are considered to contain 1 MSC. However, the fraction used in the procedures we mentioned cannot be considered purely mononuclear. To achieve this state, the fraction should undergo a laboratory procedure such as that of Ficoll, which produces an interphase between multinucleated and mononucleated cells and allows these two fractions to be identified and separated.

If the source were adipose tissue, the total MSC content in the product administered could be greater — up to 5% of all cells in the best case. Therefore, what we would refer to in medicine as an 'excipient' is made up of the other 95% of cells, which are undefined.

In these cases, when the MSC content is estimated, the estimate is made by selecting and culturing a sample separated from the product that was administered, giving it an appropriate medium for its survival that promotes its entry into the cell cycle. It is not taken into account that the cells that were administered were found in G_0 and were obligated to compete for oxygen and nutrients with millions of other cells, nor that many of them could have entered apoptosis owing to the transfer.

The conclusion is that both the benefits and the harm that may be achieved with the administration of such products should not be attributed to their 'mesenchymal stem cell' content, and therefore they should not be classified, studied or administered under this name.

The scientific community assumes that efficacy in cellular therapy requires a substantial number of 'stem cells' that are active, that is to say, in the cell cycle. To achieve this, cell selection and culture must be performed in specialised laboratories accredited by the healthcare authorities. This renders a cell product an 'advanced therapy medicine' that must be researched and used in accordance with 'Good Manufacturing Practices' pharmaceutical standards.

It is incorrect, then, to refer to a cell product as 'mesenchymal stem cells' or to use a similar term if the product does not have all the above-mentioned defining characteristics. Therefore, scientific journals should require authors to specify the exact product they are publishing on. If a cell selection and culture process has not been followed, it seems correct to refer to the product as a 'stromal vascular fraction', but never as 'MSCs' or the general term 'stem cells'.

MSCs appear to be well defined, but the emergence on the therapeutic scene of other lineages and other combinations calls for standardisation of the names of the active substances that authors of protocols and articles should follow to precisely identify the product they are dealing with.

In our community, the Spanish Agency of Medicines and Medical Devices (AEMPS) has issued guidelines that we follow and believe may be useful to circulate for general use.

The name of each cell product must include six attributes; there is a closed list of possible terms for each of them. A seventh attribute is added as free text in which cell subtypes and other specific attributes of the active ingredient that are considered to be of interest may be mentioned:

1. Product class

Cells, islet cells, laminae

2. Cell type

dendritic cells, endothelial cells, hepatocytes, chondrocytes, T lymphocytes, B lymphocytes, mononuclear cells, mesenchymal cells (categories '1' and '2' are used together in the case of MSCs), etc.

3. State of differentiation

Embryonic cells, foetal cells, stem cells, differentiated cells

4. Relationship to the patient

autologous, allogeneic, xenogeneic

5. Anatomical origin

Bone marrow, adipose tissue, umbilical cord blood, peripheral blood, cartilage, muscle, etc.

6. Manipulation

Expanded cells, non-expanded cells

7. Specific data (only used when necessary)

Information in free text considered to be of interest by the sponsor: stimulated with..., incubated with..., selected by...

As we can see, it is possible to correctly define a cell product. Even so, we have observed some inconsistencies in the use of the model described.

It is incorrect to associate some terms in a heterogeneous multicellular product derived from a simple bone marrow or adipose tissue centrifugation, for example item 2 'mesenchymal cells' and item 6 'non-expanded cells', because these products do not express any of the defining characteristics of MSCs. It would also not be correct to use item 2 'mononuclear cells' with item 6 'expanded cells', since in this case 'mesenchymal cells' and 'expanded cells' should appear.

The definition of the cell product being published on does not end with the 'active ingredient'. It should be completed with the 'dose' administered and the composition of the accompanying 'excipient', in our case, the 'suspension'. It should also contain the cell concentration in this suspension because the cell viability and the toxicity of the product administered may depend on all this.

Clearly, administering cells in a suspension that contains 0.5% albumin is not the same as administering cells in a suspension that contains 5% albumin. Likewise, transporting 10 million MSCs in a 1 cc suspension is not the same as transporting 10 million MSCs in a 0.5 cc suspension.

Ultimately, the translation of 'stem cell' knowledge and technology to clinical practice has created great expectations that we believe are more than founded, having treated more than 600 patients with expanded MSCs in accordance with GMPs and having

conducted various preclinical studies on a large animal model [2]. The problem is that Pandora's box has been opened and the ills brought about by illicit business tend to spread throughout the world and use Joseph Goebbels' well known formula: 'A lie repeated a thousand times becomes a truth' [3-7].

We would prefer President Lincoln's thinking to prevail: 'You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time.'

The journal *Insights in Stem Cells* can play a very active role in this control function by requiring appropriate use of terminology related to 'stem cells' in its articles. We are grateful for the initiative of its leaders and we wish them every success.

References

1 Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, et al. (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8: 315-317.

2 Casañas J, de la Torre J, Soler F, García F, Rodellar C, et al. (2014) Peripheral nerve regeneration after experimental sec,tion in ovine radial and tibial nerves using synthetic nerve grafts, including expanded bone marrow mesenchymal cells: morphological and neurophysiological results. Injury , Int. J. Care Injured 45 S4: S2-S6.

3 Committee for Advanced Therapies (CAT). European Medicines Agency (EMA). Reflection paper on classification of advanced therapy medicinal products. (2013).

4 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500126681.pdf

5 Orozco Ll, Soler Rich R, Morera C, Alberca M, Sanchez A, et al. (2011) Intervertebral Disc Repair by Autologous Mesenchymal Bone Marrow Cells: A Pilot Study. Transplantation Journal 92: 822-82.

6 Soler Rich R, Munar A, Soler Romagosa F, Peirau X, Huguet M, et al. (2015) Treatment of Knee Osteoarthritis with Autologous Expanded Bone Marrow Mesenchymal Stem Cells: 50 Cases Clinical and MRI Results at One Year Follow-Up. J Stem Cell Res Ther 5: 285.

7 Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, et al. (2015) Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation 99: 1681-1690.

