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THE RULE OF SCIENCE

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ABSTRACT

The use of MSCs for therapeutic purposes must be carefully considered. The scientific logic for their clinical use has recently been challenged, suggesting that the "Rule of Science" has been violated. A brief response is provided.

Paolo Bianco's recent statements try to discredit the entire translational efforts using Mesenchymal Stem Cells (MSCs) without making any distinction within the over 350 clinical trials that currently use MSCs world-wide. Trying to discredit scientists and organizations with different opinions, because they do not fit with one's myopic, narrow-minded and fundamentally misleading argument has recently raised serious concerns[1-3]. It is unfortunate to witness a pattern of out of context, selected and distorted quotes (Demystifying Mesenchymal Stem Cells, Paolo Bianco, Lecture at the 12th International Congress of The Cell Transplant Society, Milan, Italy, July 11, 2013; www.CTS2013.org). While the reasons for this attitude are not apparent, they could be misinterpreted, perhaps, as a troubled attempt to gain fame by publishing inflammatory and polarizing perspectives[4], rather than contributing to further the progress of science and clinical therapeutics.

It should be clear that we are the first to condemn the use of Mesenchymal Stem Cells (MSCs) when scientific methods are not adopted, that we consider patients' safety central to all cell therapy translational efforts and that expanded clinical trials should not be considered before safety is established in pilot (Phase I, Phase I/II) clinical trials. Nevertheless, pilot clinical trials should not necessarily require previous proof of efficacy in the selected clinical application, especially for pathologic conditions for which a valid therapeutic alternative does not exist. In addition, we believe that historical medical outcomes should be strongly considered as opposed to placebo controls, again to protect patient's safety (i.e., open label safety studies are useful when historical outcomes are known).

Before proven clinical benefits are established, well-designed clinical trials should be considered only in the presence of approval from an appropriate Institutional Review Board/Ethics Committee, with an adequate informed consent process in place and only when outcomes, possible side effects and serious adverse events are rigorously reported, monitored and reviewed by appropriate Data Safety Monitoring Boards (DSMBs), with defined stopping rules already included in the clinical protocols at their inception.

The Rules of Science requires that ALL of the facts be explained. The FACTS are:

Fact: MSCs can be isolated from a huge range of tissues and markers for their purification have been summarily published[5-11].

Explanation: MSCs are derived from perivascular cells, pericytes, and function at various sites of tissue injury[12-14].

Fact: Allogeneic or xenogeneic MSCs added systemically can CURE graft-vs-host disease, MS (EAE model), stroke, acute myocardial infarct, asthma (both acute and chronic lung inflammation), inflammatory bowel disease, kidney and liver fibrosis, urinary incontinence, sepsis, and on and on[15-19].

Explanation: MSCs stimulate powerful immunomodulatory and trophic effects[20].

Fact: MSCs are heterogeneous; only a very small fraction of these MSCs can be cloned.

Explanation: Life does not exist as a clone so if a heterogeneous mixture of cells works therapeutically, this is wonderful. Which cells do what in these therapeutic situations is what scientists are supposed to work on.

Fact: MSCs from a very limited number of tissues have been cloned and shown to possess "stem cell" properties.

Explanation: The name Mesenchymal Stem Cells does not explain their immunomodulatory or trophic effects and, therefore, Arnold Caplan who first proposed the MSC nomenclature has recently further proposed to call them "Medicinal Signaling Cells" to preserve the MSC acronym and correctly explain their function as immunomodulatory and trophic cells[21,22].

Fact: Freidenstein and Owen were among the first to describe the marrow MSC as a multipotent progenitor[23].

Explanation: There is a rich literature predating Caplan's proposal of the Mesengenic Process. However, Caplan proposed a comprehensive hypothesis (he still calls it an hypothesis) in which adult MSCs could be induced to differentiate into a variety of mesodermal phenotypes[24]. Caplan never suggested that these MSCs could differentiate into nerve, cardiac myocytes or other non-mesodermal phenotypes.

Fact: MSCs cannot differentiate into nerve or heart cells.

Explanation: Because MSCs are medicinal they can have profound therapeutic effects on stroke or AMI without differentiating into nerve or cardiac myocytes.

Fact: MSCs can have a profoundly positive effect on organ transplantation[25].

Explanation: MSCs modulate the immune-rejection chemistry and assist in the host-mediated repair of damaged vasculature and parenchymal tissue[19].

Fact: MSCs produce powerful antibiotic proteins when exposed to a range of different bacteria[26,27].

Explanation: Defensens have long been described and it is clear that they can be upregulated when bacteria are exposed to MSCs; thus, MSCs may, indeed, be a useful treatment for sepsis.

Fact: Arnold Caplan started Osiris Therapeutics and proudly publically discloses this at every public lecture.

Explanation: Caplan sued Osiris in 1997 in US Federal Court for breach of contract and has not had a formal relationship with Osiris since this time. Moreover, he owns no stock in Osiris and, thus, has nothing to gain from their successes except that many of their clinical observations support the concept that MSCs are medicinals. The data from Mesoblast, Cytori, Athersys, and other corporations likewise support the use of MSCs in various clinical contexts.

Summary

The simple Rule of Science is that with the accumulation of data, the hypotheses are proven or disproven and science progresses. Moreover, since most of biological science is tied to medical advancement and governmental (financial) support for such medical advancement, we scientist are ethically and morally obliged to extend our science into the medical arts where applicable. The use of MSCs in over 350 clinical trials listed on clinicaltrials.gov is exactly this extension. Paolo Bianco is still stuck in the 1980's and 90's and wants the *Stem Cells* to be his platform to deny us the due process of proving their therapeutic worth. Evidence Based Medicine is what we are doing and we are doing it on FIRM, PUBLISHED SCIENTIFICALLY SOUND DATA.

MSCs are, indeed, Drug Stores because they are naturally medicinals[28]. Patients in need of these therapies should not be denied access because Dr. Bianco still wants MSCs to only make bone.

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