DOI: 10.18416/crbft.2019.002 Infinite Science Publishing

MSC therapy: Donor variation and the curse of statistics

Martin James Stoddart [a,b]

[a] *AO Research Institute Davos, Davos Platz, Switzerland*
[b] *Department of Orthopedics and Trauma Surgery, G.E.R.N. Tissue Replacement, Regeneration & Neogenesis, Medical Faculty, Albert- Ludwigs-University of Freiburg, Freiburg im Breisgau, Germany*

Corresponding author, email: martin.stoddart@aofoundation.org

Abstract: *Mesenchymal stem cells (MSCs) have long been proposed as a potential cell source for musculoskeletal regeneration. Broadly speaking MSC therapies can be split into two categories; those that use freshly isolated cells, and those that use monolayer expanded cells. This distinction brings significant ramifications, both in terms of regulatory requirements and in the mechanism of action. From a scientific perspective, there have been two main challenges that have delayed the translation of MSCs into the clinic. Insufficient tools to adequately characterize the cell populations obtained and a lack of a detailed understanding of the mechanism of action of the implanted cells.*

Naïve cells are already commonly utilized in the clinic in the form of marrow stimulation techniques or intra-operative cell transfer via bone marrow aspirate concentrates (BMAC). Monolayer expansion of adherent MSCs is an attractive alternative strategy due to the increase in numbers than can then be implanted. This process is fraught with difficulties as it is known the expansion process can lead to major changes in cellular function [1]. Whether this is due to changes in cell behavior during expansion (phenotypic drift), or whether it is due to the expansion conditions preferentially selecting for a subpopulation is unclear.

The commonly used potency assays, such as in vitro differentiation, are long and labor intensive. The use of accurate markers to identify the cells being studied and assess their functional potency is the central issue around most other topics revolve. With no marker being truly MSC specific, consensus and reproducibility is almost impossible to achieve. This compounds the problem that monolayer expanded cells will vary depending on a number of factors, such as serum batch, and this makes comparisons between laboratories difficult.

Prediction of cell function at the donor level is the biggest challenge facing cell-based therapies. Especially during monolayer expansion procedures, which are expensive, the risk that the resultant cells are functionally defective, leading to a failed healing response, hampers efficacy studies. This challenge is even greater when considering the standard use of statistics, that evens out donor variation and can lead to misleading conclusions.

Author's statement

Research funding: This work was funded by the AO Foundation and a grant from the AOCMF R&D Commission. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] Bara JJ, Richards RG, Alini M, Stoddart MJ (2014) Concise review: Bone marrow-derived mesenchymal stem cells change phenotype following in vitro culture: implications for basic research and the clinic. Stem Cells 32: 1713-1723.