Cytotherapy, 2019; 00: 1–6

International Society
ISCT
Cell & Gene Therapy

Mesenchymal stem versus stromal cells: International Society for Cellular Therapy Mesenchymal Stromal Cell committee position statement on nomenclature

S. VISWANATHAN[1], Y. SHI[2,3], J. GALIPEAU[4], M. KRAMPERA[5], K. LEBLANC[6], I. MARTIN[7], J. NOLTA[8], D.G. PHINNEY[9] & L. SENSEBE[10]

[1]*Arthritis Program, University Health Network, Krembil Research Institute, University Health Network, Cell Therapy Program, University Health Network, Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Canada,*[2]*The First Affiliated Hospital, Soochow University Institutes for Translational Medicine, Suzhou, China,*[3]*Institute of Health Sciences, Chinese Academy of Sciences, Shanghai, China,*[4]*Department of Medicine, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA,*[5]*Section of Hematology, Department of Medicine, University of Verona, Verona, Italy,*[6]*Division of Clinical Immunology and Transfusion Medicine, Karolinska Institutet, Stockholm, Sweden,*[7]*Department of Biomedicine, University Hospital Basel, Basel, Switzerland,*[8]*Department of Internal Medicine, Stem Cell Program and Institute for Regenerative Cures, University of California Davis, Sacramento, California, USA,*[9]*Department of Molecular Therapeutics, The Scripps Research Institute, Jupiter, Florida, USA, and* [10]*UMR5273 STROMALab CNRS/EFS/UPS-INSERM U1031, Toulouse, France*

Abstract

The International Society for Cellular Therapy's Mesenchymal Stromal Cell (ISCT MSC) committee offers a position statement to clarify the nomenclature of mesenchymal stromal cells (MSCs). The ISCT MSC committee continues to support the use of the acronym "MSCs" but recommends this be (i) supplemented by tissue-source origin of the cells, which would highlight tissue-specific properties; (ii) intended as MSCs unless rigorous evidence for stemness exists that can be supported by both *in vitro* and *in vivo* data; and (iii) associated with robust matrix of functional assays to demonstrate MSC properties, which are not generically defined but informed by the intended therapeutic mode of actions.

Key Words: *differentiation, immunomodulation, mesenchymal stromal cells, nomenclature, paracrine secretion, self-renewal, stem cells*

Introduction

The International Society for Cellular Therapy's Mesenchymal Stromal Cell (ISCT MSC) committee issued a position paper in 2005 [1] clarifying that the term mesenchymal stem cell is not equivalent or interchangeable with mesenchymal stromal cell (MSC). The former refers to a stem cell population with demonstrable progenitor cell functionality of self-renewal and differentiation [2,3], whereas the latter refers to a bulk population with notable secretory [4], immunomodulatory [5] and homing [6] properties. The ISCT's MSC committee further issued a minimal criteria to define multipotent MSCs as being plastic adherent, expressing CD73, CD90 and CD105, lacking the expression of hematopoietic and endothelial markers CD11b, CD14, CD19, CD34, CD45, CD79a and HLA-DR and capable of *in vitro* differentiation into adipocyte, chondrocyte and osteoblast lineages [7].

These markers largely remain as minimal markers for defining *in vitro*–expanded MSCs. Nevertheless, there are issues that need to be considered. For example, CD34 negativity has been used to define MSCs; however, this is not as definitive. Depending on donors and passages, certain percentages of Adipose derived stem cells are CD34 positive. It should be noted that the Stro-1 antibody, which is also useful for the identification and isolation of MSCs, was actually produced with CD34+ bone marrow cells as immunogen [8]. It is likely that MSCs *in vivo* are

Correspondence: **Sowmya Viswanathan**, PhD, Affiliate Scientist, Krembil Research Institute, 60 Leonard Avenue, Office 3KD479, Toronto (Ontario), M5T 0S8, Canade. Yufang Shi, PhD, The First Affiliated Hospital and Soochow University Institutes for Translational Medicine, 199 Renai Road, Suzhou, 215123, China. E-mails: sowmya.viswanathan@uhnresearch.ca, yfshi@suda.edu.cn

(Received 24 June 2019; accepted 19 August 2019)

ISSN 1465-3249
https://doi.org/10.1016/j.jcyt.2019.08.002

more CD34 positive than *in vitro*–expanded counterparts, and inclusion of Insulin-like growth factor 1 in the culture media has been shown to increase CD34 expression [9]. The negativity of CD34 in MSCs could be related to plastic-adhering culture conditions [10]. Additionally, although MSCs are typically defined by lack of HLA-DR expression, this can be upregulated by exposure to interferon-γ [11] in both mouse and human MSCs, in a cell culture–dependent manner [12], indicating the plasticity of these cell surface markers. Hence, the identity of MSCs as defined by the original cell surface markers is evolving as our understanding grows.

The original position paper was meant to foster harmonization of terminology that was in keeping with the scientific evidence available then supporting functionality of the cells, "without fueling unrealistic expectations, to the general public." However, the interchangeable use of MSCs as mesenchymal stem cells or mesenchymal stromal cells has propagated, not diminished; there are in fact 54 858 results for a search string of "mesenchymal stem cells" versus 58 111 results for search string of "mesenchymal stromal cells" queried on Pubmed (February 2019). Additionally, many direct-to-consumer clinics have marketed mesenchymal stem cells to patients, sometimes even resulting in adverse reactions affecting patient safety [13]. This has prompted calls for disuse of the term "stem cells" in MSC nomenclature [14,15], reiterating the original position of the 2005 and 2006 *Cytotherapy* publications. In fact, there have been further suggestions to disqualify MSC research under the "stem cell" umbrella by funding bodies, publications and conferences organized by stem cell societies to emphasize the difference between MSCs and mesenchymal stem cells. However, the solution to this nomenclature quandary lies in more rigorous scientific examination, discussion, discourse and exchange of ideas and not exclusion of valuable research on MSC properties, function and definitions from esteemed scientific conferences and funding bodies [16]. With the advent of next-generation sequencing tools at the single-cell level and the mass cytometry technology, it is possible to decipher epigenomic, transcriptomic and proteomic level differences in heterogeneous populations composed of bulk MSCs and rarer progenitor/stem cell populations.

The aim of this position paper is to further consolidate and clarify ISCT's MSC committee position on functional definitions of mesenchymal stem versus stromal cells.

Part of the confusion lies in the use of the acronym, MSCs, which can be expanded to imply both mesenchymal stromal cells, mesenchymal stem cells, multipotent stem cells or medicinal signalling cells. The original ISCT's MSC committee position papers sought to retain the MSC acronym to provide continuity to "scientific discourse, electronic literature databases" because the term has been in use for more than three decades now. Even calls for the disuse of the "stem cell" terminology agree that retaining the MSC acronym is vital to support the continuity of scientific research and discourse [14].

Part of the contention with this terminology rises from the use of the term "mesenchymal" derived from the word mesenchyme, which is used to describe loosely organized tissue during embryonic development broadly associated with connective and bone marrow tissues. In fact, in the absence of prospective and definitive markers for MSCs, the *in vivo* equivalence of *in vitro* expanded MSCs has been much debated. There is evidence that MSCs share markers and functionality with perivascular and mural cells (pericytes and vascular smooth cells) [17]. This has led to the hypothesis that MSCs originate from perivascular cell populations and emigrate into capillary walls in surrounding fibrous tissues during times of development and injury, contributing to the repair process [18–21]. Others have highlighted that although there are similarities in between pericytes and MSCs, important differences are also present [22–24], and, in fact, MSCs share many similarities with adventitial cells [25]. Nonetheless, the controversy is less about the "mesenchymal" origin of these cells, and more centred on the "stem" versus "stromal" designation [14]. The ISCT's MSC committee does not favor abandoning the "mesenchymal" terminology, and recommends that the "MSC" acronym remain in use, but be additionally annotated with functional definitions to further clarify the designation.

Specifically, as part of this annotation, the tissue of origin of all MSCs should be provided. For example, bone marrow–derived, adipose tissue–derived and umbilical cord tissue–derived MSCs may be abbreviated appropriately as BM-MSCs, AD-MSCs and UC-MSCs, respectively. This context-dependent approach is necessary because MSCs from different tissues exhibit varied phenotypic, functional [26] and secretome behavior [27], emphasizing the need to specify tissue source ontogeny.

Second, the ISCT MSC committee recommends that functional definitions be used to clarify whether the MSC acronym stands for mesenchymal stromal cells or mesenchymal stem cells. This is particularly important because there are currently no cell surface markers to distinguish bulk populations of mesenchymal stromal cells from rarer populations of mesenchymal stem cells. Although CD146+ is a minimal surface marker that is enriched in BM-MSCs with clonogeneic colony forming unit-fibroblasts (CFU-F) potential that demonstrates *in vivo* ossicle formation and supports bone marrow hematopoiesis [2], this

marker overlaps with expression of other generic MSC markers including CD49a, CD90 and CD105 [2], rendering it common to both stromal and stem cell populations. Unless there is rigorous functional evidence *in vitro* and *in vivo* to demonstrate the self-renewal and differentiation properties, the term mesenchymal stem cells should not be used.

Previously, progenitor self-renewal and differentiation properties *in vitro* and *in vivo* have been demonstrated for mesenchymal stem cells isolated from BM, periosteum, umbilical cord blood, muscle [28], umbilical cord Wharton's jelly [29], dental pulp [30], adipose tissue [31] and growth plate [3]. Importantly, the differentiation potential of these stem/progenitor cells has varied according to the tissue of origin, method of isolation and *in vitro* propagation of the cells. Rigorous *in vitro* demonstration of self-renewal and/or multilineage differentiation should involve clonogeneic experiments as shown by Russell *et al.* [29,32–36]. Rigorous *in vivo* demonstration has not always been possible with clonogeneic cells; it has typically been limited to bone formation by skeletal stem cells under heterotropic transplantation conditions with an osteoconductive carrier [2], muscle regeneration upon local transplantation in injured-muscle tissue [37,38] or bone and cartilage formation in an intra-femoral transplantation model [39,40]. CFU-F progenitor assays and *in vitro* tri-lineage differentiation assays using inductive medium and cell staining, especially under clonal conditions, are indicative of progenitor status but not sufficient to demonstrate self-renewal capacity of mesenchymal stem cells in the absence of *in vivo* data.

Third, the ISCT MSC suggests that the moniker mesenchymal stromal cells be used to describe bulk unfractionated populations. We acknowledge that this is a heterogeneous population that includes fibroblasts, myofibroblasts and even a small proportion of stem/progenitor cells [30,33,41], but excludes hematopoietic and endothelial cells. Given this heterogeneity, we recommend the ongoing need to characterize MSCs using a matrix of assays to demonstrate secretion of trophic factors [42–44], modulation of immune cells [5,45–47] and other relevant properties including promoting angiogenesis [48–51]. Importantly, we recognize this limitation in functionally defining stromal cells, and advocate that the matrix of functional assays [52] be carefully selected based on the proposed utility of MSCs to demonstrate functionality of these cells both *in vitro* and *in vivo*. It is important to recognize that a matrix of functional assays will be needed to best capture the multimodal properties of this heterogeneous population of MSCs for their intended use. The ISCT's MSC committee had put out a consensus paper on functional matrix assays recommending three approaches, including quantitative RNA analyses of selected genes, flow cytometry of cell surface markers and protein analysis of MSC secretome [44]. The paper also speculated that characterization of exosomes and/or microRNA may be included as part of this multi-modal approach with increasing demonstration of functional roles for MSC-secreted exosomes [53–55] and microRNAs [56,57].

Use of licensed MSCs by interferon-γ or tumor necrosis factor-α or other cytokines in these functional assays is recommended because it mimics an *in vivo* diseased inflammatory environment that MSCs are likely to encounter [44]. Licensing of MSCs was previously recommended in an ISCT MSC position paper on interrogating MSC modulation of immune cells and addressing issues of culture-condition–driven immune plasticity [47]. The ISCT MSC committee also recommends using resting MSCs as internal controls or other reference materials as previously discussed [58].

Importantly, it is the paracrine and immunomodulatory properties of MSCs that largely serve as the basis for their clinical utility as exemplified in the Food and Drug Administration–authored review of 66 investigational new drug (IND) applications of MSC-based products submitted to the agency prior to 2013 [59]. Approximately half of the IND applications described MSC potency in terms of secretion of factors or expression of surface proteins on MSCs or on target cells such as lymphocytes [59]. Referring to MSCs as mesenchymal stromal cells, therefore, does not diminish their clinical utility and may more accurately reflect their functional benefit. This is especially true because many of the applications include non-homologous indications, which do not reply on the "stemness" or differentiation capacity of MSCs to connective tissue lineages, but in their interaction with tissue-specific progenitors and immune cells [60]. This is reinforced by the recent approval of Alofisel by Takeda and Tigenix for treatment of complex perianal fistulas in adult patients [61]. The primary mechanisms of action are speculated to be impairment of proliferation of activated lymphocytes and reduction in the release of pro-inflammatory cytokines, which allow the tissue around the fistula track to heal [62] in line with current understanding of the immunomodulatory properties of MSCs. Similarly, the 2017 approval by the Drug Controller General of India of Stempeucel for treatment for patients with critical limb ischemia due to Buerger's disease is predicated on the cells' anti-inflammatory and immunomodulatory properties, including inducing angiogenesis in ischemic muscle [63–65], in line with current functional definitions of MSCs.

Ultimately, the questions of whether mesenchymal stem versus stromal cells are functionally distinct

subpopulations and whether the stem and stromal cells have overlapping paracrine and immunomodulatory functions are best answered based on single-cell sequencing experiments, statistical clustering and analyses of data. From a clinical translational perspective, the secretory and immunomodulatory functions associated with clinical benefits of MSC-based therapies are thought to reside in the bulk, heterogeneous stromal cell fraction. The ISCT MSC committee strongly recommends that such cells continued to be termed and characterized as mesenchymal stromal cells through a matrix of functional assays with appropriate controls. For research and clinical translation applications, the ISCT MSC committee recommends the continued use of the acronym MSC, but with detailed annotation of tissue source and a robust matrix approach to demonstrate relevant functionality. Importantly, stringent evidence for stem cell functionality should be provided to justify the use of the "stem" moniker. The ISCT MSC committee recommends that functional distinction around definitions of stromal and stem cells be maintained. Further analysis should be focused on their secretomes and related functionalities. This will provide clarity to the field, enable stringency and continue to fuel science-based evidence for furthering research and development on both mesenchymal stromal and stem cells.

Acknowledgments

All the authors are current and active ISCT MSC committee members. The authors acknowledge ISCT as a funding source for open access.

References

[1] Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, et al. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy 2005;7:393–5. https://doi.org/10.1080/14653240500319234.

[2] Sacchetti B, Funari A, Michienzi S, Di Cesare S, Piersanti S, Saggio I, et al. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. Cell 2007;131:324–36. https://doi.org/10.1016/j.cell.2007.08.025.

[3] Chan CKF, Gulati GS, Sinha R, Tompkins JV, Lopez M, Carter AC, et al. Identification of the human skeletal stem cell. Cell 2018;175:43–56. https://doi.org/10.1016/j.cell.2018.07.029. e21.

[4] Dennis JE, Caplan AI. Advances in mesenchymal stem cell biology [Miscellaneous Article] Curr Opin Orthopaedics 2004;15:341–6.

[5] Le Blanc K, Mougiakakos D. Multipotent mesenchymal stromal cells and the innate immune system. Nat Rev Immunol 2012;12:383–96. https://doi.org/10.1038/nri3209.

[6] Kallmeyer K, Pepper MS. Homing properties of mesenchymal stromal cells. Expert Opin Biological Ther 2015;15:477–9. https://doi.org/10.1517/14712598.2015.997204.

[7] Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315–7. https://doi.org/10.1080/14653240600855905.

[8] Lin C-S, Ning H, Lin G, Lue TF. Is CD34 truly a negative marker for mesenchymal stromal cells? Cytotherapy 2012;14:1159–63. https://doi.org/10.3109/14653249.2012.729817.

[9] Bellagamba BC, Grudzinski PB, Ely PB, Nader P, de JH, Nardi NB, da Silva Meirelles L. Induction of expression of CD271 and CD34 in mesenchymal stromal cells cultured as spheroids. Stem Cells Int 2018;2018:7357213. https://doi.org/10.1155/2018/7357213.

[10] Simmons PJ, Torok-Storb B. CD34 expression by stromal precursors in normal human adult bone marrow. Blood 1991;78:2848–53.

[11] Stagg J, Pommey S, Eliopoulos N, Galipeau J. Interferon-gamma-stimulated marrow stromal cells: a new type of nonhematopoietic antigen-presenting cell. Blood 2006;107:2570–7. https://doi.org/10.1182/blood-2005-07-2793.

[12] Romieu-Mourez R, François M, Boivin M-N, Stagg J, Galipeau J. Regulation of MHC class II expression and antigen processing in murine and human mesenchymal stromal cells by IFN-γ, TGF-β, and cell density. J Immunol 2007;179:1549–58. https://doi.org/10.4049/jimmunol.179.3.1549.

[13] Jabr F.In the Flesh: The Embedded Dangers of Untested Stem Cell Cosmetics. Scientific American n.d. https://www.scientificamerican.com/article/stem-cell-cosmetics/(accessed February 20, 2019).

[14] Caplan AI. Mesenchymal stem cells: time to change the name! Stem Cells Transl Med 2017;6:1445–51. https://doi.org/10.1002/sctm.17-0051.

[15] Sipp D, Robey PG, Turner L. Clear up this stem-cell mess. Nature 2018;561:455. https://doi.org/10.1038/d41586-018-06756-9.

[16] Galipeau J, Weiss DJ, Dominici M. Response to Nature commentary "Clear up this stem-cell mess". Cytotherapy 2019;21:1–2. https://doi.org/10.1016/j.jcyt.2018.11.007.

[17] Crisan M, Yap S, Casteilla L, Chen C-W, Corselli M, Park TS, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. Cell Stem Cell 2008;3:301–13. https://doi.org/10.1016/j.stem.2008.07.003.

[18] Brighton CT, Lorich DG, Kupcha R, Reilly TM, Jones AR, Woodbury RA. The pericyte as a possible osteoblast progenitor cell. Clin Orthop Relat Res 1992;275:287–99.

[19] Canfield AE, Doherty MJ, Kelly V, Newman B, Farrington C, Grant ME, et al. Matrix Gla protein is differentially expressed during the deposition of a calcified matrix by vascular pericytes. FEBS Lett 2000;487:267–71.

[20] Bianco P, Robey PG. Stem cells in tissue engineering. Nature 2001;414:118–21. https://doi.org/10.1038/35102181.

[21] Tavian M, Péault B. The changing cellular environments of hematopoiesis in human development *in utero*. Exp Hematol 2005;33:1062–9. https://doi.org/10.1016/j.exphem.2005.06.025.

[22] Covas DT, Panepucci RA, Fontes AM, Silva JW, Orellana MD, Freitas MC, et al. Multipotent mesenchymal stromal cells obtained from diverse human tissues share functional properties and gene-expression profile with CD146+ perivascular cells and fibroblasts. Exp Hematol 2008;36:642–54. https://doi.org/10.1016/j.exphem.2007.12.015.

[23] Blocki A, Wang Y, Koch M, Peh P, Beyer S, Law P, et al. Not all MSCs can act as pericytes: functional *in vitro* assays to distinguish pericytes from other mesenchymal stem cells in angiogenesis. Stem Cells Dev 2013;22:2347–55. https://doi.org/10.1089/scd.2012.0415.

[24] Guimarães-Camboa N, Cattaneo P, Sun Y, Moore-Morris T, Gu Y, Dalton ND, et al. Pericytes of multiple organs do not behave as mesenchymal stem cells *in vivo*. Cell Stem Cell 2017;20:345–59. https://doi.org/10.1016/j.stem.2016.12.006. e5.

[25] Corselli M, Chen C-W, Sun B, Yap S, Rubin JP, Péault B. The tunica adventitia of human arteries and veins as a source of mesenchymal stem cells. Stem Cells Dev 2012;21:1299–308. https://doi.org/10.1089/scd.2011.0200.

[26] Melief SM, Zwaginga JJ, Fibbe WE, Roelofs H. Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. Stem Cells Transl Med 2013;2:455–63. https://doi.org/10.5966/sctm.2012-0184.

[27] Phinney DG, Sensebé L. Mesenchymal stromal cells: misconceptions and evolving concepts. Cytotherapy 2013;15:140–5. https://doi.org/10.1016/j.jcyt.2012.11.005.

[28] Sacchetti B, Funari A, Remoli C, Giannicola G, Kogler G, Liedtke S, et al. No identical "mesenchymal stem cells" at different times and sites: human committed progenitors of distinct origin and differentiation potential are incorporated as adventitial cells in microvessels. Stem Cell Reports 2016;6:897–913. https://doi.org/10.1016/j.stemcr.2016.05.011.

[29] Sarugaser R, Hanoun L, Keating A, Stanford WL, Davies JE. Human mesenchymal stem cells self-renew and differentiate according to a deterministic hierarchy. PLOS ONE 2009;4:e6498. https://doi.org/10.1371/journal.pone.0006498.

[30] Gronthos S, Brahim J, Li W, Fisher LW, Cherman N, Boyde A, et al. Stem cell properties of human dental pulp stem cells. J Dent Res 2002;81:531–5. https://doi.org/10.1177/154405910208100806.

[31] Zannettino ACW, Paton S, Arthur A, Khor F, Itescu S, Gimble JM, et al. Multipotential human adipose-derived stromal stem cells exhibit a perivascular phenotype *in vitro* and *in vivo*. J Cell Physiol 2008;214:413–21. https://doi.org/10.1002/jcp.21210.

[32] Russell KC, Phinney DG, Lacey MR, Barrilleaux BL, Meyertholen KE, O'Connor KC. *In vitro* high-capacity assay to quantify the clonal heterogeneity in trilineage potential of mesenchymal stem cells reveals a complex hierarchy of lineage commitment. Stem Cells 2010;28:788–98. https://doi.org/10.1002/stem.312.

[33] Guilak F, Lott KE, Awad HA, Cao Q, Hicok KC, Fermor B, et al. Clonal analysis of the differentiation potential of human adipose-derived adult stem cells. J Cell Physiol 2006;206:229–37. https://doi.org/10.1002/jcp.20463.

[34] Muraglia A, Cancedda R, Quarto R. Clonal mesenchymal progenitors from human bone marrow differentiate *in vitro* according to a hierarchical model. J Cell Sci 2000;113:1161–6.

[35] Lee CCI, Christensen JE, Yoder MC, Tarantal AF. Clonal analysis and hierarchy of human bone marrow mesenchymal stem and progenitor cells. Exp Hematol 2010;38:46–54. https://doi.org/10.1016/j.exphem.2009.11.001.

[36] Friedenstein AJ, Chailakhyan RK, Gerasimov UV. Bone marrow osteogenic stem cells: *in vitro* cultivation and transplantation in diffusion chambers. Cell Tissue Kinet 1987;20:263–72.

[37] Linard C, Brachet M, L'homme B, Strup-Perrot C, Busson E, Bonneau M, et al. Long-term effectiveness of local BM-MSCs for skeletal muscle regeneration: a proof of concept obtained on a pig model of severe radiation burn. Stem Cell Res Ther 2018;9:299. https://doi.org/10.1186/s13287-018-1051-6.

[38] Winkler T, von Roth P, Schuman MR, Sieland K, Stoltenburg-Didinger G, Taupitz M, et al. *In vivo* visualization of locally transplanted mesenchymal stem cells in the severely injured muscle in rats. Tissue Eng Part A 2008;14:1149–60. https://doi.org/10.1089/ten.tea.2007.0179.

[39] Mazurier F, Doedens M, Gan OI, Dick JE. Rapid myeloerythroid repopulation after intrafemoral transplantation of NOD-SCID mice reveals a new class of human stem cells. Nat Med 2003;9:959–63. https://doi.org/10.1038/nm886.

[40] McKenzie JL, Gan OI, Doedens M, Dick JE. Human short-term repopulating stem cells are efficiently detected following intrafemoral transplantation into NOD/SCID recipients depleted of CD122+ cells. Blood 2005;106:1259–61. https://doi.org/10.1182/blood-2005-03-1081.

[41] Kuznetsov SA, Krebsbach PH, Satomura K, Kerr J, Riminucci M, Benayahu D, et al. Single-colony derived strains of human marrow stromal fibroblasts form bone after transplantation *in vivo*. J Bone Miner Res 1997;12:1335–47. https://doi.org/10.1359/jbmr.1997.12.9.1335.

[42] Meirelles Lda S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine Growth Factor Rev 2009;20:419–27. https://doi.org/10.1016/j.cytogfr.2009.10.002.

[43] Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell 2011;9:11–5. https://doi.org/10.1016/j.stem.2011.06.008.

[44] Galipeau J, Krampera M, Barrett J, Dazzi F, Deans RJ, DeBruijn J, et al. International Society for Cellular Therapy perspective on immune functional assays for mesenchymal stromal cells as potency release criterion for advanced phase clinical trials. Cytotherapy 2016;18:151–9. https://doi.org/10.1016/j.jcyt.2015.11.008.

[45] Iyer SS, Rojas M. Anti-inflammatory effects of mesenchymal stem cells: novel concept for future therapies. Expert Opin Biol Ther 2008;8:569–81. https://doi.org/10.1517/14712598.8.5.569.

[46] Jones BJ, McTaggart SJ. Immunosuppression by mesenchymal stromal cells: from culture to clinic. Exp Hematol 2008;36:733–41. https://doi.org/10.1016/j.exphem.2008.03.006.

[47] Krampera M, Galipeau J, Shi Y, Tarte K, Sensebe L, MSC Committee of the International Society for Cellular Therapy (ISCT). Immunological characterization of multipotent mesenchymal stromal cells—The International Society for Cellular Therapy (ISCT) working proposal. Cytotherapy 2013;15:1054–61. https://doi.org/10.1016/j.jcyt.2013.02.010.

[48] Kinnaird T, Stabile E, Burnett MS, Shou M, Lee CW, Barr S, et al. Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. Circulation 2004;109:1543–9. https://doi.org/10.1161/01.CIR.0000124062.31102.57.

[49] Gruber R, Kandler B, Holzmann P, Vögele-Kadletz M, Losert U, Fischer MB, et al. Bone marrow stromal cells can provide a local environment that favors migration and formation of tubular structures of endothelial cells. Tissue Eng 2005;11:896–903. https://doi.org/10.1089/ten.2005.11.896.

[50] Wang C-Y, Yang H-B, Hsu H-S, Chen L-L, Tsai C-C, Tsai K-S, et al. Mesenchymal stem cell-conditioned medium facilitates angiogenesis and fracture healing in diabetic rats. J Tissue Eng Regen Med 2012;6:559–69. https://doi.org/10.1002/term.461.

[51] Hoffmann J, Glassford AJ, Doyle TC, Robbins RC, Schrepfer S, Pelletier MP. Angiogenic effects despite limited cell survival of bone marrow-derived mesenchymal stem cells under ischemia. Thorac Cardiovasc Surg 2010;58:136–42. https://doi.org/10.1055/s-0029-1240758.

[52] Chinnadurai R, Rajan D, Qayed M, Arafat D, Garcia M, Liu Y, et al. Potency analysis of mesenchymal stromal cells using a combinatorial assay matrix approach. Cell Rep 2018;22:2504–17. https://doi.org/10.1016/j.celrep.2018.02.013.

[53] Kordelas L, Rebmann V, Ludwig A-K, Radtke S, Ruesing J, Doeppner TR, et al. MSC-derived exosomes: a novel tool to treat therapy-refractory graft-versus-host disease. Leukemia 2014;28:970–3. https://doi.org/10.1038/leu.2014.41.

[54] Del Fattore A, Luciano R, Pascucci L, Goffredo BM, Giorda E, Scapaticci M, et al. Immunoregulatory effects of mesenchymal stem cell-derived extracellular vesicles on T lymphocytes. Cell Transplant 2015;24:2615–27. https://doi.org/10.3727/096368915X687543.

[55] Favaro E, Carpanetto A, Caorsi C, Giovarelli M, Angelini C, Cavallo-Perin P, et al. Human mesenchymal stem cells and derived extracellular vesicles induce regulatory dendritic cells in type 1 diabetic patients. Diabetologia 2016;59:325–33. https://doi.org/10.1007/s00125-015-3808-0.

[56] Concise Review: MicroRNA Function in Multipotent Mesenchymal Stromal Cells - Clark - 2014 - STEM CELLS - Wiley Online Library n.d. https://stemcellsjournals.onlinelibrary.wiley.com/doi/full/10.1002/stem.1623 (accessed April 1, 2019).

[57] Collino F, Deregibus MC, Bruno S, Sterpone L, Aghemo G, Viltono L, et al. Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. PLoS ONE 2010;5:e11803. https://doi.org/10.1371/journal.pone.0011803.

[58] Viswanathan S, Keating A, Deans R, Hematti P, Prockop D, Stroncek DF, et al. Soliciting strategies for developing cell-based reference materials to advance mesenchymal stromal cell research and clinical translation. Stem Cells Dev 2014;23:1157–67. https://doi.org/10.1089/scd.2013.0591.

[59] Mendicino M, Bailey AM, Wonnacott K, Puri RK, Bauer SR. MSC-based product characterization for clinical trials: an FDA perspective. Cell Stem Cell 2014;14:141–5. https://doi.org/10.1016/j.stem.2014.01.013.

[60] Martin I, Galipeau J, Kessler C, Blanc KL, Dazzi F. Challenges for mesenchymal stromal cell therapies. Science Translational Medicine 2019;11:1–3. https://doi.org/10.1126/scitranslmed.aat2189. eaat2189.

[61] Anonymous. Alofisel. European Medicines Agency - Commission 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/alofisel. (accessed February 20, 2019).

[62] Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet 2016;388:1281–90. https://doi.org/10.1016/S0140-6736(16)31203-X.

[63] Ranganath SH, Levy O, Inamdar MS, Karp JM. Harnessing the mesenchymal stem cell secretome for the treatment of cardiovascular disease. Cell Stem Cell 2012;10:244–58. https://doi.org/10.1016/j.stem.2012.02.005.

[64] Gupta PK, Krishna M, Chullikana A, Desai S, Murugesan R, Dutta S, et al. Administration of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells in critical limb ischemia due to Buerger's disease: phase II study report suggests clinical efficacy. STEM CELLS Translational Medicine 2017;6:689–99. https://doi.org/10.5966/sctm.2016-0237.

[65] Stempeutics Reserch Pvt Lts, Stempeucell, Stempeutron, Stempeucare, Cutisera, Stem Cells n.d.http://www.stempeutics.com/clinical-trials-CLI.html (accessed February 20, 2019).