**ML 18 (22/05/2017)**

Cell Reprogram. 2017 May 18. doi: 10.1089/cell.2016.0062. [Epub ahead of print]

# Mesenchymal Stem/Stromal Cells in Regenerative Medicine: Past, Present, and Future.

Trohatou O[1,2], Roubelakis MG[1,2].
**Author information**

**Abstract**

The concept of Regenerative Medicine combined with Cell based Therapy and Tissue Engineering represents the fourth pillar of healthcare and provides a promising approach for the treatment of serious diseases. Recently, cell based therapies are focused on the use of mesenchymal stem/stromal cells (MSCs). Human MSCs, that represent a mesoderm derived population of progenitors, are easily expanded in culture. They are capable to differentiate into osteoblasts, chondrocytes, and adipocytes and exhibit the potential to repair or regenerate damaged tissues. The best characterized source of human MSCs to date is the bone marrow; recently, fetal sources, such as amniotic fluid, umbilical cord, amniotic membranes, or placenta, have also attracted increased attention. Thus, MSCs may represent a valuable tool for tissue repair and cell therapeutic applications. To this end, the main focus of this review is to summarize and evaluate the key characteristics, the sources, and the potential use of MSCs in therapeutic approaches and modalities.

Tissue Eng Part B Rev. 2017 May 17. doi: 10.1089/ten.TEB.2017.0083. [Epub ahead of print]

# Mesenchymal stem cell-based cartilage regeneration approach and cell senescence: can we manipulate cell aging and function?

Szychlinska MA[1], Stoddart MJ[2,3], D'Amora U[4], Ambrosio L[5], Alini M PhD[6], Musumeci G[7].
**Author information**

**Abstract**

Aging is the most prominent risk factor triggering several degenerative diseases, such as Osteoarthritis (OA). Due to its poor self-healing capacity, once injured cartilage needs to be re-established. This process mighmight be approached bythrough resorting to cell-based therapies and/or tissue engineering. Human mesenchymal stem cells (hMSC) represent a promising approach due to their chondrogenic differentiation potential. Presently, in vitro chondrogenic differentiation of MSCs is limited by two main reasons: Aging aging of MSCs, which determines the loss of cell proliferative and differentiationed capacity and MSC-derived chondrocyte hypertrophic differentiation, which limits the use of these cells in cartilage tissue regeneration approach. The effect of aging on MSCs is fundamental for stem cell-based therapy development, especially in older subjects. In the present review we focus on homeostasis alterations occurring in MSC-derived chondrocytes with during in vitro aging. Moreover, we deal with potential cell aging regulation approaches, such as cell stimulation through telomerase activators, mechanical stimulation strain and epigenetic regulation. Future

investigations in these this fields might provide new insights into innovative strategies for cartilage regeneration in understanding the regulation of stem cell aging and will potentially open inspire novel therapeutic avenues approaches for OA treatments.

Curr Protoc Stem Cell Biol. 2017 May 16;41:1F.17.1-1F.17.12. doi: 10.1002/cpsc.29.

# Isolation of Ready-to-Use Adipose-Derived Stem Cell (ASC) Pellet for Clinical Applications and a Comparative Overview of Alternate Methods for ASC Isolation.

Raposio E[1], Bertozzi N[2].
**Author information**

**Abstract**

Current literature does not offer a standardized method to isolate adipose-derived stem cells (ASCs) for clinical applications and hence clinical studies using ASCs often show inconsistent results. Most of these studies borrow laboratory or benchside-derived protocols, which are complex, time consuming, and involve the use of chemical, animal-derived reagents. In this unit we describe a relatively simple and faster isolation protocol that allows collection of a ready-to-use ASC pellet for clinical application. All steps are performed in a closed circuit in order to guarantee maximum process sterility. Once the adipose tissue is harvested by means of a standard liposuction procedure, it undergoes a first centrifugation in order to remove the oil and serous fractions. Then ASCs are released by enzymatic digestion from the surrounding connective tissue scaffold. Finally a double series of washing and centrifugation allows one to obtain the ASC pellet alone. We usually graft this ASC pellet onto the skin edge and to the bottom of chronic skin ulcers as ASCs proved to be effective in promoting wound healing processes. Moreover, an increasing number of clinical studies are currently ongoing to test their potential in every medical field, from orthopedics to cardiology, oncology, autoimmune diseases, and tissue engineering

J Transl Med. 2017 May 19;15(1):107. doi: 10.1186/s12967-017-1210-z.

# Standardization of platelet releasate products for clinical applications in cell therapy: a mathematical approach.

Agostini F[1], Polesel J[2], Battiston M[1], Lombardi E[1], Zanolin S[1], Da Ponte A[1], Astori G[3], Durante C[1], Mazzucato M[4].

**Author information**

**Abstract**

***BACKGROUND:***

Standardized animal-free components are required for manufacturing cell-based medicinal products. Human platelet concentrates are sources of growth factors for cell expansion but such products are characterized by undesired variability. Pooling together single-donor products improves consistency, but the minimal pool sample size was never determined.

***METHODS:***

Supernatant rich in growth factors (SRGF) derived from n = 44 single-donor platelet-apheresis was obtained by $CaCl_2$ addition. n = 10 growth factor concentrations were measured. The data matrix was analyzed by a novel statistical algorithm programmed to create 500 groups of random data from single-donor SRGF and to repeat this task increasing group statistical sample size from n = 2 to n = 20. Thereafter, in created groups (n = 9500), the software calculated means for each growth factor and, matching groups with the same sample size, the software retrieved the percent coefficient of variation (CV) between calculated means. A 20% CV was defined as threshold. For validation, we assessed the CV of concentrations measured in n = 10 pools manufactured according to algorithm results. Finally, we compared growth rate and differentiation potential of adipose-derived stromal/stem cells (ASC) expanded by separate SRGF pools.

***RESULTS:***

Growth factor concentrations in single-donor SRGF were characterized by high variability (mean (pg/ml)-CV); VEGF: 950-81.4; FGF-b: 27-74.6; PDGF-AA: 7883-28.8; PDGF-AB: 107834-32.5; PDGF-BB: 11142-48.4; Endostatin: 305034-16.2; Angiostatin: 197284-32.9; TGF-β1: 68382-53.7; IGF-I: 70876-38.3; EGF: 2411-30.2). In silico performed analysis suggested that pooling n = 16 single-donor SRGF reduced CV below 20%. Concentrations measured in 10 pools of n = 16 single SRGF were not different from mean values measured in single SRGF, but the CV was reduced to or below the threshold. Separate SRGF pools failed to differently affect ASC growth rate (slope pool A = 0.6; $R^2$ = 0.99; slope pool B = 0.7; $R^2$ 0.99) or differentiation potential.

***DISCUSSION:***

Results deriving from our algorithm and from validation utilizing real SRGF pools demonstrated that pooling n = 16 single-donor SRGF products can ameliorate variability of final growth factor concentrations. Different pools of n = 16 single donor SRGF displayed consitent capability to modulate growth and differentiation potential of expanded ASC. Increasing the pool size should not further improve product composition.

J Bone Joint Surg Am. 2017 May 17;99(10):809-819. doi: 10.2106/JBJS.16.00793.

# Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): Platelet-Rich Plasma and Mesenchymal Stem Cells.

Murray IR[1], Geeslin AG, Goudie EB, Petrigliano FA, LaPrade RF.

**Author information**

## Abstract

***BACKGROUND:***

A comprehensive approach to the evaluation of biologic therapies for musculoskeletal conditions is required to guide appropriate future use. Clinical studies evaluating platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are limited by inadequate reporting of scientific details critical to

outcome. We developed minimum reporting requirements for clinical studies evaluating PRP and MSCs using Delphi consensus methods.

***METHODS:***

The need for consensus on the minimum reporting requirements for studies evaluating biologics was identified at the American Academy of Orthopaedic Surgeons/Orthopaedic Research Society (AAOS/ORS) Biologic Treatments for Orthopaedic Injuries Symposium in 2015 and the American Orthopaedic Society for Sports Medicine (AOSSM) Biologic Treatments for Sports Injuries II Think Tank in 2015. A working group facilitated the development of 2 expert consensus statements for PRP and MSCs using Delphi techniques. Exhaustive lists of items that could be reported on by clinical studies evaluating PRP or MSCs were generated by searching the published literature and protocols. PRP and MSC expert groups, each made up of 24 invited speakers at the AAOS and AOSSM symposia, were surveyed on 3 occasions to establish consensus on the inclusion of each item within minimum reporting guidelines. In addition to rating their agreement, the experts were encouraged to propose further items or modifications. Predefined criteria were used to refine item lists after each survey. Final lists were compiled into checklist statements by the working group.

***RESULTS:***

For PRP, the working group identified 93 experimental information items from the literature. Twenty-three experts (96%) completed 3 rounds of surveys. After 3 rounds, 58 items generated consensus with >75% agreement and <5% disagreement. These items were compiled into a 23-statement checklist. For MSCs, 103 items were identified from the published literature. Twenty-three experts (96%) completed 3 rounds of surveys. After 3 rounds, the 61 items for which consensus was reached were compiled into a 25-statement checklist.

***CONCLUSIONS:***

This study has established expert consensus on the minimum reporting requirements for clinical studies evaluating PRP and MSCs.

***CLINICAL RELEVANCE:***

These checklists provide specifications for the minimum information that should be reported by clinical studies evaluating PRP or MSCs.