

Stem Cells: What Should the Clinician Know?

UCSF Trauma Course 2022

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Where are the Endogenous Fracture Progenitor Cells



Bragdon & Bahney. Curr Osteoporos Rep. 2018 Aug;16(4):490-503. PMCID: PMC6041151

Preserve Endogenous Stem Cells in Periosteum and Muscle

Direct contribution of skeletal muscle mesenchymal progenitors to bone repair

Anais Julien, Anuya Kanagalingam, Ester Martínez-Sarrà, Jérome Megret, Marine Luka, Mickaël Ménager, Frédéric Relaix & Céline Colnot ⊡

Nature Communications 12, Article number: 2860 (2021) | Cite this article



Circulating Progenitor Cells are NOT the Primary Cell Source in Fracture Repair



macrophages

Xing et al, 2010

Chondrocytes Give Rise to Osteoblasts During Fracture Healing



Chondrocytes Give Rise to Osteoblasts During Fracture Healing



RESEARCH ARTICLE 🖞 Open Access 💿 🛈

Chondrocyte-to-osteoblast transformation in mandibular fracture repair

Sarah A. Wong, Diane P. Hu, Joshua Slocum, Charles Lam, Michael Nguyen, Theodore Miclau III, Ralı S. Marcucio 🕱, Chelsea S. Bahney 🕿

First published: 03 November 2020 | https://doi.org/10.1002/jor.24904





Cartilage Grafts as a Template for Bone Tissue Engineering



The Lifecycle of the Stem Cells within the Fracture Callus



Marcucio, Micalu, Bahney. Metaplasia during Regeneration of the Cranial and Appendicular Skeleton. Journal of Dental Research 2022

Exogenous Applications of Stem Cells: What is an MSC??



Nature Reviews | Molecular Cell Biology

MacArthur BD et al. Systems biology of stem cell fate and cellular reprogramming. Nature Reviews Molecular Cell Biology 10, 672-681. (2009)

Mesenchymal Stem Cell Mesenchymal Stromal Cell **Mesenchymal Signaling Cell**

There is no one MSC

tSNE_1

Single-cell RNA sequencing deconvolutes the in vivo heterogeneity of human bone marrow-derived mesenchymal stem cells

Zun Wang, Xiaohua Li, Junxiao Yang, Yun Gong, Huixi Zhang, A Jonathan Greenbaum, Liang Cheng, Yihe Hu, Jie Xie, Xucheng Si-Yuan Tang, Hui Shen, Hong-Mei Xiao, Hong-Wen Deng doi: https://doi.org/10.1101/2020.04.06.027904

bioRχiv THE PREPRINT SERVER FOR BIOLOGY



How do MSCs Impart a Regenerative Function?



https://www.nature.com/articles/s41585-019-0169-3 https://www.mdpi.com/1422-0067/20/12/2853

nature medicine

Article | Published: November 2000

Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after *in utero* transplantation in sheep

Kenneth W. Liechty, Tippi C. MacKenzie, Aimen F. Shaaban, Antoneta Radu, AnneMarie B. Moseley, Robert Deans, Daniel R. Marshak & Alan W. Flake 🖂



International Journal of *Molecular Sciences*



Review

Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine

Francisco J. Vizoso ^{1,*}, Noemi Eiro ¹, Sandra Cid ¹, Jose Schneider ² and Roman Perez-Fernandez ^{3,*}

How do MSCs Impart a Regenerative Function?



Clinical Application of "MSCs"



The FDA is going after stem cell clinics that peddle unproven treatments

The clinics claim they can treat serious diseases with stem cells from fat. The FDA doesn't buy it.





Bone Joint J. 2020 Feb; 102-B(2): 148–154. Published online 2020 Feb 1. doi: <u>10.1302/0301-620X.102B2.BJJ-2019-1104.R1</u>

PMCID: PMC7002842 PMID: <u>32009438</u>

Rogue stem cell clinics

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Bone Marrow Aspirate Stem Cell Concentration: Could it be Effective?

Chelsea S Bahney, PhD

SPRI Program Director, Bone Repair & Regenerative therapeutics

Associate Professor, UCSF







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Bone Marrow Concentrate: The Process





NS Piuzzi et al. J Knee Surgery 2018

Protein Composition of the MSC Secretome





Does BMC Deliver the Complex Protein Supplementation Beneficial to Repair??









Shrivats *et al*. Bone Regeneration. Ch 55, Principals of Tissue Engineering. 2014

Patient Factors Influencing BMC Secretome





Concentration increases the number of "stem cells"



El-Jawhari et al. European Cells and Materials Vol. 40 2020 (pages 58-73) DOI: 10.22203/eCM.v040a04

OPEN QUESTION: How many MSCs are in BMC and how many do you need?

HYPOTHESIS: The fist fraction of bone marrow contains all the "important cells"

Single Provider, Patient demographics^{*a*}. (n=13)

Age (years) 60.0 ± 12.2 years (range 30.0 - 77.0)Gender (Male or Female)9 Male, 4 FemaleBMI (kg/m²) 24.4 ± 3.8 (range 21.0 - 32.1)

^{α}Values represent median ± standard deviation (range) or number of patients



Stem Cell Concentration is Consistent Across BM Fractions



Secretome Differs Across Fractions → Therapeutic Application Matters!



- □ Bone Marrow Concentration Improves Angiogenesis?
- □ First fraction is more anti-inflammatory and pro-osteogenic???



Orthobiologics and Age – Are These Effective When we Need Them?





Orthobiologics and Age – Are These Effective When we Need Them?





K Miclau et al. Aging Cell 2022 (in press)

Aging and Senescence



Aging and Senescence: Impact on Orthobiologics



Senolytics to Improve Orthobiologics





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(A) Fisetin treatment on hBMAC (Time-course)





The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Concentrate for Osteoarthritis



Sponsor: Johnny Huard, Ph.D. Clinical Principal Investigator: Leslie Vidal, M.D. Principal Investigators: Scott Tashman, Marc Philippon, MD Funding: National Institutes of Health

NIAMS Regenerative Medicine Innovation Program (RMIP) Phase I/II Randomized 2x2 Factorial Clinical Trial

Hypothesis 1:

Senolytic drugs will eliminate senescent cells and improve the beneficial effect of BMAC treatment for knee OA Subjects.

Study Population: 100 subjects with symptomatic unilateral or bilateral knee OA (KL grade II-IV).

Study Arms:

Group 1-n=25: Control (BMA concentrate + Fisetin Placebo + Losartan Placebo)

Group 2-n=25: BMA concentrate + Fisetin Placebo + Active Losartan

Group 3-n=25: BMA concentrate + Active Fisetin + Losartan Placebo

Group 4-n=25: BMA concentrate + Active Fisetin + Active Losartan





The Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis



Primary: <u>Safety and tolerability</u> of Fisetin and Losartan alone and both given in sequence as compared to injection of BMAC alone

Secondary: To define in combination with injection of BMAC into the osteo arthritic knee the <u>effectiveness</u> of Fisetin and Losartan alone and both given in sequence as compared with injection of BMAC alone:

- 1. Structural improvement of the injected joint;
- 2. Effect on pain, function, and quality of life;
- 3. Characterization of synovial fluid content prior to injection;
- 4. Characterization of BMAC cell content prior to injection;
- 5. Characterization of BMAC derived plasma biomarkers prior to injection;
- 6. Effect on local and systemic SASP and OA-associated biomarkers as compared to placebo in peripheral blood plasma/serum;
- 7. Functional performance, strength and movement as compared to placebo;
- 8. Time to rescue treatment.



Thank You !



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