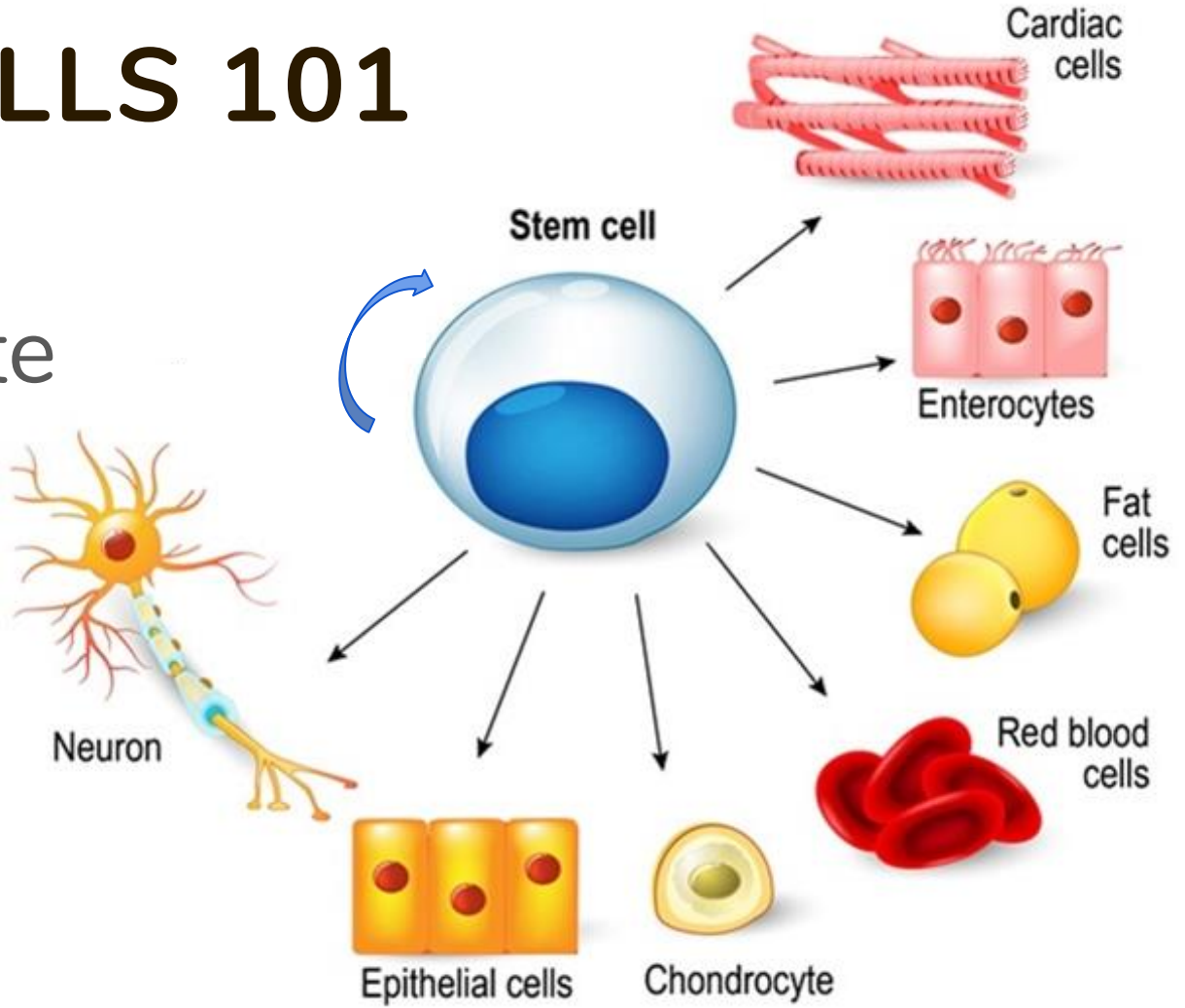
INTRODUCTION TO STEM CELL THERAPY FOR AESTHETICS

DAVID GREENE, MD, MBA
FOUNDER/CEO

STEM CELLS 101

- Self-renew
- Differentiate



Classification

Source of Origin

- Embryonic
- Adult

Action Potential

- Totipotent
- Pluripotent
- Multipotent
- Unipotent

Totipotent Stem Cell

Can make:

- The embryo
- Placenta
- Support cells

Mesoderm Endoderm Ectoderm

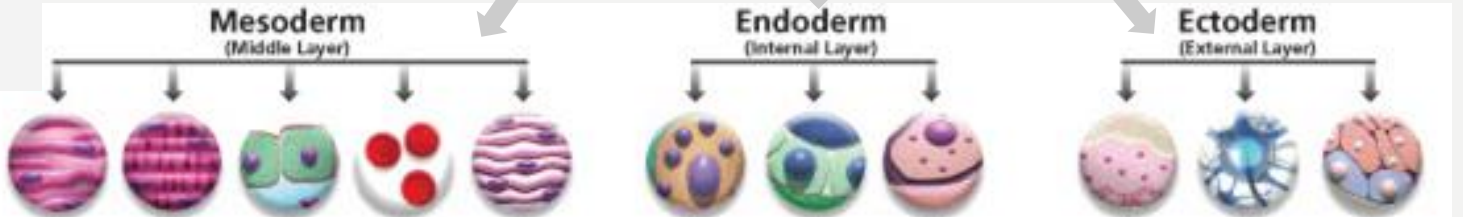
Pluripotent Stem Cells

Can generate all the cells of the body

Induced Pluripotent Stem Cells

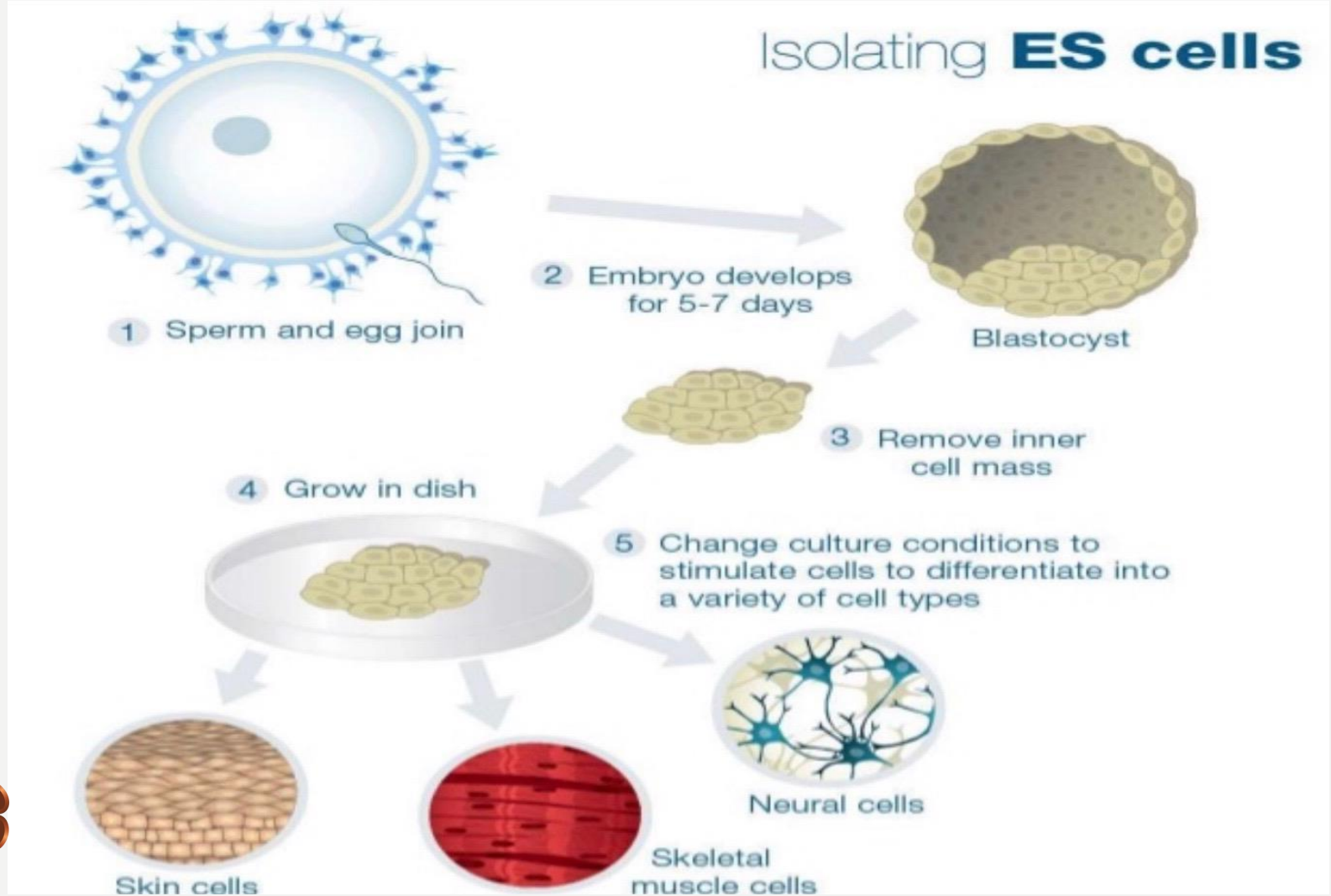
Multipotent Stem Cells

Committed to a cell line



Cardiac Muscle Kidney RBC Smooth Mm Thyroid Lung Pancreas Skin Nerve Pigment

Differentiation


Isolating ES cells
1 Sperm and egg join
2 Embryo develops for 5-7 days
Blastocyst
3 Remove inner cell mass
4 Grow in dish
5 Change culture conditions to stimulate cells to differentiate into a variety of cell types
Neural cells
Skeletal muscle cells
Skin cells

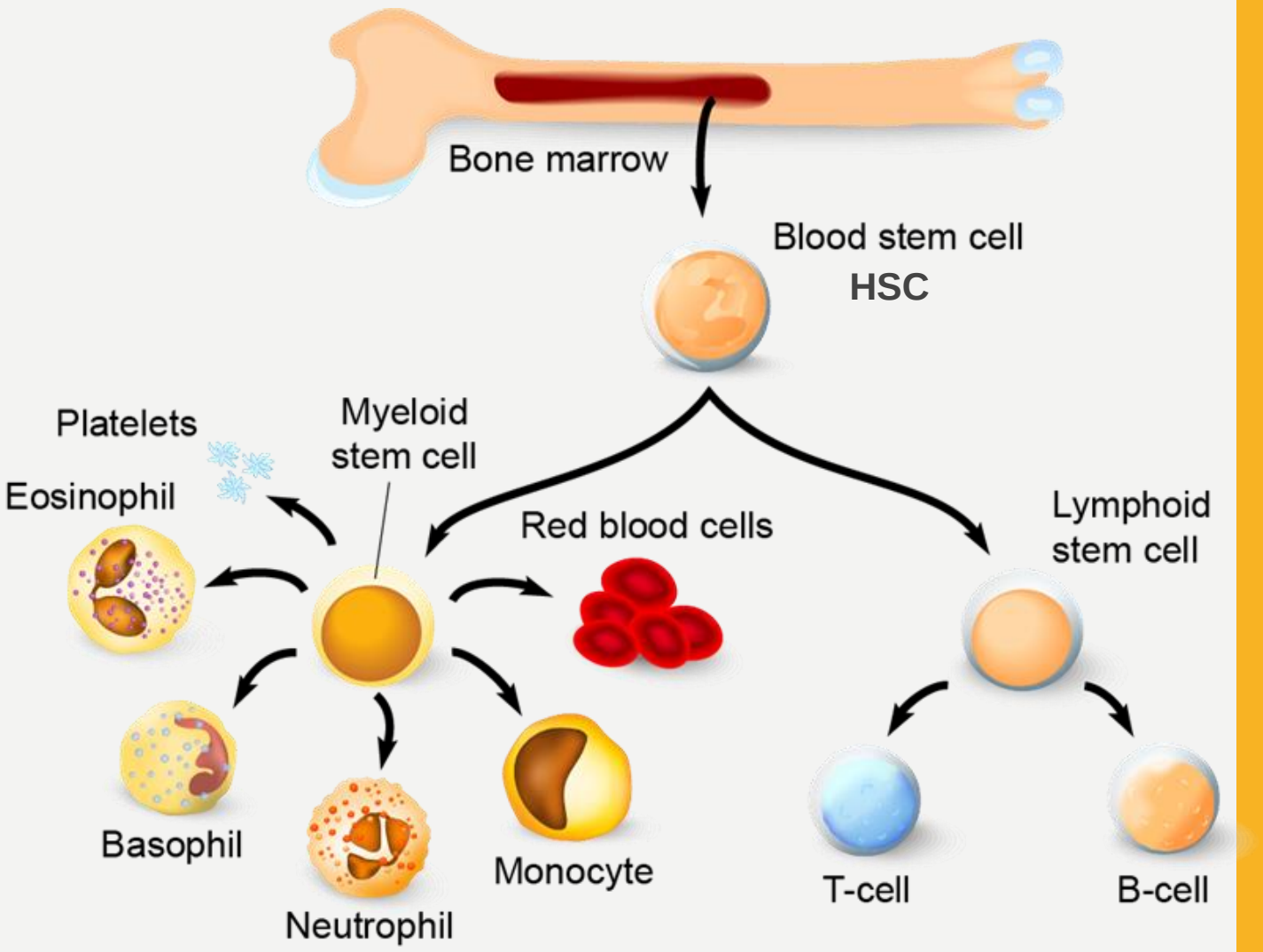
Adult Stem Cells

Bone Marrow

Adipose Tissue

Post Partum Birth Tissues

Bone Marrow Stem Cells (HSC)



Bone Marrow Aspiration & Concentration- BMAC

FDA Approved

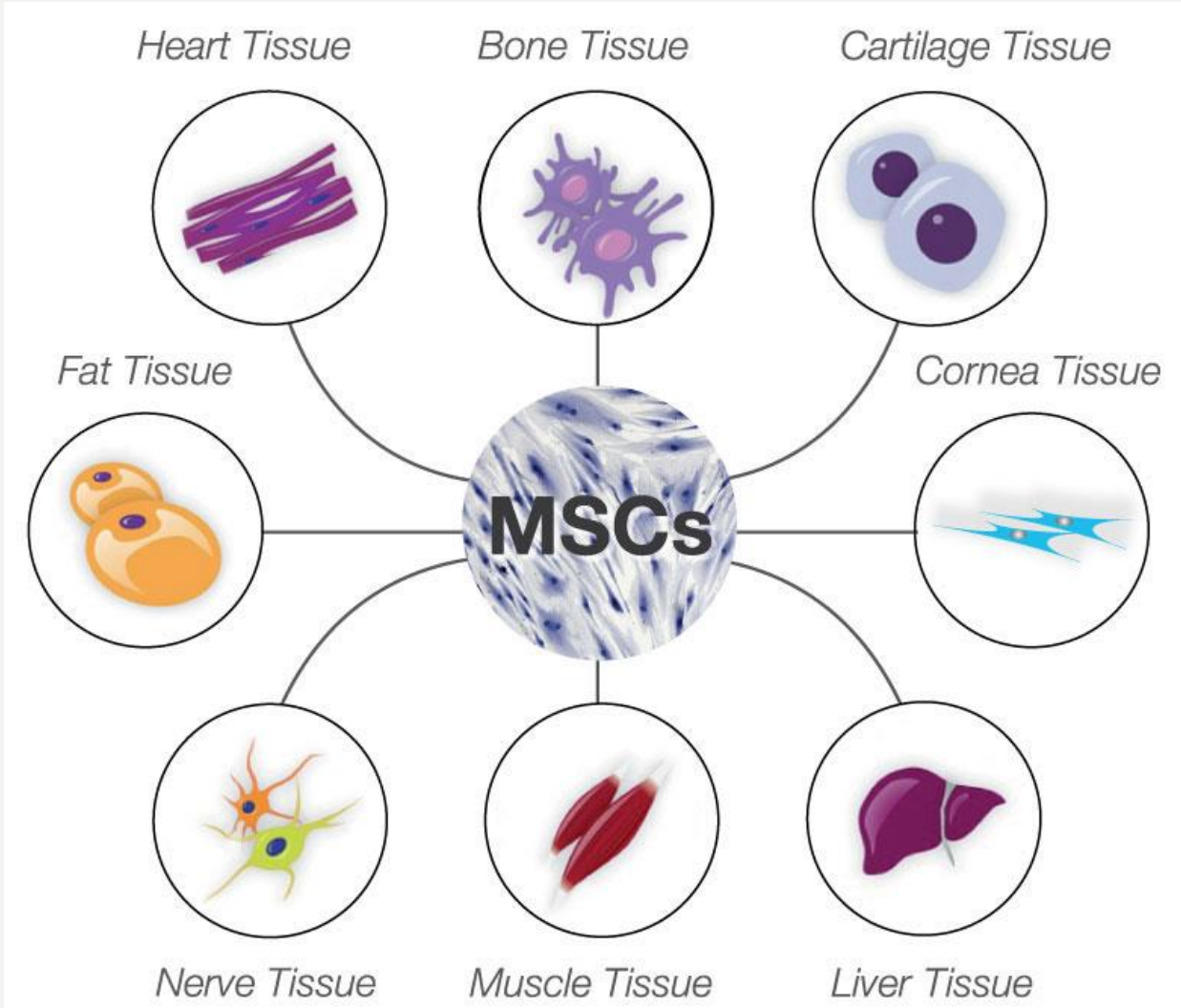
PROS:

- Autologous

CONS:

- painful
- time consuming
- risk of infection
- mainly HSCs

ADULT MULTIPOTENT STEM CELLS (MSCS)

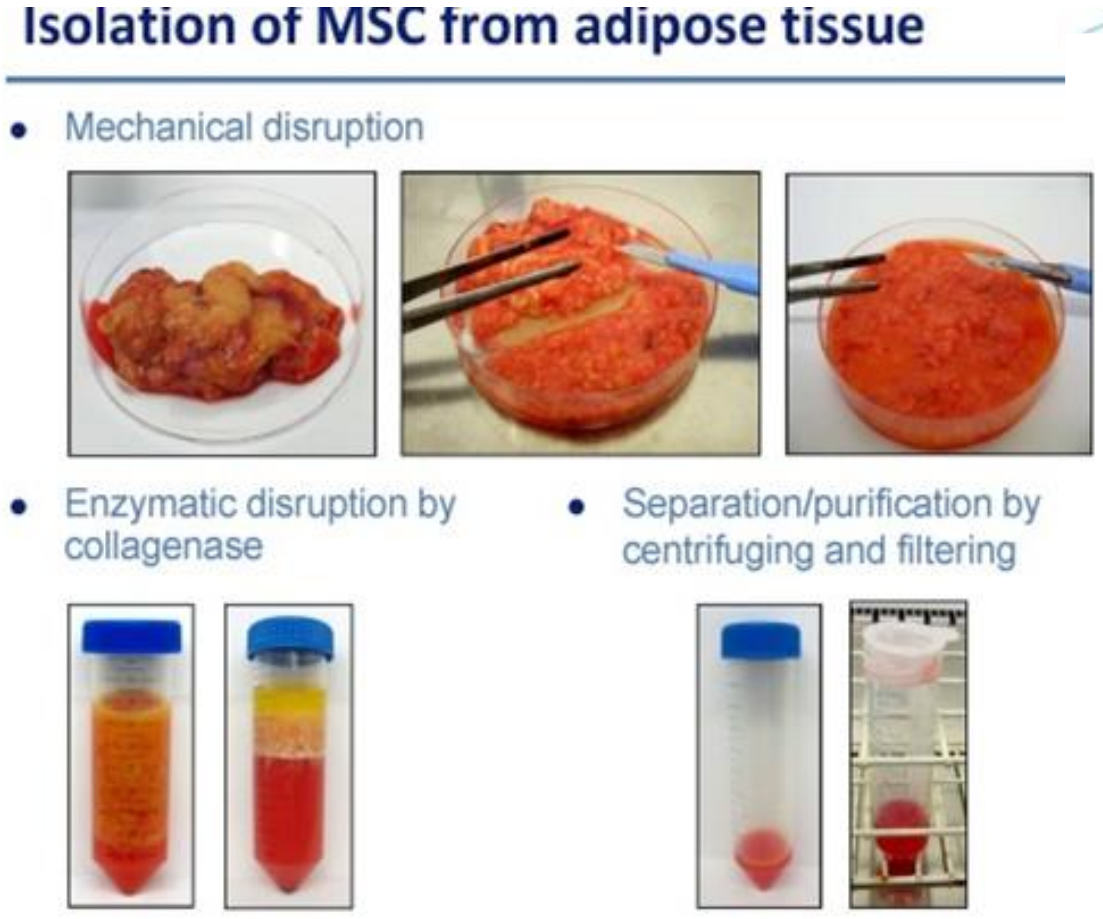


Adipose Stromal Vascular Fraction

Good source of **older** adult MSCs.

PROS:
- Autologous

CONS:
- painful
- time consuming
- risk of infection
- potential tumor promoter



www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 10

Adipose-derived stem cells promote tumor initiation and accelerate tumor growth by interleukin-6 production

Hong-Jian Wei[1,2], Rong Zeng[3], Jui-Hua Lu[1], Wen-Fu T. Lai[4], Wei-Hong Chen[2], Hen-Yu Liu[2], Ya-Ting Chang[1] and Win-Ping Deng[1,2,3]

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[2] Stem Cell Research Center, Taipei Medical University, Taipei, Taiwan

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[4] Graduate Institute of Clinical Medicine, Taipei Medical University, Taipei, Taiwan

In conclusion, we demonstrated that ADSCs play a pro-malignant role in tumor development of breast and colon cancer cells. Interaction of ADSCs and cancer cells stimulated secretion of IL-6 in ADSCs, which in turn acted in a paracrine manner on cancer cells to enhance their malignant properties, including tumor initiation

Published in final edited form as:
Prostate. 2010 November 1; 70(15): 1709–1715. doi:10.1002/pros.21206.

Adipose Tissue Derived Stem Cells Promote Prostate Tumor Growth

Lukas Prantl[1], **Fabian Muehlberg**[1], **Nora M. Navone**[2], **Yao-Hua Song**[1], **Jody Vykoukal**[1], **Christopher J. Logothetis**[2], and **Eckhard U. Alt**[1,*]

[1]Department of Molecular Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[2]Department of Genitourinary Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

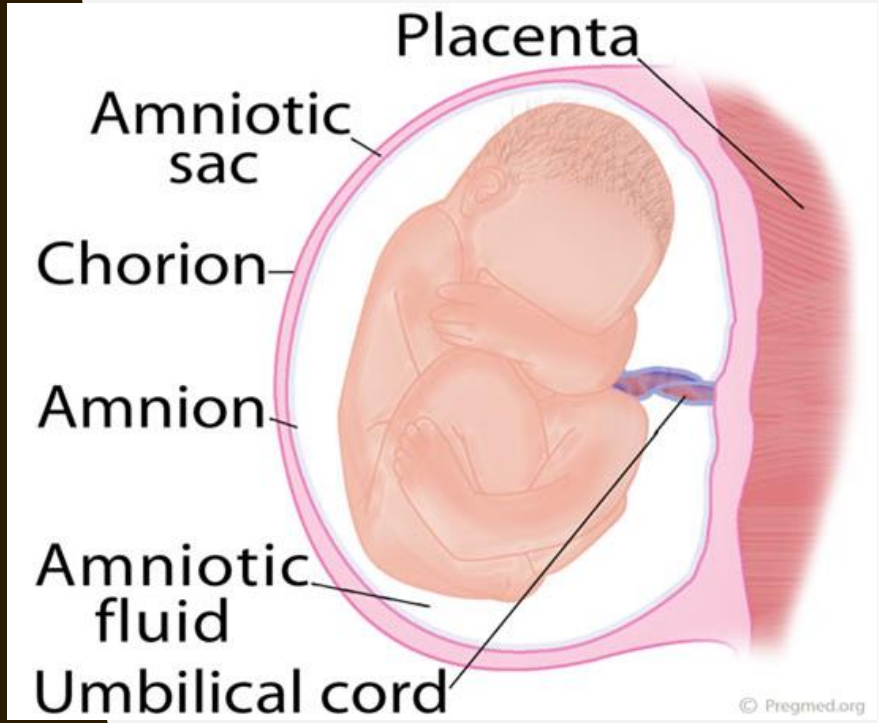
Abstract

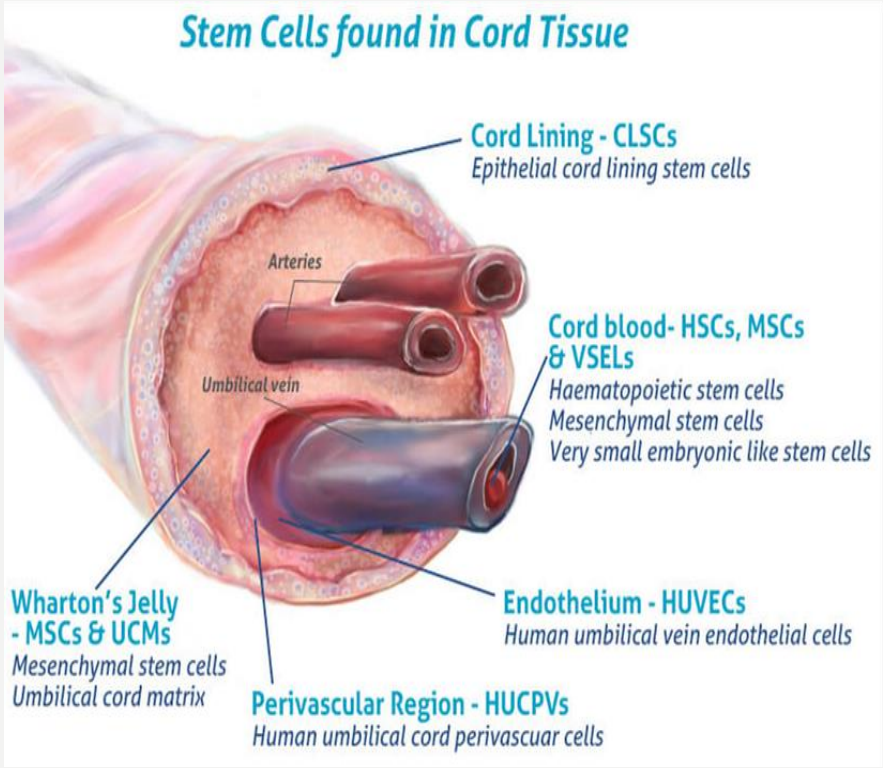
BACKGROUND—Recent evidence indicates that cancer stem cells play an important role in tumor initiation and maintenance. Additionally, the effect of tissue-resident stem cells located in

OLDER ADULT MESENCHYMAL STEM CELLS

- More likely to have accumulated cellular damage
- Less vigorous response
- Require typing and cross matching
- 1:2,000,000 (scarce)

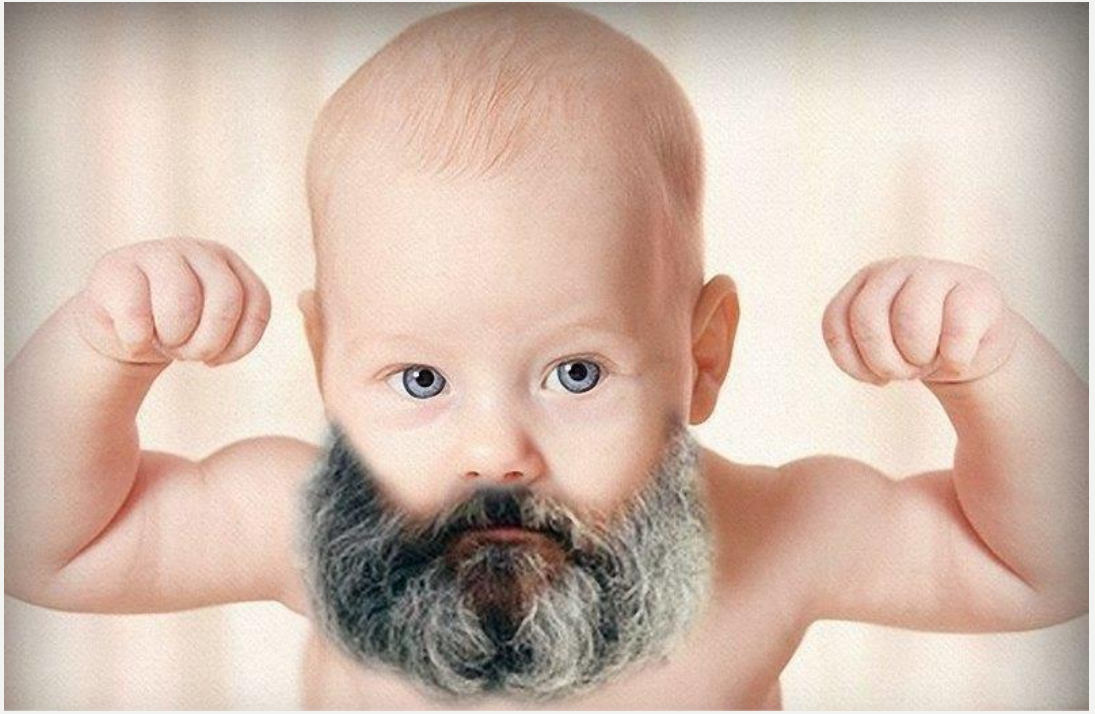
POST NATAL ADULT MESENCHYMAL STEM CELLS





POST NATAL MESENCHYMAL STEM CELLS

- Robust
- Less likely to have genetic errors
- Not the same as mature adult
- Immune Priviledged
- 1:10,000 (Plentiful)

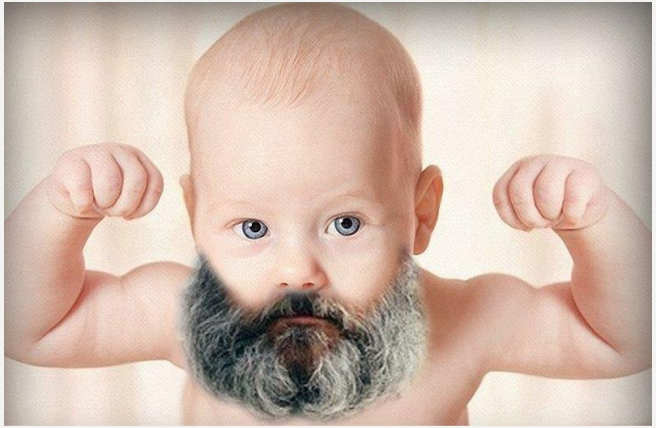


Fan M. The effect of age on the efficacy of human mesenchymal stem cell transplantation after a myocardial infarctation. *Rejuv Research*, 2010.

POST NATAL MESENCHYMAL STEM CELLS

- **MSC from young individuals can undergo neuroectodermal differentiation in vitro, but MSC from elderly patients cannot**

Heremann A. Age dependent neuroectodermal differentiation capacity of human mesenchymal stromal cells: limitations for autologous cell replacement strategies. *Cytotherapy*, 2010.



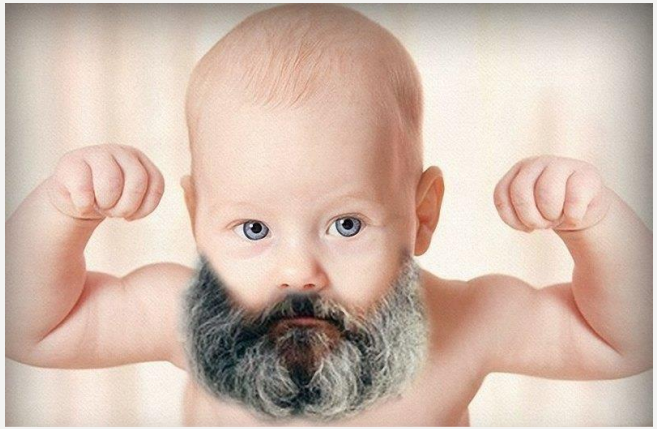
- **Adult MSC are exposed to a lifetime of factors, eg NSAIDS -- may inhibit MSC chondrogenic differentiation and disrupt endochondral bone formation.**

Pountos I. NSAIDS inhibit in vitro MSC chondrogenesis: implications for mechanisms of bone formation inhibition in man. *J of Cell and Mol Medicine* 2011.

POST NATAL MESENCHYMAL STEM CELLS

- **Lifestyle affects the quality of MSCs- animal study where mice fed a high fat diet had a lower endothelial differentiation potential in vitro vs control group.**

  Lamontgne V. High-fat diets-induced metabolic alterations alter the differentiation potential of adipose tissue-derived stem cells. *Open J of Endocr & Metabol* Dis, 2013.



- **Osteogenic potential impaired in obese patients, and diminished capacity of adult stem cells to form a vascular network in patients with metabolic diseases such as DM**

  Roldan M. Obesity short-circuits stemness gene network in human adipose multipotent stem cells. *The FASEB Journal*. 2011.

  Rennert RC. Diabetes impairs that angiogenic potential of adipose-derived stem cells by selectively depleting cellular subpopulations. *Stem Cell Research & Therapy*. 2014.

Measure	Bone Marrow	Adipose Tissue	Umbilical Cord Blood
Proliferative capacity	Growth arrest at pass 11-12	Growth arrest at pass 11-12	Growth arrest at pass 14-16
Growth Rate/ Doubling Time	Moderate	Lowest	Highest
Colony Forming Ability	Moderate	Lowest	Highest
Senescence (Passage 6)	11%	13%	0%
Anti-Inflammation	Some	Some	Greatest

Hye JJ. Comparative analysis of human MSC from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. I*nt J Mol Sci* 2013

Measure	Bone Marrow	Umbilical Cord Blood
Collagen Formation*	1x	3x
Mineralization in bone culture**	Moderate	Highest
Size of chondrogenic pellets	Small	Large

*Fong CY. Human umbilical cord Wharton's jelly stem cells undergo enhanced chondrogenic differentiation when grown in nanofibrous scaffolds and in sequential two-stage culture medium environment. Stem Cell Rev & Report, 2012.

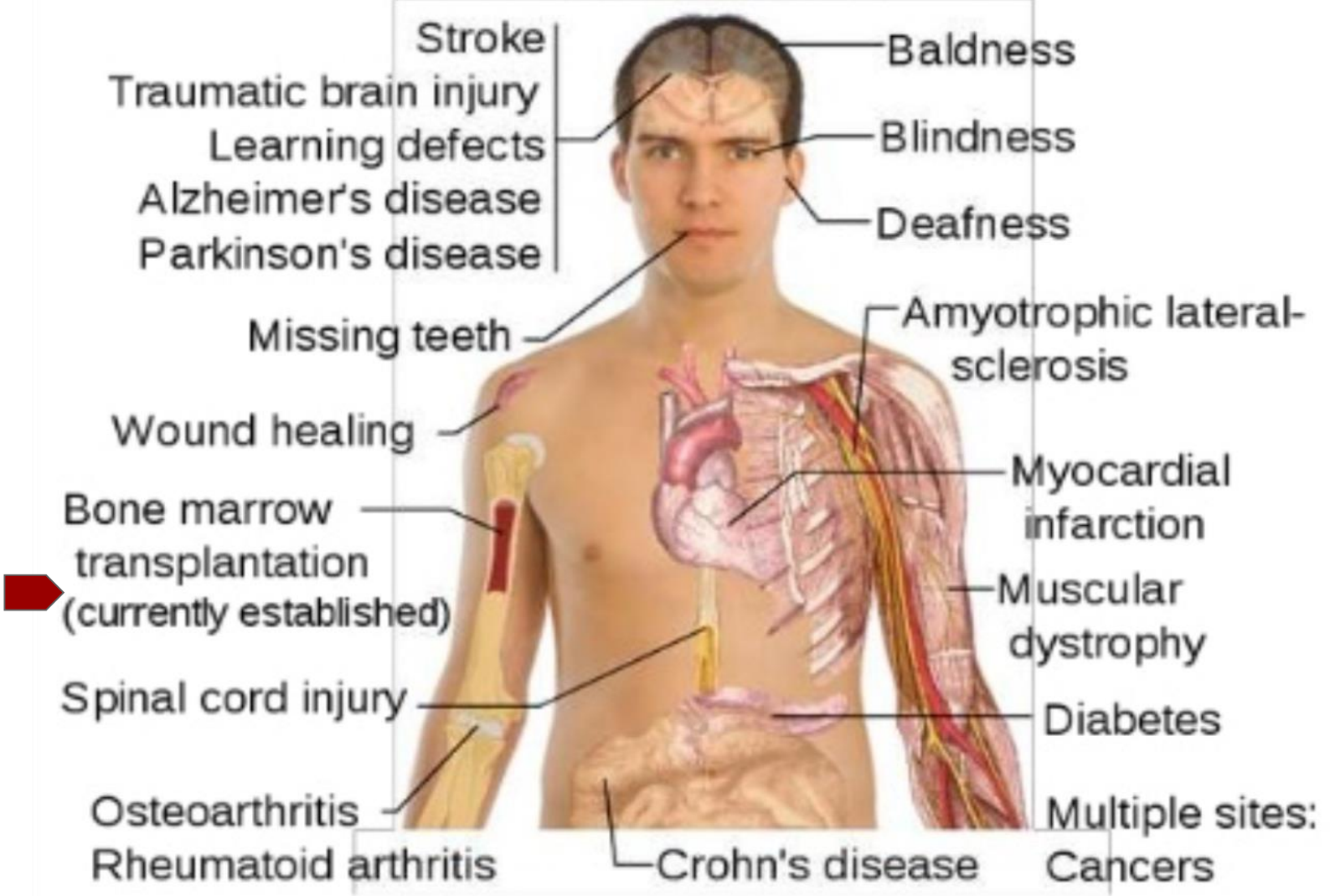
**Baksh D. Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow stem cells, 2007.

Measure	Adipose Tissue	Umbilical Cord Blood	Wharton' Jelly
Effect of Tumor Growth*	Promoted	Inhibited	
Apoptosis*	Mild	Stronger	
Teratoma/Tumors			Not Induced
Abrogate Solid tumors			Yes

*Akimoto K. Umbilical cord blood derived MSCs inhibit, but adipose tissue-derived MSCs promote glioblastoma multiforme proliferation. *Stem Cells & Development*, 2012.

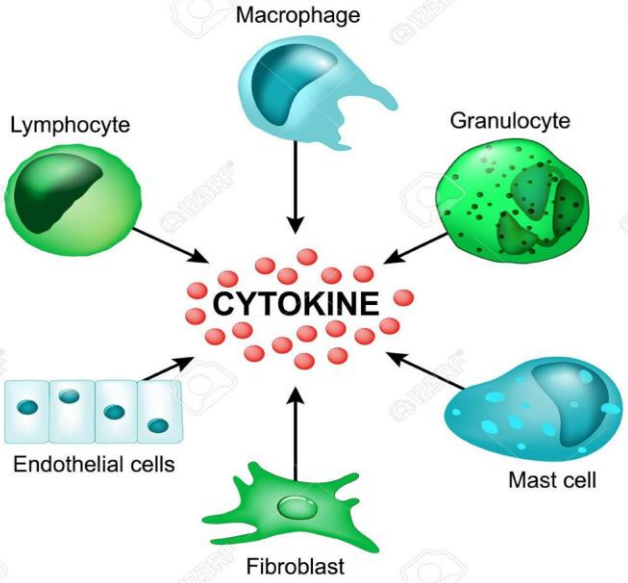
Gauthaman K. Human umbilical cord Wharton's jelly stem cell (hWJSC) extracts inhibit cancer cell growht in vitro. J Cell Biochem, 2012.

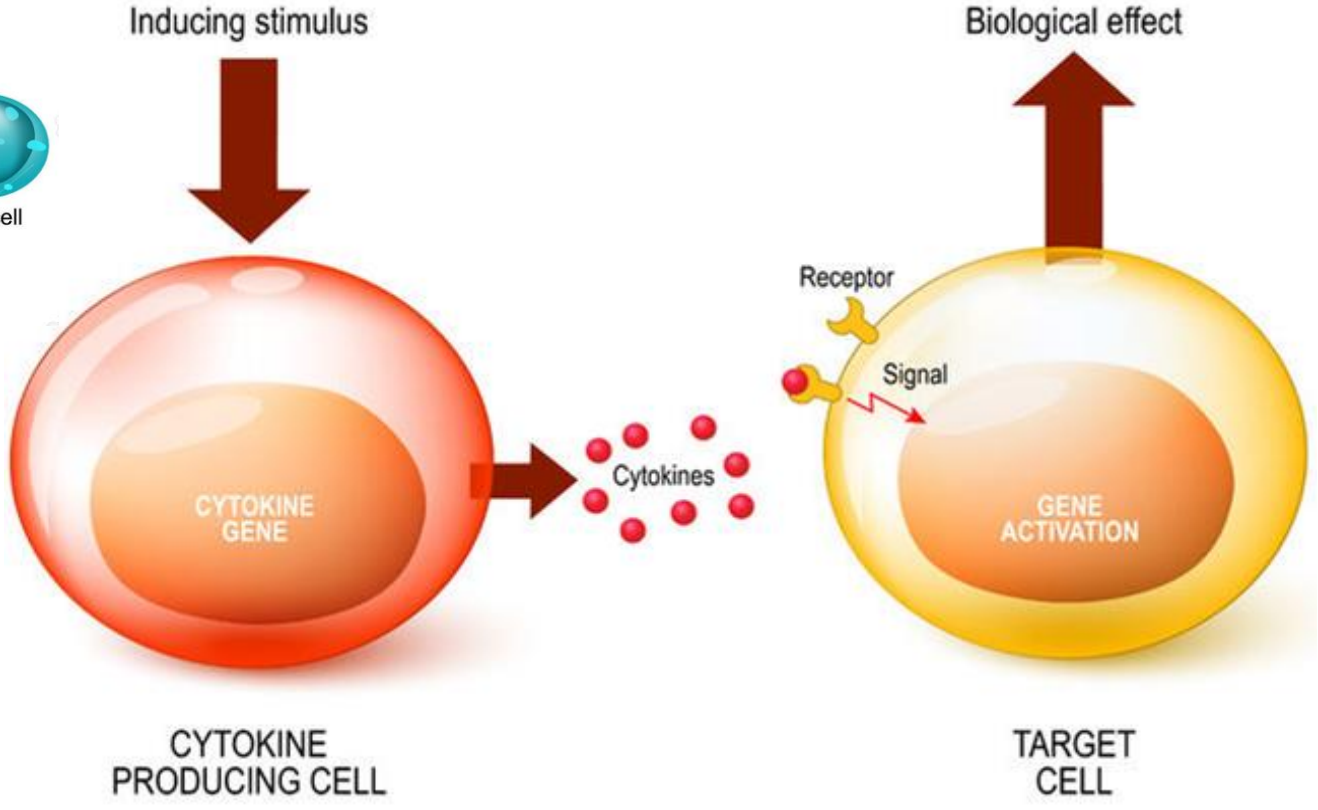
Potential Uses of Stem Cells (MSCs)

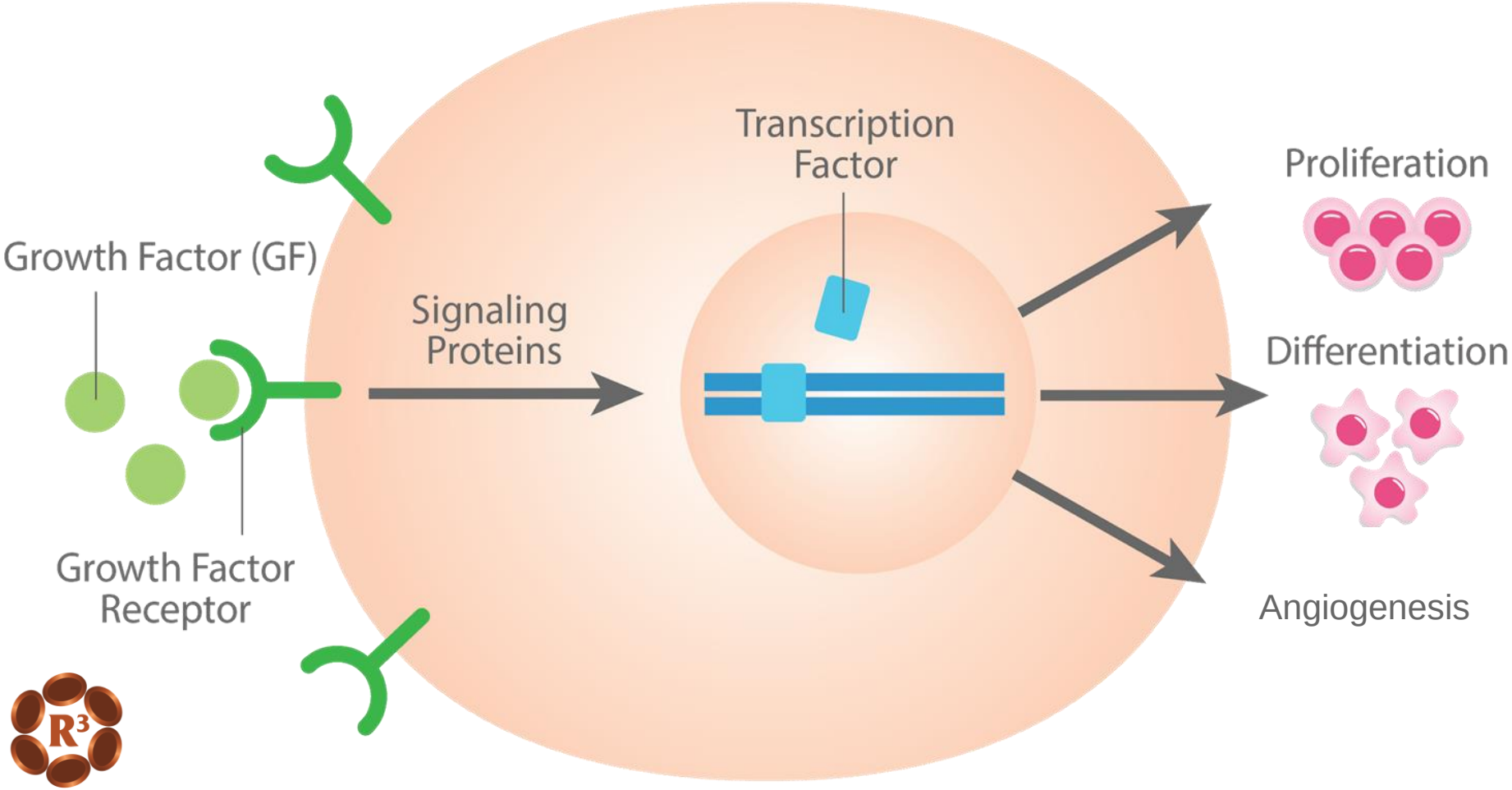


Cytokines

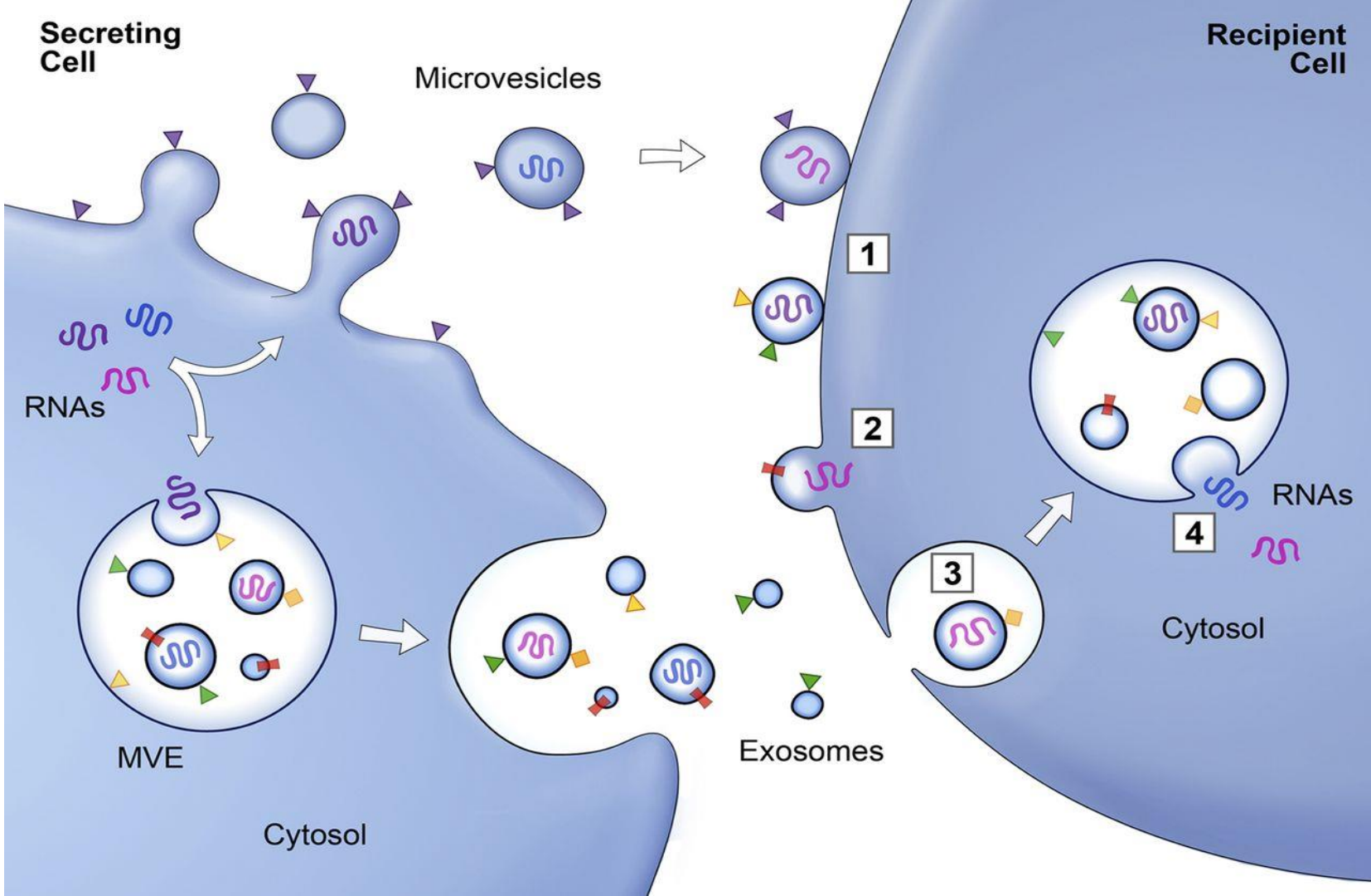
Regulate Cellular Differentiation



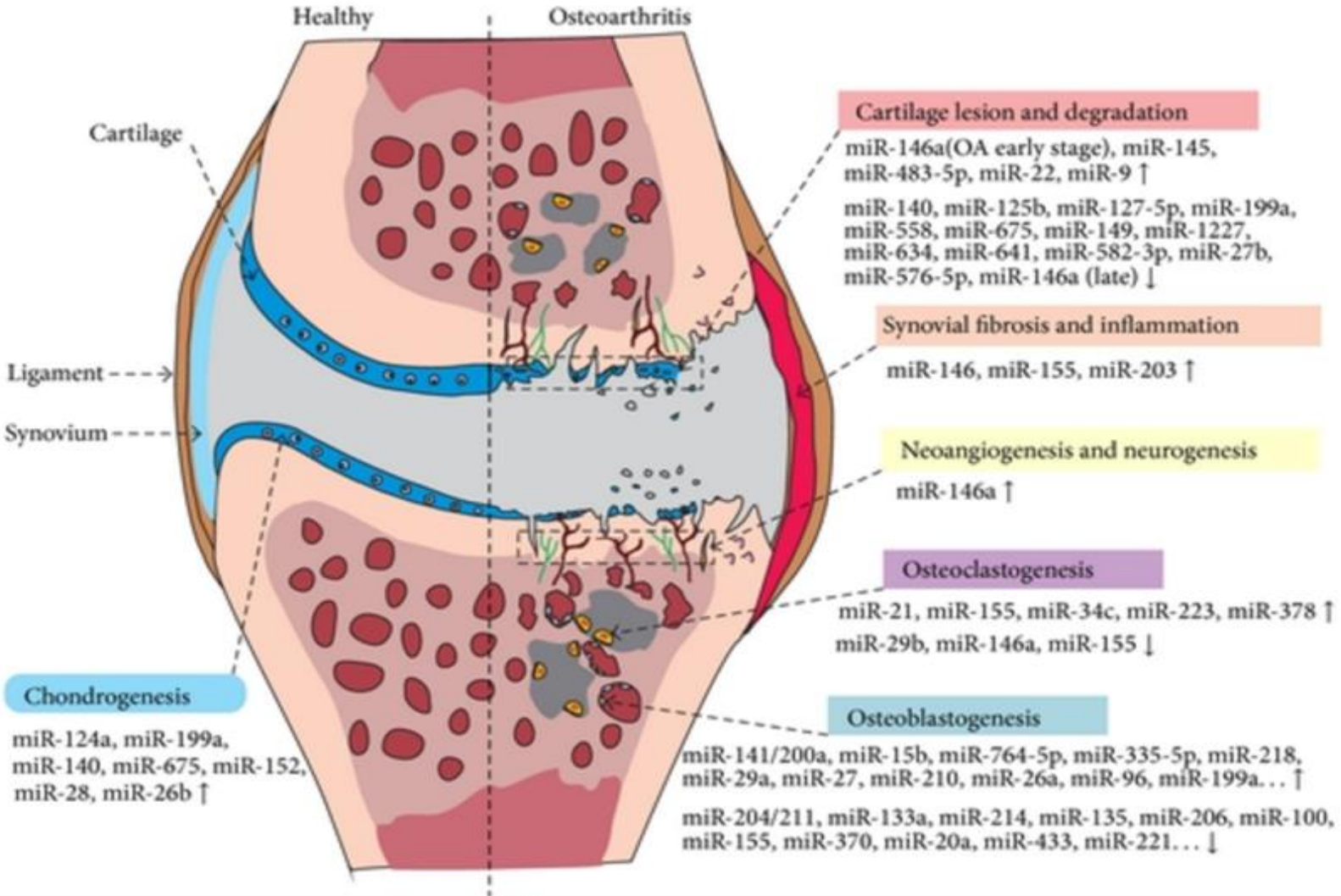



Growth Factor (GF)
Growth Factor Receptor
Signaling Proteins
Transcription Factor
Proliferation
Differentiation
Angiogenesis

Exosomes


Secreting Cell
Microvesicles
Recipient Cell
RNAs
1
2
3
4
RNAs
MVE
Cytosol
Exosomes
Cytosol

Micro RNA


Healthy
Osteoarthritis
Cartilage
Ligament
Synovium
Cartilage lesion and degradation
miR-146a(OA early stage), miR-145, miR-483-5p, miR-22, miR-9 ↑
miR-140, miR-125b, miR-127-5p, miR-199a, miR-558, miR-675, miR-149, miR-1227, miR-634, miR-641, miR-582-3p, miR-27b, miR-576-5p, miR-146a (late) ↓
Synovial fibrosis and inflammation
miR-146, miR-155, miR-203 ↑
Neoangiogenesis and neurogenesis
miR-146a ↑
Osteoclastogenesis
miR-21, miR-155, miR-34c, miR-223, miR-378 ↑
miR-29b, miR-146a, miR-155 ↓
Chondrogenesis
miR-124a, miR-199a, miR-140, miR-675, miR-152, miR-28, miR-26b ↑
Osteoblastogenesis
miR-141/200a, miR-15b, miR-764-5p, miR-335-5p, miR-218, miR-29a, miR-27, miR-210, miR-26a, miR-96, miR-199a... ↑
miR-204/211, miR-133a, miR-214, miR-135, miR-206, miR-100, miR-155, miR-370, miR-20a, miR-433, miR-221... ↓

MESENCHYMAL STEM CELLS

- One MSC can inhibit the proliferation of up to 100 T cells
- MSCs suppress proliferation of activated CD4 T and CD8 T cells
- Extensive immunomodulatory potential of MSCs and the ability of **infused MSCs to resolve inflammation and promote tissue repair** are shown in models of disease (GvHD, SLE, MS, renal injury, fibrosis and arthritis)
- **Hypoxia induces MSCs to secrete IL-6, VEGF**, and chemokines in a model of myocardial infarction

COLLAGEN FORMATION - EXOSOMES

J Cosmet Dermatol. 2019 Nov 21. doi: 10.1111/jocd.13215. [Epub ahead of print]

Prospective application of exosomes derived from adipose-derived stem cells in skin wound healing: A review.

Qiu H[1], Liu S[1], Wu K[1], Zhao R[1], Cao L[1], Wang H[1].

RESULTS: Most studies have shown the possible roles of ASCs-derived exosomes (ADSCs-Exos) in cutaneous wound healing through regulation of the inflammatory response and promotion of cell proliferation, migration, differentiation, angiogenesis and matrix reconstruction to provide a new perspective strategy for the use of ASCs-Exos in skin wound healing.

ERECTILE DYSFUNCTION

7 men with T2DM, mean age 69.5 with no erection for 6 months despite medications, awaiting prostheses

- UC-MSC injected in corpus cavernosum
- 3 participants regained morning erections
- Maintained erections for 6 months
- Increased rigidity requiring PDE5 for penetration
- 1 maintained erection sufficient for coitus for 11 months
- HbA1c improvement for 3-4 months

Bahk et al. *Experimental and Clinical Transplantation* 2010

ERECTILE DYSFUNCTION

Andrologia. 2018 Mar;50(2). doi: 10.1111/and.12871. Epub 2017 Oct 23.

Transplantation of adipose tissue-derived stem cell-derived exosomes ameliorates erectile function in diabetic rats.

Zhu LL[1], Huang X[1], Yu W[2], Chen H[2], Chen Y[2], Dai YT[2].

Author information

Abstract

Mesenchymal stem cells (MSCs) have been considered as an attractive tool for the therapy of diseases. Accumulating evidence indicates that the healing effects of MSCs are mainly related to paracrine action rather than transdifferentiation. Exosomes excreted from MSCs have emerged as physiologically relevant and powerful components of the MSC secretome. However, whether MSC-derived exosomes can improve erectile function of streptozotocin-induced diabetic rats and its mechanism remains unknown. Our previous work showed that adipose tissue-derived stem cells (ADSCs) transplantation could increase endothelial and smooth muscle contents and improve erectile function of diabetic rats. In this study, ADSC-derived exosomes (ADSC-Exo) exhibited in vitro proangiogenic properties, induced the proliferation of endothelial cells and restored erectile function in vivo, as well as decreased fibrosis of corpus cavernosum. In further experiments, we found that ADSC-Exo contained some proangiogenic (miR-126, miR-130a and miR-132) microRNAs and an antifibrotic microRNA family (miR-let7b and miR-let7c). Thus, it is reasonable to postulate that ADSC-Exo transports key functional miRNAs to target cells in a specific manner to improve functional recovery or to activate endogenous repair mechanisms. This proof-of-concept study provides a novel approach for the treatment of diabetic erectile dysfunction.

HAIR RESTORATION

Aesthet Surg J. 2019 May 20. pii: sjz146. doi: 10.1093/asj/sjz146. [Epub ahead of print]

Platelet-Rich Plasma and Stem Cells for Hair Growth: A Review of the Literature.

Semsarzadeh N[1], Khetarpal S[1].

Author information

Abstract

The prevalence of hair loss, its psychological consequences, and historically subpar treatments present a unique challenge to the physician. The current FDA approved treatments for hair loss are plagued by ineffectiveness, noncompliance and adverse effects. Recently, the understanding of hair physiology has fueled the development of more efficacious, minimally invasive, and safe treatment options for hair restoration including plasma-rich protein and stem cell therapy. Plasma-rich protein, the autologous preparation of concentrated platelets in plasma, when injected into the scalp of patients with both androgenetic alopecia (AGA) and alopecia areata (AA) has been shown to increase hair count and density. The clinical findings have been supported on histological evaluation of the scalp skin. These findings have been recapitulated in numerous randomized controlled trials. Stem cell therapy, although newer in its application in hair restoration, has also been effective in both AGA and AA. The isolation technique of stem cells are varied, but regardless have shown promising results in early prospective and retrospective studies.

HAIR RESTORATION

Facial Plast Surg Clin North Am. 2018 Nov;26(4):503-511. doi: 10.1016/j.fsc.2018.06.010. Epub 2018 Aug 16.

Mesenchymal Stem Cells and Stromal Vascular Fraction for Hair Loss: Current Status.

Epstein GK[1], Epstein JS[2].

Author information

Abstract

The current state of the applicability of cell therapy for the treatment of various conditions of hair loss reveals a promising and potentially effective role. Further research, based on published work to date, is indicated to further explore the potential roles of autologous fat grafting, mesenchymal stem cells, and stromal vascular fraction therapy. The authors' evolving experience matches these promising scientific findings.

Published by Elsevier Inc.

ANTI-AGING

20 patients with chronic inflammatory conditions also desiring anti-aging treated with UC-MSC IV.

- 10 had significantly improved inflammatory markers
- Significant improvement in
  - Hair and nail growth
  - Skin
  - Libido
  - Energy, mood, sleep and pain

Mehling et al. Journal of Stem Cell Research & Therapy 2015

ANTI-AGING

30 patients, average age 75 with frailty treated with IV MSCs

- Improved 6 min walk test
- Improved FEV1
- Improved markers of immunity (serum TNF-a, B cell intracellular TNF-a)
- No adverse events

Tompkins et al. Gerontological Society of America 2017.

ANTI-AGING

PERSPECTIVE ARTICLE

Front. Cell Dev. Biol., 22 November 2016 | https://doi.org/10.3389/fcell.2016.00135

Amniotic Epithelial Cells: A New Tool to Combat Aging and Age-Related Diseases?

- Persistent low grade inflammation accelerates aging process – "inflammaging"
- Following transplantation, exogenous stem cells can graft and replace dysfunctional tissues or improve the tissue milieu, possibly through anti-inflammatory and anti-fibrotic mechanisms.

MODES OF DELIVERY

- **IV**- animal studies show MSC in lungs at 1hr, decreased at 24 hours, some still detectable at 6 weeks.
- **Subcutaneous**- remained at site, undetectable after 30 days
- **Intrathecal**
- **Intranasal**- 3% proliferative at 4.5 months (spinal cord, brainstem, cerebellum, cortex, etc)
- **Direct Injection**
  - **Intraarticular – best we can tell is a few weeks.**
  - **Intramuscular**- detectable for 104 days, metabolically active
- **Nebulized – 72% survive the journey.**

MEDICATIONS THAT AFFECT STEM CELLS

(-)

ACE Inhibitors

Steroids

Local Anesthetics

Chemotherapy Agents

Antibiotics

NSAIDS

PPI

(+)

Plavix

Melatonin

STEM CELL PROGRAM VS PROCEDURE

1. Intelligent Advertising
2. Proper Consent
3. Use Peer Reviewed Protocols
4. Join an IRB
5. Offer ancillary therapies to help activate the biologic cells to the max.
6. E.G. Supplements, acupuncture, electrical stimulation, PT