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Mesenchymal Stem Cells

Science and therapeutic applications

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GRIFOLS SA

May 10th, 2010

EMA

Discovery and Definition of Mesenchymal Stem Cells

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- MSC must be plastic-adherent if maintained in standard culture conditions
- MSC must express CD105, CD73 and CD90; lack expression of hematopoietic markers such as CD45, CD34, CD14 or CD11b.
- MSC must be capable of differentiation to osteoblasts, adipocytes and chondroblasts under differentiating conditions

Minimal criteria for defining multipotent mesenchymal stromal cells.
The International Society for Cellular Therapy position statement (Dominici et al., 2006)

Wikipedia: *Mesenchymal stem cells*

*Mesenchymal stem cells (MSCs) are of **stromal origin** and may differentiate into a variety of tissues. MSCs have been isolated from **placenta (2004)**, **adipose tissue (2001)**, **lung (2004)**, **bone marrow (1994)** and **blood (2001)**, **Wharton's jelly** from the **umbilical cord (2001)**, and **teeth (2000)** (perivascular niche of dental pulp and periodontal ligament).*
*MSCs are attractive for clinical therapy due to their ability to **differentiate**, provide **trophic support**, and **modulate innate immune response**.*

Publications

Pubmed: http://www.ncbi.nlm.nih.gov/ (April 2010)

- Mesenchymal stem cells: **10774** (1556 reviews)
- Mesenchymal stem cells + Differentiation: **6177** (848 reviews)
- Mesenchymal stem cells + Secretion: **421** (42 reviews)
- Mesenchymal stem cells + Inflammation **301** (73 reviews)
- Mesenchymal stem cells + Immune system **919** (152 reviews)
- Mesenchymal stem cells + Autoimmune **148** (63 reviews)
- Mesenchymal stem cells + Disease **1593** (422 reviews)

Clinical trials

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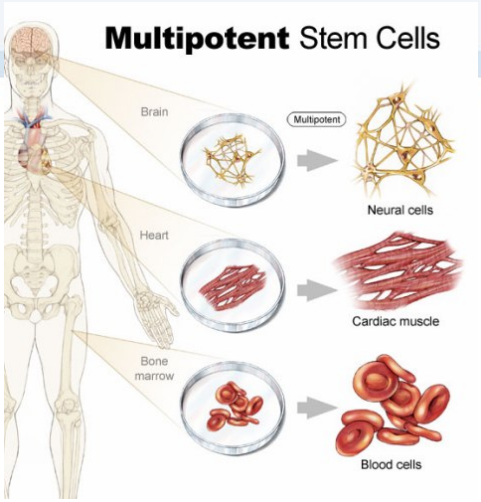
http://www.clinicaltrials.gov

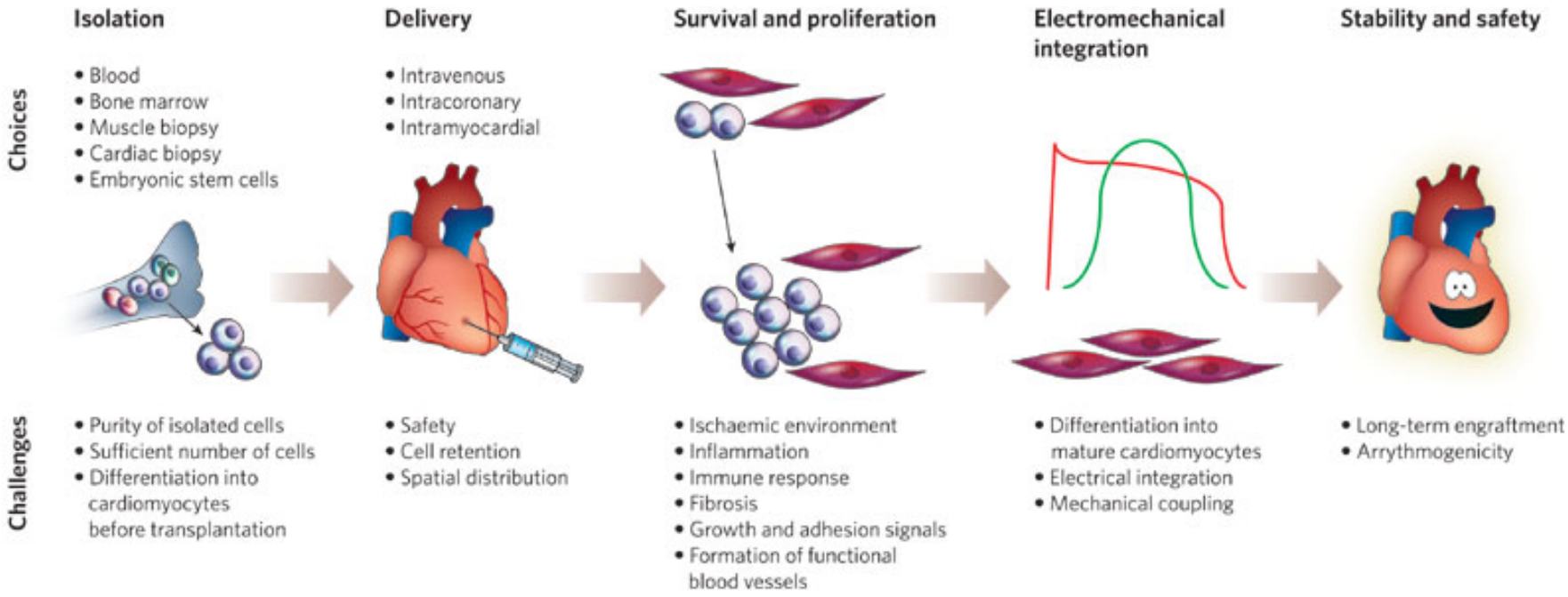
Search term: Mesenchymal stem cells => 102 trials (April 2010)

- Secondary Progressive Multiple Sclerosis
- Graft Rejection and Graft Versus Host Disease
- Diabetic Foot
- Primary Sjögren's Syndrome
- Chronic Allograft Nephorpathy
- Type 1 Diabetis
- Subclinical Rejection (Organ Transplants)
- Moderate-to-Severe Crohn's Disease
- Ischemic Stroke
- Lupus Nephritis
- Sytemic Lupus Erythematosus
- Systemic Sclerosis
- Chronic Critical Limb Ischemia
- Compex Peri-anal Fistula
- Chronic obstructive Pulmonary Disease
- Inflammatory Response After Muscle and Skeleton Trauma (IRAMST)
- Osteonecrosis of the Femoral Head
- Liver Cirrhosis (injection of progenitor of hepatocyte derived from Mesenchymal stem cell)
- Treatment of Articular Cartilage Defects
- Cardiac Surgery
- Myocardial Ischemia
- MSCs in AMI (Acute Myocardial Infarction)
- Parkinson's Disease
- Osteogenisis Imperfecta
- Oestoarthritis
- Epidermolysis Bullosa
- Regeneration of Peridontal Tissue
- Intra-Articular Injection Following Meniscectomy

Origin and usage



Adult stem cells: Multipotent
use = differentiation (regeneration)
use = immunomodulation
use = screening (?)



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CD235a
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NGFR
D7-FIB
b2 microglob.

eASCs

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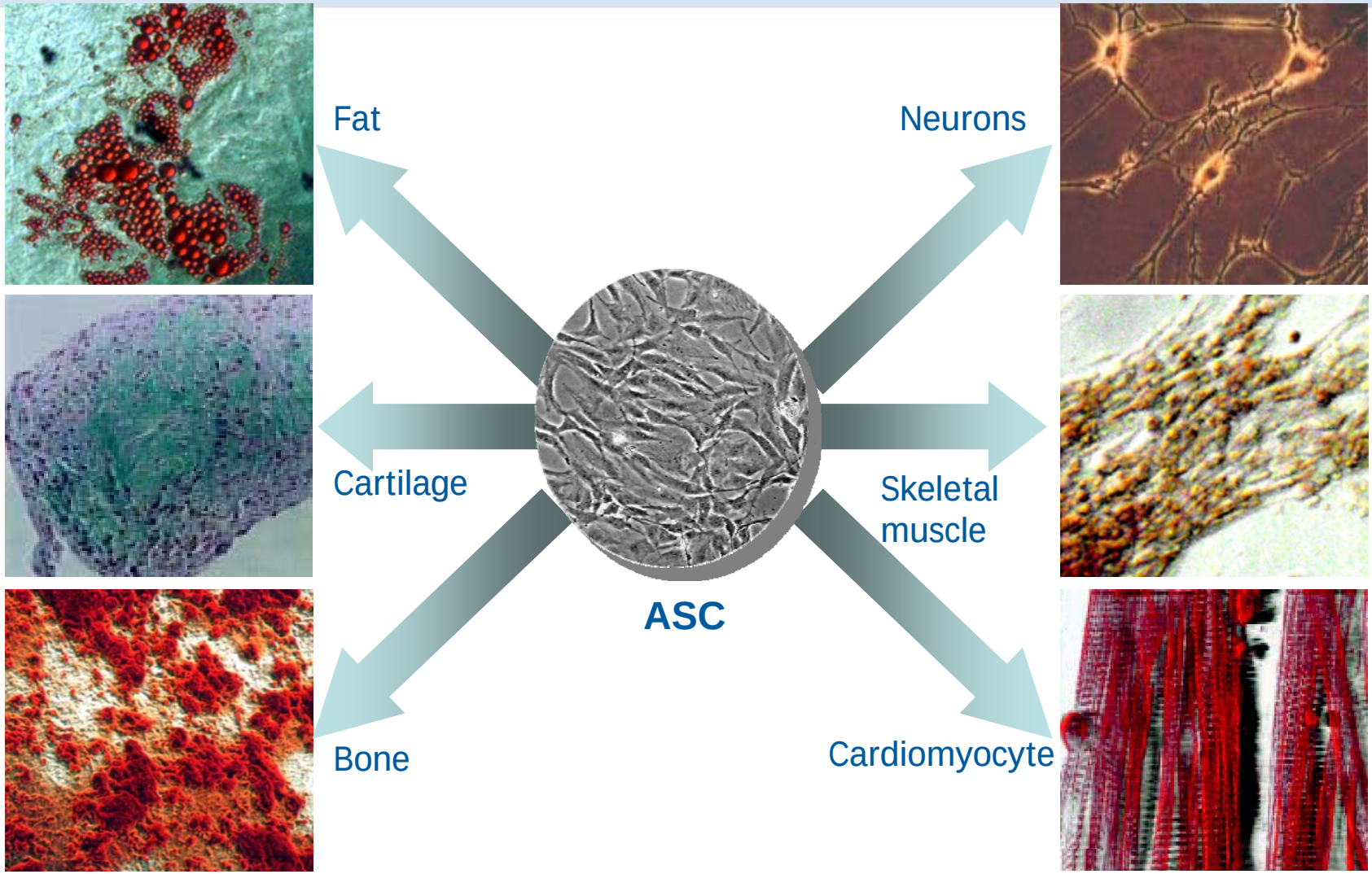
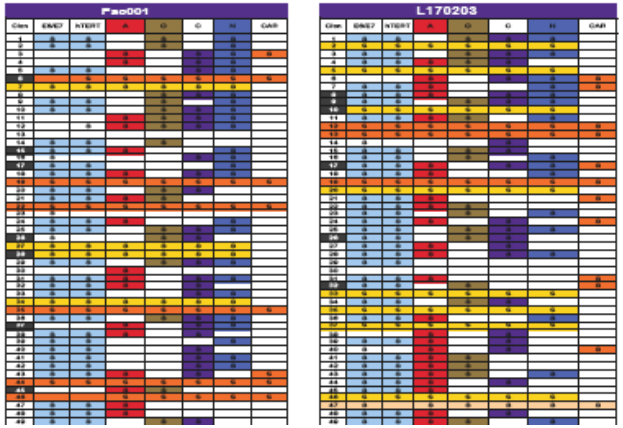
Differentiation: Mechanism of Action I



Clonality and stemness

Clonal differentiation in ASCs



Clonal heterogeneity in differentiation potential of immortalized human mesenchymal stem cells

Takeshi Okamoto,[a,b] Tomoki Aoyama,[a,b] Tomitaka Nakayama,[b] Takeharu Nakamata,[a,b] Taisuke Hosaka,[a,b,1] Koichi Nishijo,[a,b] Takashi Nakamura,[b] Tohru Kiyono,[c,2] and Junya Toguchida[a,*]

Clonal Analysis of the Differentiation Potential of Human Adipose-Derived Adult Stem Cells

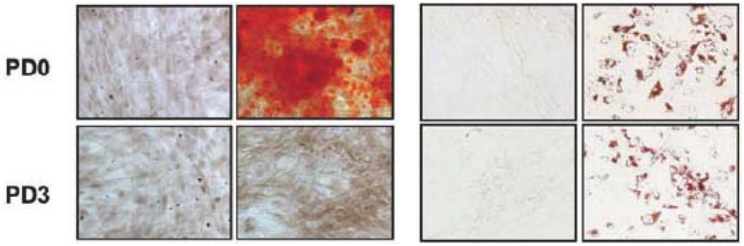
FARSHID GUILAK,[1]* KRISTEN E. LOTT,[1] HANI A. AWAD,[1] QIONGFANG CAO,[1] KEVIN C. HICOK,[1] BEVERLEY FERMOR,[1] AND JEFFREY M. GIMBLE[2]

Dynamics of adipogenic promoter DNA methylation during clonal culture of human adipose stem cells to senescence

Agate Noer, Andrew C Boquest and Philippe Collas*

Differentiation after expansion

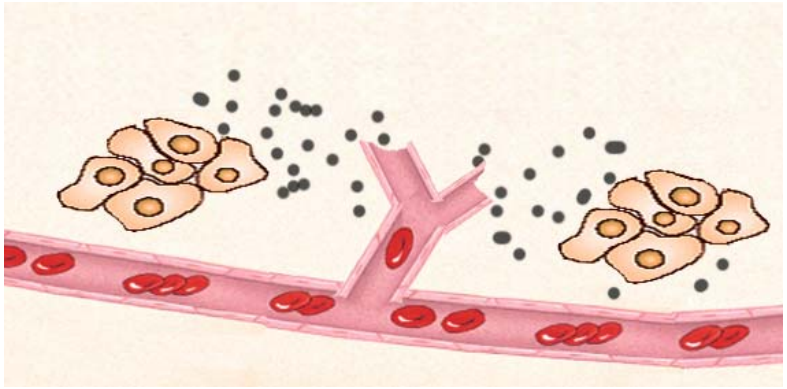
Osteocytes Adipocytes



Aging of mesenchymal stem cell in vitro

Mandana Mohyeddin Bonab*[1], Kamran Alimoghaddam[1], Fatemeh Talebian[2], Syed Hamid Ghaffari[1], Ardeshir Ghavamzadeh[1] and Behrouz Nikbin[2]

Secretome: Mechanism of Action II



Angiogenesis

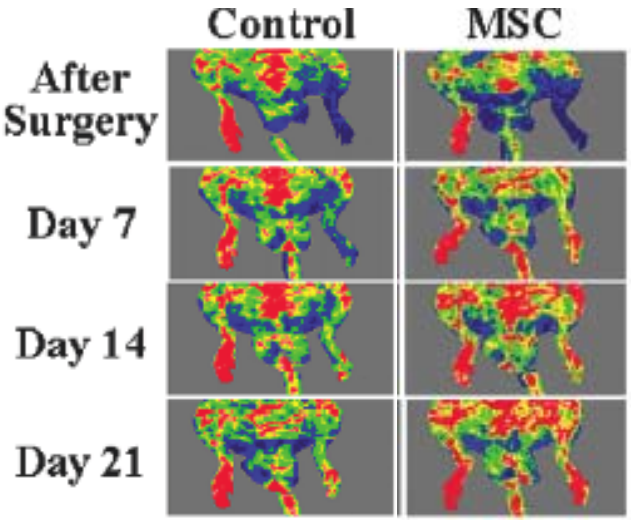
- Inhibition of apoptosis in ischemia
- Secretion of trophic factors such as:
    - IL6, IL11, GM-CSF, WNTs
- Secretion of VEGF
- Angiogenesis and repair of tissue

Expression Profiling and Functional Analysis of Wnt Signaling Mechanisms in Mesenchymal Stem Cells

S. Leah Etheridge,[a] Gary J. Spencer,[a] Deborah J. Heath,[b] Paul G. Genever[a]

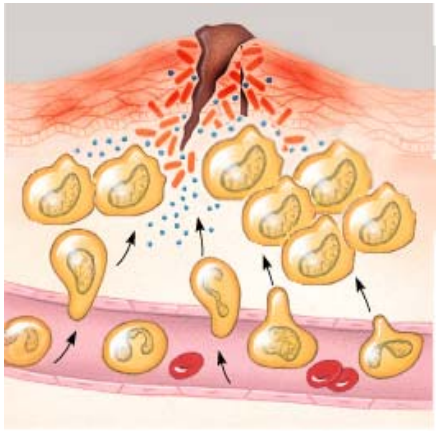
MicroSAGE Analysis of 2,353 Expressed Genes in a Single Cell-Derived Colony of Undifferentiated Human Mesenchymal Stem Cells Reveals mRNAs of Multiple Cell Lineages

Nicola Tremain,[a] Jarmo Korkko,[a] David Ibberson,[a] Gene C. Kopen,[b] Carla DiGirolamo,[a] Donald G. Phinney[a]



Iwase et al 2005

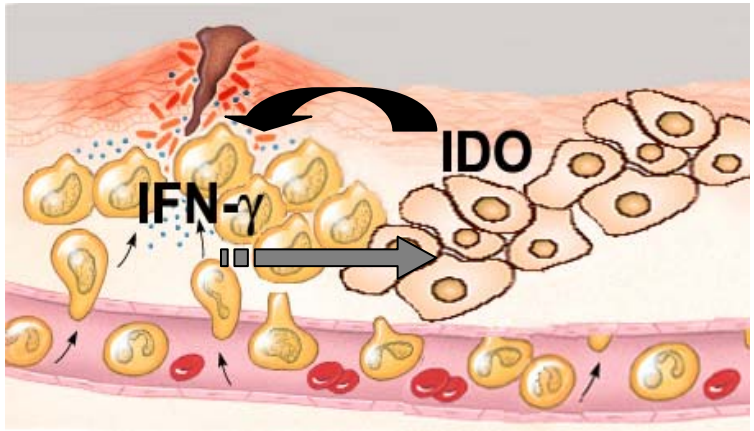
Mechanism of Action III



A

Inflammation

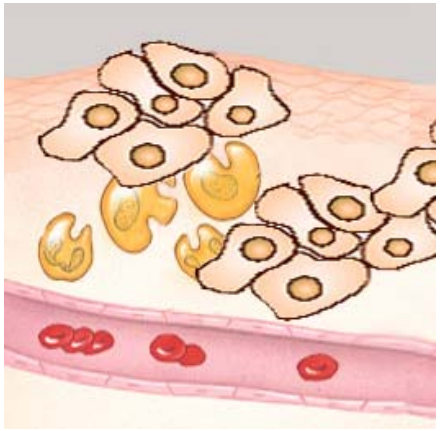
- Infiltration of lymphocytes (PBLs) in wound area
- Secretion of pro-inflammatory cytokines
- Sensation of pain



B

Delivery of eASCs/MSCs

- Activation of eASC by a cytokine called IFN-γ
- Expression of an enzyme called IDO by eASCs
- Suppression the proliferation of activated PBLs
- Suppression of production of inflammatory signals

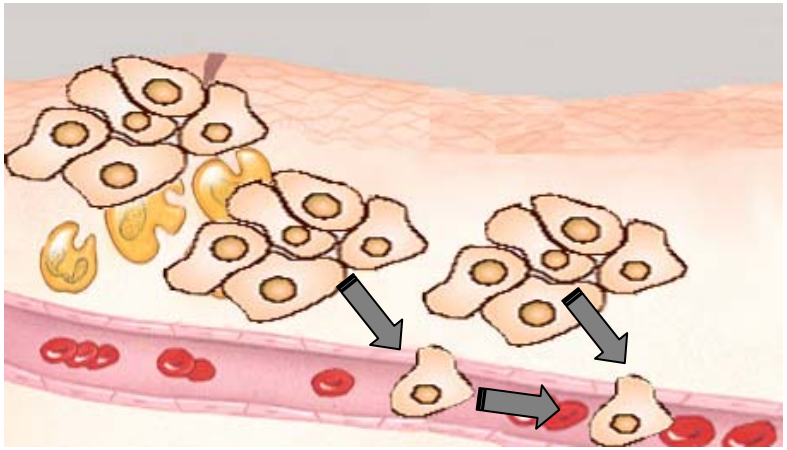


C

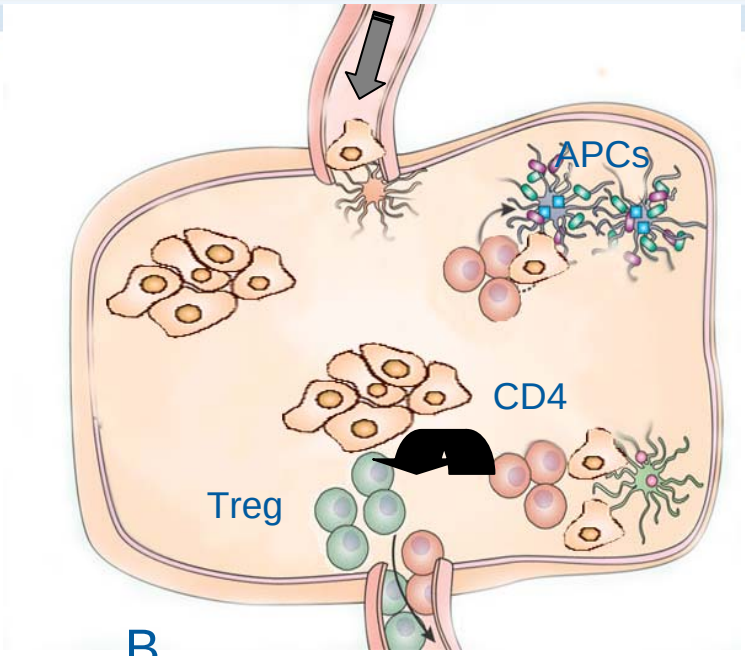
Healing

- Elimination of activated PBLs
- Abrogation of pro-inflammatory cytokines
- Cessation of pain
- Repair of tissue

Mechanism of Action IV



A



B

Migration

- Active movement out of a local environment (bone marrow, connective tissue)
- Entering into the blood stream

and/or

- Entering into the lymph system

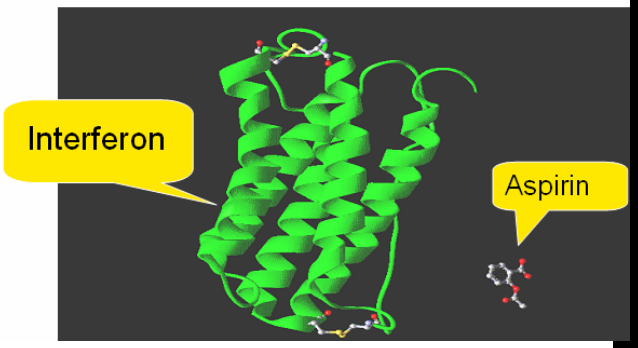
Immuno-modulation

- Migration into secondary lymph organs
- Physical contact with APCs and T/B cells
- Induction of new Treg cells

and/or

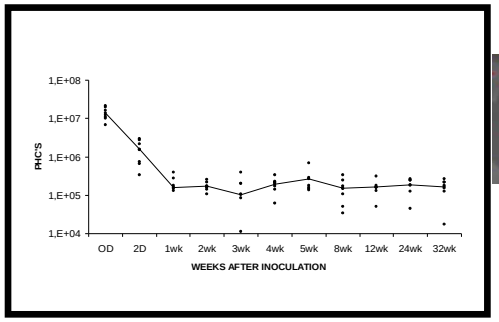
- Selective expansion of Treg cells

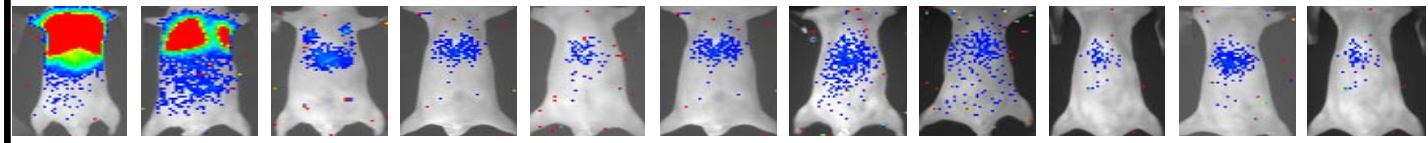
Size does matter



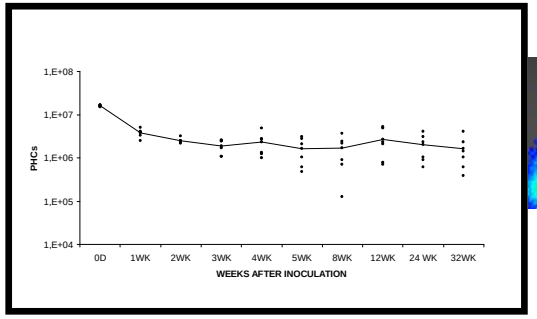
Survival of MSCs: Safety and Function

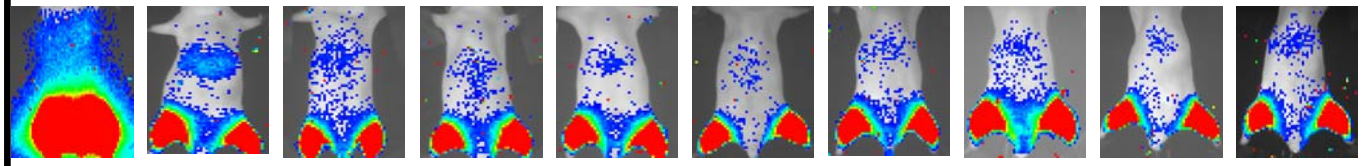
Intra-venous





Intra-muscular





Vilalta et al., 2008

Autologous versus Allogeneic

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AUTOLOGOUS

Pros

- No rejection
- Simpler quality control requirements

Cons

- Single batch production per patient
- Several weeks are needed to have the product ready to be implanted in the patient
- Patient “biopsies” required
- Difficult logistics
- High cost of production

ALLOGENEIC

Pros

- Universal medicine: Standardized product
- Medicine ready to use when needed
- No patient “biopsies” required:
  - Simplification of logistics
  - Patient's benefit
- Reduction of costs

Cons

- (Theoretical) risk of rejection
- Additional regulatory issues (i.e. more quality control needed)

MSCs: Immuno-privileged

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Other cell types

Surface antigens

- High levels of MHC I (HLA-A, B, C)
- MHC II: depending on cell type
- Co-stimulatory molecules
  - Depending on cell type
- CD55 and CD59: depending on cell type

Other Factors

- Lack of IDO induction

MSCs

Surface antigens

- Low levels of MHC I (HLA-A, B, C)
- Lack of MHC II (HLA-DR, DQ, DP)
- Lack of co-stimulatory molecules
  - CD40 (TNFR), CD80 (B7-1), CD86 (B7-2)
- High levels of CD55 (DAF) and CD59 (Protectin) => protectors of complement associated lysis

Other Factors

- Strong IDO induction

THANK YOU FOR YOUR ATTENTION