CERSI MTG
BALTIMORE,MD
MAY 8,2013
ARNOLD I CAPLAN

The Science of MSCs & REGENERATIVE MEDICINE :

CELL-BASED THERAPY =

the NEW MEDICINE.

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May 8, 2013

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FDA

Cells and cell-based therapies are being managed by the FDA under the same logics as DRUGS are managed. Cells are not single molecular agents but are ,rather, site-regulated, adaptive agents capable of very complex functions involving a multitude of bioactive factors and reactivities.

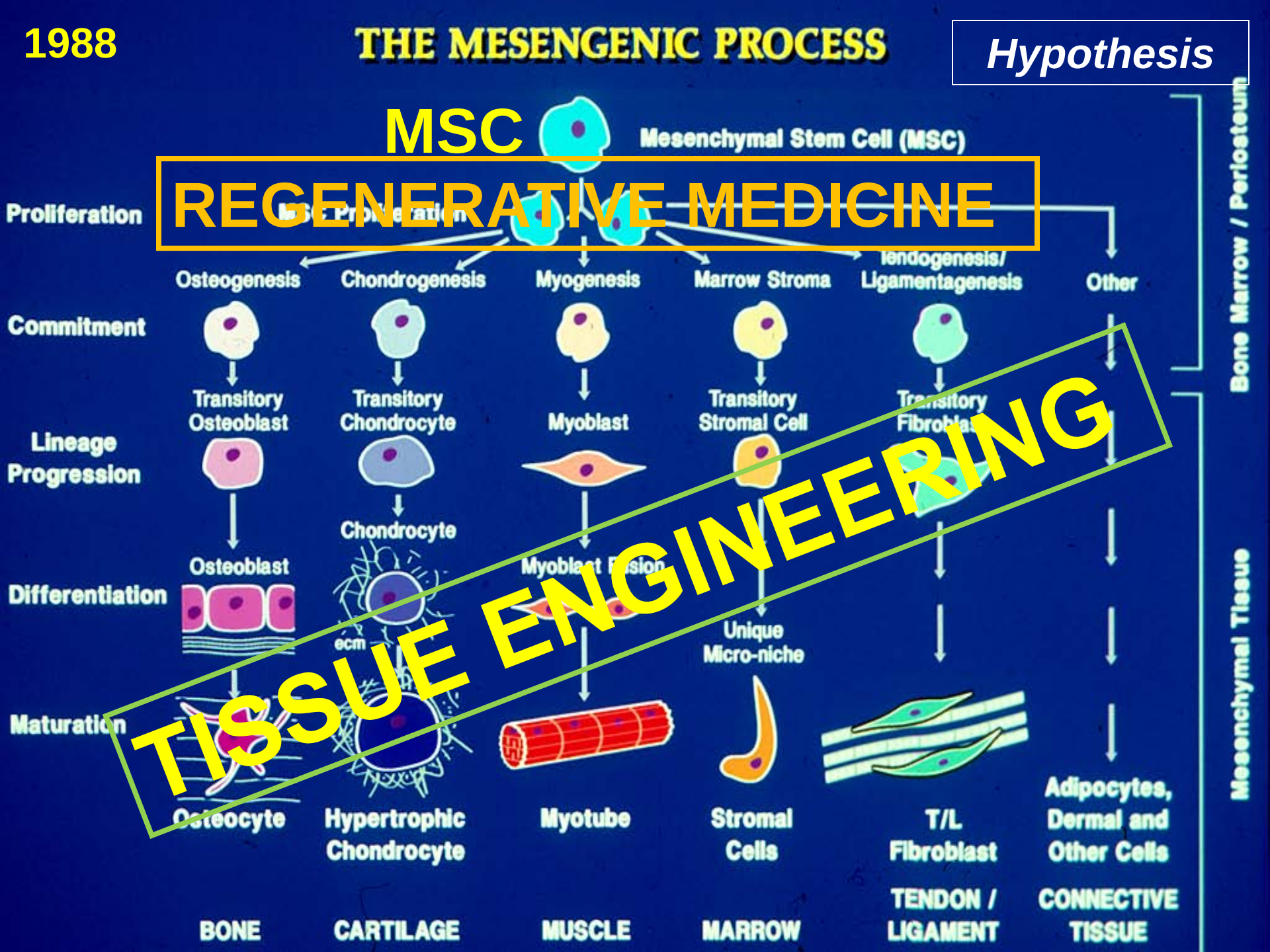
These facts require new management logics and regulatory values.

Progressive Approval:

A Proposed Regulatory Pathway for Cell-Based Therapies and Regenerative Medicine.

ARNOLD I. CAPLAN , MICHAEL WEST, ANDREW C von ESCHENBACH

- Phase I: Safety Study.
- Product APPROVAL, thus, paid for at market.
- Phase IV: Post Marketing , Long Term follow up with outcomes listed in real-time on a publically accessible website with protection for patients' identity with 3-10 year reporting.
- Statistical Significance= label approval.
- Adverse Events: All scientists/clinicians assist.


1988
THE MESENGENIC PROCESS
Hypothesis
MSC
REGENERATIVE MEDICINE
TISSUE ENGINEERING
Mesenchymal Stem Cell (MSC)
Proliferation
Osteogenesis
Chondrogenesis
Myogenesis
Marrow Stroma
Tendogenesis/ Ligamentagenesis
Other
Commitment
Transitory Osteoblast
Transitory Chondrocyte
Myoblast
Transitory Stromal Cell
Lineage Progression
Chondrocyte
Osteoblast
Differentiation
ecm
Unique Micro-niche
Maturation
Osteocyte
Hypertrophic Chondrocyte
Myotube
Stromal Cells
T/L Fibroblast
Adipocytes, Dermal and Other Cells
BONE
CARTILAGE
MUSCLE
MARROW
TENDON / LIGAMENT
CONNECTIVE TISSUE
Bone Marrow / Periosteum
Mesenchymal Tissue

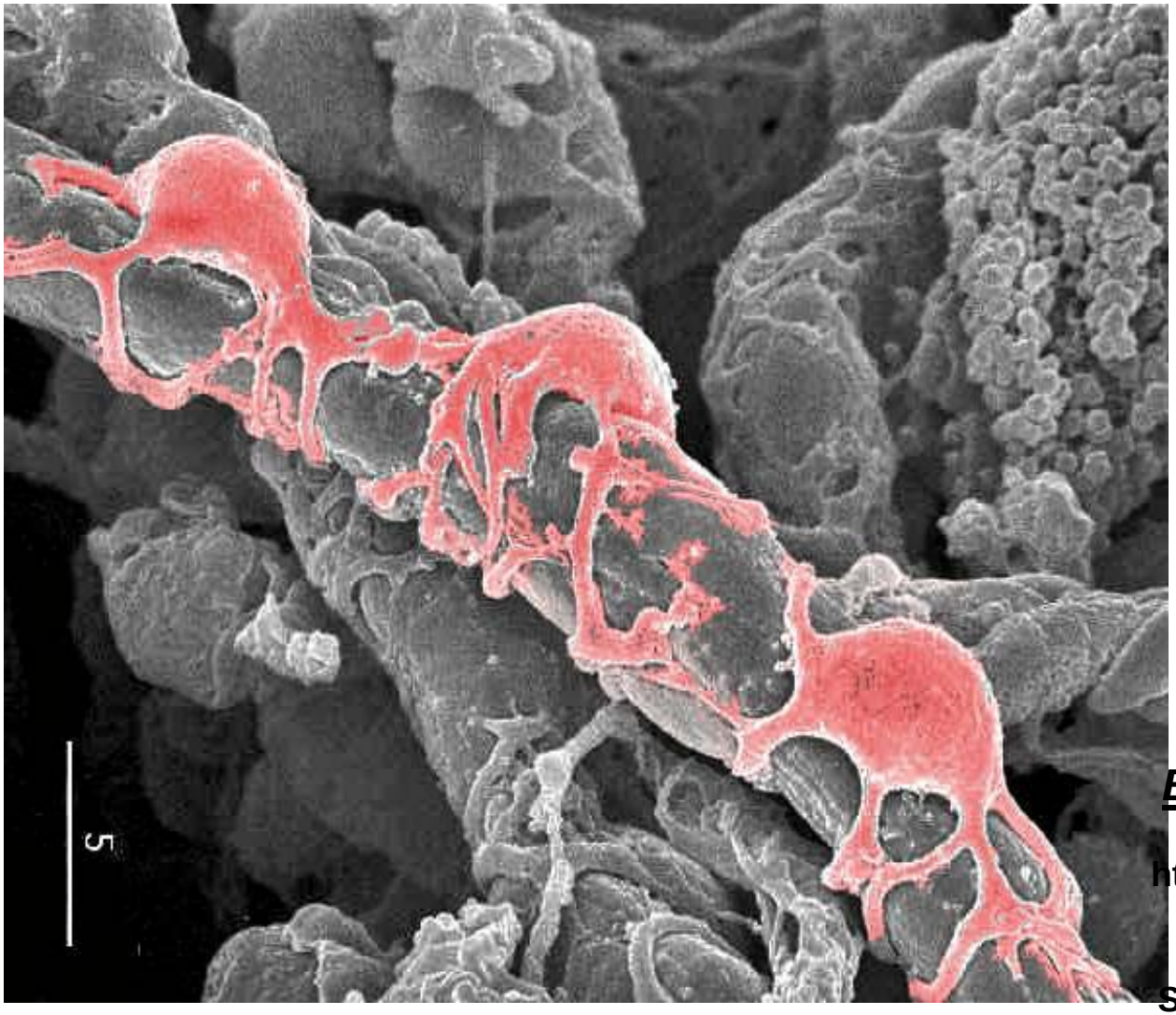
Stem Cell Publications Based on Type of Stem Cell

Class of Stem Cell	Number of publications Containing the Particular Stem Cell Class in Title or Abstract*
HSC [Hematopoietic Stem Cell]	75,995
MSC [Mesenchymal Stem Cell]	26,905
NSC [Neural Stem Cell]	17,060
hESC[Human Embryonic Stem Cells]	14,121
EnSC [Endothelial Stem Cell]	10,018
CSC [Cancer Stem Cells]	9,334
CBSC [Cord-Blood Stem Cell]	9,197
IPSC[Induced Pluripotent Stem Cell]	3,778
AdSC [Adipose-derived Stem Cell]	2,015

*The total number of publications in this table is more than 144,317 since a given publication may reference more than one type of stem cell, in which case it would be classified within each of the various stem cell classes.

Pericytes: cells on capillaries and microvessels.

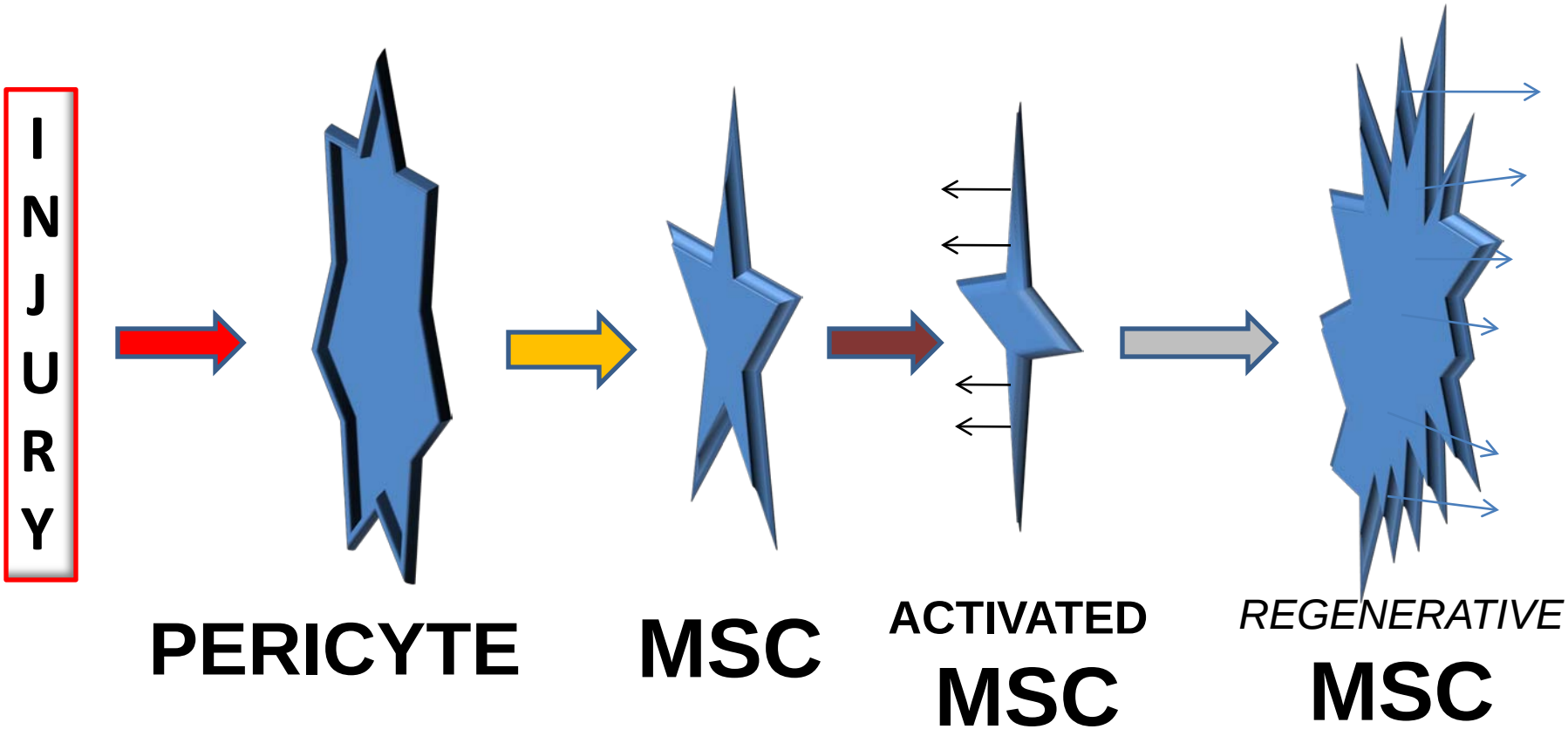
ALL MSCs are PERICYTES!



modified by
BRUNO PEAULT
from
http://www.geocities.co.jp/HeartLand-Suzuran/9389/kekkan

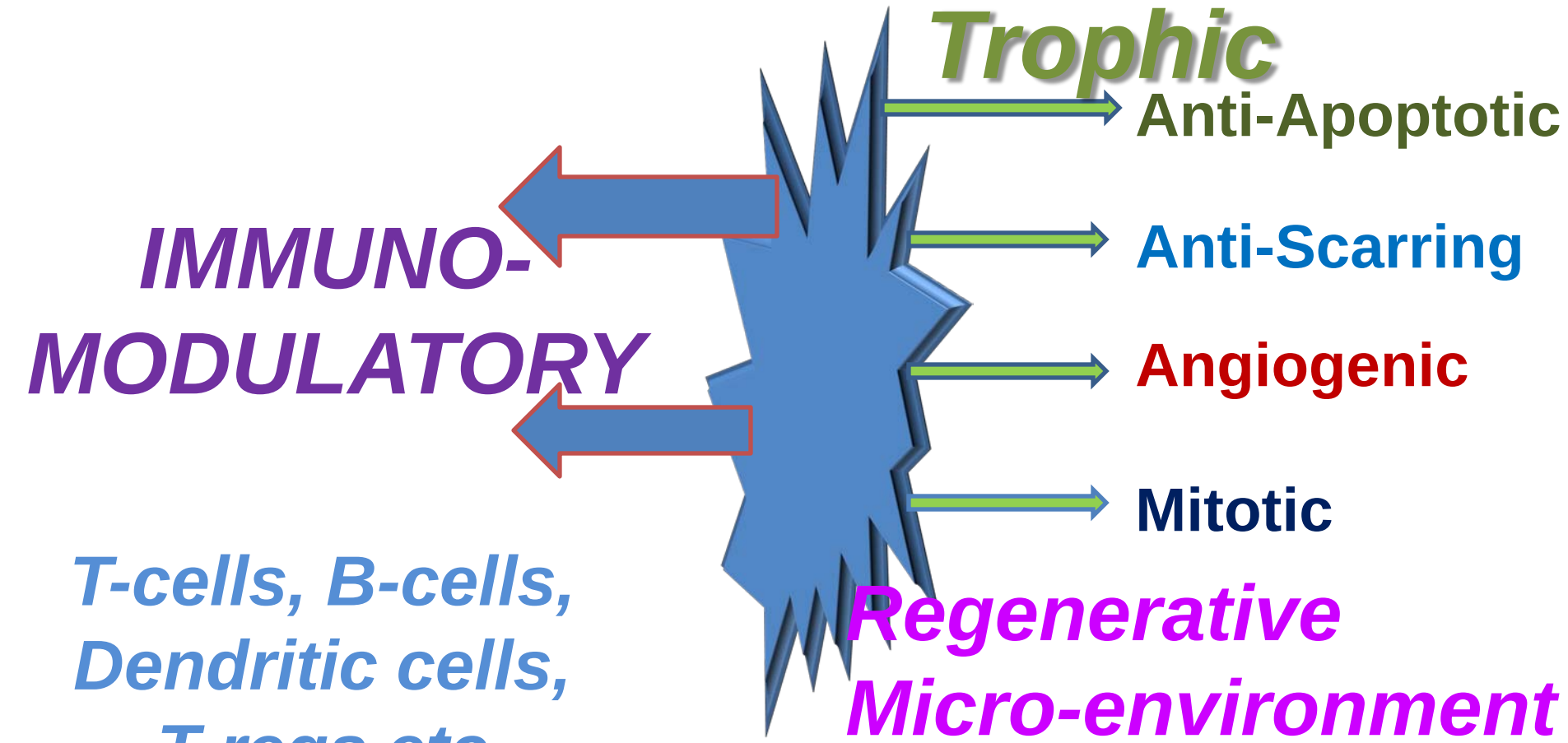
2013

PROPOSED SEQUENCE OF CHANGE DUE TO INJURY:



2013

natural INJURY RESPONSE



MSC=*pericyte*

MSC =

Medicinal Signaling Cell.

(the injury-specific DRUG STORE)

Cultured Pericytes Express Markers of hMSCs.

Pericytes

Events

CD10 CD13 CD44

CD73 CD90 CD105

hMSCs

CD34 CD133 CD45

hHSCs

negative

CD146 aSMA CD56

M Crisan *et al, 2008*

Perivascular *Niche* and Implications:

All MSCs are Pericytes

Caplan AI, *Cell Stem Cell (2008)*

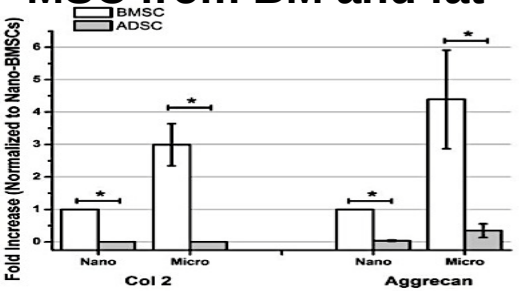
Present throughout the body.

Crisan M et al: *Cell Stem Cells (2008)*

All blood vessel cells REFLECT the tissue in which they function. Thus, since each tissue is different, THE CELLS OF THE BLOOD VESSELS ARE DISTINCTLY DIFFERENT.

All MSCs are "different"… They are specified by their instructive microenvironment.

Chondrogenesis using MSC from BM and fat



Bean AC et al: *TERMIS (2011)*

Marrow MSCs require exposure to TGF-β to be chondrocytes; ASCs require both TGF-β and BMP-6 to be chondrocytes. Therefore, marrow MSCS ≠ ASCs.

Endogenous Bone Marrow MSCs are Dynamic, *FATE-RESTRICTED* Participants in BONE Maintenance and Regeneration.

Park *et al*, *Cell Stem Cell*, 10,259-272, 2012

- $Mx1^+$ murine MSCs are multi-potent *in vitro*.
- $Mx1^+$ MSCs are capable of local & systemic translocation and serial transplantation.
- $Mx1^+$ MSCs are **OSTEO-LINEAGE restricted**.
- FATE-RESTRICTED potential fits into the high replacement demands of the adult skeleton.

- **One million knees and hips this year will be surgically replaced . ALL of the surgical patents' Bone , Marrow and Stem Cells will be discarded.**
- **As with Cord Blood, *CellBank* will process and store this autograft for future reconstructive procedures in a patient-pay business model. There is no FDA-regulation of the use of this banked ,autologous graft material.**
- **CellBank enrolled their first patients in Feb, 2013.**

CLINICALTRIALS.GOV

4-2013. Found 307 studies with search of: Mesenchymal Stem Cells:

Clinical Conditions for MSC-therapy: ~25% autologous.

Ulcerative Colitis, Diabetes Mellitus, Type 1, Liver Cirrhosis,Nonunion Fractures, Diabetic Foot, Critical Limb Ischemia, Dilated Cardiomyopathy, Autoimmune Diseases; Immune System Diseases; Demyelinating Diseases; Nervous System Diseases; Demyelinating Autoimmune Diseases, CNS; Autoimmune Diseases of the Nervous System(MS), Sjogren's Syndrome, Graft Versus Host Disease; Chronic and Expanded Graft Versus Host Disease, Middle Cerebral Artery Infarction, Osteoarthritis, Aplastic Anemia, Maxillary Cyst; Bone Loss of Substance, Spinal Cord Injury, Parkinson's Disease, Crohn's Disease, Acute Myocardial Infarction, Multiple Sclerosis, Hematological Malignancies, Organ Transplantation, Ischemia; Stroke, Systemic Sclerosis, Hereditary Ataxia, Liver Failure, Retinitis Pigmentosa, Kidney Transplant; Rheumatoid Arthritis, Lumbar Spondylolisthesis Involving L4-L5, Chronic Allograft Nephropathy, Degenerative Arthritis; Chondral Defects; Osteochondral Defects, Progressive Multiple Sclerosis; Neuromyelitis Optica, Primary Biliary Cirrhosis, Osteonecrosis of the Femoral Head, Pened Chest Surgery for Programmes Coronary Bypass, Lupus Nephritis, Wilson's Disease, Multiple System Atrophy, Burns, Intervertebral Disc Disease, Chronic Myocardial Ischemia; Left Ventricular Dysfunction, Relapsing-Remitting Multiple Sclerosis; Secondary Progressive Multiple Sclerosis; Progressive Relapsing Multiple Sclerosis, Tibial Fracture, Bone Cyst,Buerger's Disease, Amyotrophic Lateral Sclerosis, Allogeneic Stem Cell Transplantation, Idiopathic Pulmonary Fibrosis, Type 2 Diabetes Mellitus, Refractory Systemic Lupus Erythematosus, Leukemia, Myeloid, Acute; Leukemia, Lymphoblastic, Acute; Leukemia, Myelocytic, Chronic; Myeloproliferative Disorders; Myelodysplastic Syndromes; Multiple Myeloma; Leukemia, Lymphocytic, Chronic; Hodgkin's Disease; Lymphoma, Non-Hodgkin, Degenerative Arthritis, Myelodysplastic Syndrome, ST-Elevation Myocardial Infarction, Pulmonary Disease, Chronic Obstructive; Pulmonary Emphysema; Chronic Bronchitis, Lower Back Pain; Disc Degeneration, Articular Cartilage Lesion of the Femoral Condyle, Osteoporotic Fractures, Bone Neoplasms, Solid Tumors; Acute Kidney Injury, Hereditary Cerebellar Ataxia, Primary Disease, Autism, Limbus Corneae Insufficiency Syndrome, Wound Healing, Dementia of the Alzheimer's Type, Non-ischemic Dilated Cardiomyopathy, Stroke, Epidermolysis Bullosa, Tibia or Femur Pseudo-arthrosis, Recovery Following Partial Medial Meniscectomy, Human Immunodeficiency Virus, Stable Angina; Heart Failure; Atherosclerosis; Multivessel Coronary Artery Disease, Osteogenesis Imperfecta, Emphysema, Progressive Hemifacial Atrophy; Romberg's Disease, Complex Perianal Fistula, Multiple Trauma, Osteodysplasia, Tibiotalar Arthrodesis; Subtalar Arthrodesis; Calcaneocuboid Arthrodesis; Talonavicular Arthrodesis; Double Arthrodesis (i.e. Calcaneocuboid and Talonavicular); Triple Arthrodesis (i.e. Subtalar, Calcaneocuboid, and Talonavicular), Recto-vaginal Fistula, Peripheral Vascular Diseases, Prostate Cancer; Erectile Dysfunction, Diabetic Wounds; Venous Stasis Wounds, Ovarian Cancer; Sarcoma; Small Intestine Cancer.

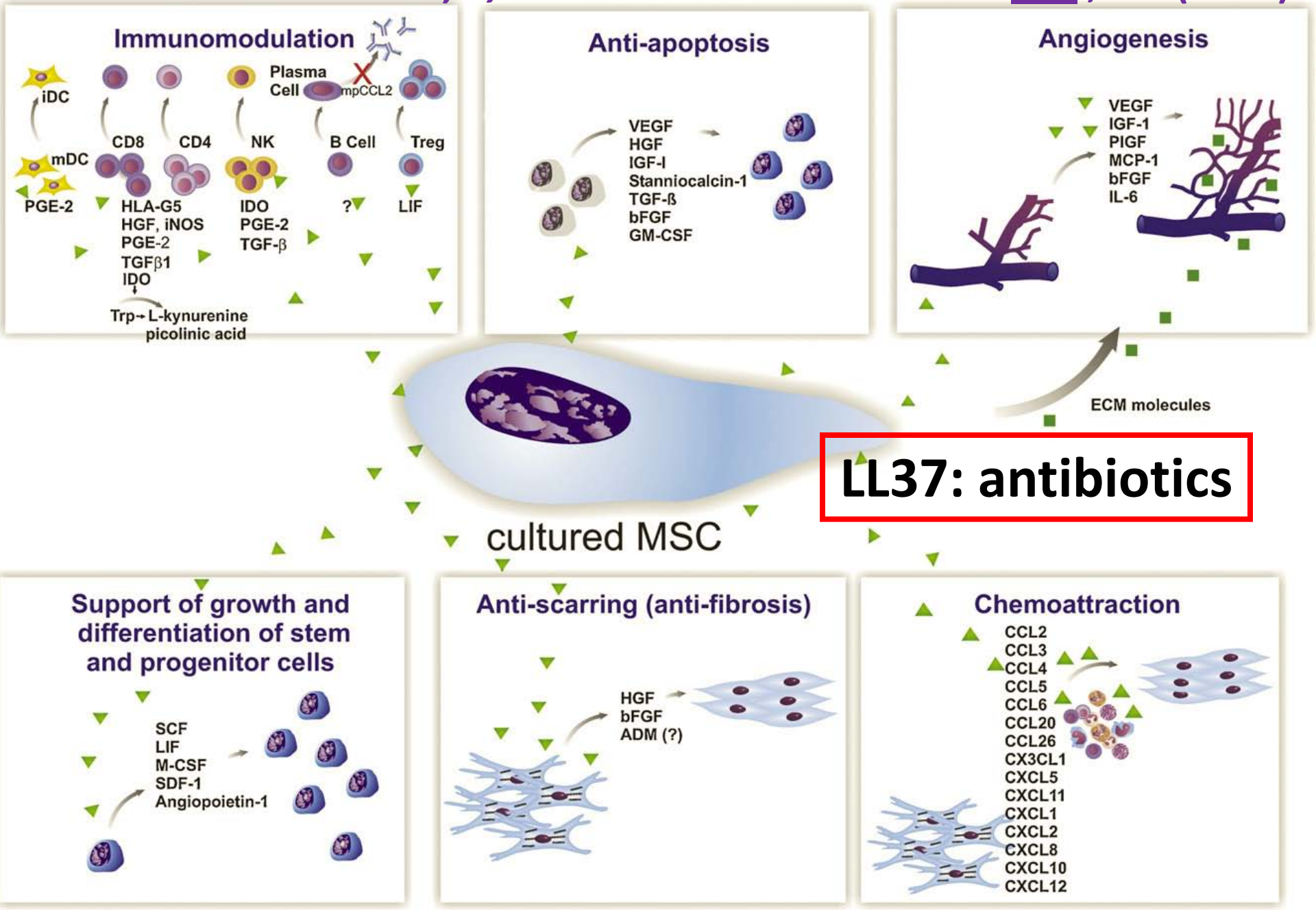
Induction Therapy with Autologous MSCs in Kidney Transplants:

J Tan et al & Camillo Ricordi, JAMA,307,1169-77.

159 patients were enrolled in a single site, prospective, open-label, randomized study to compare anti-IL-2 receptor antibody induction therapy with marrow-derived, culture expanded, autologous MSCs.

The infused MSCs (1-2x 10^6/kg at reperfusion and at 2wks) **lowered the incidence of acute rejection, decreased the risk of opportunistic infection, and provided better estimated renal function at 1year.**

L. da Silva Meirelles et al, *Cytokine & Growth Factor Reviews*: *550* , 1–9(2009)



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