MSCs are not Stem Cells; *the New Medicine.*

Innate Regenerative Potential

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October 26, 2019

Case Western Reserve University

Cleveland, Ohio

Disclosure Information:

1. **Osiris Therapuetic, Inc. :**

   Former Officer and Founder

   Current status: NO association or equity; receive royalties thru CWRU.

2. **Consulting:**

   Provide advice globally within the Regenerative Medicine space.

QUESTIONS

- Why do women who have open bleeding uterine wounds not have monthly issues of sepsis???

- Can we regenerate **fingers** or toes??
- How does breast milk inhibit infections?
- Can we regenerate our broken spinal discs??
- Can we reverse the effects of my heart attack?
- Will my knee /hip need to be replaced??

CONCLUSION: **MSCs**

MSCs = **M**esenchymal **S**tem **C**ells

AI Caplan. Mesenchymal Stem Cells. *J Ortho Res* 9:641-650 (**1991**).

MSC = Medicinal Signaling Cell.

(the injury-specific DRUG STORE)

Al Caplan.
What's in a name?
Tiss Eng, A, 16: 2415-2417, **2010**

CONCLUSIONS

MSCs are NOT Stem Cells

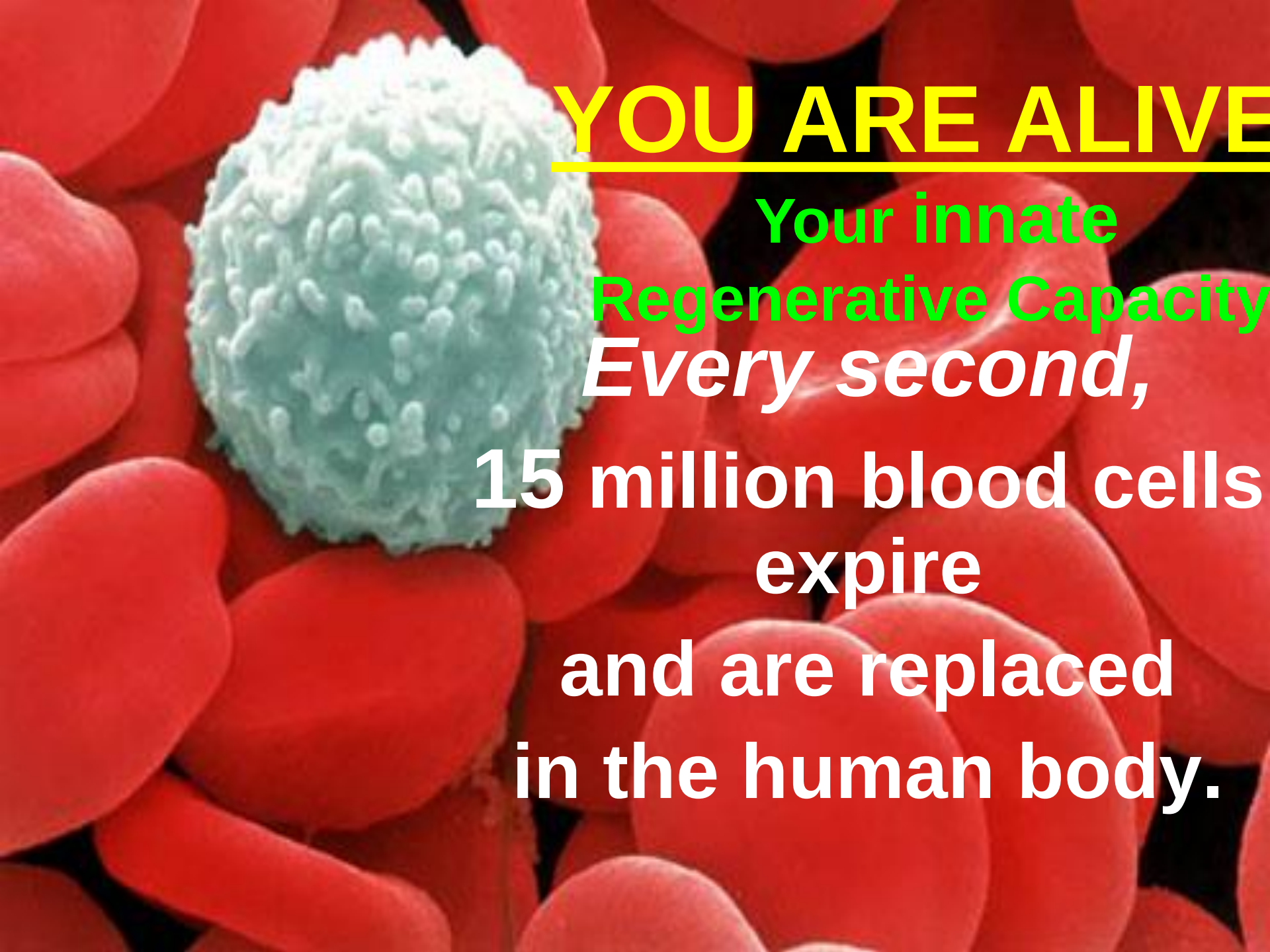
- **MSCs arise from *PERICYTES* at sites of injury.**
- **MSCs do not arise from *stroma*.**
- **MScs do not differentiate into *mesenchymal tissues*.**
- **MSCs make DRUGS at sites of injury:**

1. **MSCs are immuno-modulatory(*decreases pain*).**
2. **MSCs make TROPHIC/Regenerative molecules.**
3. **MSCs make molecules that occupy *Opioid* Receptors.**
4. **MSCs make antibiotic proteins that kill bacteria.**

MSCs are NOT Stem Cells *except*

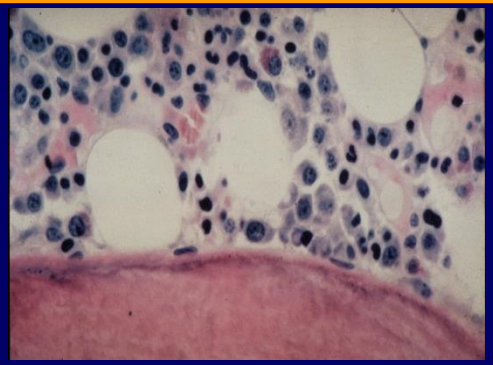
in Cell or Tissue Cultures. MSCs are multi-potent and can be used in tissue engineered constructs to fabricate skeletal tissues like CARTILAGE.

MSCs function *in vivo* to manage the *innate capacity* of tissues to regenerate.


YOU ARE ALIVE
Your innate
Regenerative Capacity
Every second,
15 million blood cells
expire
and are replaced
in the human body.

Adult

BONE MARROW



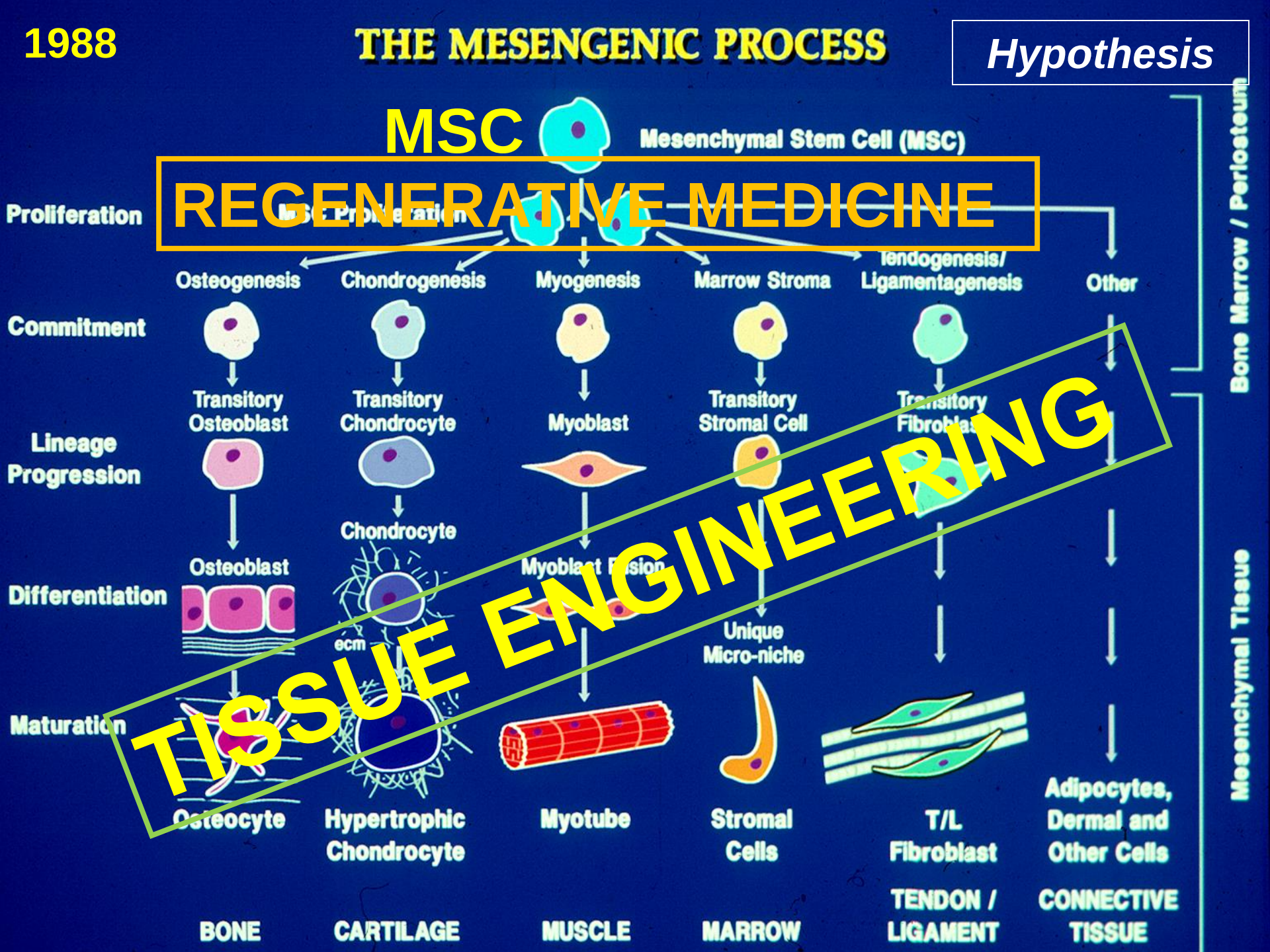
Hematopoietic Stem Cell

HSC

ALL BLOOD CELLS

MSC

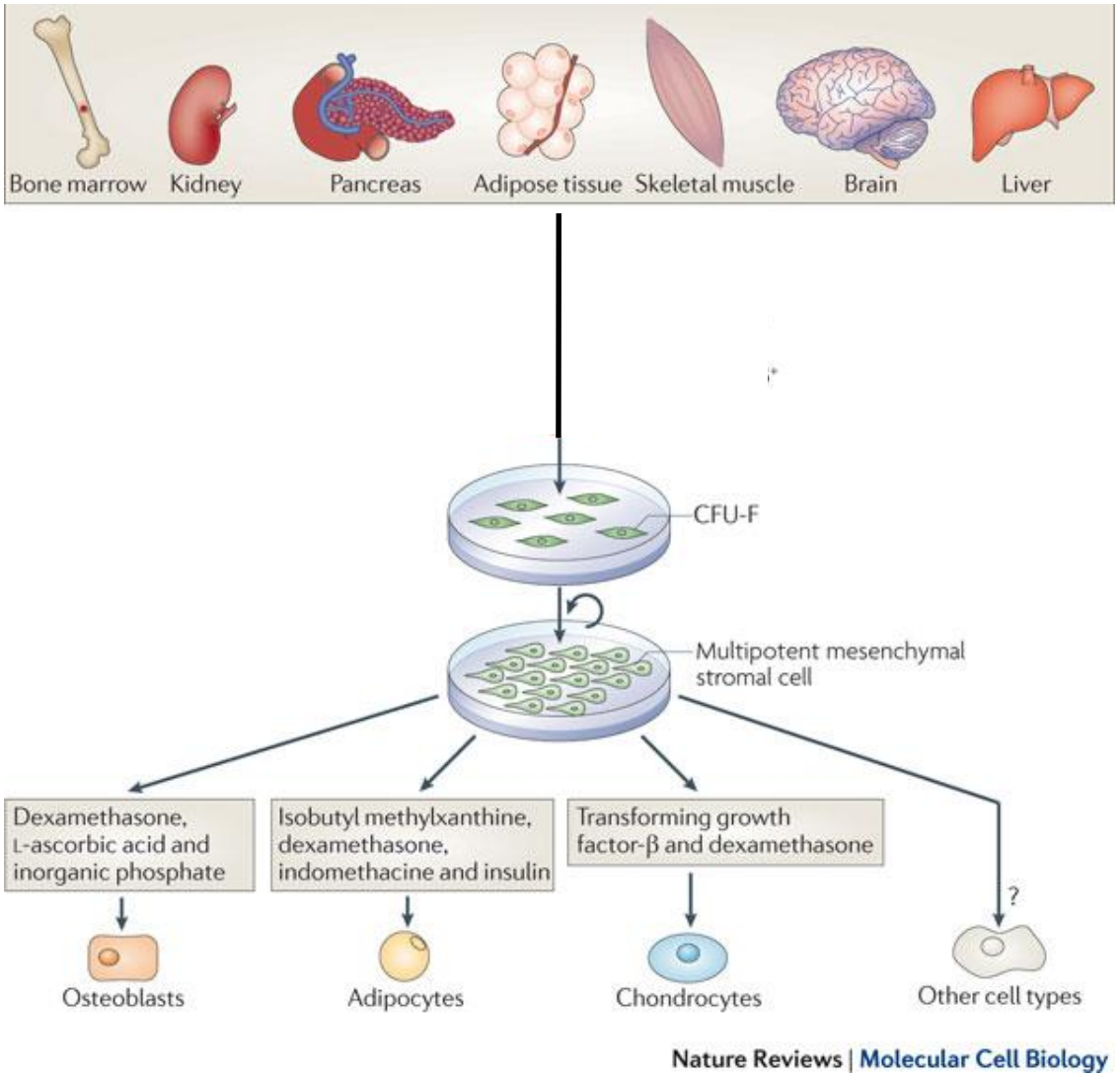
MESENCHYMAL STEM CELLS


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
Osteoblast
Chondrocyte
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

MSCs can be derived from multiple tissue sources

- Aorta
- Adipose
- Amniotic fluid
- Bone marrow
- Blood
- Brain
- Cartilage
- Cord blood
- Dental pulp
- Endometrium
- Eye
- Gut
- Heart
- Kidney
- Liver
- Lung
- Muscle
- Pancreas
- Perichondrium
- Periodontal ligament
- Placenta
- Salivary gland
- Skin
- Spleen
- Synovial membrane
- Tendon
- Thymus
- Umbilical cord
- Vein

Murray et al, 2014



Nombela-Arrieta et al., 2011

TODAY:

MSCs

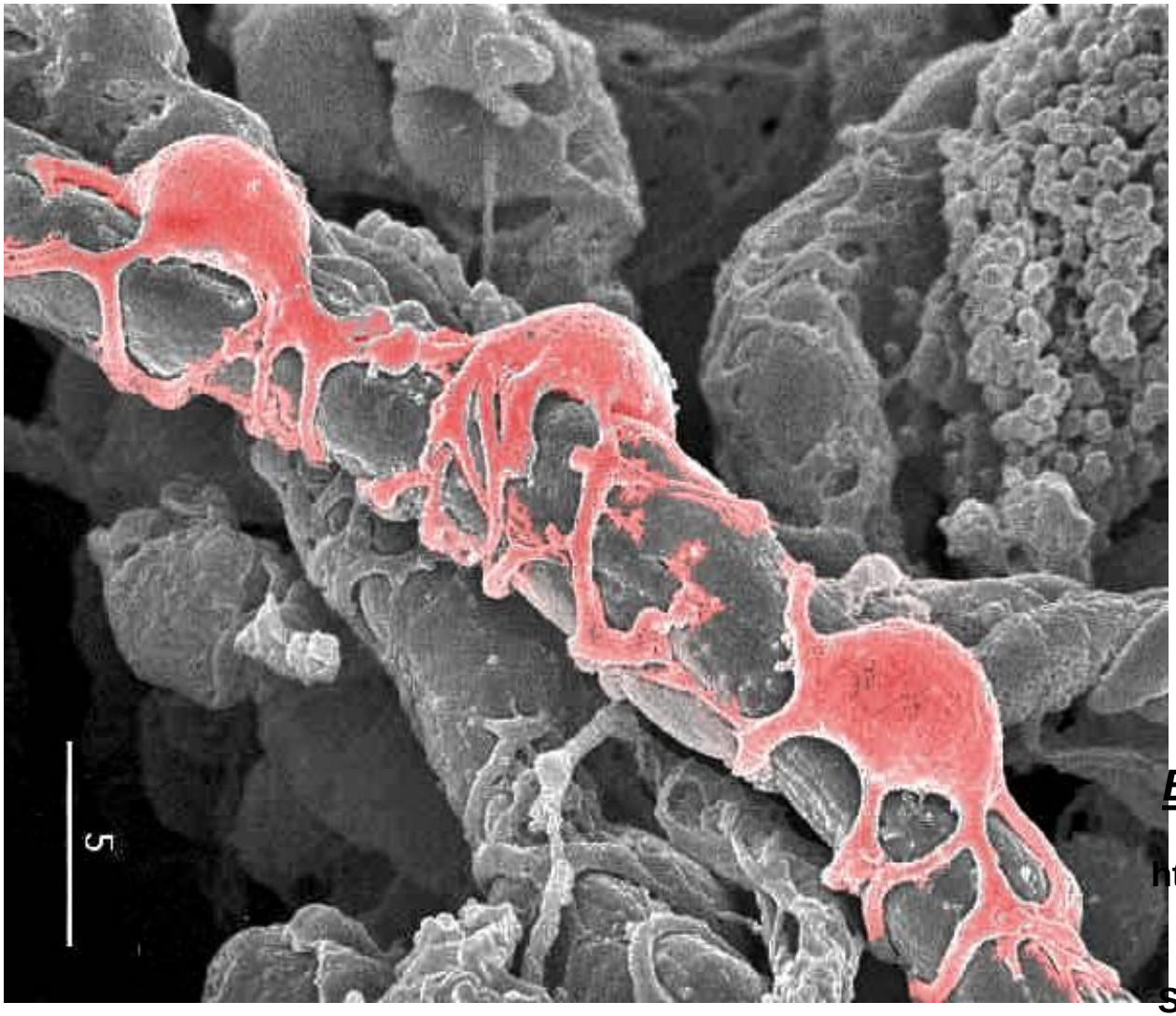
"Mesenchymal Stem Cells"

and

Regenerative Medicine.

Pericytes: cells on capillaries and microvessels.

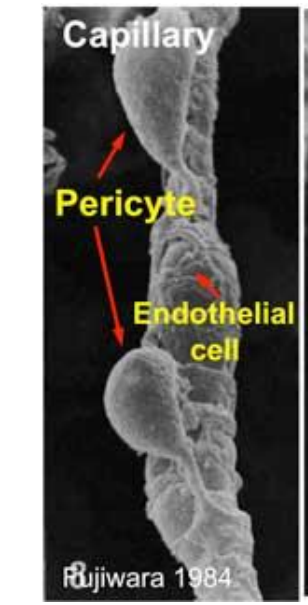
ALL MSCs are PERICYTES!

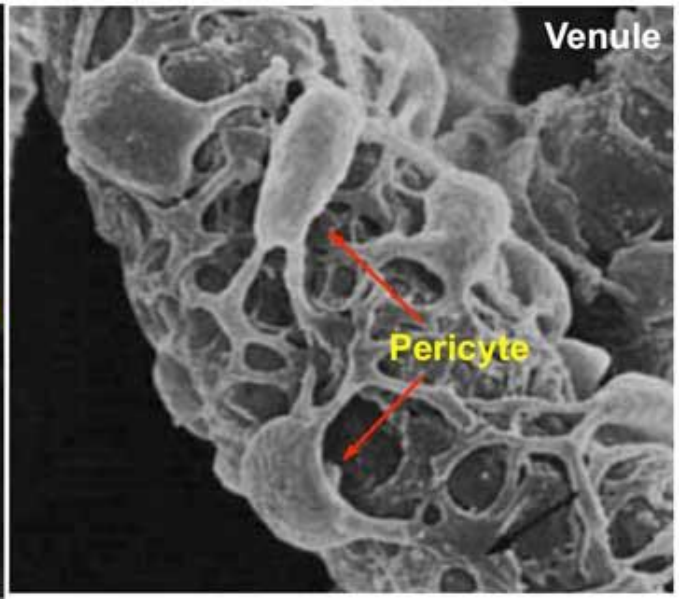


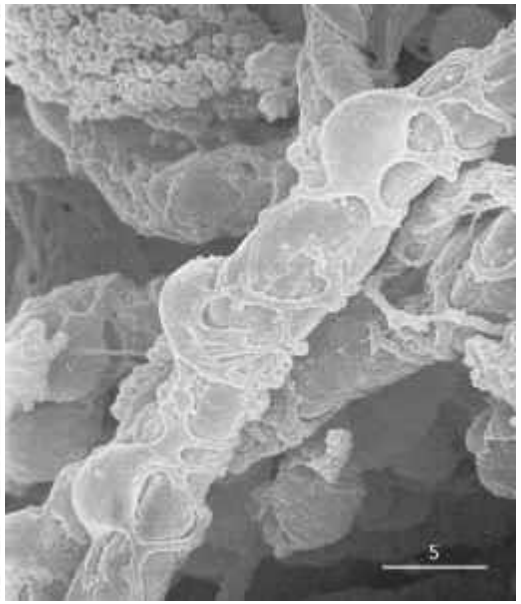
Al Caplan. Cell Stem Cell, 3:229-30, 2008.

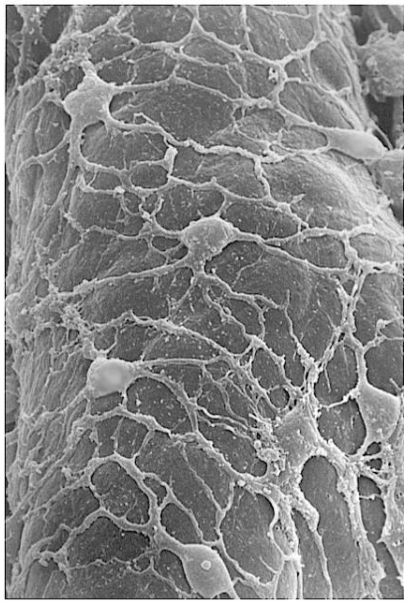
modified by ***BRUNO PEAULT*** from http://www.geocities.co.jp/HeartLand-Suzuran/9389/kekkan

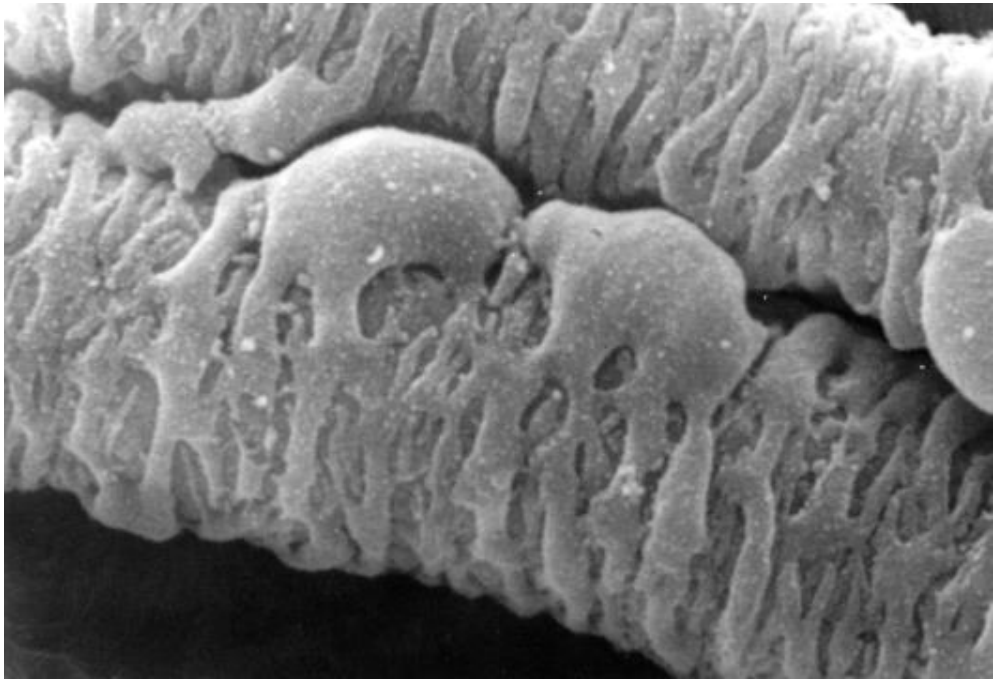
In vivo identity of preMSCs: pericytes

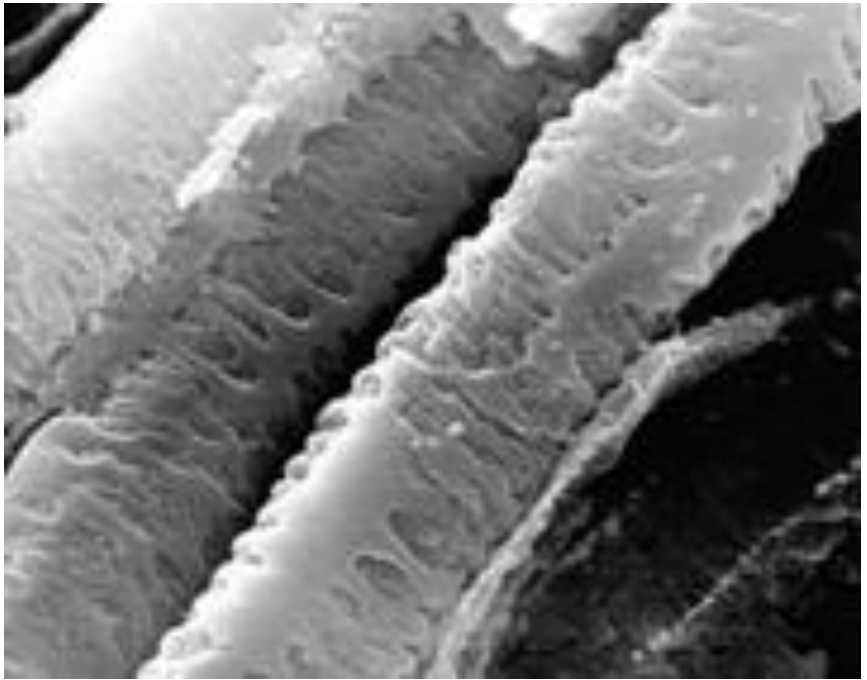




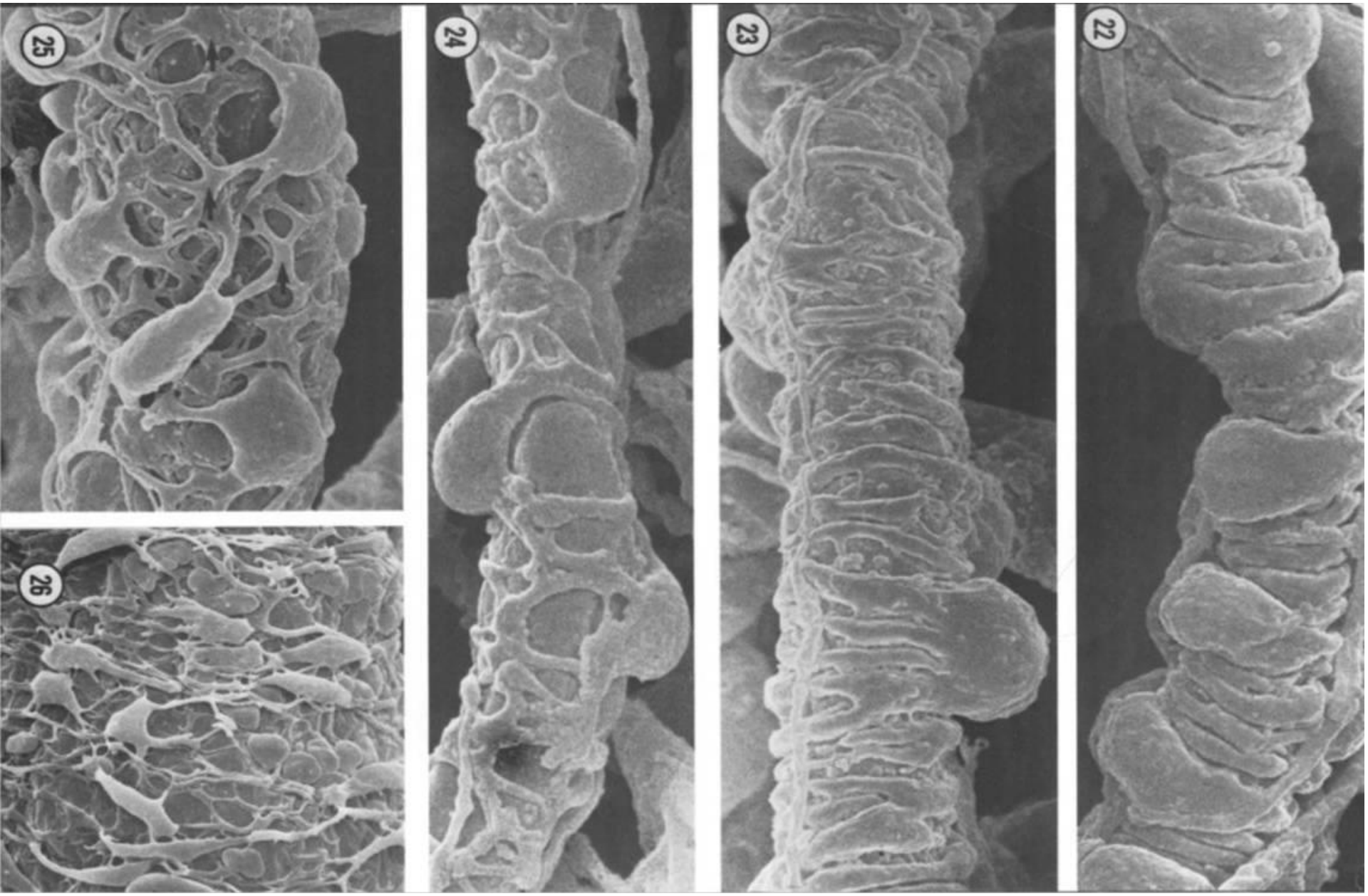


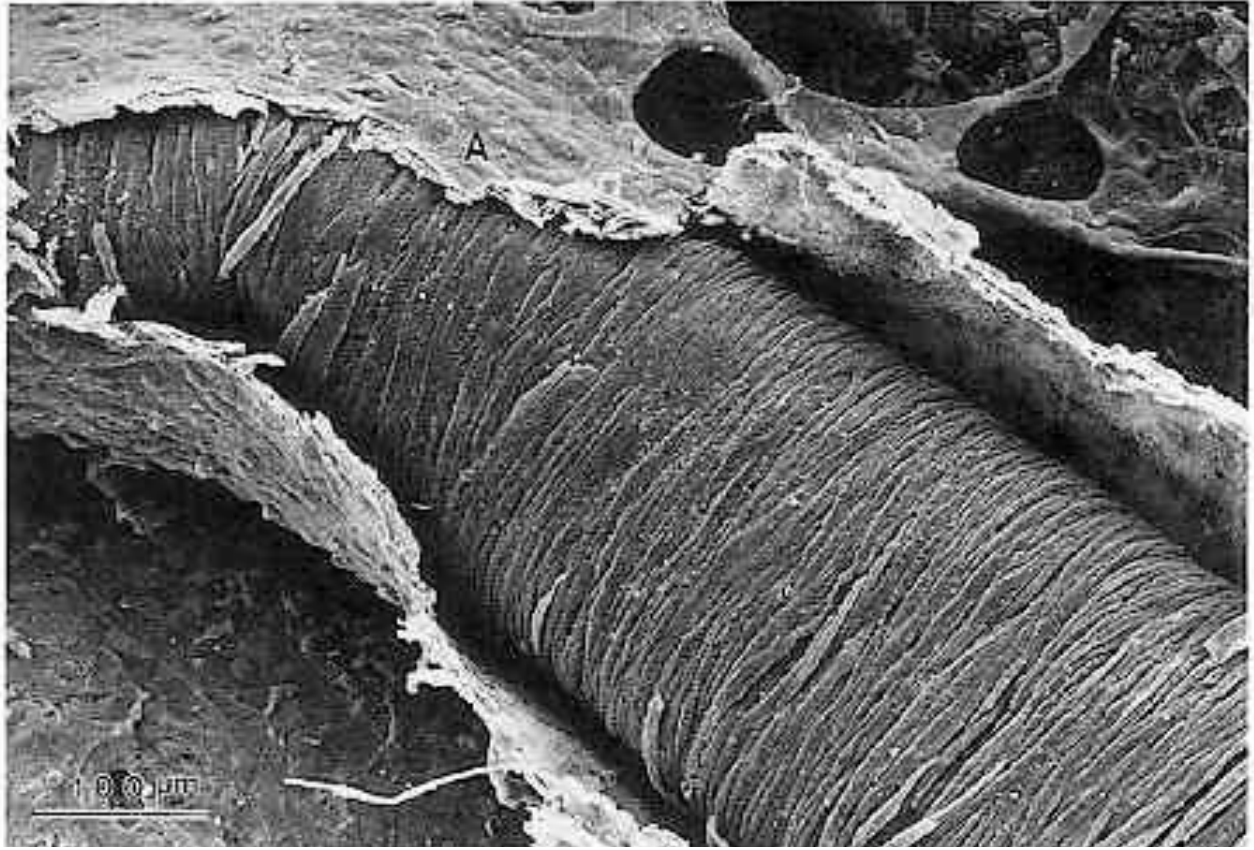


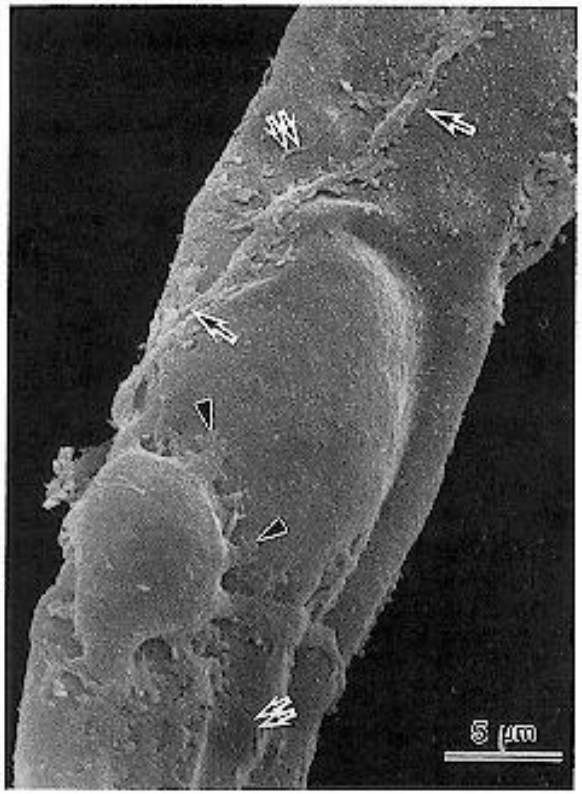


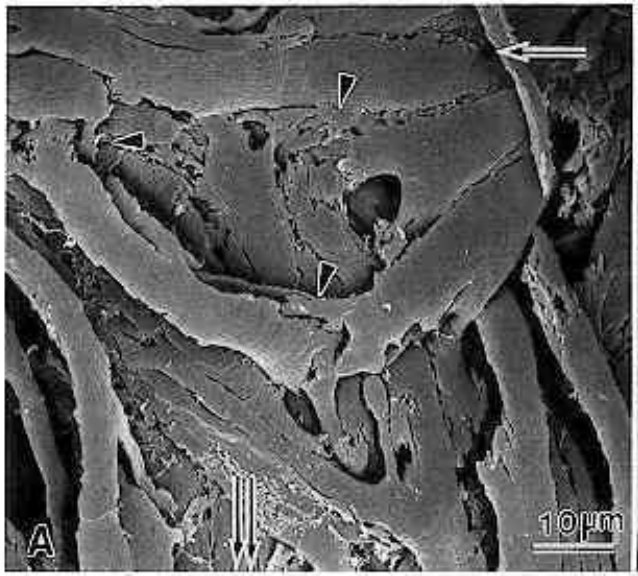


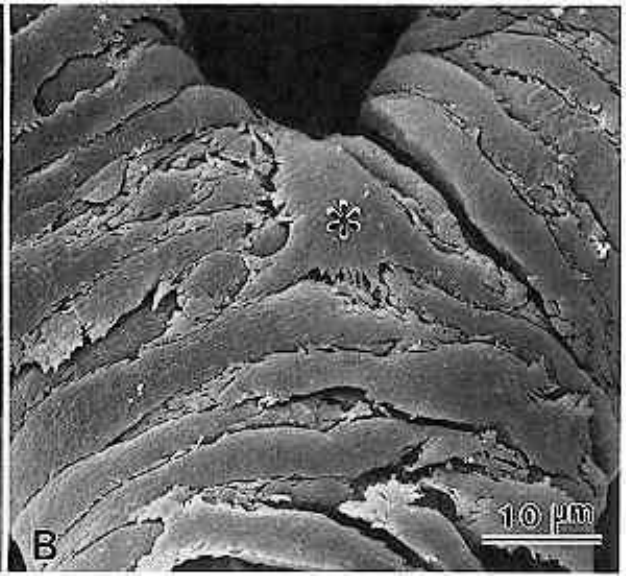
David E. Sims: “The Pericyte-A Review”. *Tissue & Cell*,18,153-174, 1986.

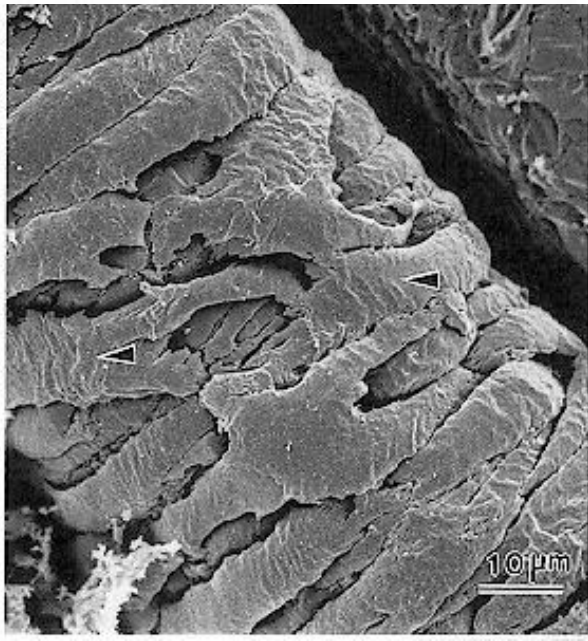


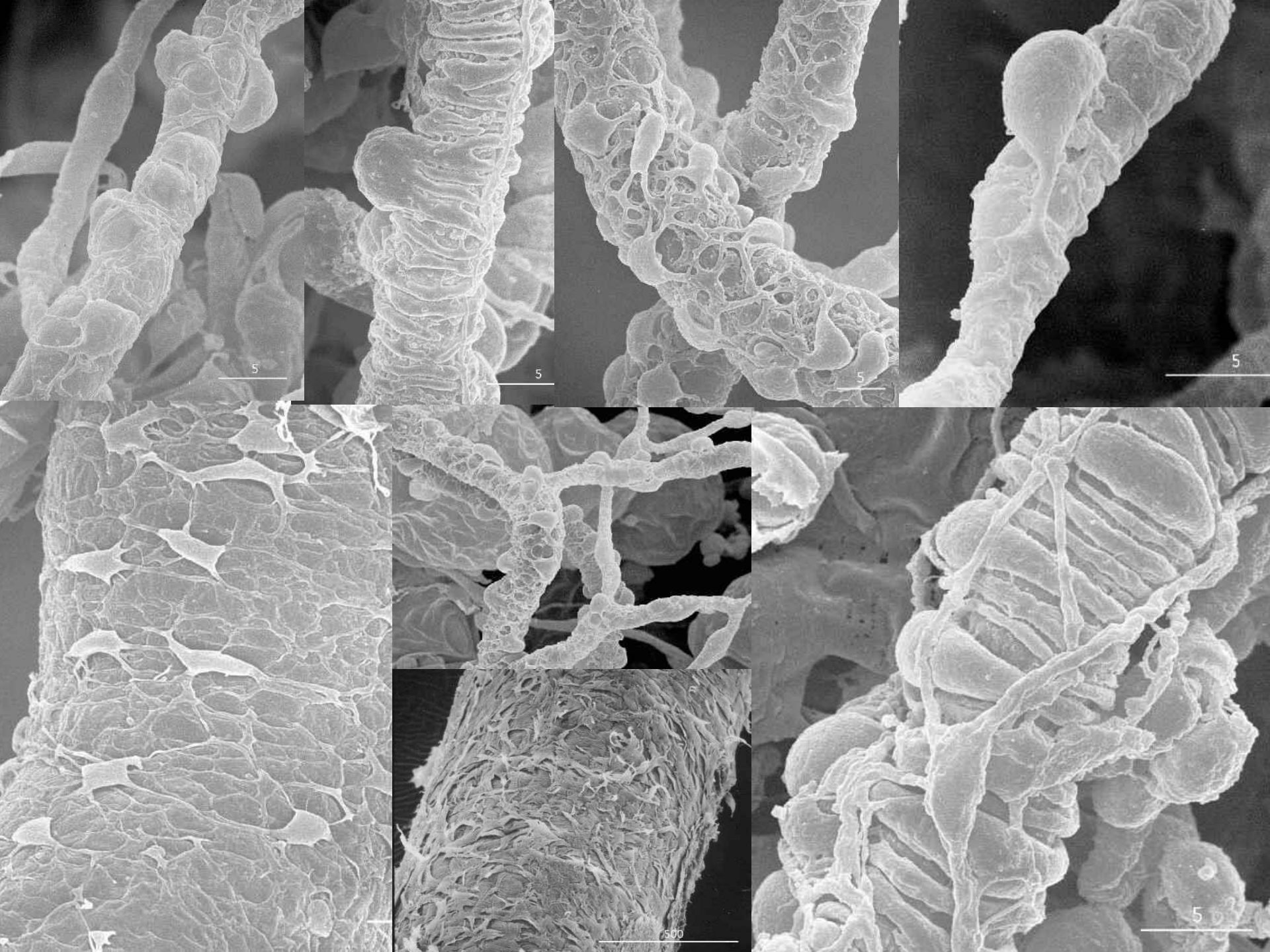

A
100 µm


5 µm

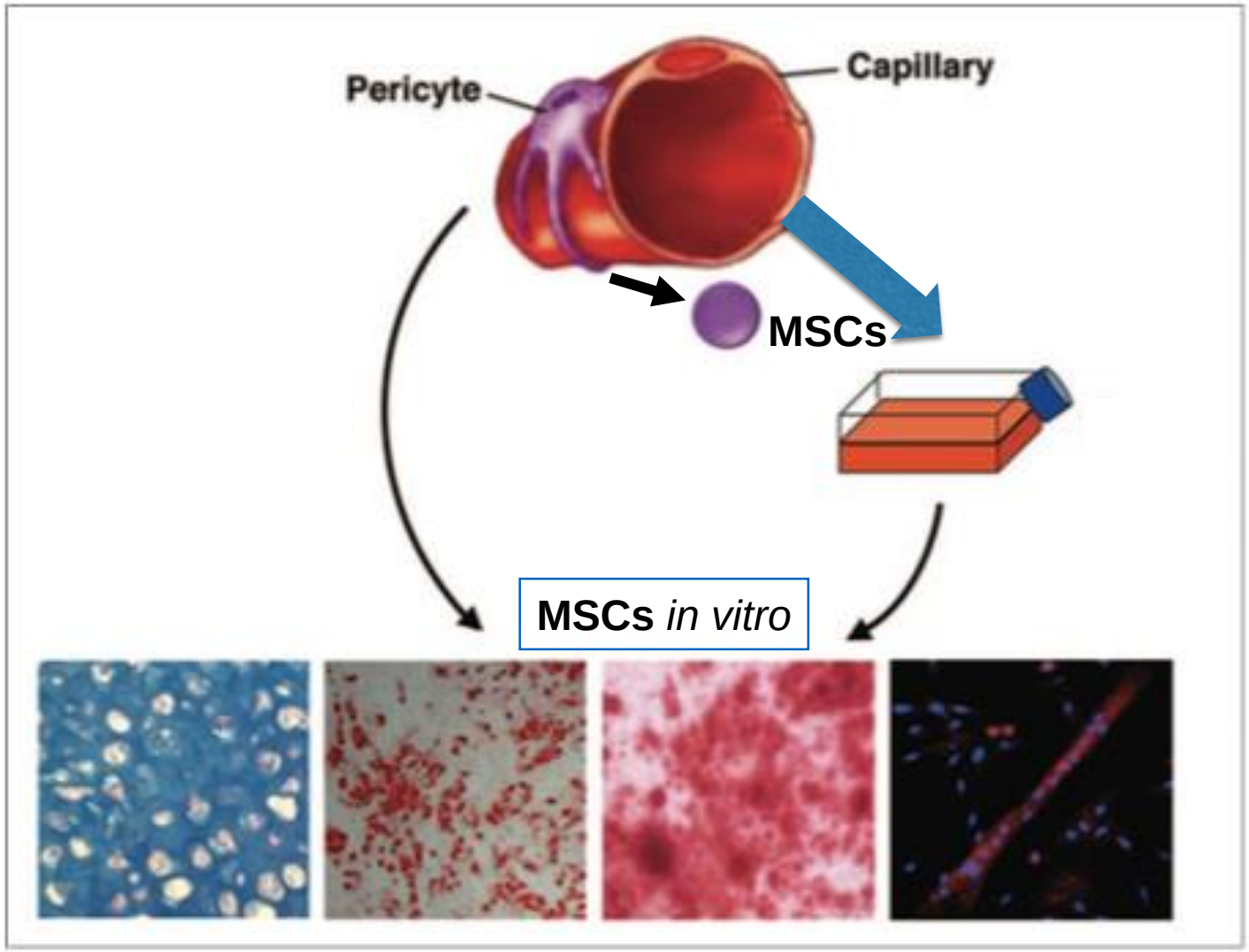

A
10µm


B
10 µm


10µm


5
5
5
5
500
5

MSCs *in vitro* **are multi-potent but NOT** *in vivo*

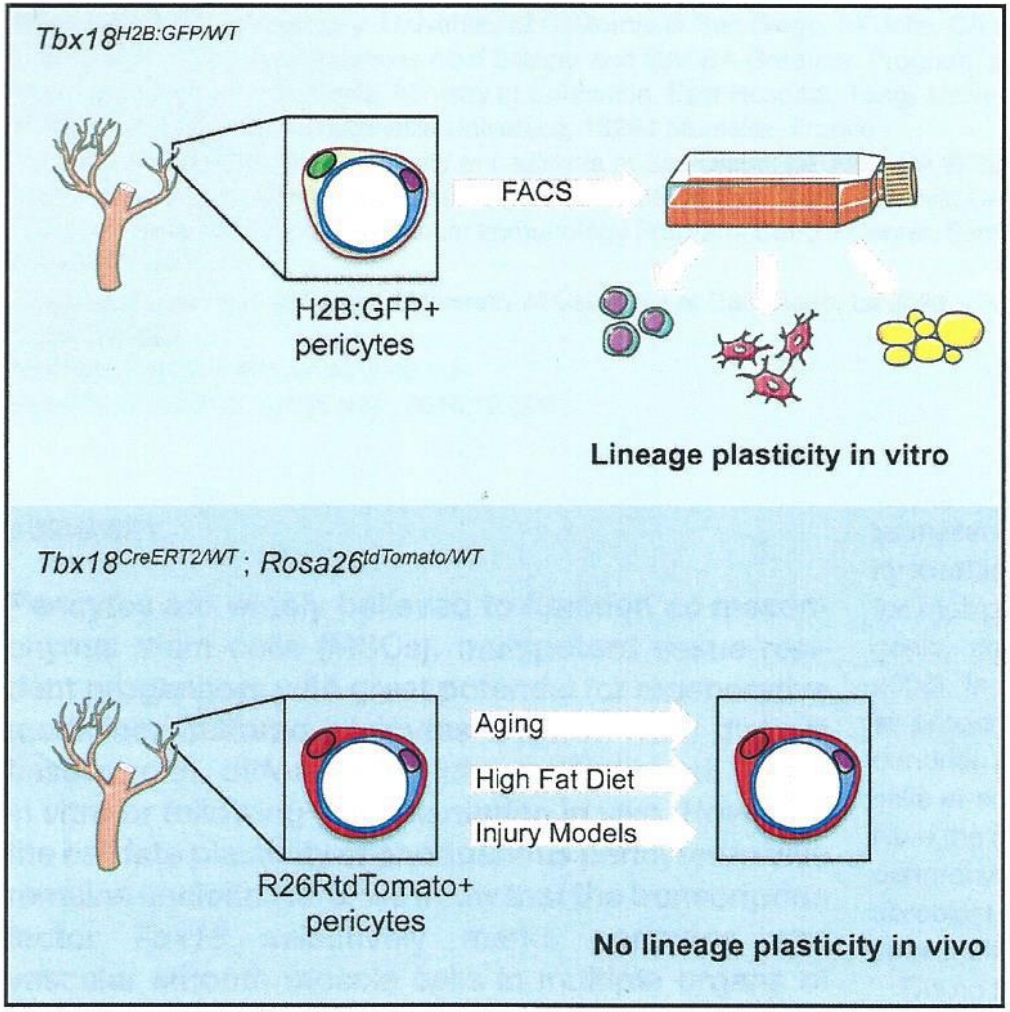


Corselli et al, 2011

Cell Stem Cell, 20, 1-15 (2017)

Pericytes of Multiple Organs Do Not Behave as Mesenchymal Stem Cells In Vivo

Graphical Abstract



Authors

Nuno Guimarães-Camboa, Paola Cattaneo, Yunfu Sun, ..., William B. Stallcup, Ju Chen, Sylvia M. Evans

Correspondence

syevans@ucsd.edu

In Brief

Guimarães-Camboa et al. permanently labeled pericytes and vascular smooth muscle of multiple organs in vivo and followed the fate of these cells in aging and injury models. Their analyses showed that, in vivo, pericytes did not behave as stem cells, challenging the current view of pericytes as tissue-resident multipotent progenitors.

MSCs can be derived from multiple tissue sources

- Aorta
- Adipose
- Amniotic fluid
- Bone marrow
- Blood
- Brain
- Cartilage
- Cord blood
- Dental pulp
- Endometrium
- Eye
- Gut
- Heart
- Kidney
- Liver
- Lung
- Muscle
- Pancreas
- Perichondrium
- Periodontal ligament
- Placenta
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- Skin
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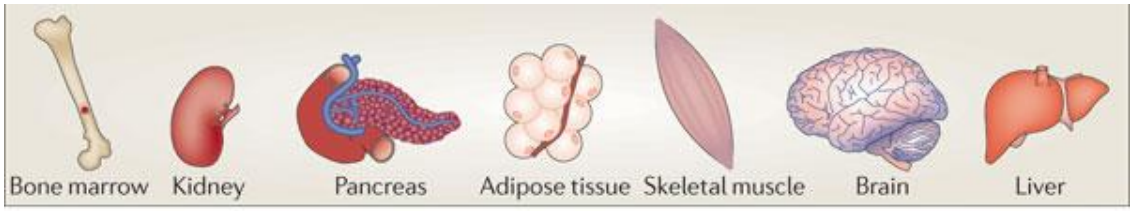
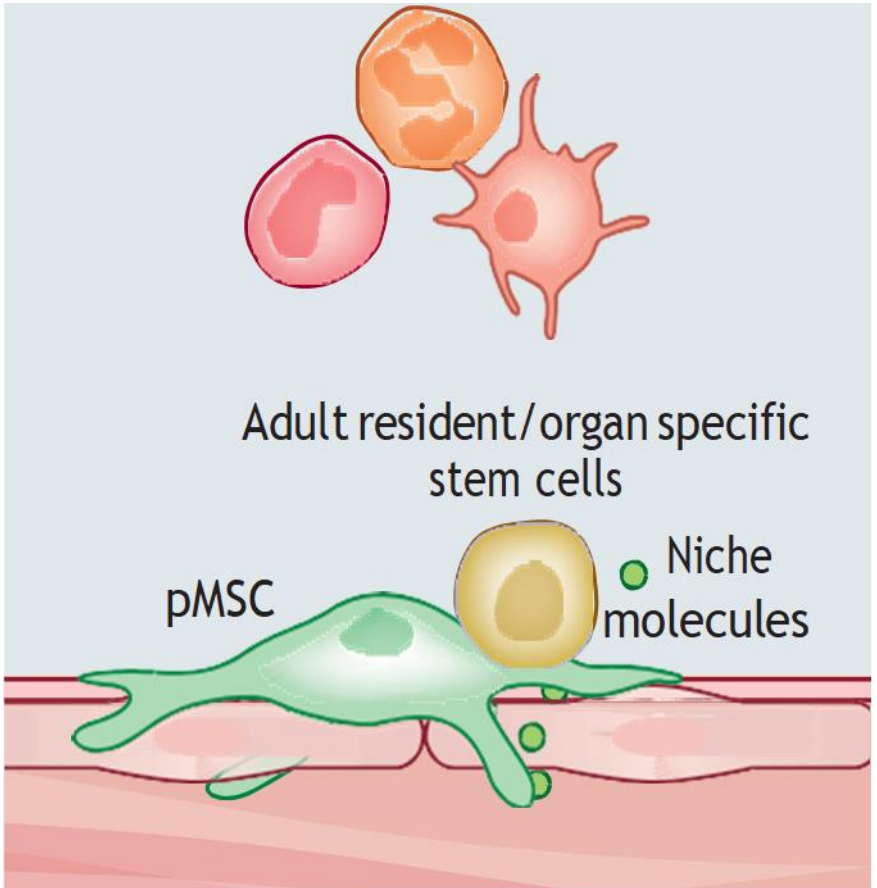
- Synovial membrane
- Tendon
- Thymus
- Umbilical cord
- Vein

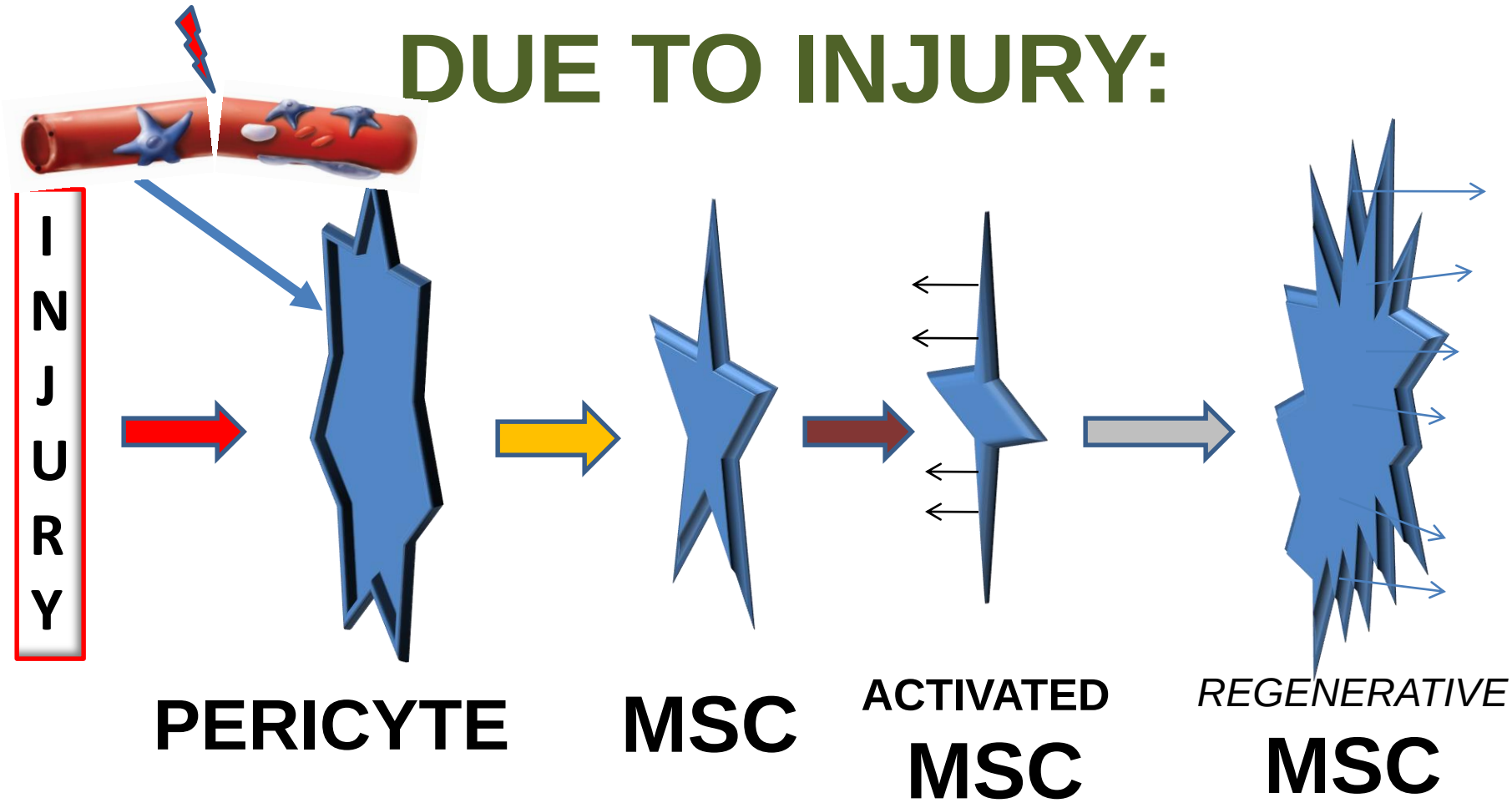


The Universal Stem Cell Niche



2019

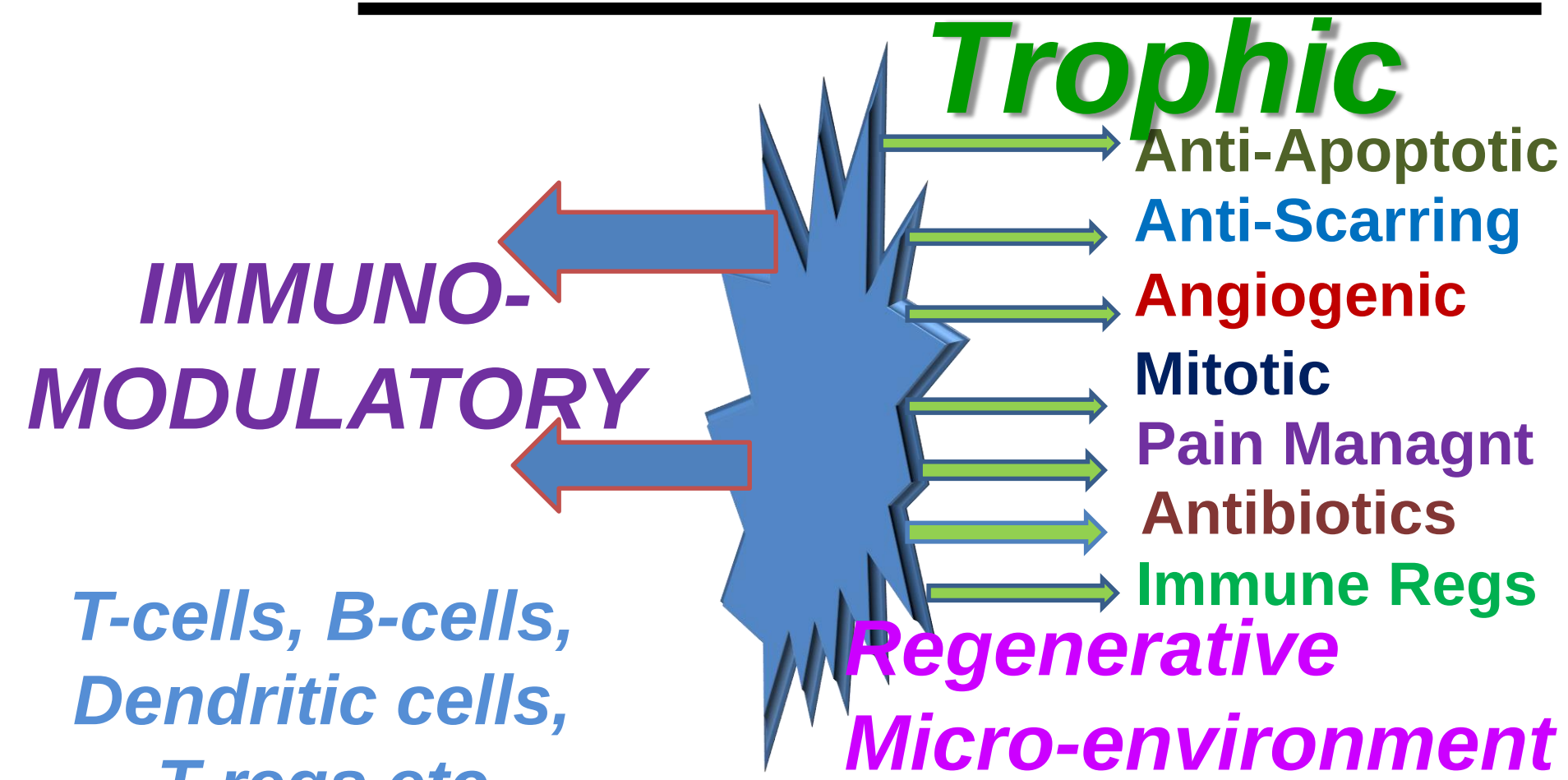
PROPOSED SEQUENCE OF CHANGE DUE TO INJURY:



AI Caplan. MSCs as Therapeutics. In: *Stem Cell Biology and Regenerative Medicine. Mesenchymal Stromal Cells: Biology and Clinical Applications, Stem Cell Biology and Regenerative Medicine*. P. Hematti and A. Keating (Eds.), Springer Science+Business Media New York, Chapter 5. Pp.79-90, **2012**.

2019

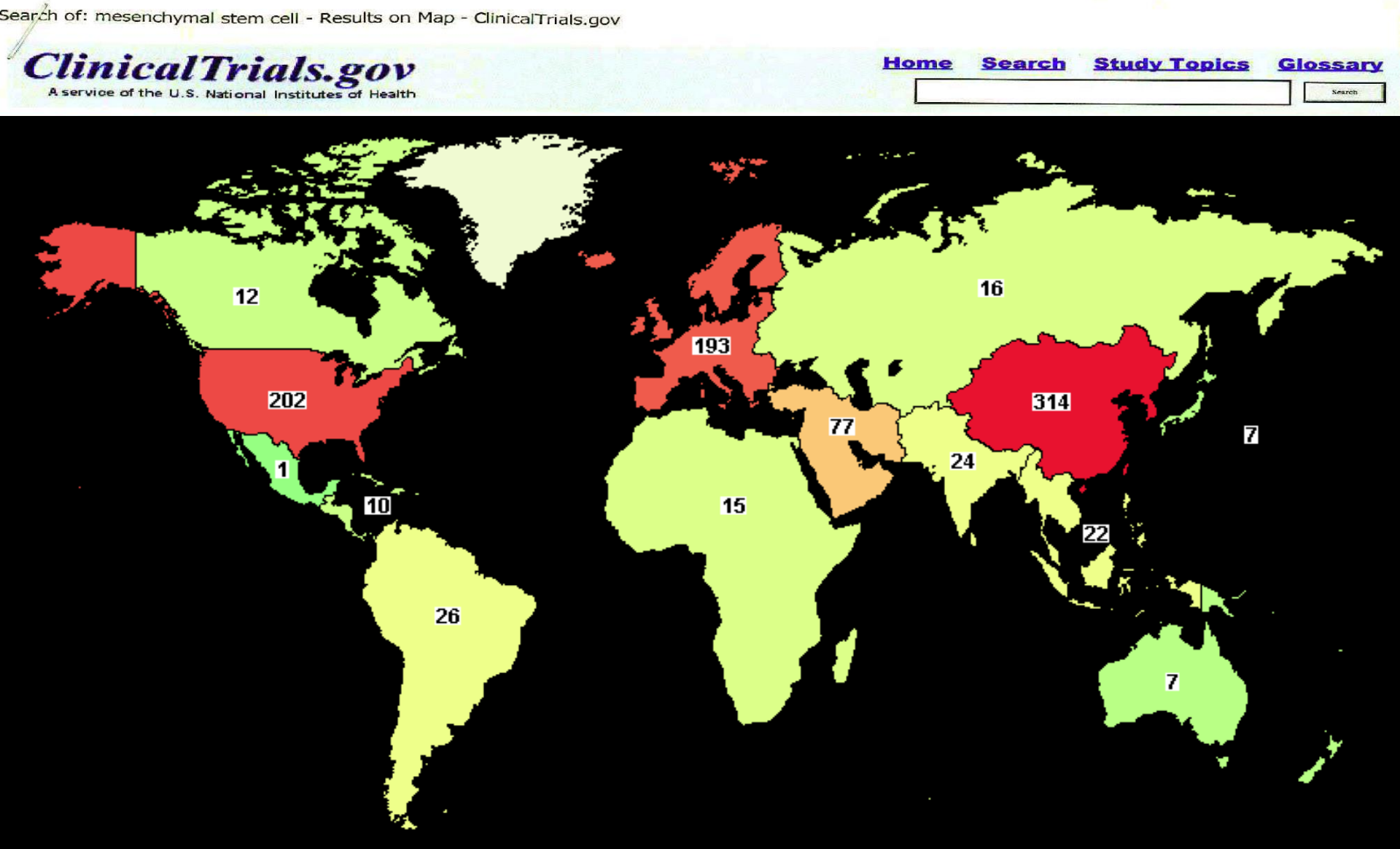
natural INJURY RESPONSE



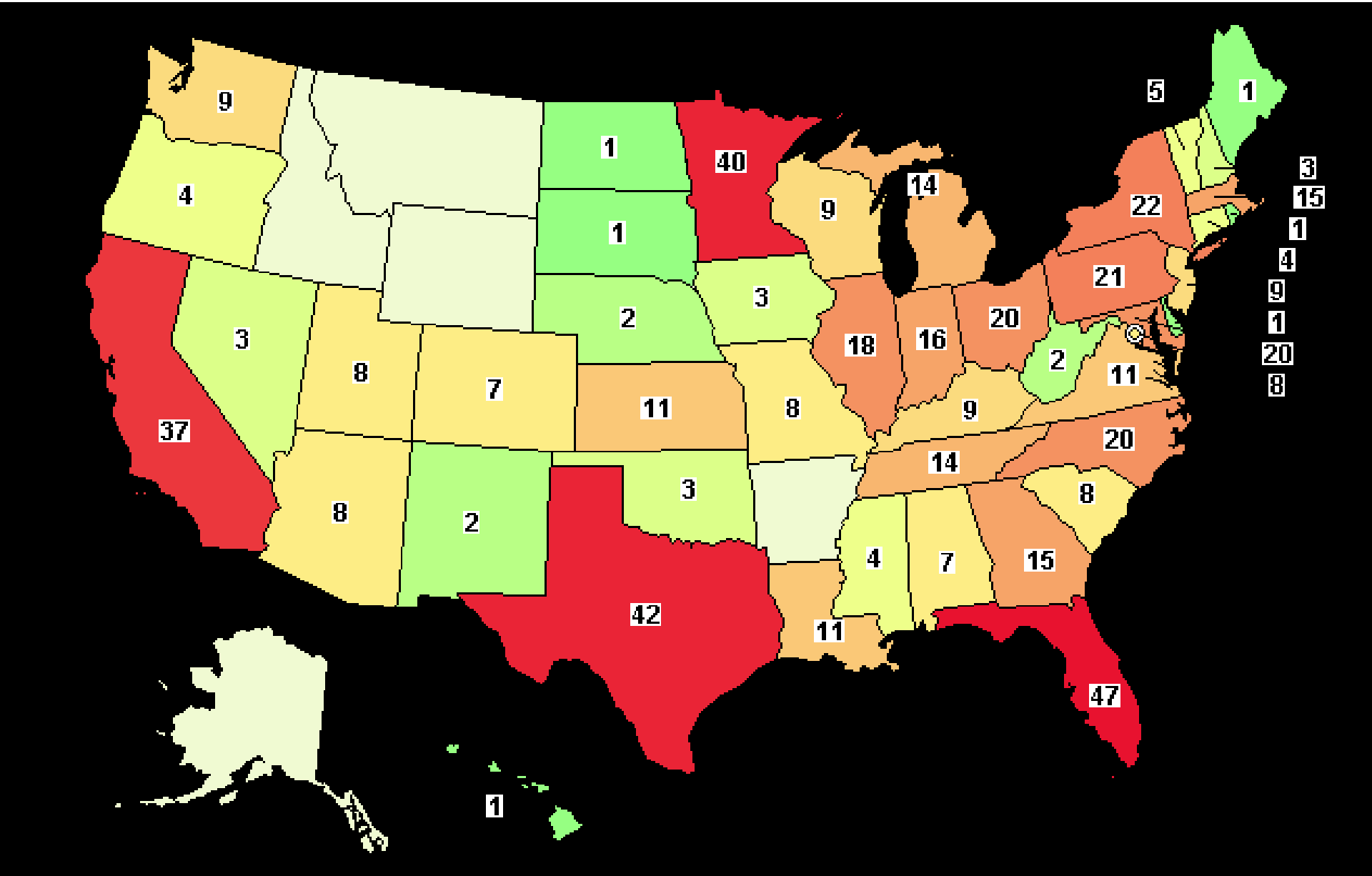
MSC=*pericyte*

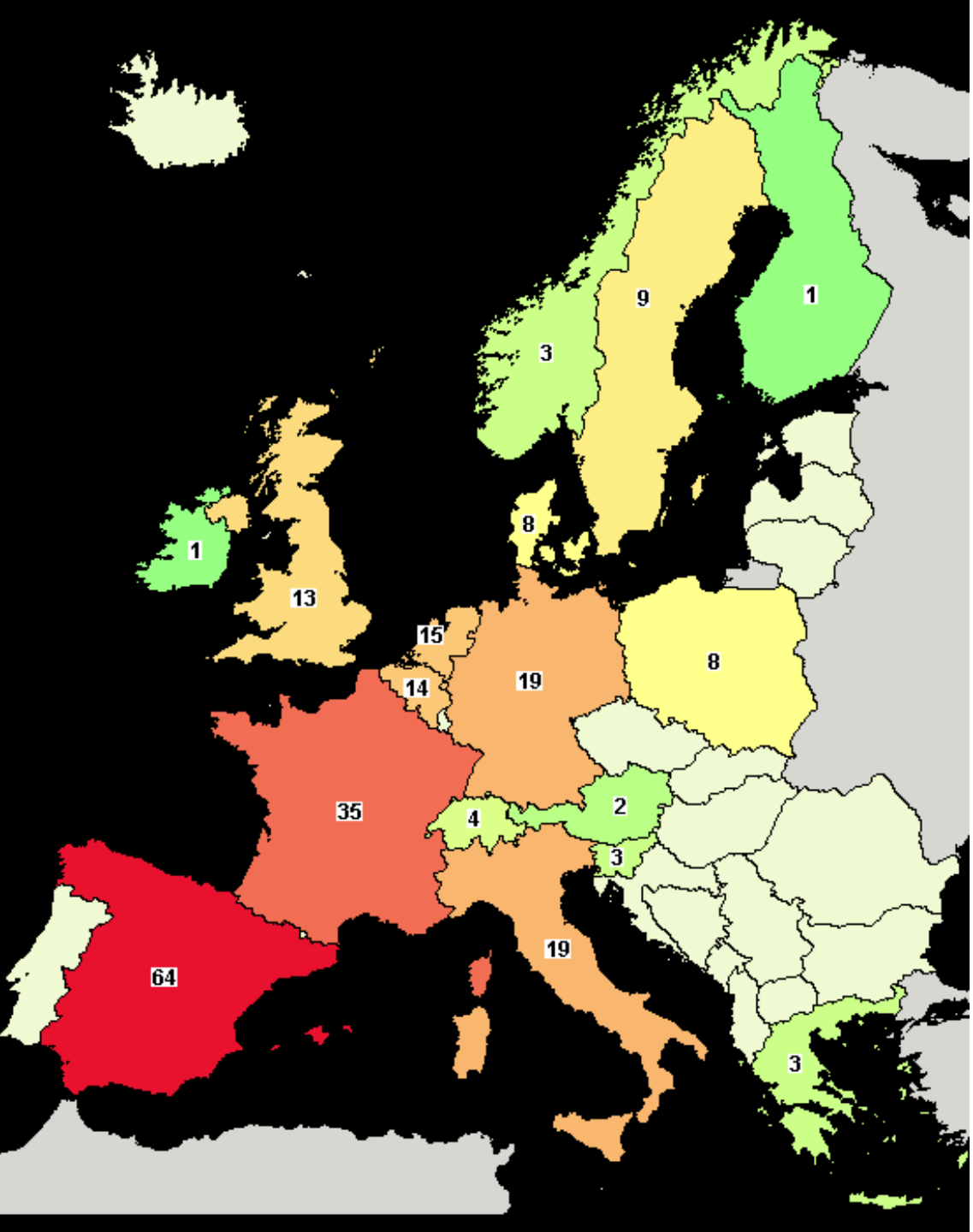
1004 MSC-CLINICAL TRIALS, 10-2019:

~380 are active



202 USA: *clinicaltrials.gov* 10-2019





193 EUROPE MSC-CLINICAL TRIALS, 10-2019

CLINICALTRIALS.GOV

10-2019. Found 1,004+ studies with search of: Mesenchymal Stem Cells:

Clinical Conditions for MSC-therapy: ~45% autologous.

Ulcerative C… …ion Fractures, Diabetic F… …hemia, Dilated Cardiomyopathy, Autoimmun… …eases; Nervous System … …ng Autoimmune Diseases, CNS; Autoimmun… …e, Graft Versus Host Dise… …anded 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 Sclero… …5, Chron… …Optica, Prima… …ase, 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 Sclero… …2 Diabetes Mellitus, Refractory Systemic Lupus Erythematos… …locytic, Chronic; Myeloproliferative Disorders; Myelodyspla… …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… …eudo-arthrosis, Recovery Following Partial Medial Menisce… …Multivessel Coronary Artery Disease, Osteogenesis Imperfect… …stula, 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.

Crohn's Disease

GvHD

MS, ALS, other nervous system diseases

Kidney Transplantation

AMI,Chronic Heart Failure

Rheumatoid Arthritis, Lupus, Autism

MSCs are NOT stomal cells:

- **Stroma is a generic term for connective tissue found in and around almost all organs and tissues.**
- **MSCs are found as perivascular cells and, even in large vessels ,in the adventitia but, again, not in the generic connective tissue.**
- **To best understand the native, functional properties of MSCs, think PERICYTES.**

The management of the Body's Innate Regenerative Potential.

Not a STEM CELL

MSC =

Medicinal Signaling Cell.

(the injury-specific DRUG STORE)

Al Caplan. What's in a name? Tiss Eng, Part A, 16: 2415-2417, 2010

MSC- based Therapies:

MSCs dock at sites of broken or inflamed blood vessels.

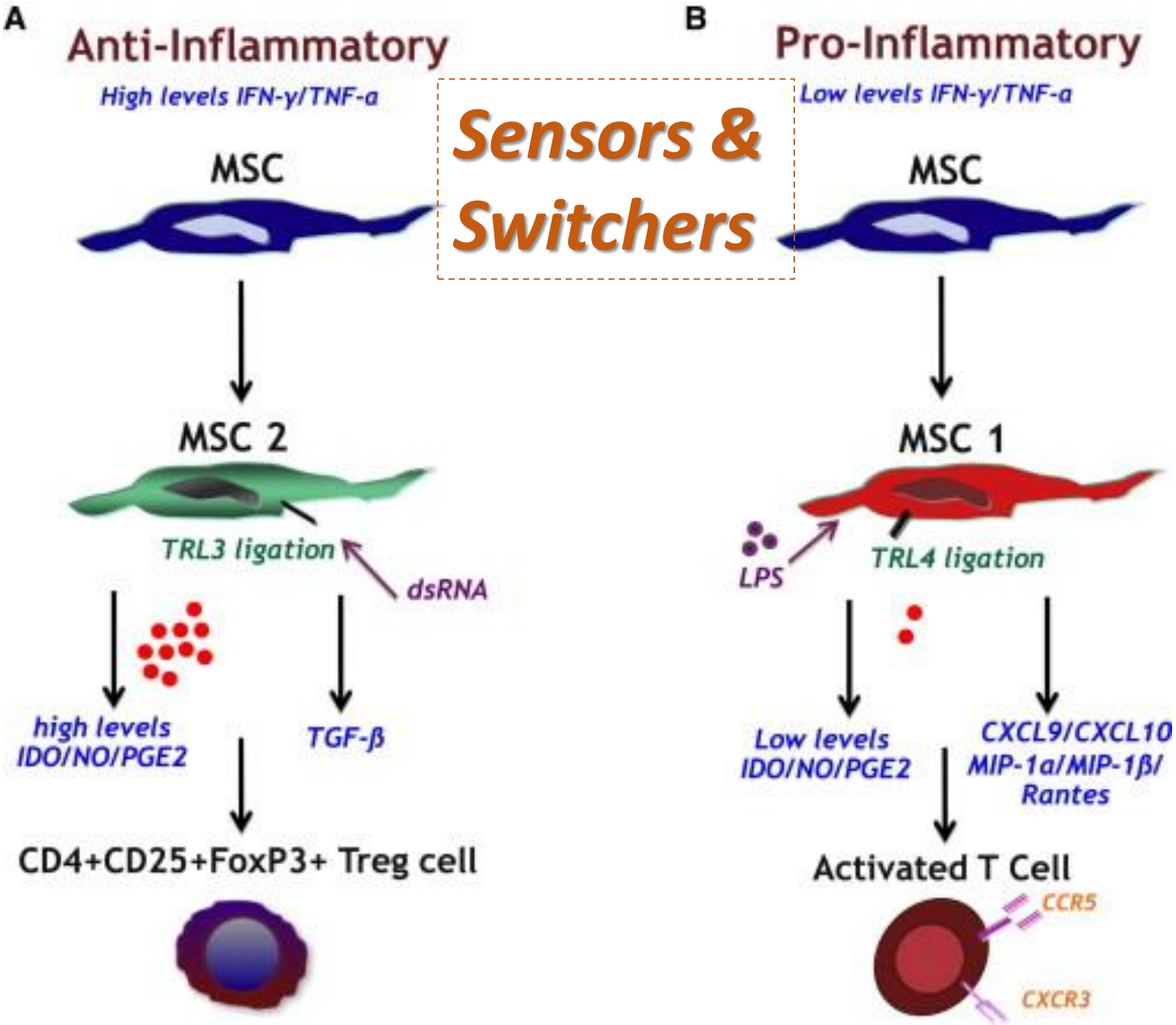
MSC-action: An Immuno-component.

A Regenerative component.

Management of the body's innate regenerative capacity.

CELLS(MSCs) are multi-factorial SITE-Specific **SENSORS** with genetically wired molecular RESPONSES.

MSC-***Cell Therapy*** *works everywhere in the body.*



Sensors & Switchers

M. E. Bernardo[1], W. E. Fibbe; Mesenchymal Stromal Cells: Sensors and Switchers of Inflammation. **Cell Stem Cell** ,13,392-402(2013)

bump into object = blood vessels break = hurt = hurt goes away =

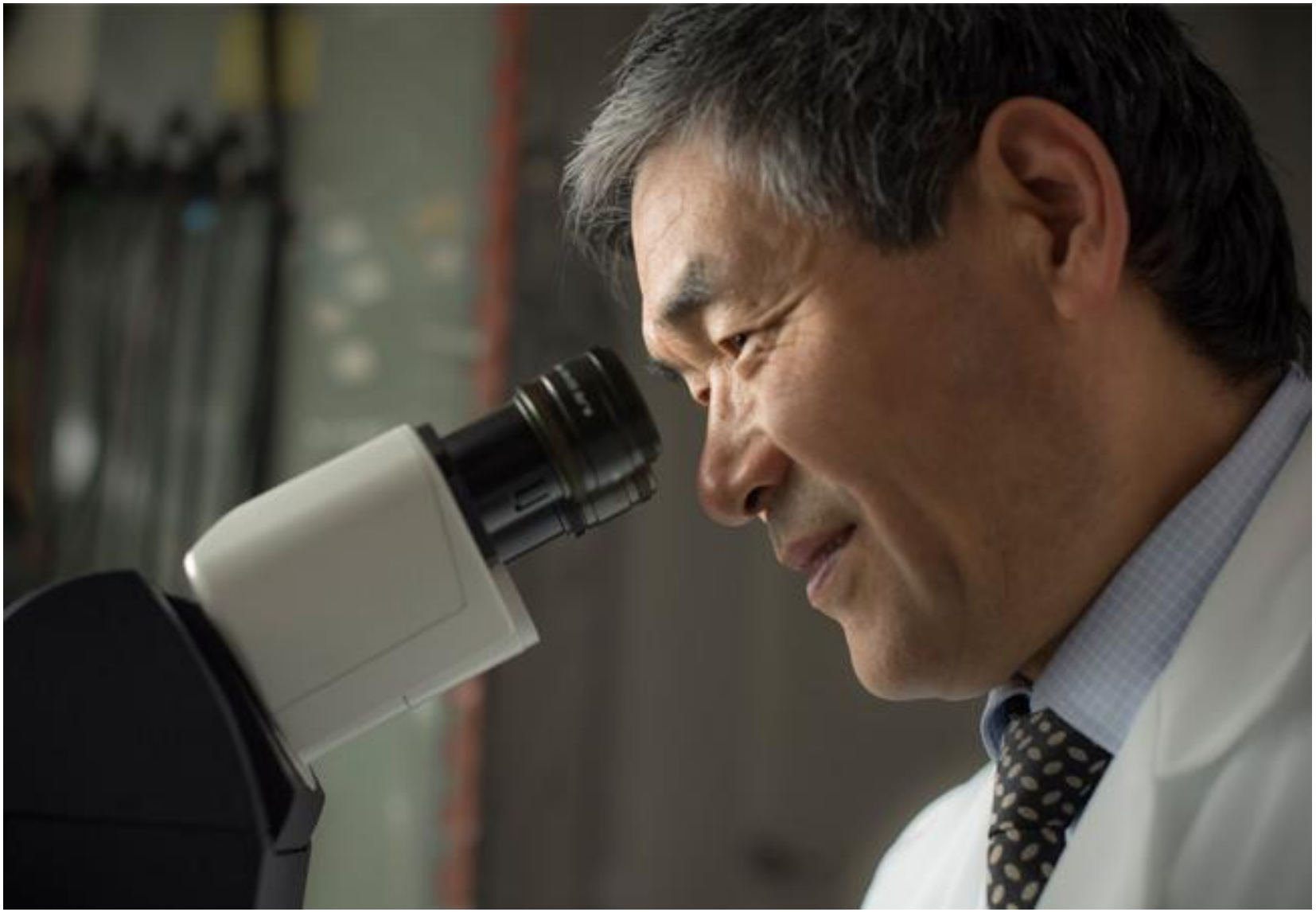
BLACK-and-BLUE MARK

Break a blood vessel, release MSCs.

MSC Therapy for Neuropathic Pain

- Animal studies have demonstrated the effectiveness of mesenchymal stem cells (**MSCs**) transplantation in reducing hyperalgesia due to nerve injury. MSC transplantation is effective in reducing pain induced by sciatic nerve injury in rats and mice and significantly reduced pain sensitivity evaluated by foot withdrawal thresholds in animals in response to thermal or mechanical stimulation. The MSCs produced immune modulatory and anti-inflammatory effects, promoted sensory nerve repair, and showed strong analgesic properties that could provide a treatment in the management of neuropathic pain.
- A comparison of the analgesic effects of MSCs-derived from **bone marrow** with MSCs-derived from adipose tissue showed that a**dipose-derived** MSCs were as efficacious as bone marrow-derived cells in reducing neuropathic pain in rats.

Zhen Hua *et al*, Scientific Reports | 6:32096 | DOI: 10.1038/srep32096/24 August **2016**



Jianguo Cheng, MD, PhD

Professor of Anesthesiology and Director of the **Cleveland Clinic Foundation**
Multidisciplinary Pain Medicine Fellowship Program

Annual Meeting of the American Academy of Pain Medicine.

Director of Communications American Academy of Pain Medicine

Cleveland Clinic Researchers First to Demonstrate Significant Blocking of Opioid Tolerance With Mesenchymal Stem Cell Transplant

March 19, 2015, NATIONAL HARBOR, Md. – Mesenchymal stem cell (MSC) transplantation reduced opioid tolerance and opioid-induced hyperalgesia caused by daily morphine injections in rats, according to new research. The results could herald stem cell transplantation as an innovative, safe, efficacious and cost-effective therapy to treat pain and opioid tolerance, said researchers, who presented results today in a Plenary Research Highlight session at the 31st

Not only was opioid tolerance prevented when the rats were transplanted with hMSC before repeated morphine injections, but tolerance was reversed when the rats were treated after opioid tolerance had developed, results demonstrated:

"MSCs have a remarkable anti-inflammatory effect and a powerful anti-tolerance effect," said the study's principal investigator, **Jianguo Cheng, M.D., Ph.D.**, who led the research team from the Cleveland Clinic, in Ohio. "The results may apply to millions of patients with a wide range of pain states, including cancer pain and other intractable chronic pain that requires long-term opioid therapy."

Published: F. Li, L. Liu, K. Cheng, Z. Chen and **J. Cheng: The Use of Stem Cell Therapy to Reverse Opioid Tolerance. CLIN PHARMAC & THERAPE,2017**

Bone Marrow Stromal Cells Produce Long-Term Pain Relief in Rat Models of Persistent Pain.

W.Guo *et a*l, *Stem Cells.29*:1294–1303,2011.

- A single systemic (intravenous) or local injection (into the lesion site) of rat primary BMSCs reversed pain hypersensitivity in rats after injury and that the effect lasted until the conclusion of the study at 22 weeks.
- The pain hypersensitivity was rekindled by naloxone hydrochloride, an opioid receptor antagonist that acts peripherally and centrally, when tested at 1–5 weeks after BMSC infusion.
- In contrast, naloxone methiodide, a peripherally acting opioid receptor antagonist, only rekindled hyperalgesia in the first 3 weeks of BMSC treatment.
- Focal downregulation of brainstem mu opioid receptors by RNA interference (RNAi) reversed the effect of BMSCs, when RNAi was introduced at 5- but not 1-week after BMSC transplantation.
- Thus, BMSCs produced long-term pain relief ;this effect involved activation of peripheral and central opioid receptors in distinct time domains.
- **The early effect of BMSCs on mechanical hypersensitivity mainly involved peripheral opioids and the late effect of BMSCs depended on activation of opioids in brainstem descending pathways.**

A Preliminary Reort on STEM CELL THERAPY FOR NEUROPATHIC PAIN in Humans.

ER Vickers, E Karsten, J Flood, R Lilischkis. J Pain Res.,7, 255-263(2014)

- **10 female patients (27-80) with neuropathic trigeminal pain**
- **Tooth extraction, Idiopathic, dental work, etc.**

  Diagnosis= Atypical Odontalgia;4m to 5yrs.
- **Liposuction(100-2000g) from the bilateral lumbar region to yield SVF containing MSCs (3-5 injections;4-8ml total).**
- **SVF viability** 62-91%;**CD90=**45%;**CD31=**16%;**CD45=**45%±7%.
- **Injections directly in the pain field and adjacent branches of the trigeminal nerve (0,1wk,1,3, 6m pain scores follow-up).**
- **Pain scores go from 9 to 1 for 7responders out of 9 with 5 patients reducing gabapentin.**

Intrathecal administration of autologous bone marrow MSCs improves neuropathic pain, NP, in patients with spinal cord injury, SCI.

J. Vaquero et al, Neuroscience Letters, 670: 14–18(2018)

Intrathecal bone marrow MSCs inhibit neuropathic pain via TGF-β secretion.

G. Chen et al, J Clin Invest.;125:3226-3240(2015)

Interleukin-1β pre-treated marrow MSCs alleviate neuropathic pain through CCL7-mediated inhibition of microglial activation in the spinal cord.

J.Li et al, Scientific Reports 7:42260(2017)

PAIN MANAGEMENT:

- **MSCs control or affect pain by their paracrine capacity.**
- **MSCs are effective in the central and peripheral nervous system:** reducing inflammation and enhancing regenerative activity.
- Bump into a wall=black/blue + short-lived pain=MSCs
- **Pain management by MSCs involves molecules that occupy opioid receptors and thru other molecular mediators.**

MSC- based Therapies:

MSCs dock at sites of broken or inflamed blood vessels.

MSC-action: An immuno-component.

A Regenerative component.

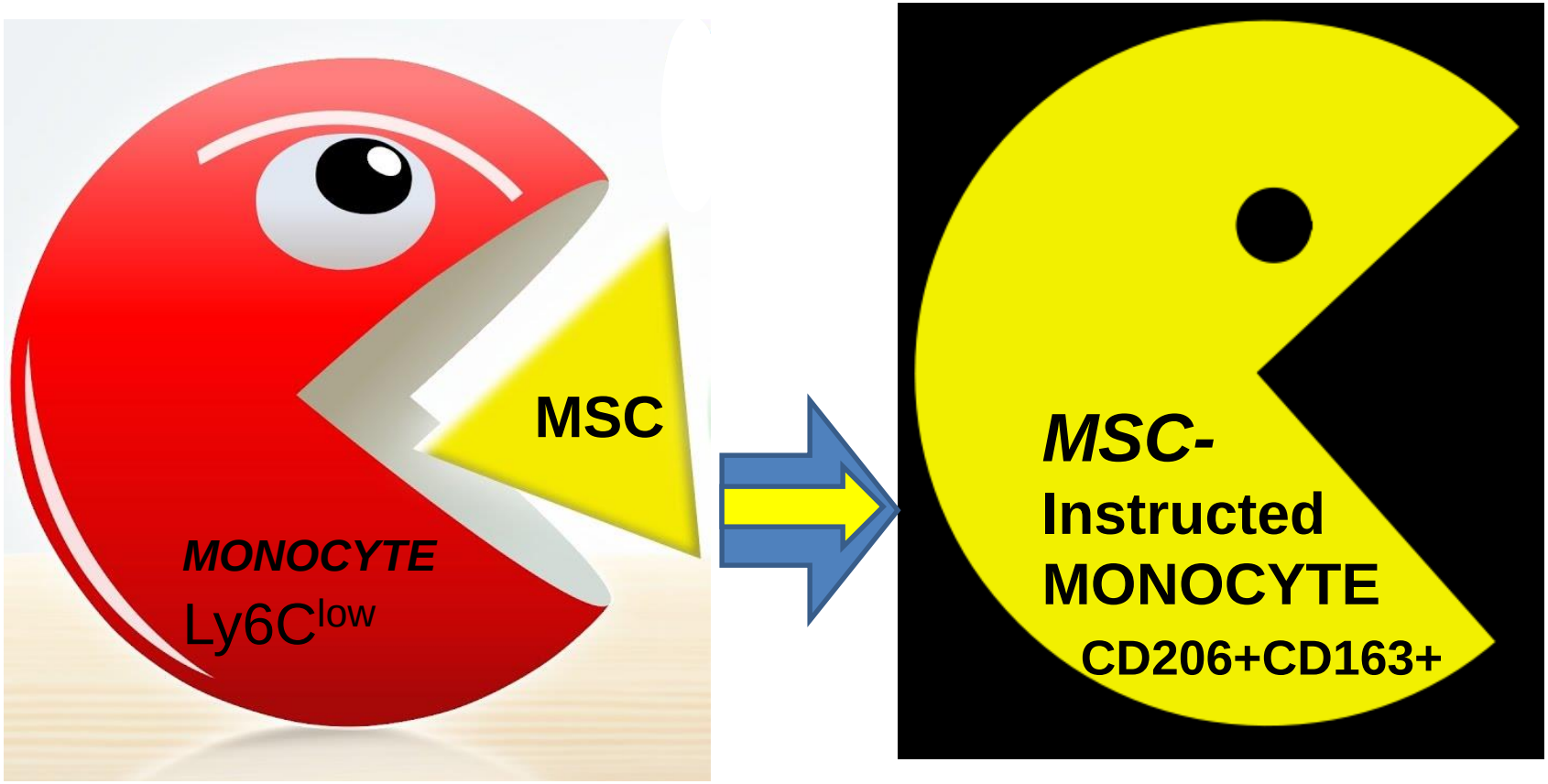
Management of the body's innate regenerative capacity.

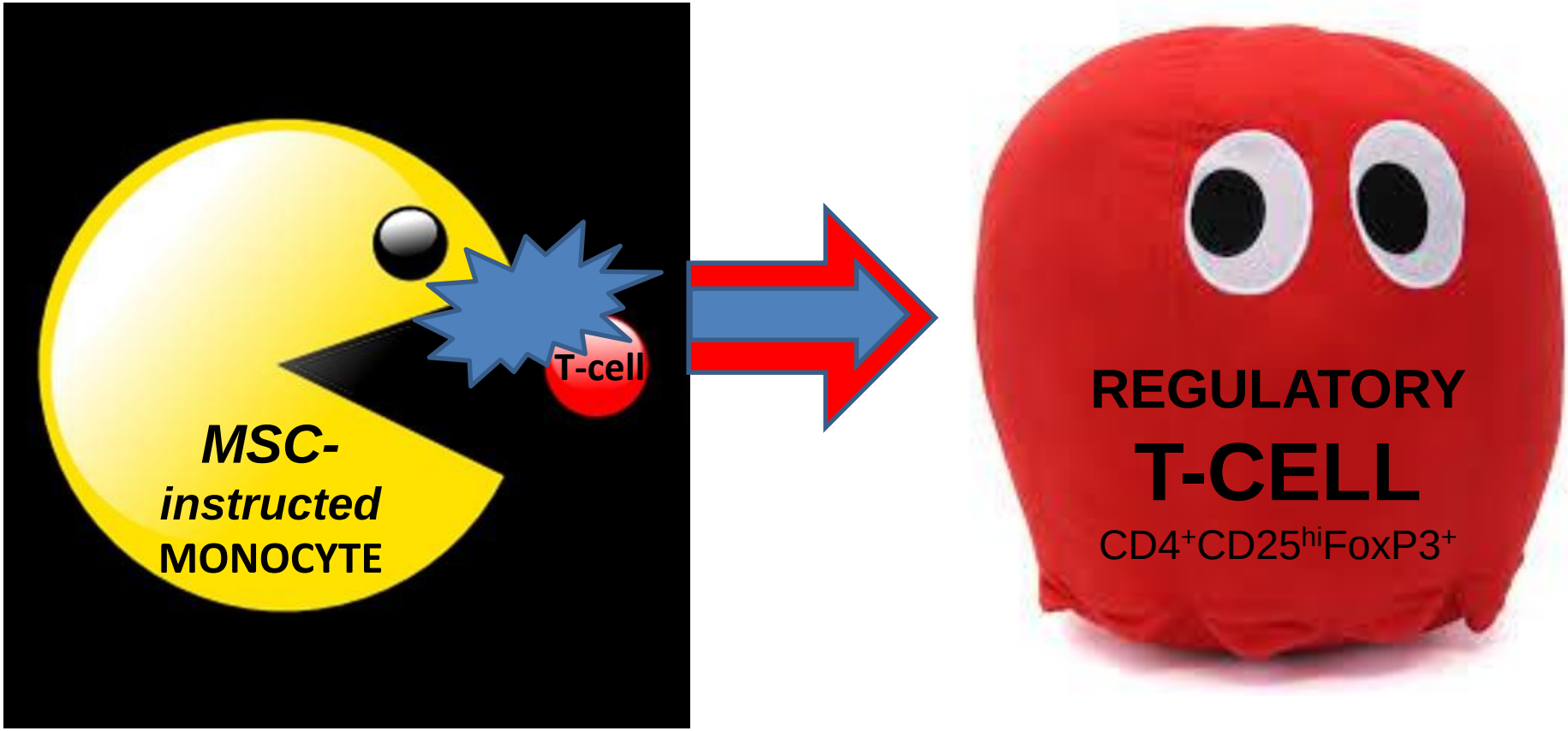
LONGTERM THERAPUETIC EFFECTS???

Immunomodulation by hMSCs is triggered by phagocytosis of the hMSCs by MONOCYTIC CELLS.

S. de Witte *et al* , Stem Cells, 2018

- Infused human umbilical cord MSCs into mice disappear within 24hrs and their remnants are found in Ly6C^{low} monocytes found in the lungs and circulation.
- These **monocytes** upregulate CD206 after phagocytosing ucMSCs to become CD206^{+}CD163^{+} which regulate the generation of CD4^{+}CD25^{hi}FoxP3^{+} T-cells (TREGS).
- **Phagocytosis of ucMSCs induces phenotypic and functional changes in monocytes, which subsequently modulates cells of the adaptive immune system. =*Exosome phagocytosis??***


MSC
MONOCYTE
Ly6C^low
MSC-
Instructed
MONOCYTE
CD206+CD163+


T-cell
MSC-
instructed
MONOCYTE
REGULATORY
T-CELL
CD4+CD25hiFoxP3+

Immunomodulation by hMSCs is triggered by phagocytosis of the hMSCs by MONOCYTIC CELLS.

S. de Witte *et al* , Stem Cells, 2018

- Infused human umbilical cord MSCs [illegible] disappear within 24hrs and th[illegible] found in Ly6C^{low} mon[illegible] lungs and circulatio[illegible]
- The[illegible] regulate CD206 after engulfing ucMSCs to become CD206^{+}CD163^{+} which regulate the generation of CD4^{+}CD25^{hi}FoxP3^{+} T-cells (TREGS).
- **Phagocytosis of ucMSCs induces phenotypic and functional changes in monocytes, which subsequently modulates cells of the adaptive immune system. =*Exosome phagocytosis??***

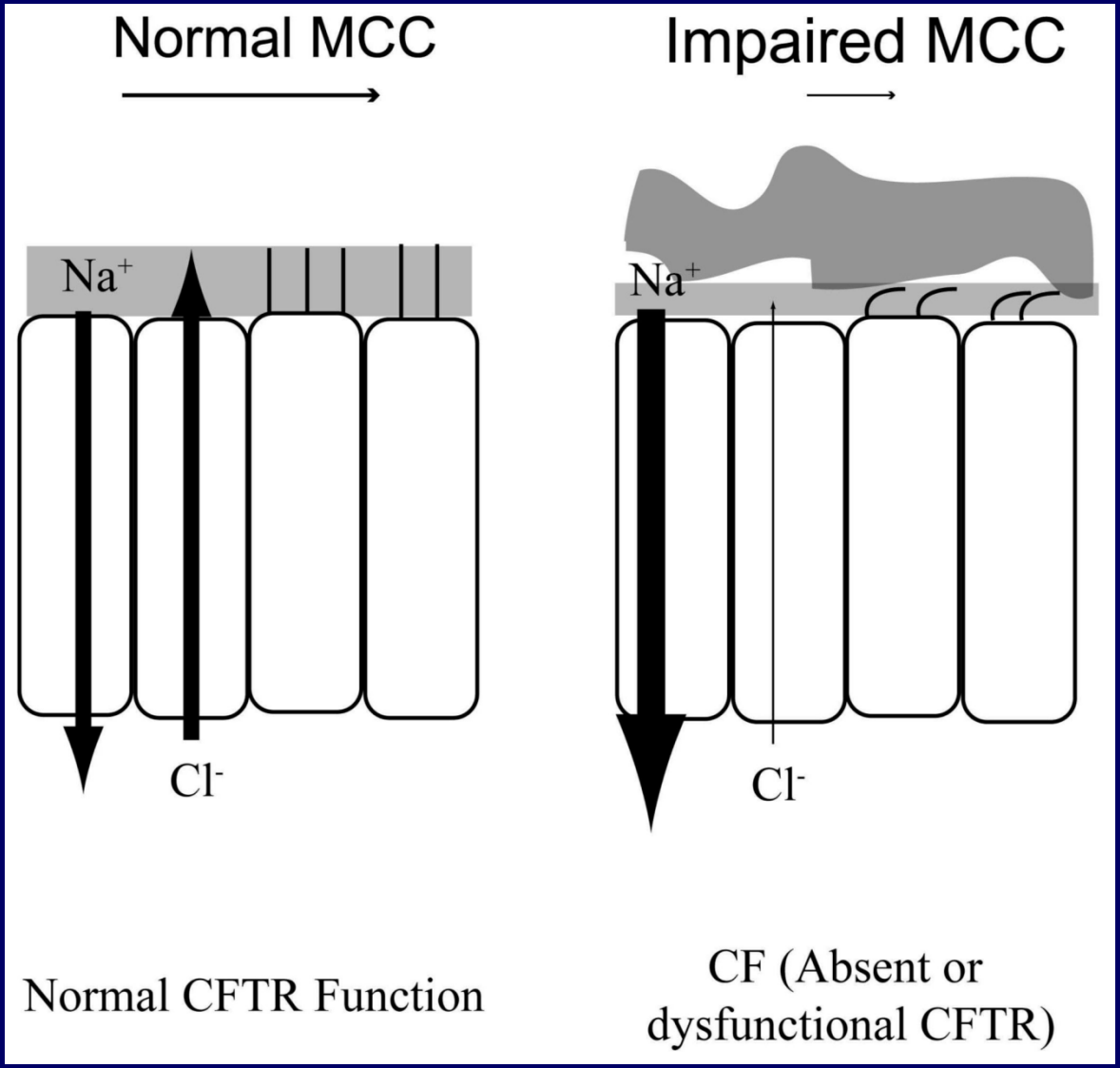
MSCs stay at the injury site for a short time. Long-term therapeutic outcomes are from secondary influences.

Tracey Bonfeild,PhD

Pediatric Pulmonary Dept, Rainbow Babies and Children's Hospital.

Cystic Fibrosis

- Known to be inherited in an autosomal recessive pattern, located on chromosome 7.
- Gene defect is in the cystic fibrosis transmembrane conductance regulator (CFTR).
- Mutations in the gene result in dysfunction of the epithelia resulting in inefficient sodium and chloride transport.



James L. Kreindler, Pharmacol Ther. 2010 ; 125(2): 219–229.

Cystic Fibrosis (CF)

- ***Lung*** **disease is the major cause of morbidity and mortality in CF.**
- **Airway inflammation plays a central role in the progression of CF lung disease.**
- **CF has been characterized as a perpetuating cycle involving airway obstruction, chronic bacterial infection and robust inflammatory response.**

Knock-out mCF Gene:

- **Wild type mice + *P. aeruginosa* = most alive at day 7.**
- **CF Knock-out + *P. aeruginosa* = *all dead by day 7.***
- ***CF Knock-out* + *P. aeruginosa* + (day 2) hMSCs = alive at day 7.**

Antibacterial Effects of hMSCs

Krasnodembskaya, et al. *Stem Cells*,28,2229-38 (2010)

- The human cathelicidin antimicrobial peptide, **hCAP-18/LL37** is secreted by hMSCs.
- In vivo hMSCs effect sepsis induced by bacterial infections.
- LL37 is in breast milk and it inhibits infections.
- *DEFENSINS*

DEFENSINS

ANIMALS LICK THEIR WOUNDS

QUESTIONS

- Why do women who have open bleeding uterine wounds not have monthly issues of sepsis???

- Can we regenerate fingers or toes??
- How does breast milk inhibit infections?
- Can we regenerate our broken spinal discs??
- Can we reverse the effects of my heart attack?
- Will my knee /hip need to be replaced??

CONCLUSION: **MSCs**

Welcome to LifeCell Femme India

where every month holds a miracle

Monthly Miracle

With the launch of an exclusive and revolutionary service, LifeCell Femme, you have the power now to prepare for a better tomorrow and whatever it may bring by acting on the promise of stem cell research. Thanks to Cryo-Cell's patent-pending technology and an easy-to-use collection kit you can have the reassurance and peace of mind you need, when it comes to collecting, processing and preserving menstrual blood stem cells.

Menstrual stem cell banking in city soon

THE PROCESS

These cells can be used to treat many conditions, including heart disease

Menstrual blood can save a life

research Syed Akbar

MONTHLY MIRACLE

Women can now take control of their future health by banking their menstrual blood stem cells in an affordable, painless and non-invasive manner

India's Most Promising Brands 2011

LifeCell International, has been honored the most prestigious award of **"India's Most Promising Brands 2011"** by 4Ps Business & Marketing & ICMR. Besides, being recognized as the Most Promising Brand, LifeCell was also shortlisted for the category of 'India's Most Popular Brands 2011' survey that make India Inc. Proud. This is a significant achievement for LifeCell since LifeCell

MSCs from Uterine blood flow:

Human Menstrual Blood-Derived Stem Cell Transplantation for Acute Hind Limb Ischemia Treatmentin Mouse Models Ngoc Bich Vu et al. *Regenerative Medicine: Using Non-Fetal Sources of Stem Cells*, 205 DOI 10.1007/978-1-4471-6542-2_20, © Springer-Verlag London 2015

Characterization of menstrual stem cells: angiogenic effect, migration and hematopoietic stem cell support in comparison with bone marrow mesenchymal stem cells

Alcayaga-Miranda et al. Stem Cell Research & Therapy (2015) 6:32

The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy.

Maroun Khoury et al Frontiers in Immunology,5,1-8,2014

Multi-site **MSC-based Therapies:**

MSCs dock at sites of broken or inflamed blood vessels.

MSC-action: An Immuno-component.

A Regenerative component.

Management of the body's innate regenerative capacity.

TROPHIC

CELL-PRODUCED, BIOACTIVE FACTOR-MEDIATED *REGENERATIVE MILIEU.*

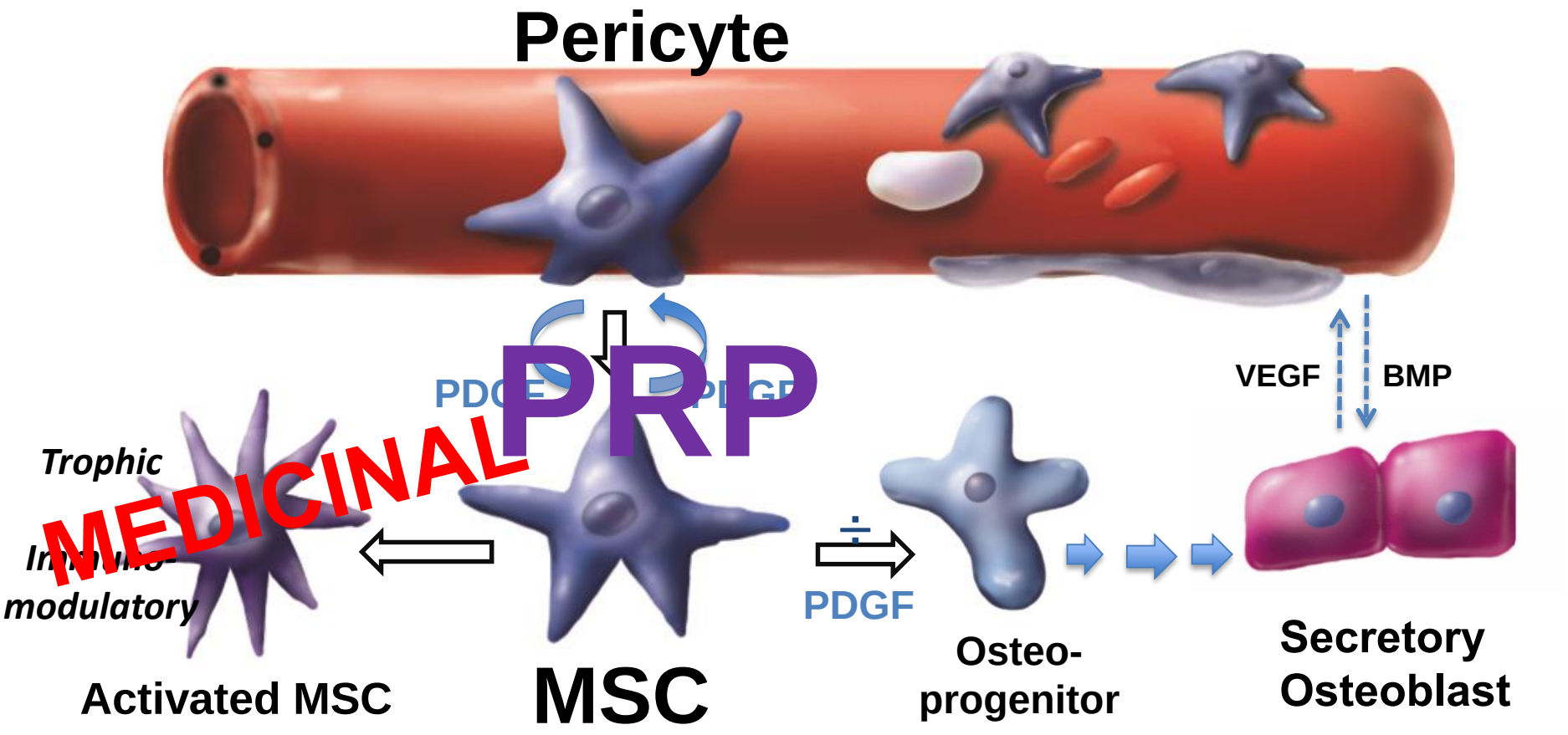
MSCs as site*-regulated *multi-drug delivery vehicles.

MSCs as DRUG STORES.

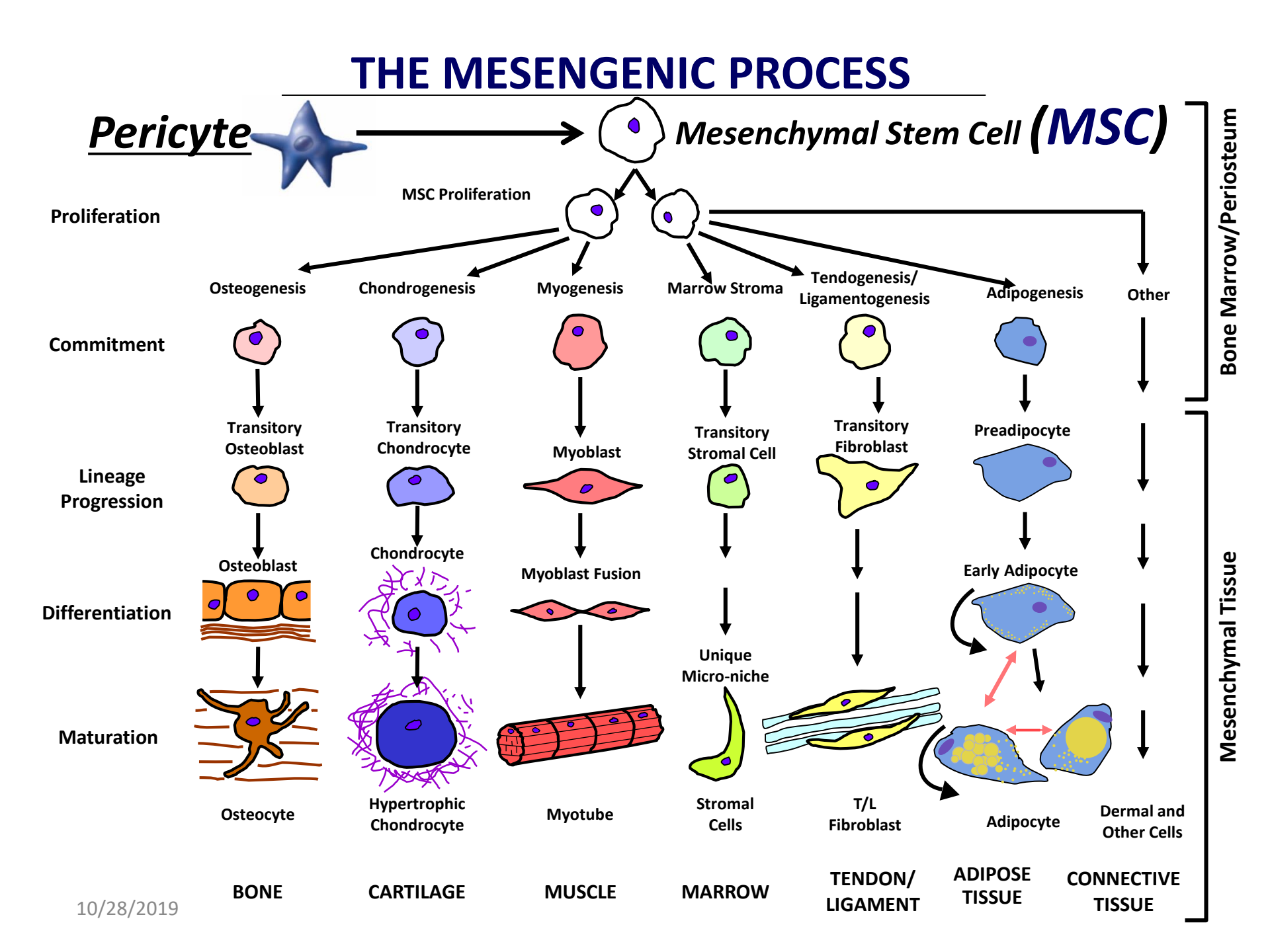
The Paramedic-ER analogy:

MSC Transitions:

Osteogenic, Trophic and Immunomodulatory.



THE MESENGENIC PROCESS



MSC = most sexy caplan

Medicinal Signaling Cell.

Not a STEM CELL!

CONCLUSIONS

MSCs are Not Stem Cells

- MSCs arise from their release from perivascular locations.
- MSCs inhibit scar formation.
- MSCs modulate the immune system.
- MSCs are immuno-evasive and thus allo-MSCs can be used.
- MSCs manage pain by secreting molecules that occupy opioid receptors.
- MSCs secrete molecules that are angiogenic.
- MSCs secrete proteins that are anti-bacterial.
- MSCs secrete molecules that are mitogenic to tissue-intrinsic stem cells.
- MSCs survey, sense and respond to their microenvironments.
- MSCs secrete pro- or anti-inflammatory molecules based on their microenvironment.
- MSCs are eaten by $Ly6C^{low}$ monocytes which then change T-cells to *Regulatory T-cells* which can account for long-term therapy.
- MSCs are NOT Stem Cells.

MANAGE YOUR REGENERATIVE POTENTIAL

Management of the patients innate regenerative resources will be the new treatment plan.

Mesenchymal Stem Cells (MSCs) at their perivascular niche.

Nature Protocols

Rodrigo Somoza, PhD

Diego Correa MD, PhD

Arnold I Caplan, PhD

Skeletal Research Center, Case Western Reserve University

Diego Correa

Rodrigo Somoza

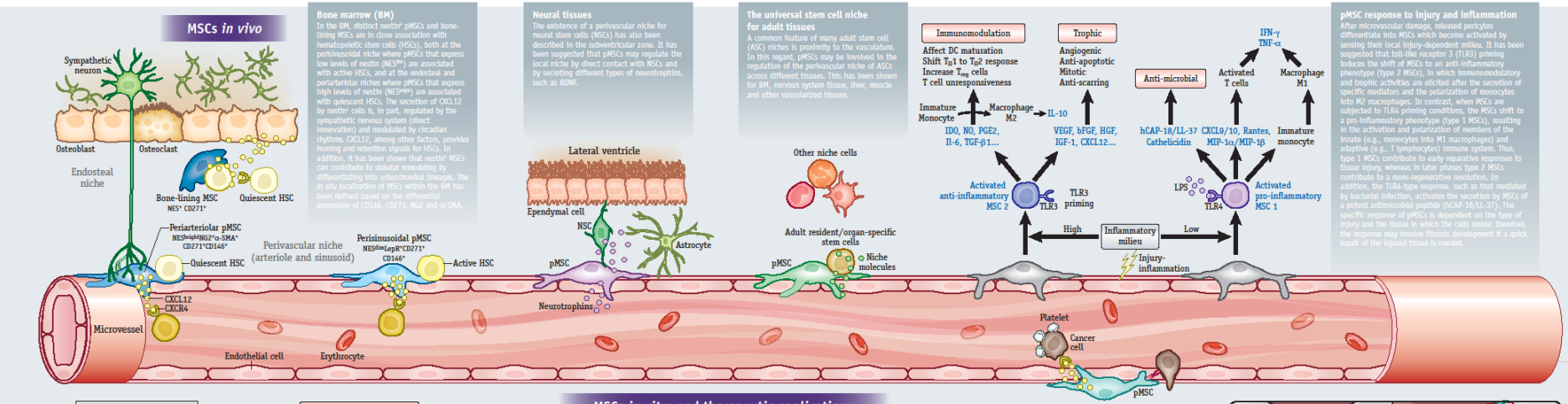
http://www.nature.com/nprot/posters/msc/index.html

nature protocols
Recipes for Researchers
January 2016 Vol 11 No 1

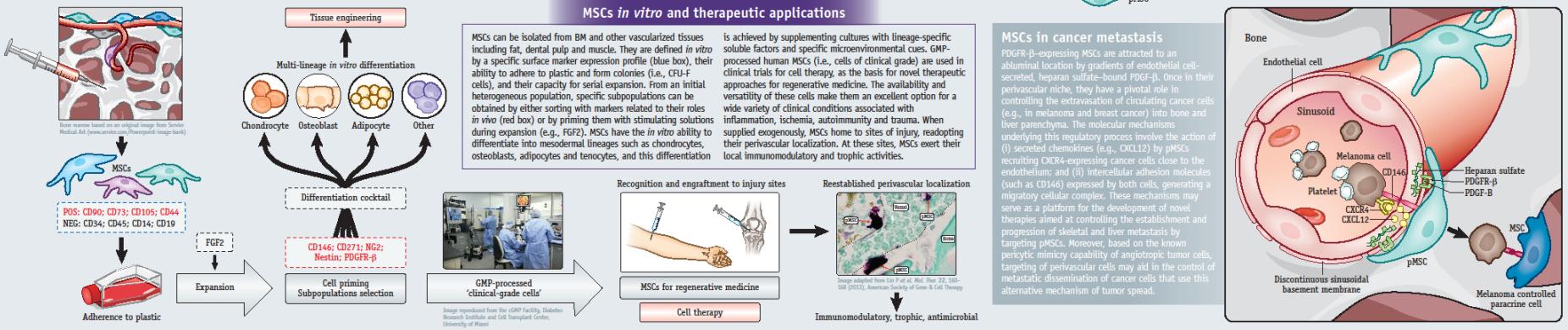
Roles for mesenchymal stem cells as medicinal signaling cells

Rodrigo A Somoza[1], Diego Correa[1,2] & Arnold I Caplan[1]

Understanding the *in vivo* identity and function of mesenchymal stem cells (MSCs) is vital to fully exploiting their therapeutic potential. New data are emerging that demonstrate previously undescribed roles of MSCs *in vivo*. Understanding the behavior of MSCs *in vivo* is crucial as recent results suggest these additional roles enable MSCs to function as medicinal signaling cells. This medicinal signaling activity is in addition to the contribution of MSCs to the maintenance of the stem cell niche and homeostasis. There is increasing evidence that not all cells described as MSCs share the same properties. Most MSCs reside in a perivascular location and have some functionalities in common with those of the pericytes and adventitial cells located around the microvasculature and larger vessels, respectively. Here we focus on the characteristics of MSCs that have been demonstrated to be similar to those of pericytes located around the microvasculature, defined as perivascular MSCs (pMSCs). Although we focus here on pMSCs, it is important to bear in mind that pericytes are found in many types of blood vessels, and that not all pericytes are thought to be MSCs.



MSCs *in vitro* and therapeutic applications



MSCs can be isolated from BM and other vascularized tissues including fat, dental pulp and muscle. They are defined *in vitro* by a specific surface marker expression profile (blue box), their ability to adhere to plastic and form colonies (i.e., CFU-F cells), and their capacity for serial expansion. From an initial heterogeneous population, specific subpopulations can be obtained by either sorting with markers related to their roles *in vivo* (red box) or by priming them with stimulating solutions during expansion (e.g., FGF2). MSCs have the *in vitro* ability to differentiate into mesodermal lineages such as chondrocytes, osteoblasts, adipocytes and tenocytes, and this differentiation is achieved by supplementing cultures with lineage-specific soluble factors and specific microenvironmental cues. GMP-processed human MSCs (i.e., cells of clinical grade) are used in clinical trials for cell therapy, as the basis for novel therapeutic approaches for regenerative medicine. The availability and versatility of these cells make them an excellent option for a wide variety of clinical conditions associated with inflammation, ischemia, autoimmunity and trauma. When supplied exogenously, MSCs home to sites of injury, readopting their perivascular localization. At these sites, MSCs exert their local immunomodulatory and trophic activities.

MSCs in cancer metastasis

PDGFR-β–expressing MSCs are attracted to an abluminal location by gradients of endothelial cell–secreted, heparan sulfate–bound PDGF-β. Once in their perivascular niche, they have a pivotal role in controlling the extravasation of circulating cancer cells (e.g., in melanoma and breast cancer) into bone and liver parenchyma. The molecular mechanisms underlying this regulatory process involve the action of (i) secreted chemokines (e.g., CXCL12) by pMSCs recruiting CXCR4-expressing cancer cells close to the endothelium; and (ii) intercellular adhesion molecules (such as CD146) expressed by both cells, generating a migratory cellular complex. These mechanisms may serve as a platform for the development of novel therapies aimed at controlling the establishment and progression of skeletal and liver metastasis by targeting pMSCs. Moreover, based on the known pericytic mimicry capability of angiotropic tumor cells, targeting of perivascular cells may aid in the control of metastatic dissemination of cancer cells that use this alternative mechanism of tumor spread.

MesenCult™: Your High-Performance System for MSC Isolation, Culture & Differentiation

STEMCELL Technologies is committed to serve scientists along the basic to translational research continuum by providing high-quality, standardized media and reagents for mesenchymal stem cells (MSCs). Choose from a comprehensive range of MesenCult™ specialty products designed to standardize your cell culture system and minimize experimental variability. Optimized products for the isolation, expansion, quantification (CFU-F Assay) and differentiation of human and mouse MSCs to adipocytes, osteoblasts and chondrocytes are available.

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Please visit www.stemcell.com/MesenCult for additional information on all products and resources available to help your MSC research, including cell enrichment and selection kits, antibodies and a range of primary cell products, or contact our knowledgeable technical support team for detailed protocol information at techsupport@stemcell.com.

Abbreviations

α-SMA: Alpha smooth muscle actin; ASC: Adult stem cell; BDNF: Brain-derived neurotrophic factor; CCL5: C-C motif chemokine 5 (Rantes); CXCR4: Chemokine (C-X-C motif) receptor 4; CXCL9: Chemokine (C-X-C motif) ligand 9; CXCL10: Chemokine (C-X-C motif) ligand 10; CXCL12: Chemokine (C-X-C motif) ligand 12; DC: Dendritic cell; FGF2: Fibroblast growth factor 2; GMP: Good manufacturing practice; hCAP-18/LL-37: Human cationic antimicrobial protein; HGF: Hepatocyte growth factor; HSC: Hematopoietic stem cell; IDO: Indoleamine 2,3-dioxygenase; LPS: Lipopolysaccharide; IGF-1: Insulin-like growth factor-1; IL-6: Interleukin-6; IL-10: Interleukin-10; IFN-γ: Interferon gamma; LepR: Leptin receptor; MIP: Macrophage inflammatory protein; NES: Nestin; NG2: Neural/glial antigen 2; NO: Nitric oxide; NSC: Neural stem cell; PDGFR-β: Platelet-derived growth factor receptor beta; PGE2: Prostaglandin E2; pMSC: Perivascular mesenchymal stem cell; TH: T helper; TLR3: Toll-like receptor-3; TLR4: Toll-like receptor-4; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor

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[1]Department of Biology, Skeletal Research Center, Case Western Reserve University, Cleveland, Ohio, USA. [2]Department of Orthopaedics, Division of Sports Medicine and Diabetes Research Institute (DRI) University of Miami, Miller School of Medicine, Miami, Florida, USA.

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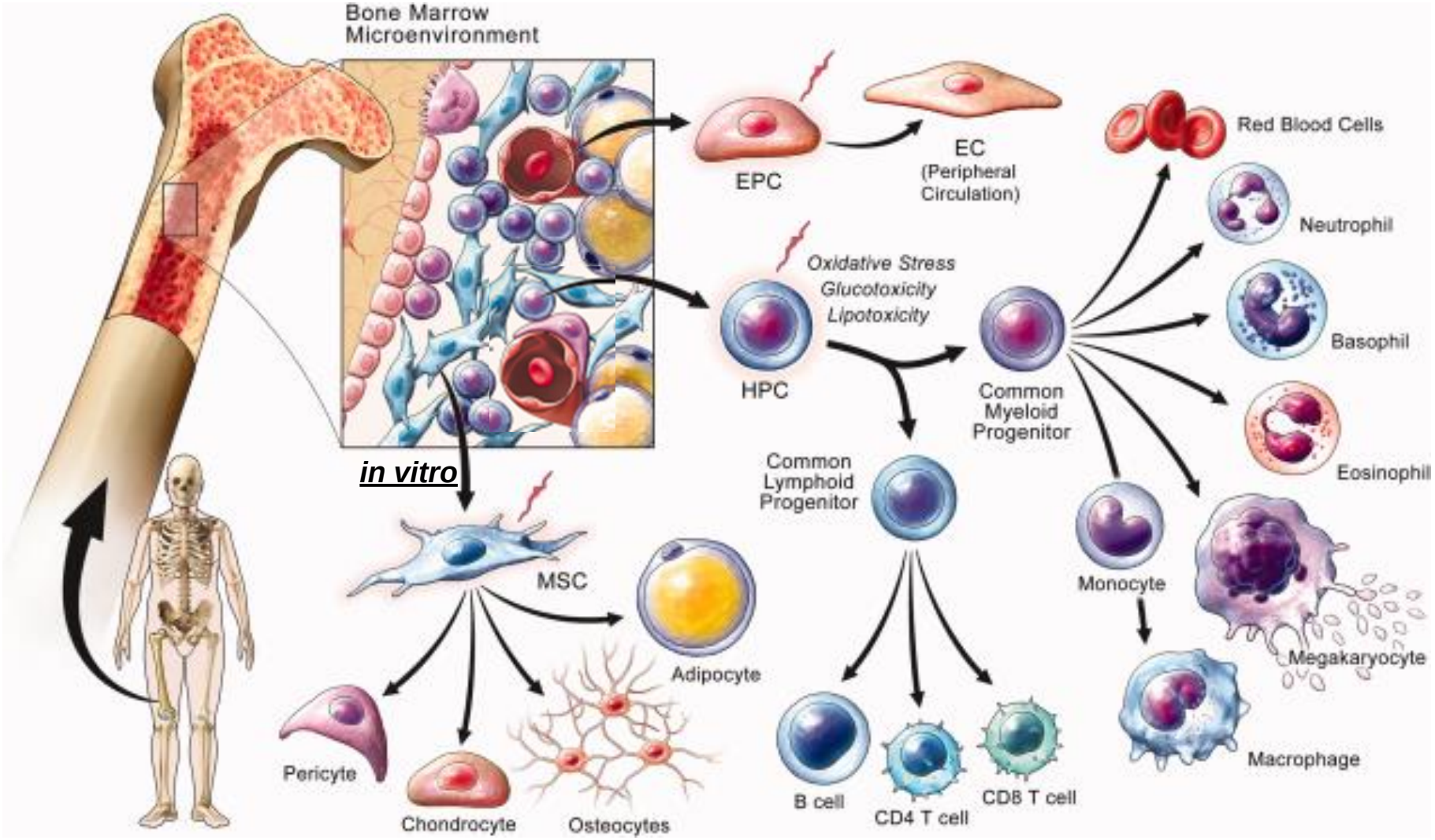
http://www.nature.com/nprot/posters/msc/index.html

Concise Review: Cell Therapy for Critical Limb Ischemia: An Integrated Review of Preclinical and Clinical Studies



STEM CELLS
3 JAN 2018 DOI: 10.1002/stem.2751
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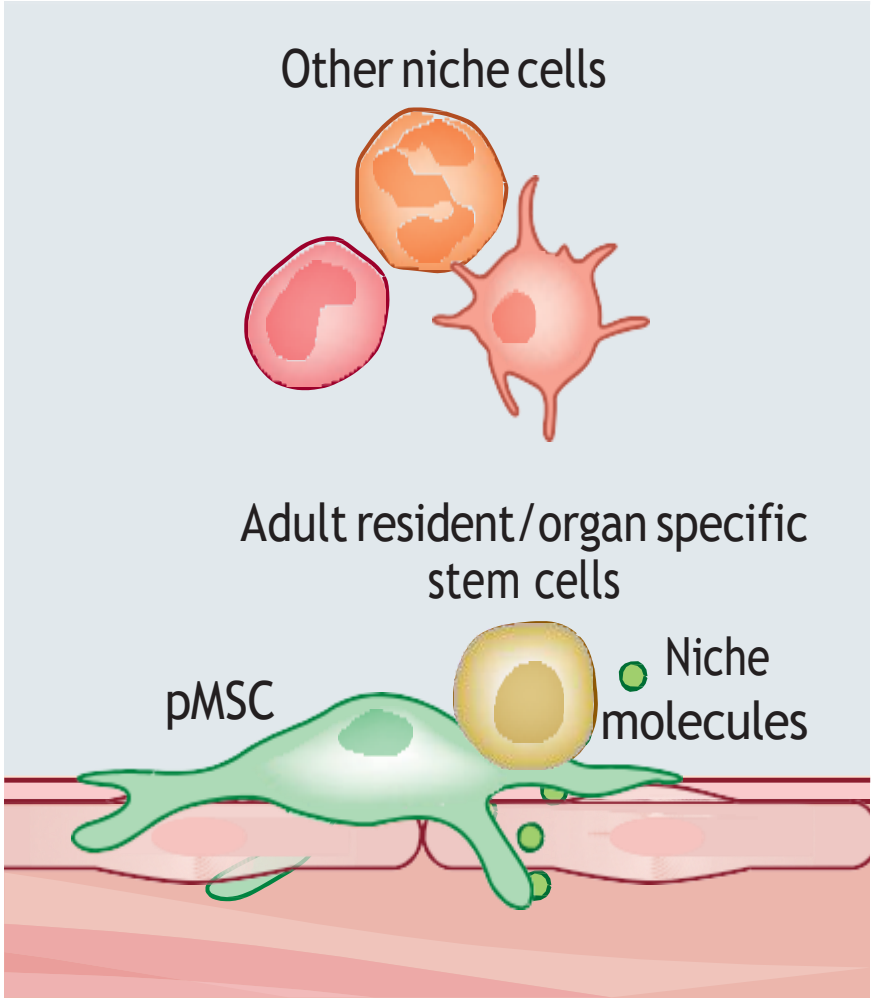
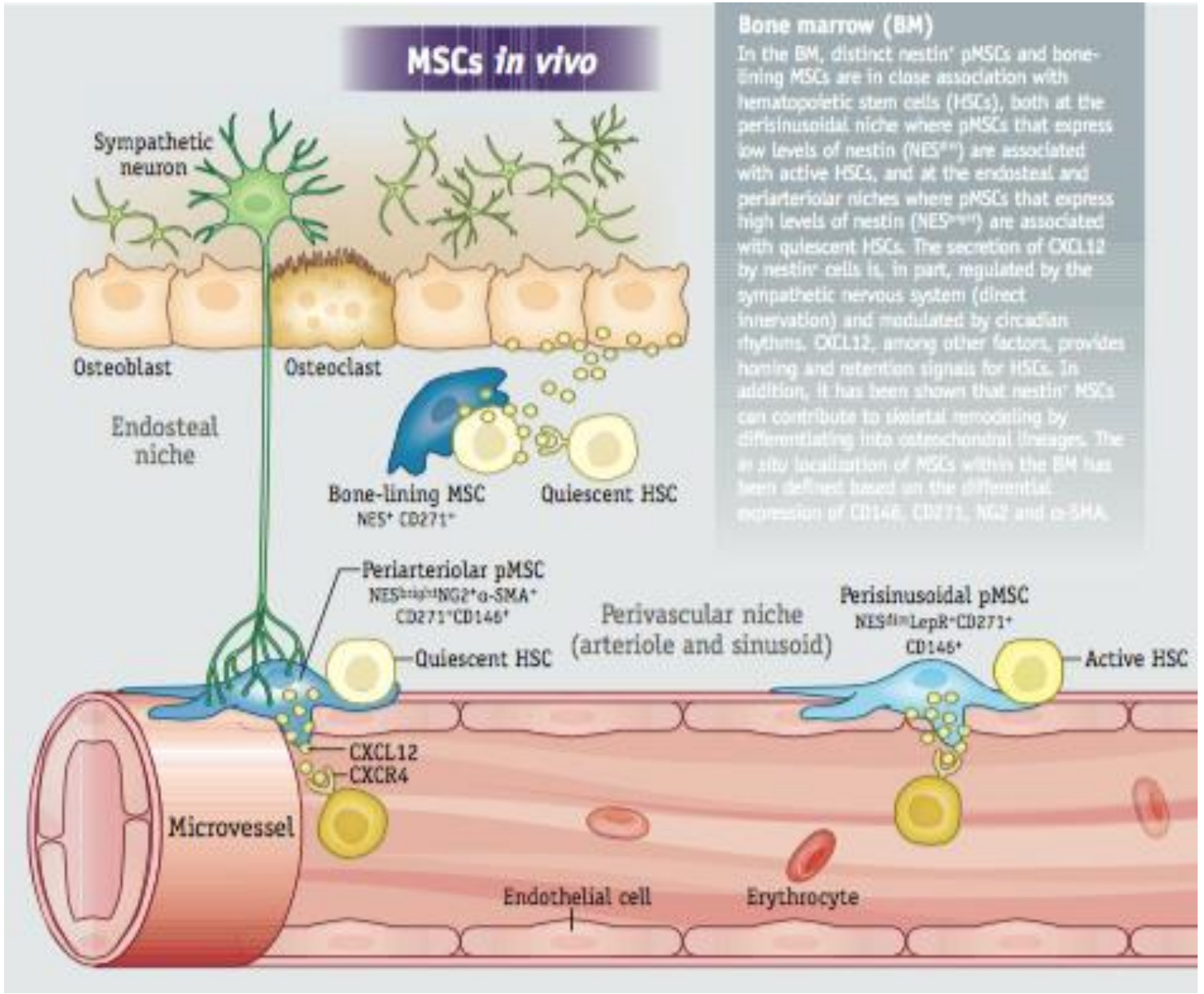
The Universal Stem Cell Niche

for ADULT TISSUES(Liver, Heart, Skeletal Muscle, Others)



MSCs *in vivo: Bone* marrow niche



Somoza et al., 2016

http://www.nature.com/nprot/posters/msc/index.html

nature protocols
Recipes for Researchers
January 2016 Vol 11 No 1

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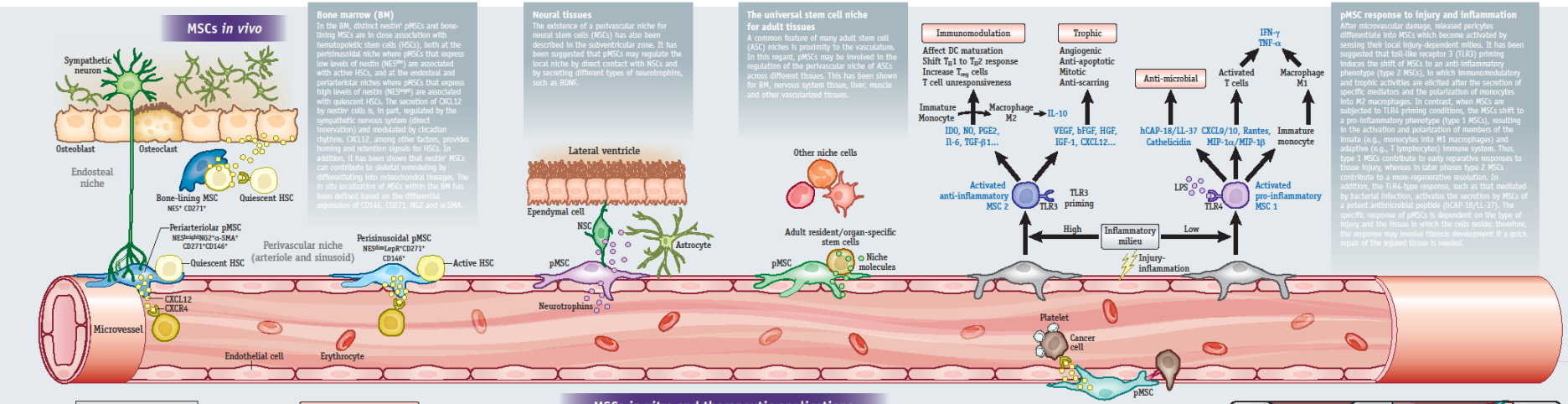

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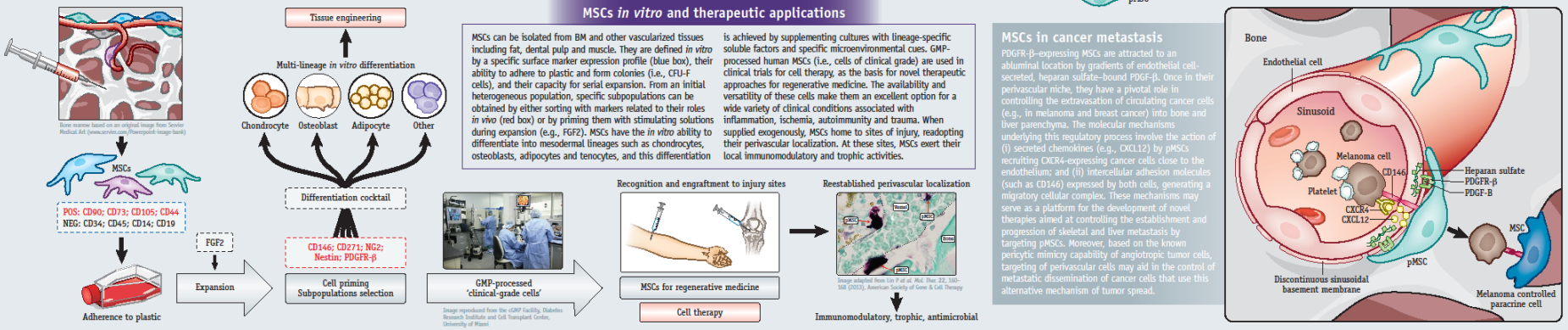

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Abbreviations

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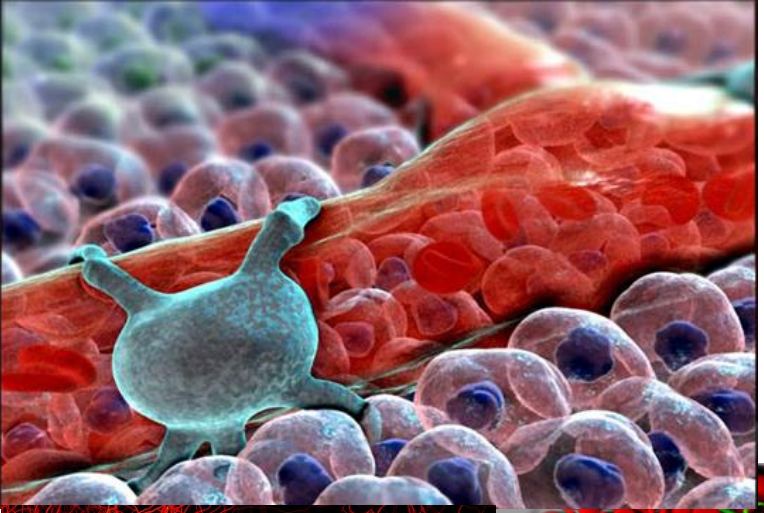
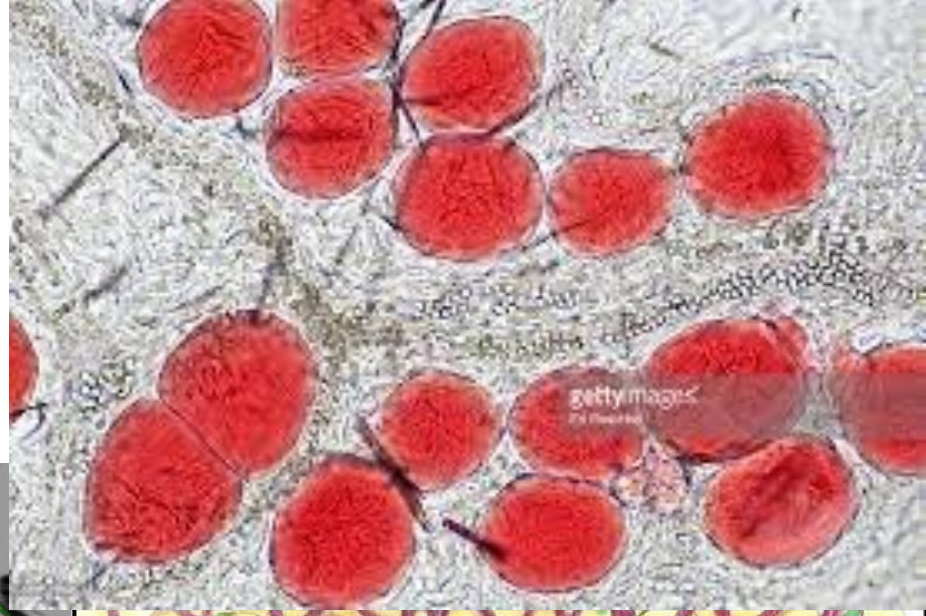
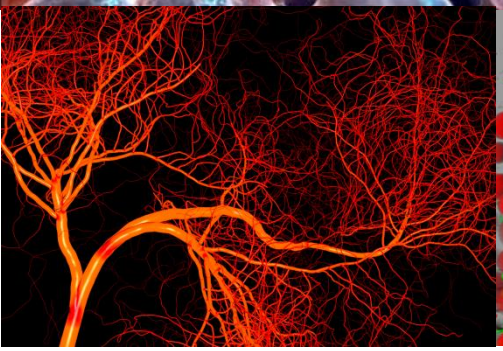
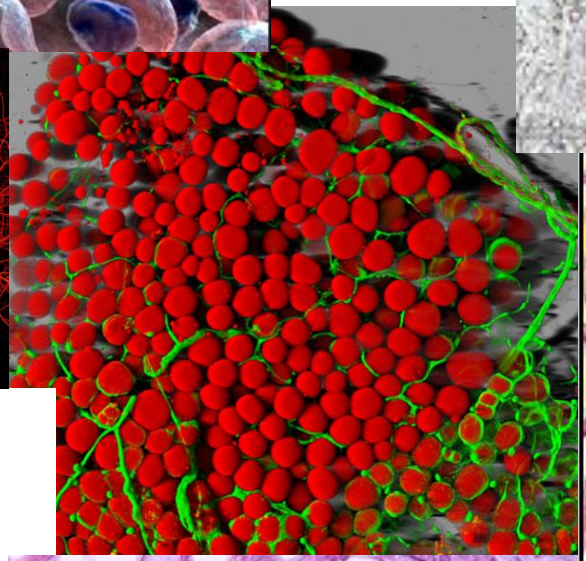
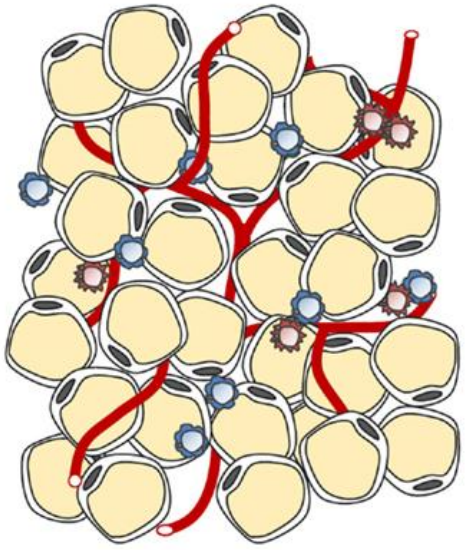
300-500 fold more MSCs than marrow

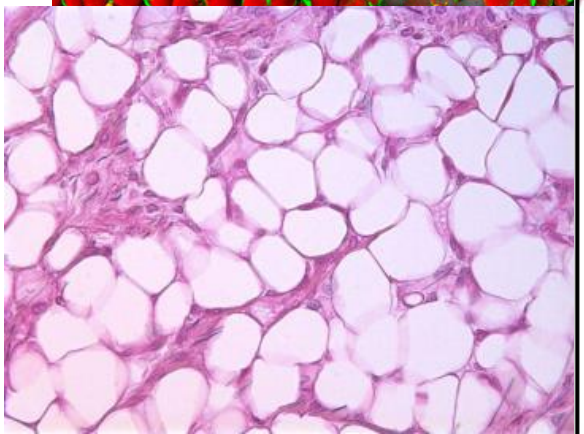


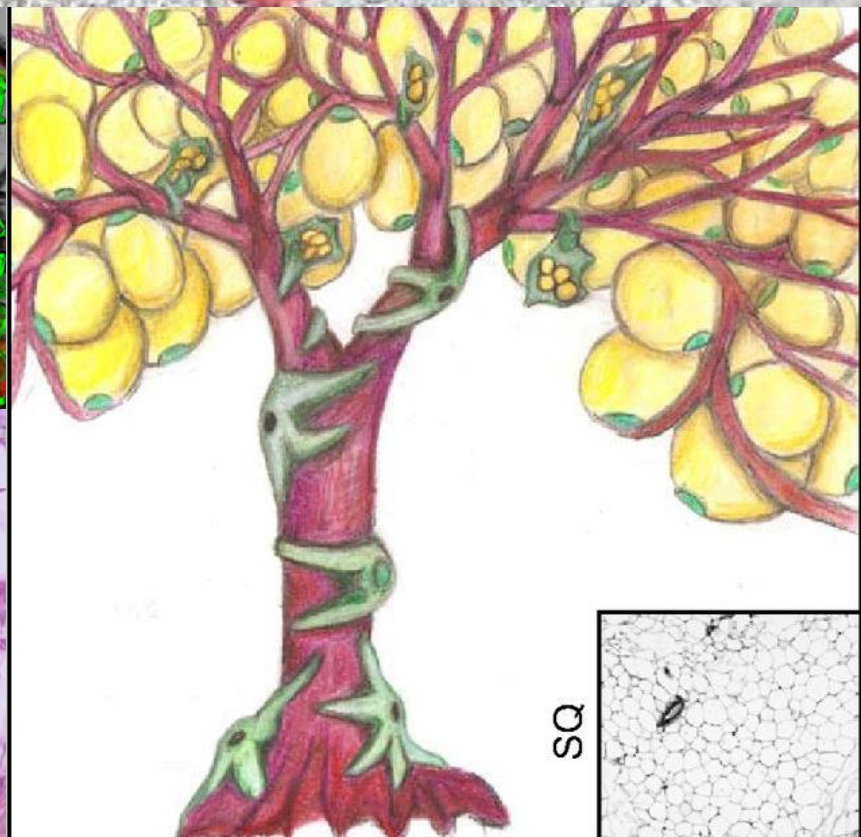






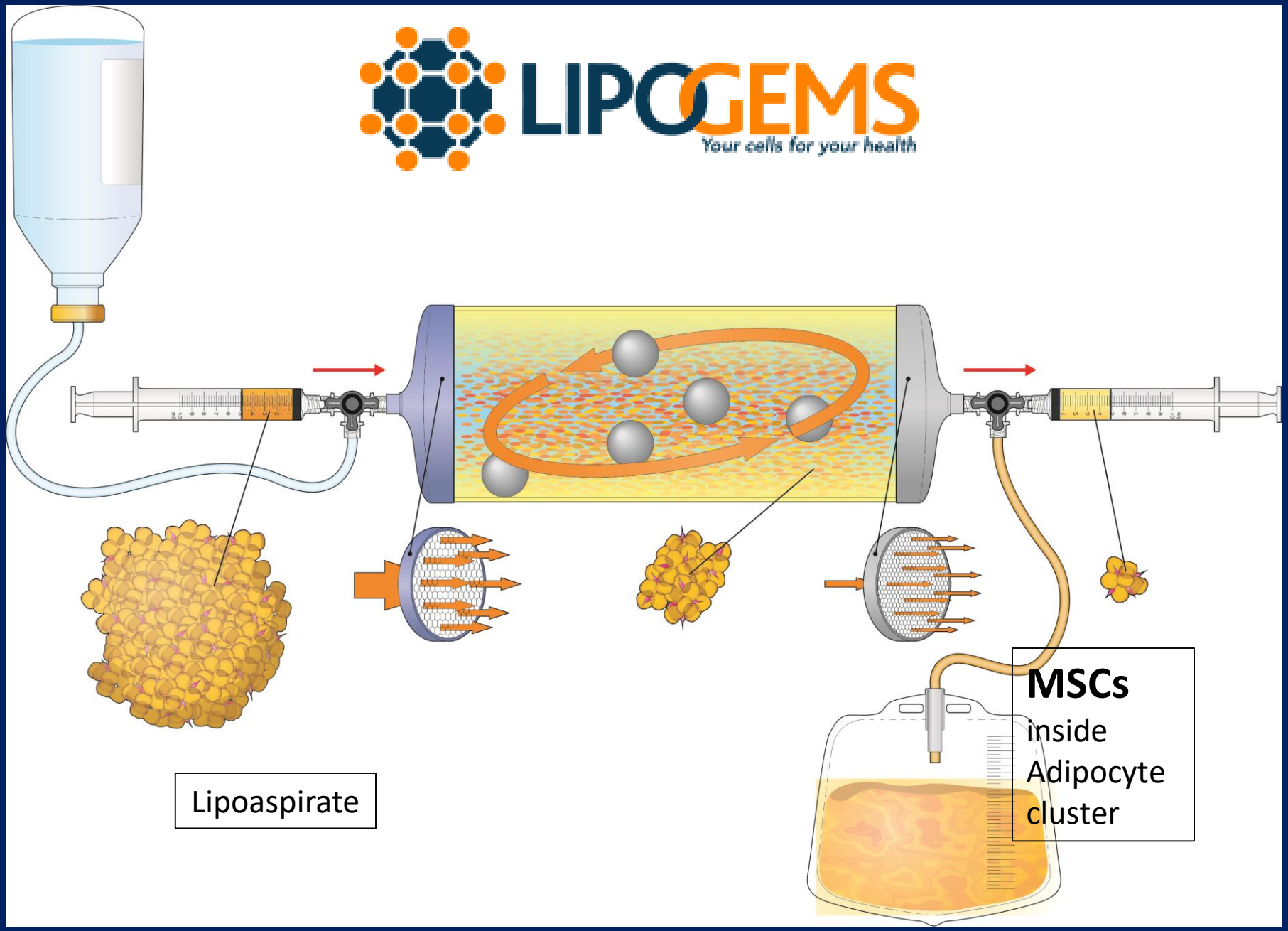






LIPOGEMS

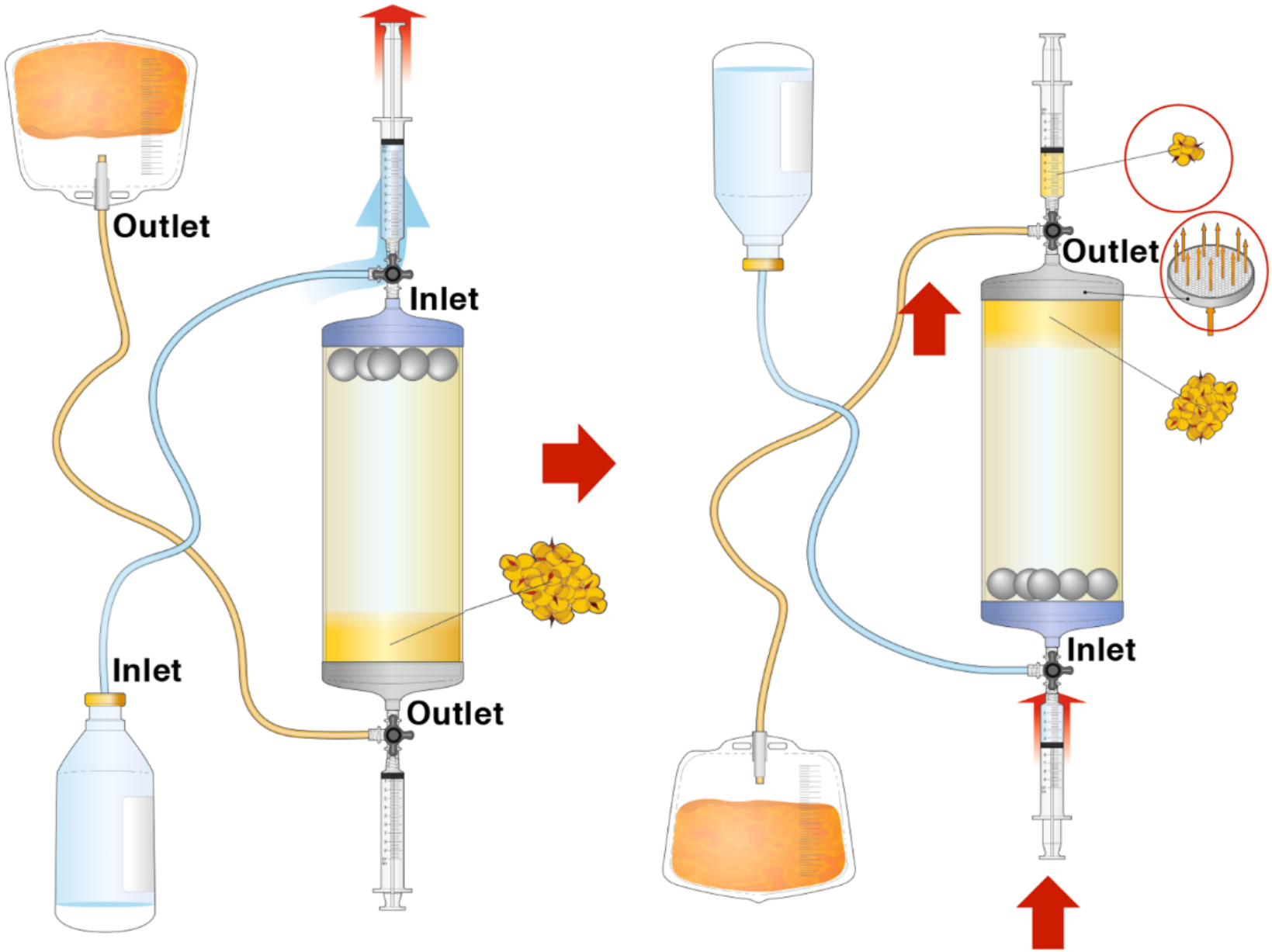
Your cells for your health



Lipoaspirate

MSCs
inside
Adipocyte
cluster

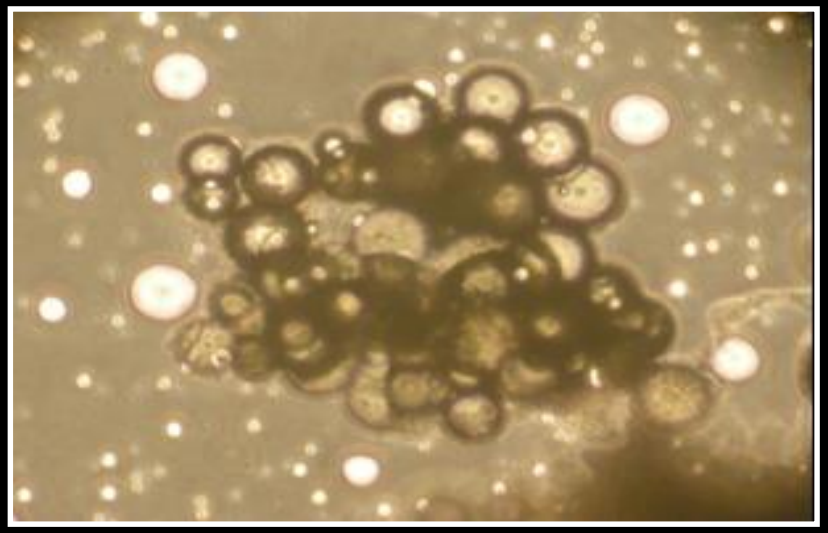
Second Cluster Size Reduction and Lipogems Tissue Harvesting



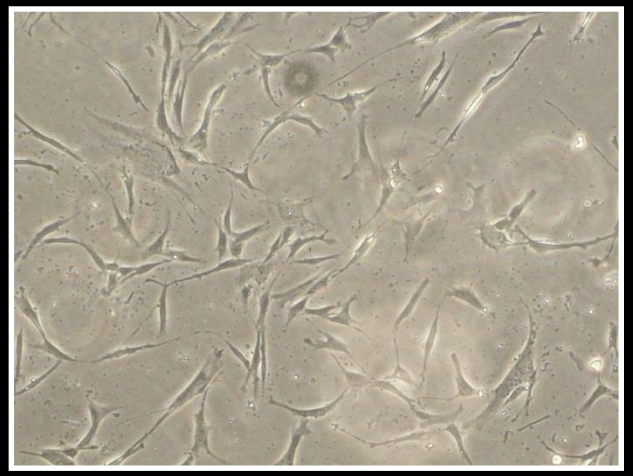
Adipose Tissue and Stem Cells

Prof. Sbarbati- University of Verona

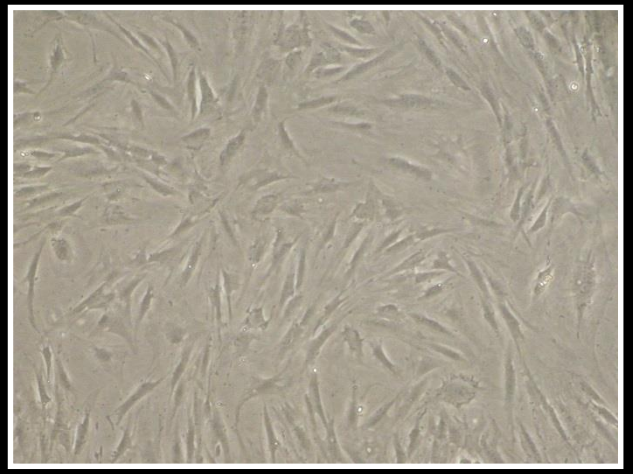
Lipogems clusters in culture:



Day 4



Day 6



Day 12