

MSCs are not Stem Cells;
the New Medicine.

Innate Regenerative Potential

ARNOLD I. CAPLAN, PhD

Texas Pain Soc., San Antonio, TX

October 26, 2019

**Case Western Reserve University
Cleveland, Ohio**



Disclosure Information:

1. Osiris Therapeutic, 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

Al 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 multipotent and can be used in tissue engineered constructs to fabricate skeletal tissues like CARTILAGE.

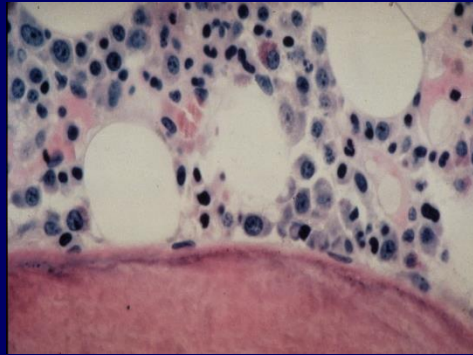
MSCs function *in vivo* to manage the *innate capacity* of tissues to regenerate.

A microscopic view of blood cells. The background is filled with numerous red blood cells, which are biconcave and reddish in color. In the upper left quadrant, there is a single white blood cell, which is larger, spherical, and has a light blue, granular surface.

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

MSC

MESENCHYMAL STEM CELLS

ALL BLOOD CELLS

1988

THE MESENGENIC PROCESS

Hypothesis

MSC

Mesenchymal Stem Cell (MSC)

REGENERATIVE MEDICINE

Proliferation

MSC Proliferation

Osteogenesis

Chondrogenesis

Myogenesis

Marrow Stroma

Endogenesis/
Ligamentogenesis

Other

Commitment



Transitory
Osteoblast

Transitory
Chondrocyte

Myoblast

Transitory
Stromal Cell

Transitory
Fibroblast

Lineage
Progression



Chondrocyte

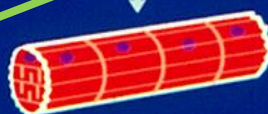
Myoblast Fusion

Unique
Micro-niche

Differentiation



Hypertrophic
Chondrocyte



Maturation

Osteocyte

BONE

CARTILAGE

Myotube

MUSCLE

Stromal
Cells

MARROW

T/L
Fibroblast

TENDON /
LIGAMENT

Adipocytes,
Dermal and
Other Cells

CONNECTIVE
TISSUE

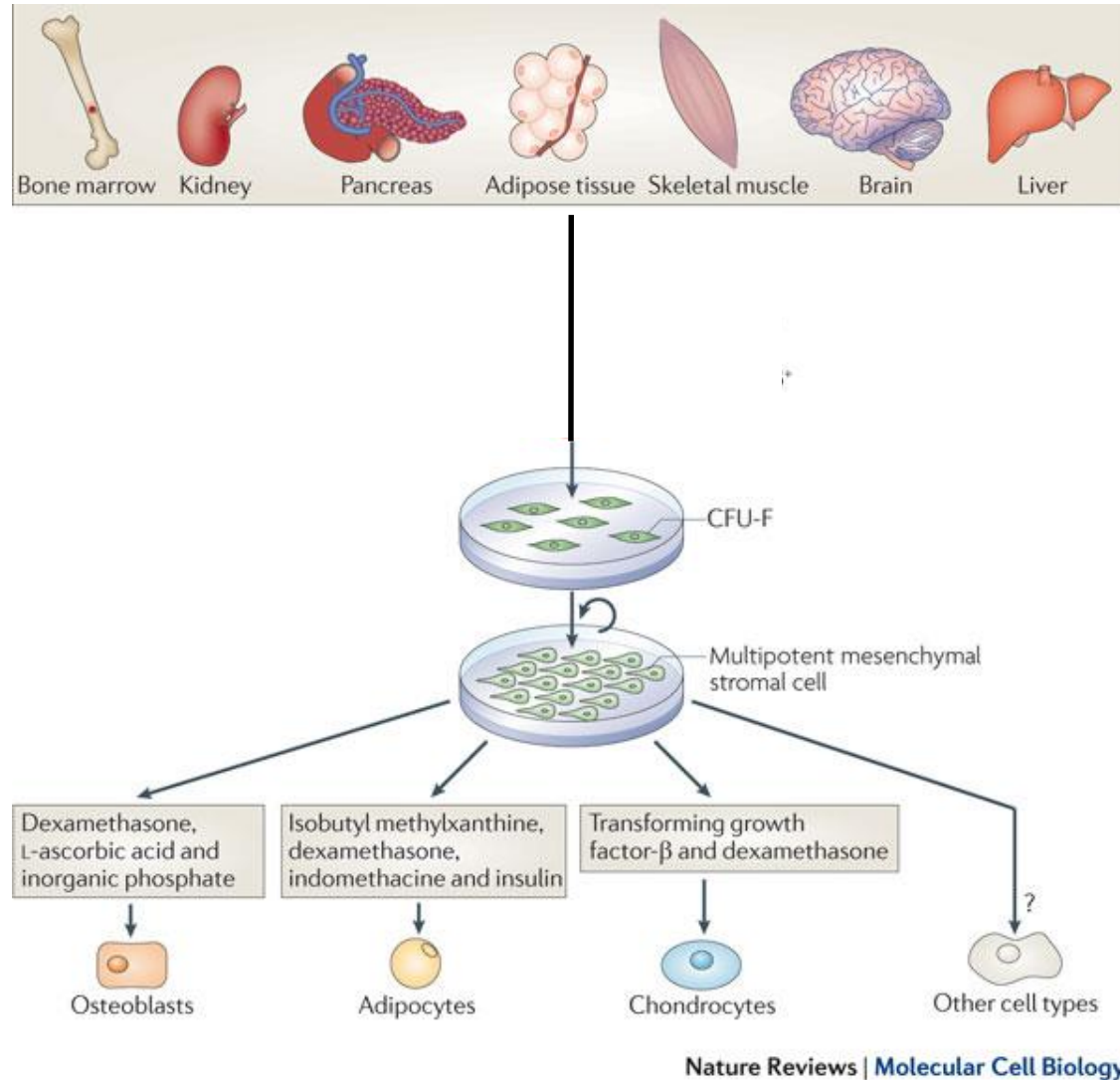
Bone Marrow / Periosteum

Mesenchymal Tissue

TISSUE ENGINEERING

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



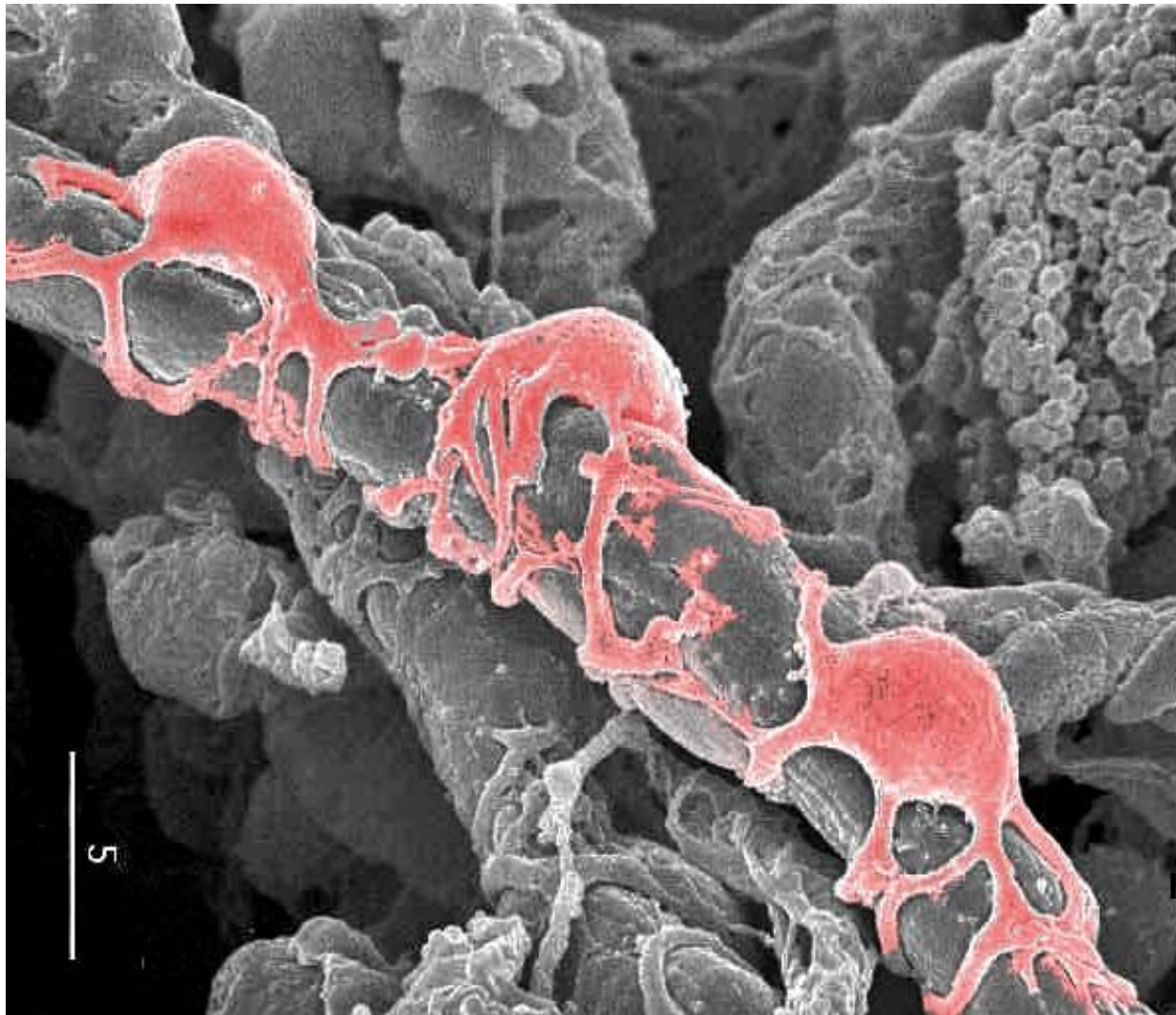
TODAY:

MSCs

*“Mesenchymal Stem Cells”
and
Regenerative Medicine.*

Pericytes: cells on capillaries and microvessels.

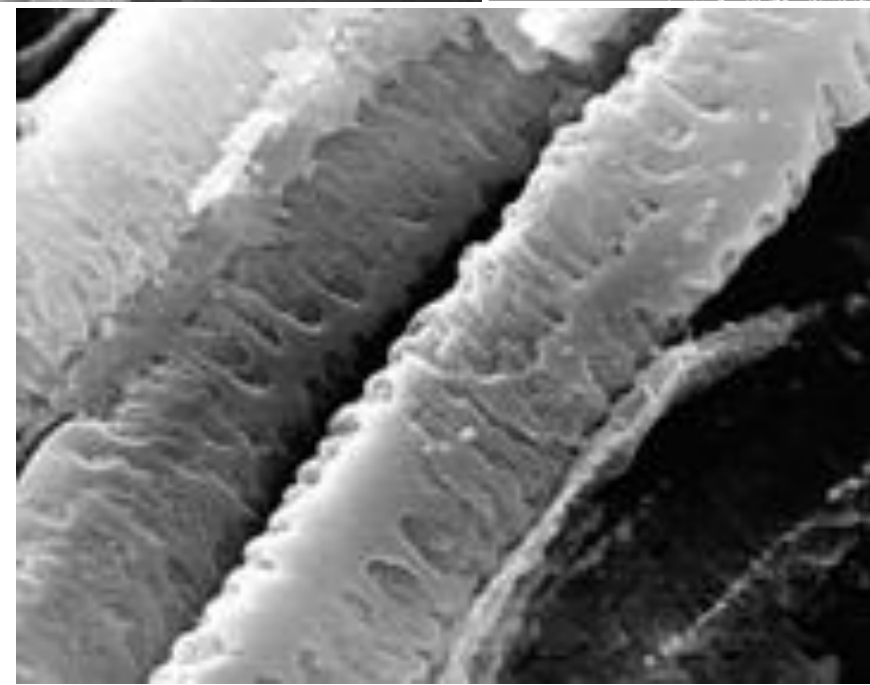
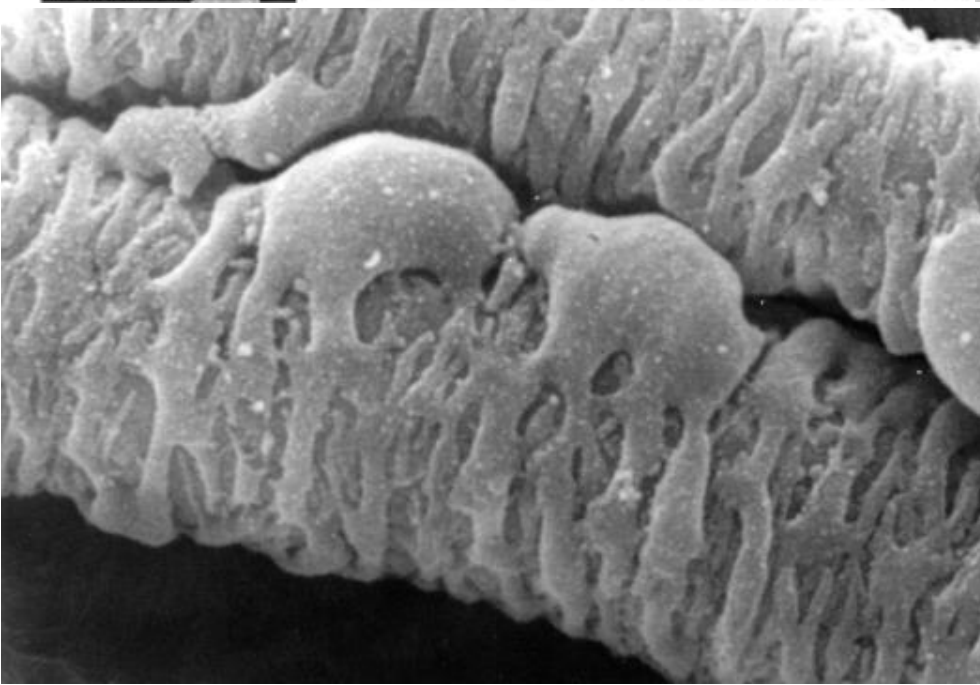
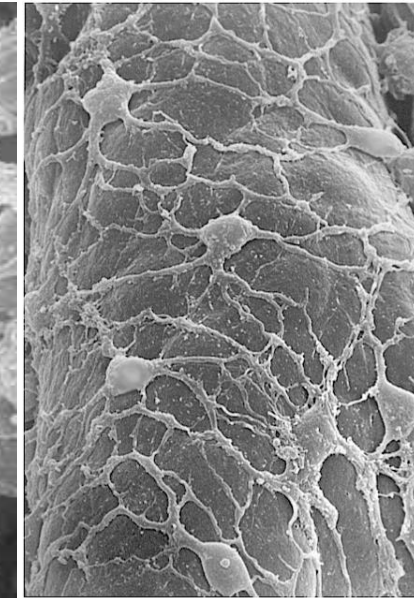
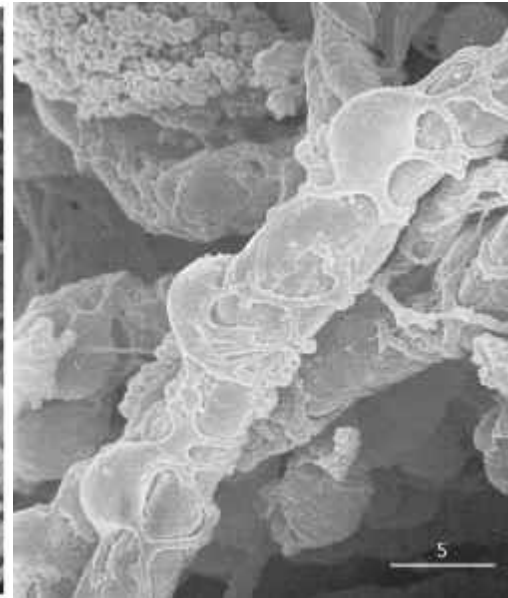
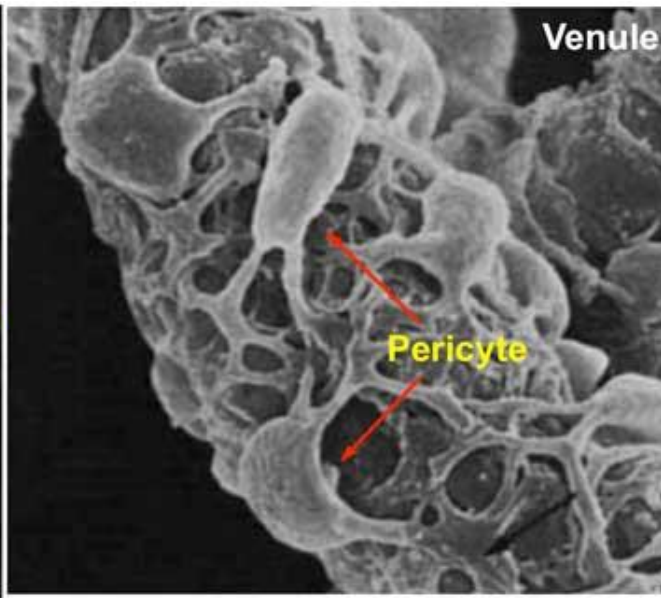
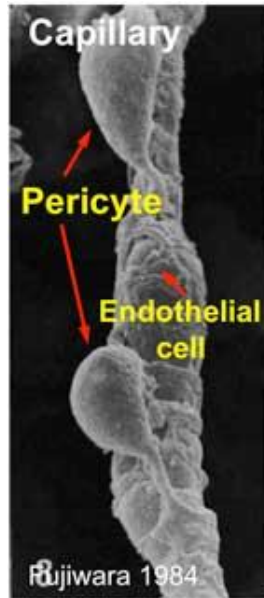
ALL MSCs are PERICYTES!



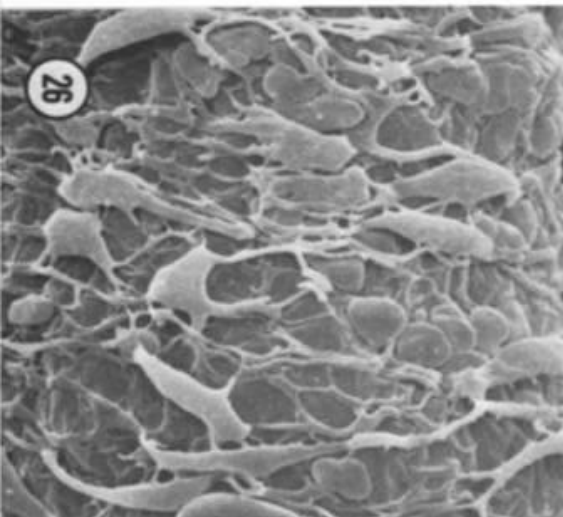
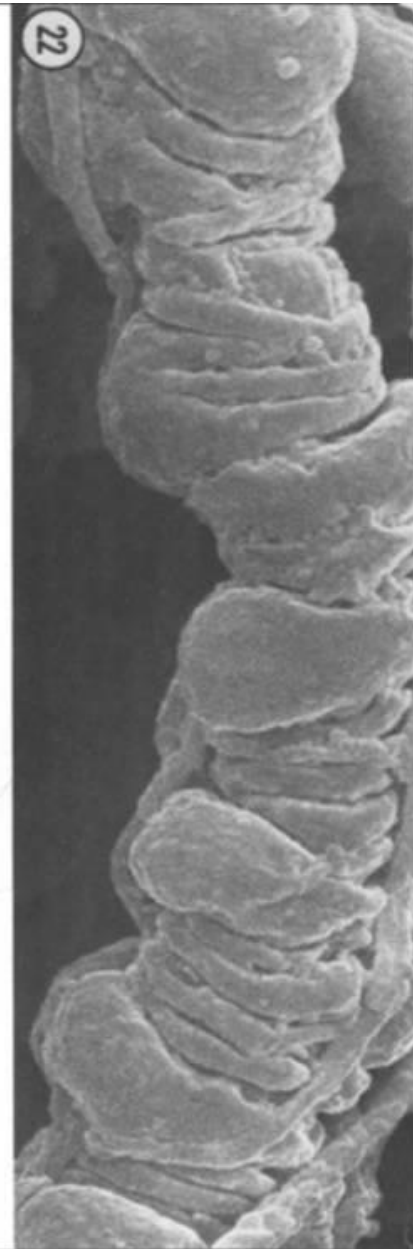
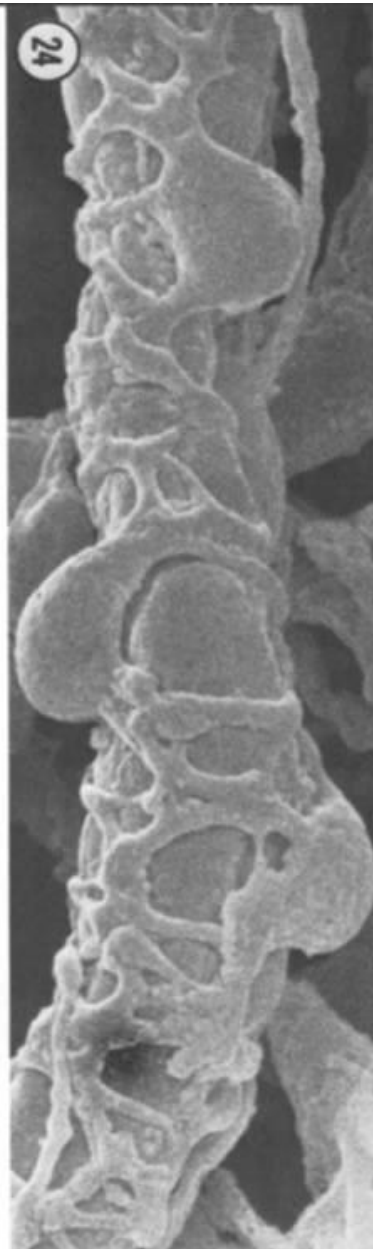
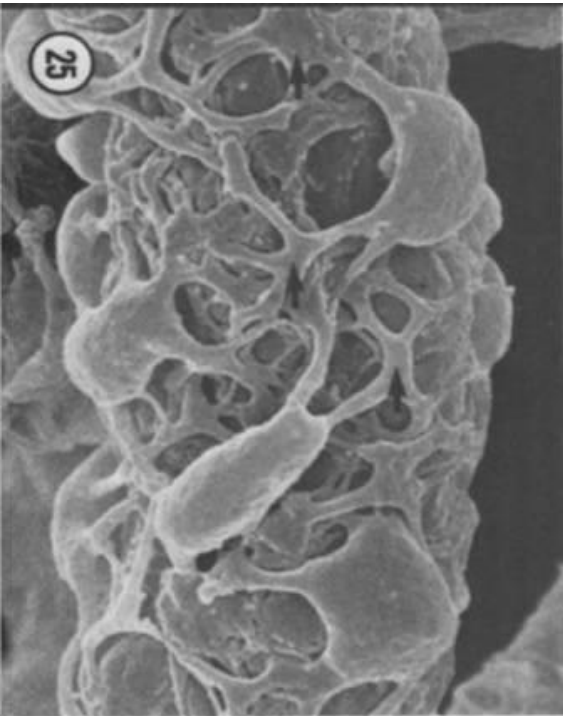
Al Caplan.
Cell Stem
Cell, 3:229-
30, 2008.

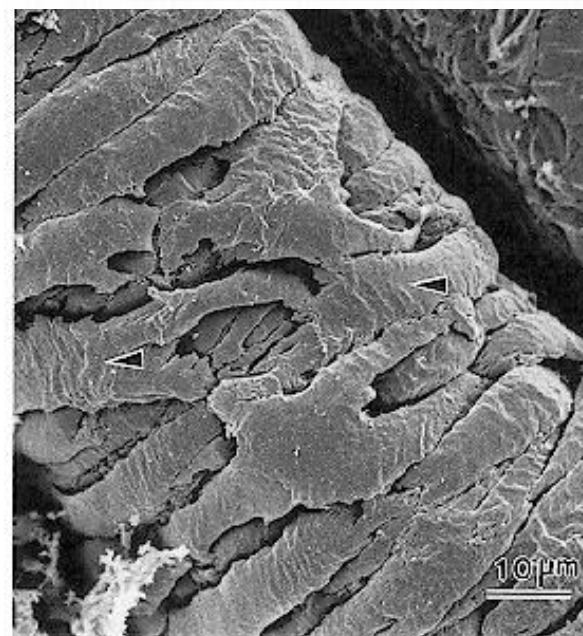
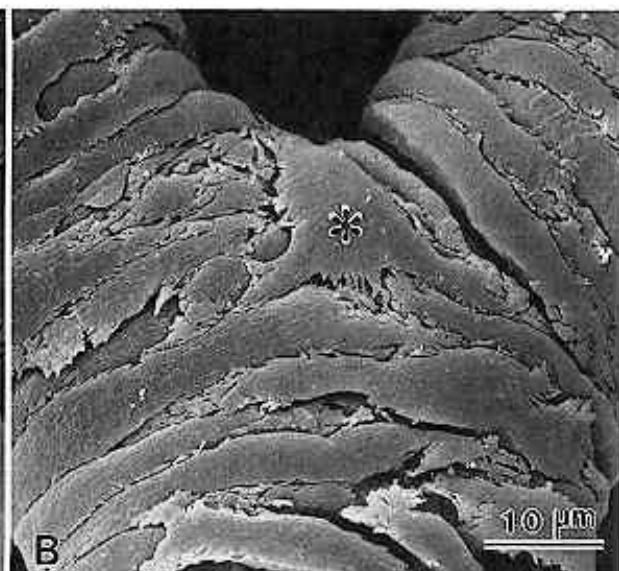
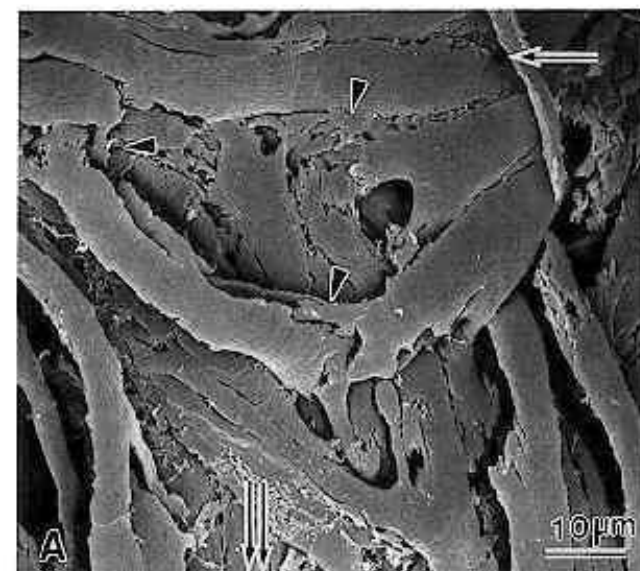
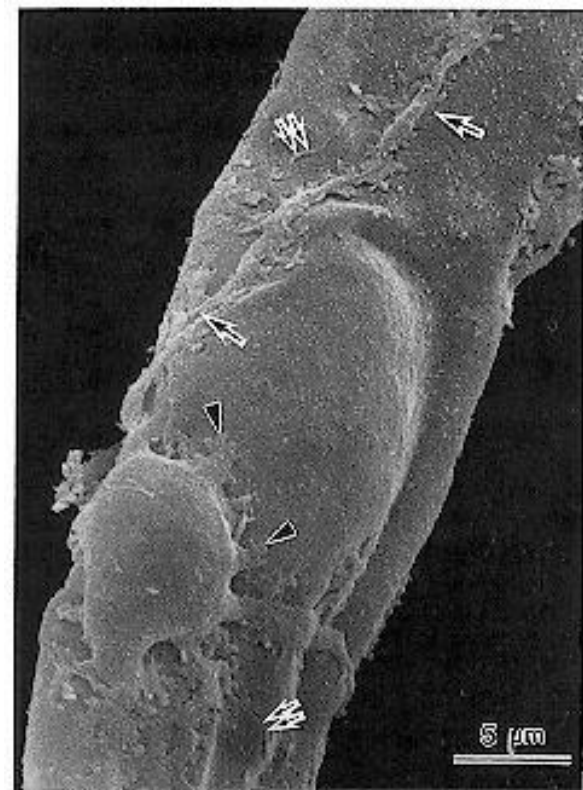
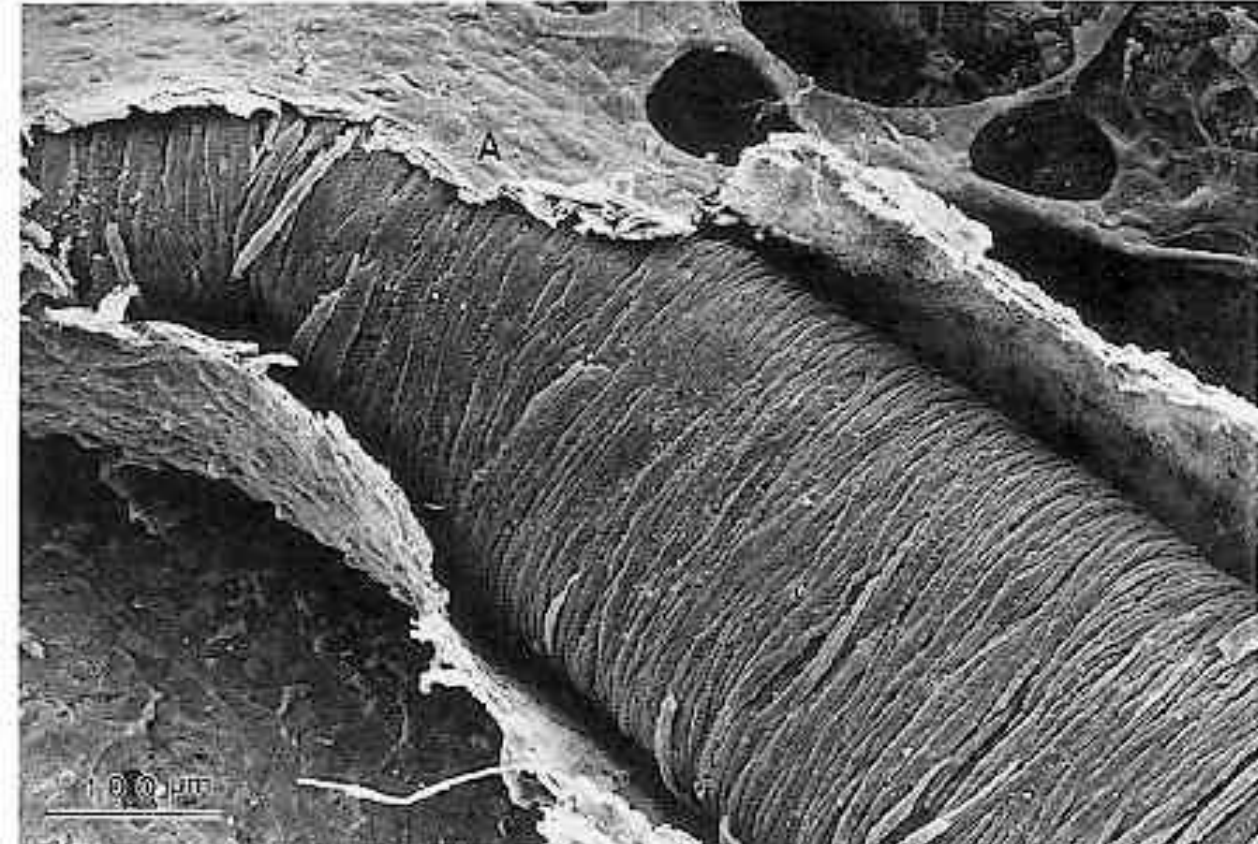
modified by
BRUNO PEULT
from
<http://www.geocities.com/HeartLand-Suzuran/9389/kekkan>

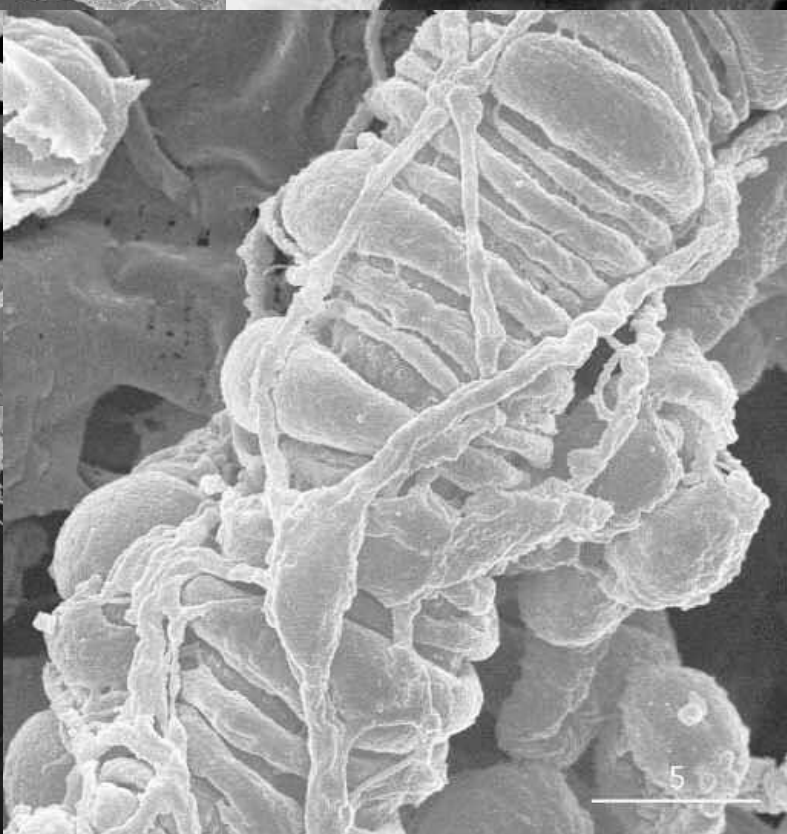
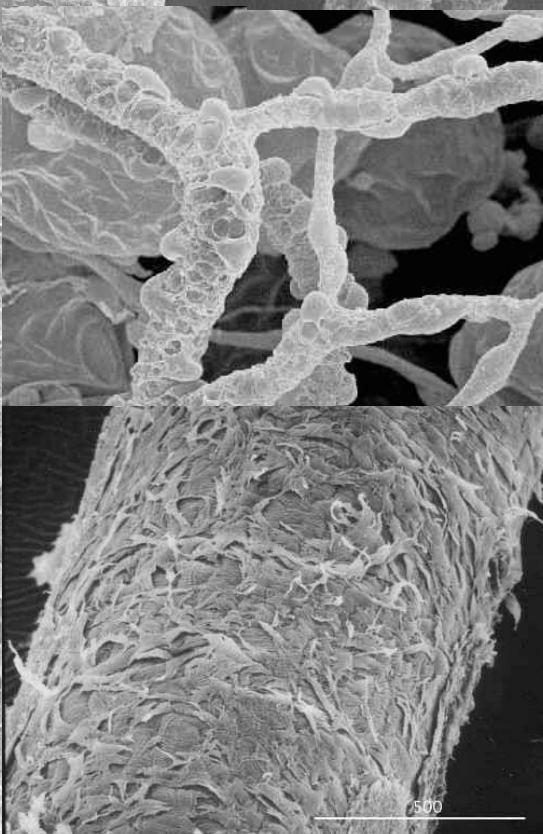
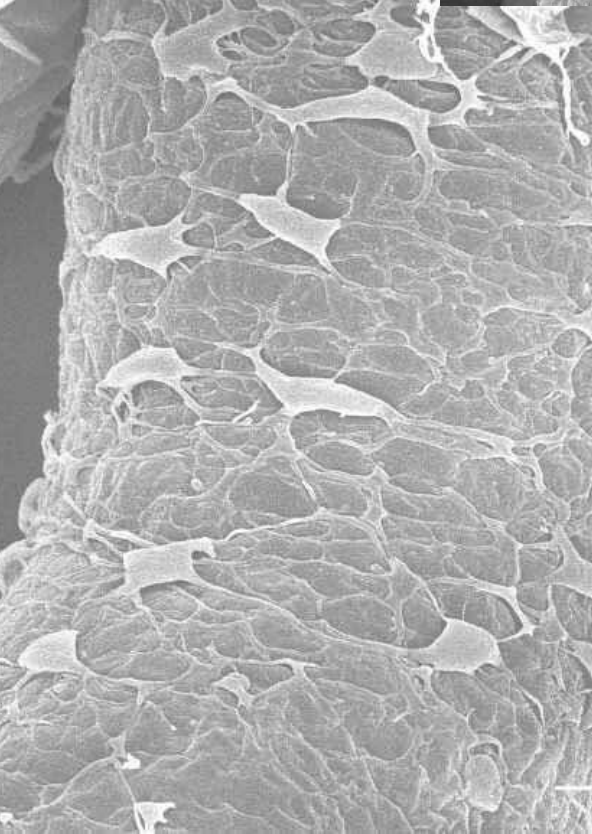
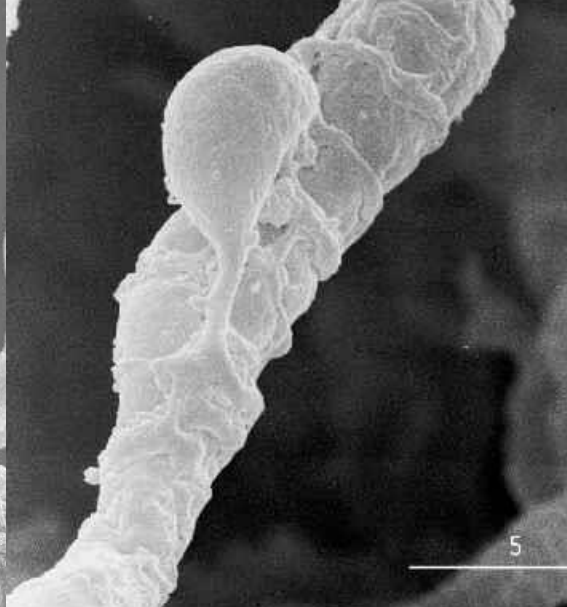
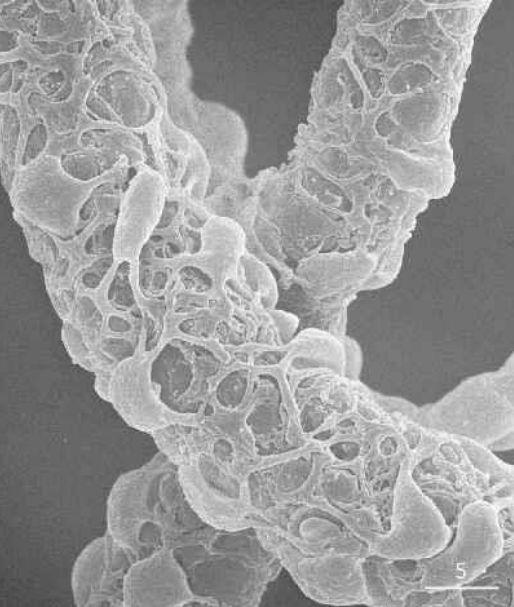
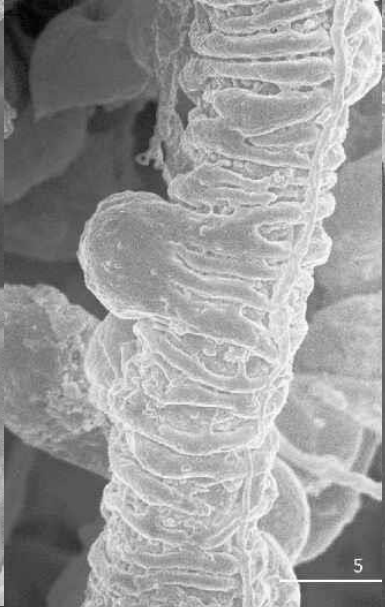
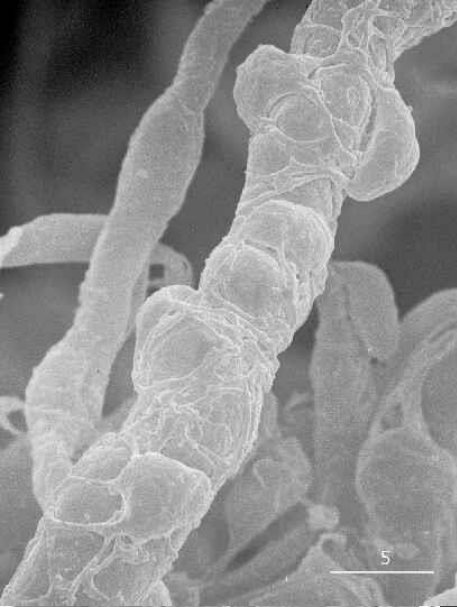
In vivo identity of preMSCs: pericytes



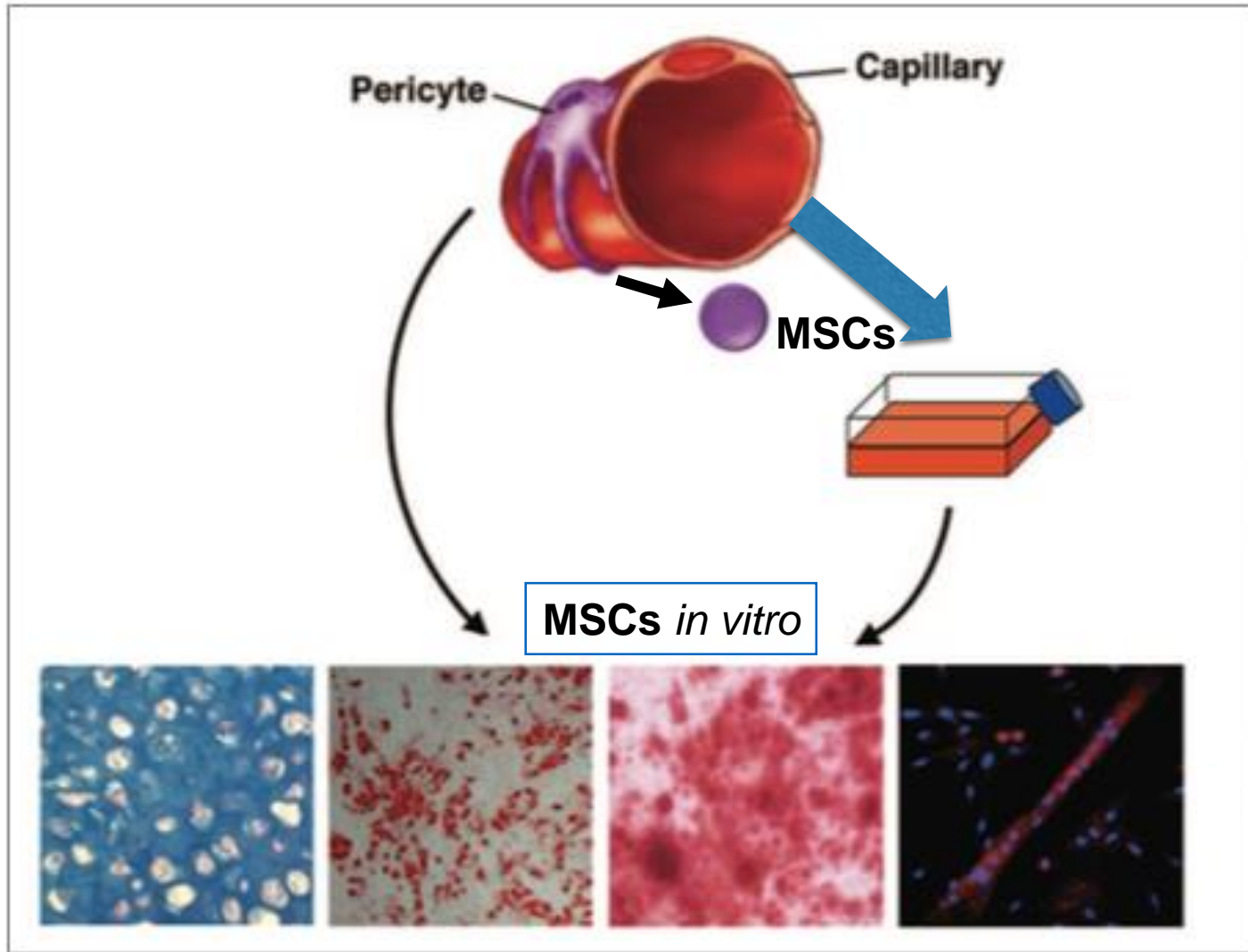
David E. Sims: "The Pericyte-A Review". *Tissue & Cell*, 18, 153-174, 1986.







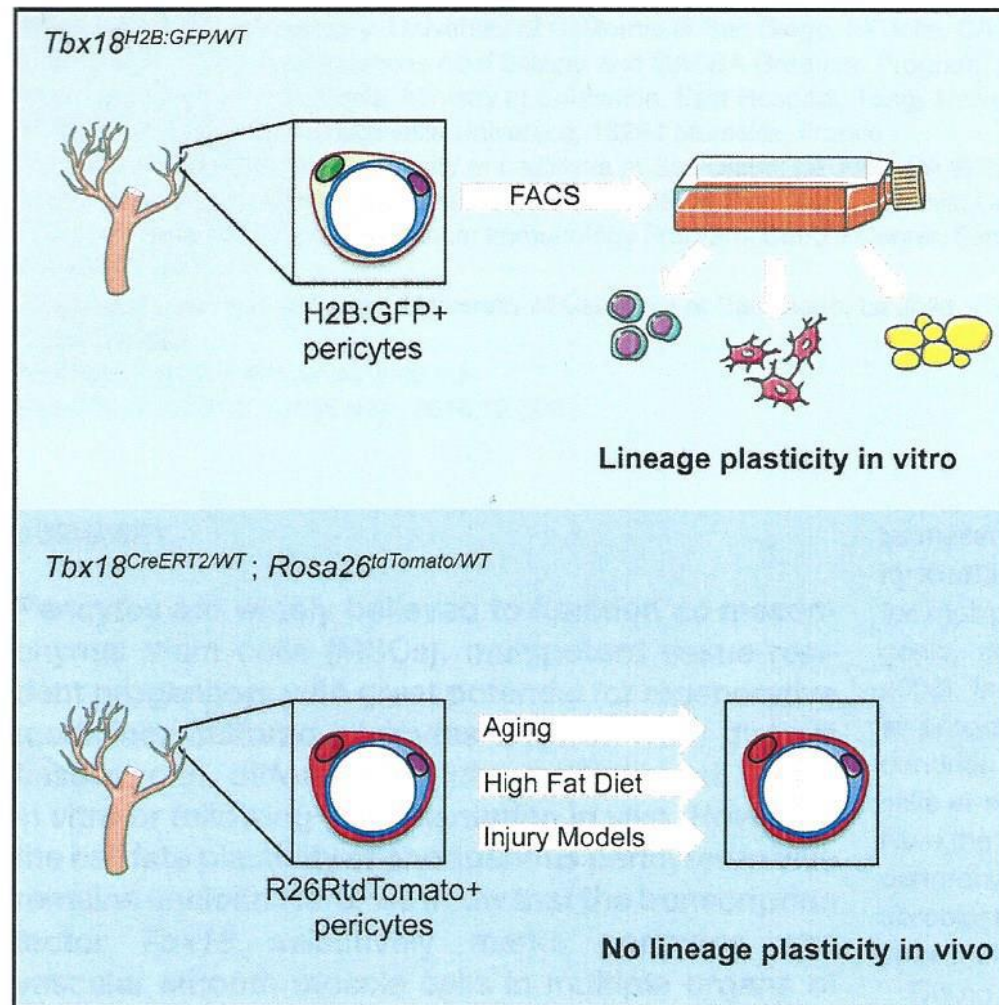
MSCs *in vitro* are multi-potent but NOT *in vivo*



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

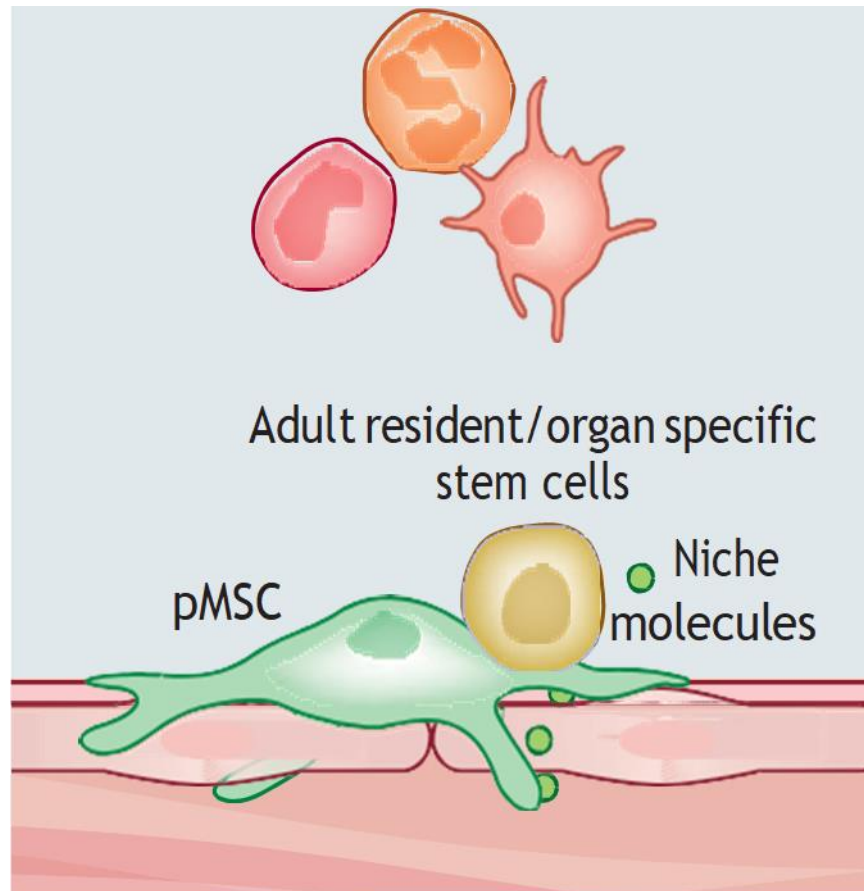
Guimarães-Camboa et al. permanently labeled pericytes and vascular smooth muscle of multiple organs in vivo and followed the fate of these cells in aging and injury models. Their analyses showed that, in vivo, pericytes did not behave as stem cells, challenging the current view of pericytes as tissue-resident 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
Salivary gland
Skin
Spleen
Synovial membrane
Tendon
Thymus
Umbilical cord
Vein

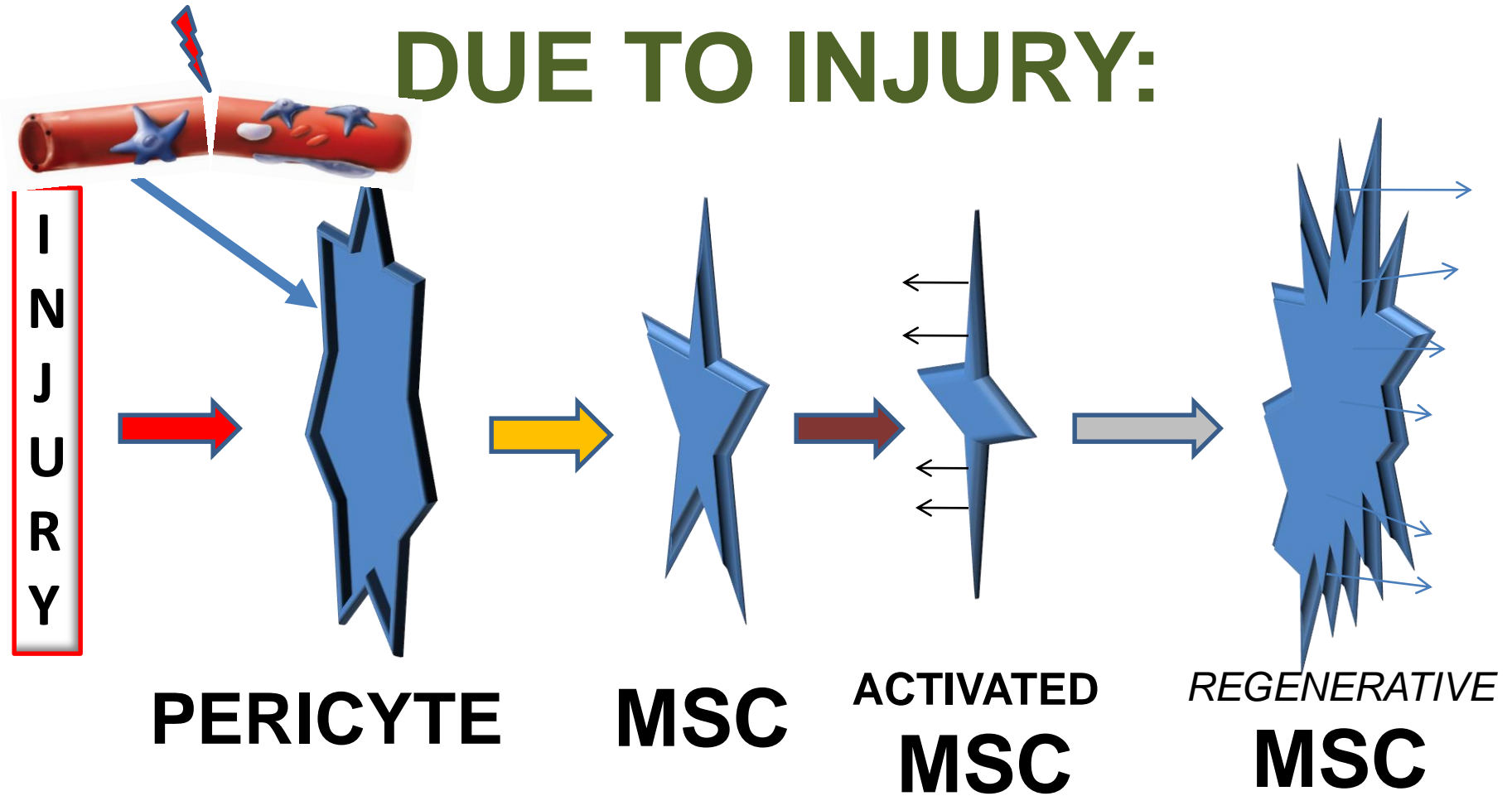


The Universal Stem Cell Niche



2019

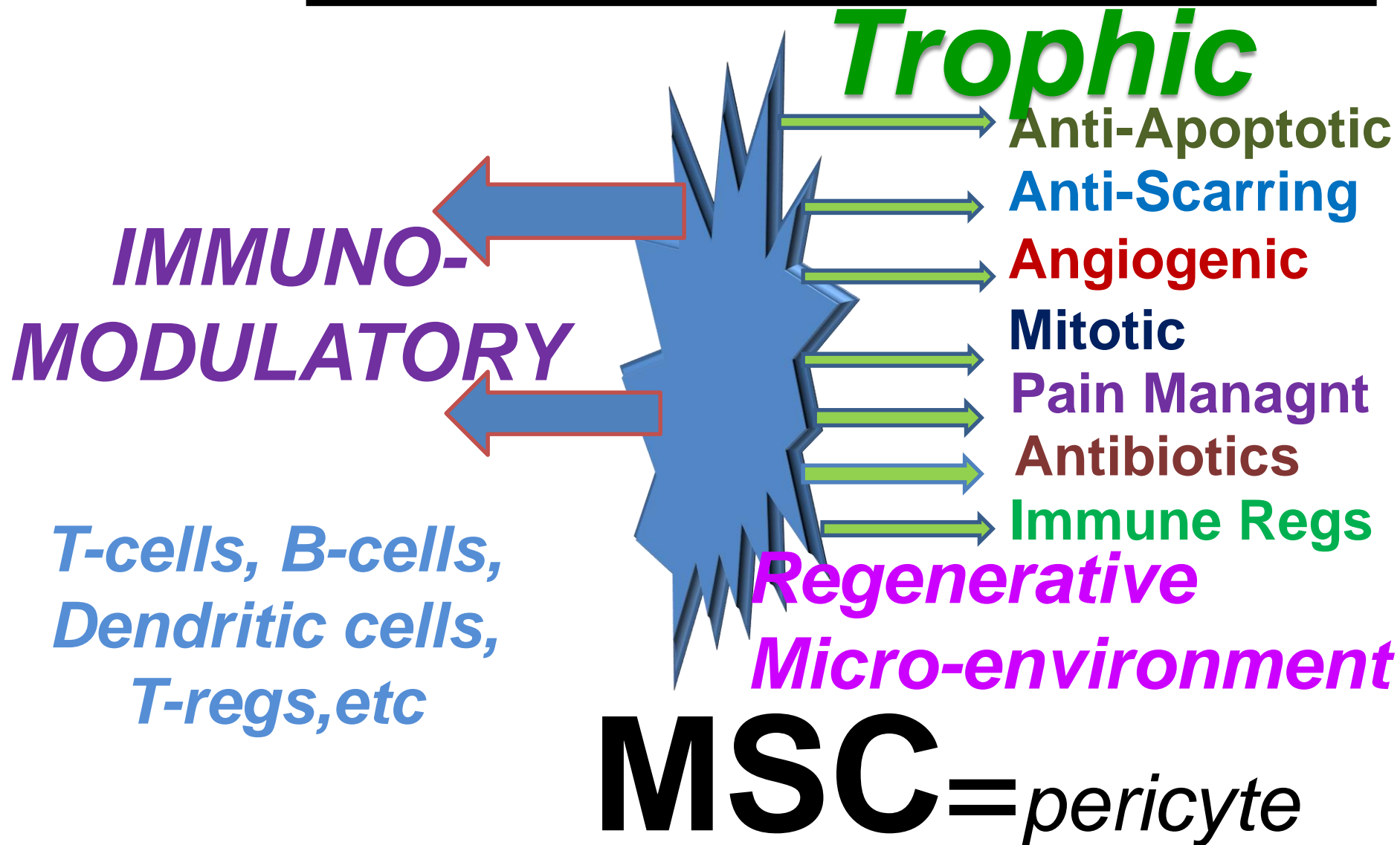
PROPOSED SEQUENCE OF CHANGE DUE TO INJURY:



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



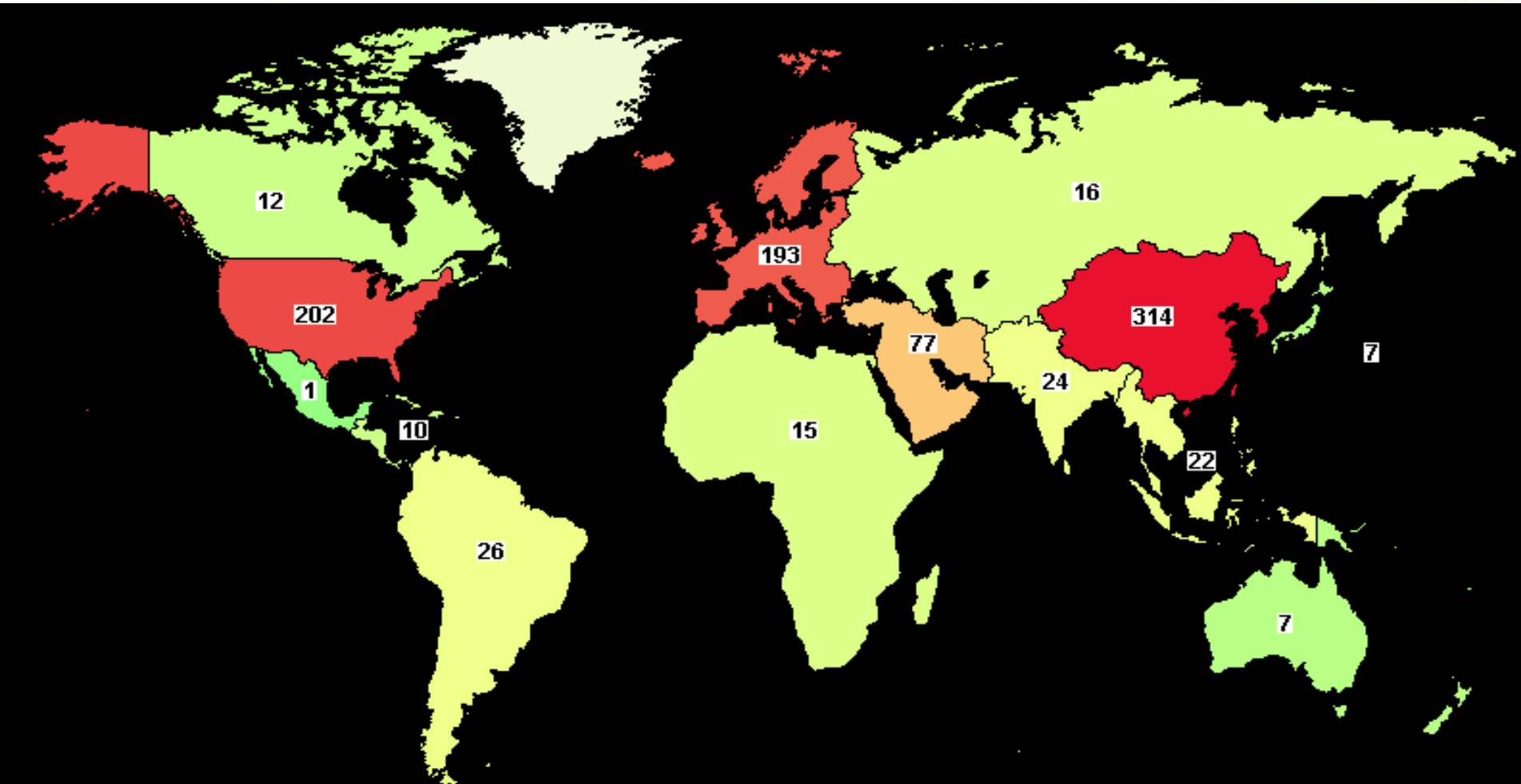
1004 MSC-CLINICAL TRIALS, 10-2019:

~380 are active

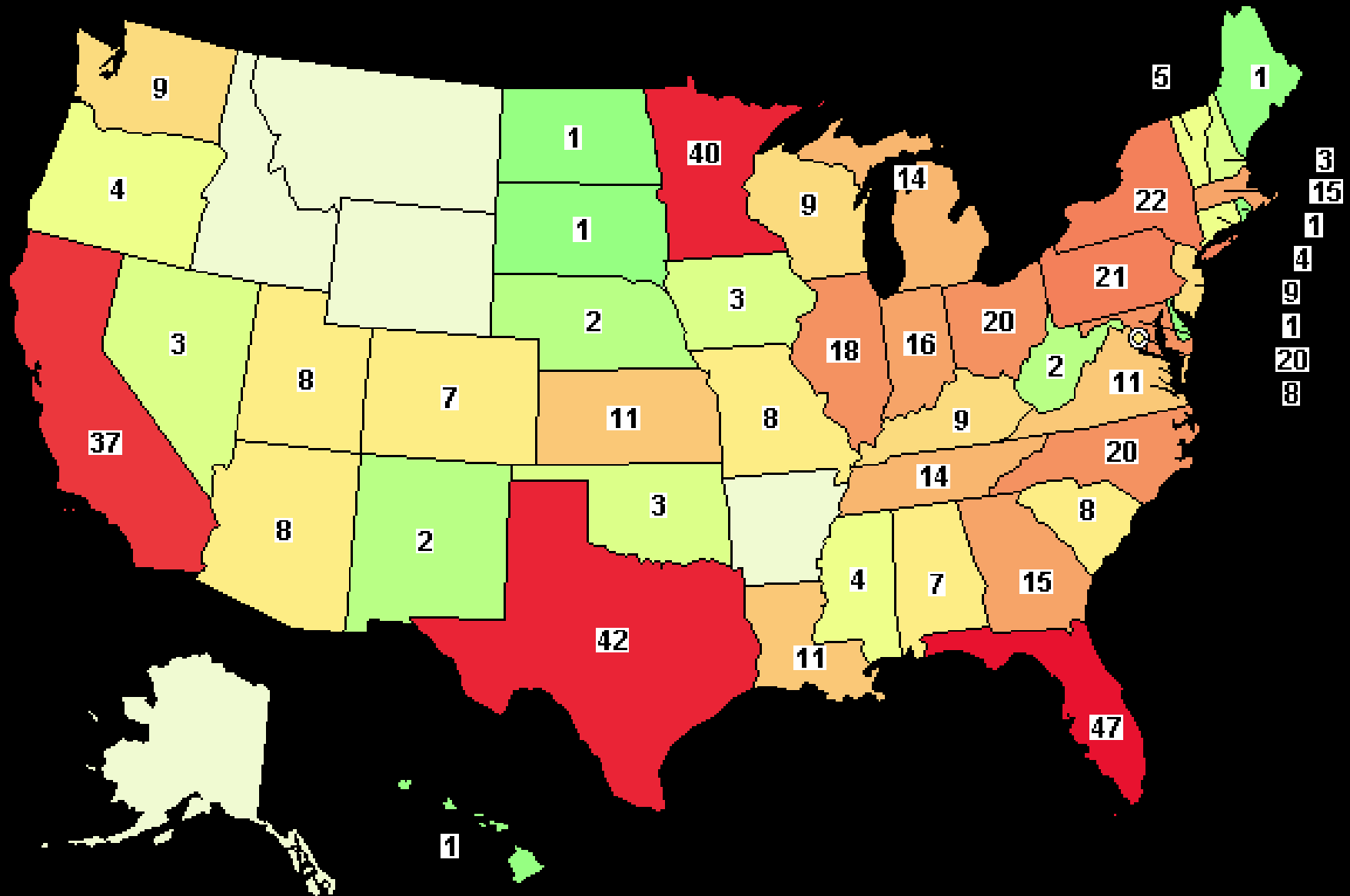
Search of: mesenchymal stem cell - Results on Map - ClinicalTrials.gov

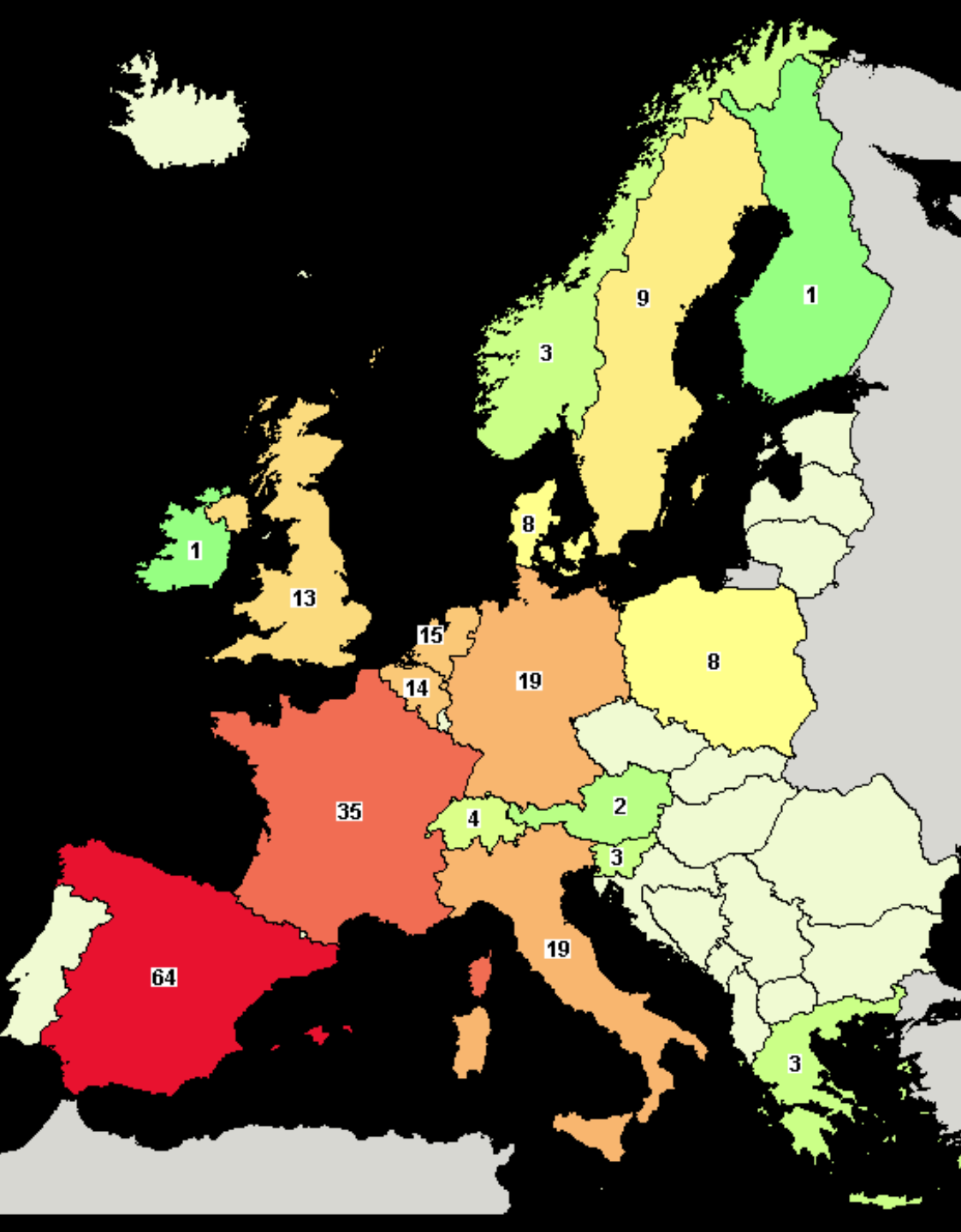
ClinicalTrials.gov
A service of the U.S. National Institutes of Health

[Home](#) [Search](#) [Study Topics](#) [Glossary](#)



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
Autoimmun
Autoimmun
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 Scler
Chor
Prim
Crohn's Disease GvHD
ion Fractures, Diabetic F... GvHD... Hemia, Dilated Cardiomyopathy, eases; Nervous System... ng Autoimmune Diseases, CNS; ie, Graft Versus Host Dise... ended Graft Versus Host 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 Scler
Erythematos
Myelodyspla
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
Partial Medial Menisce
Osteogenesis Imperfect
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.

Rheumatoid Arthritis, Lupus, Autism

MSCs are NOT stromal 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.

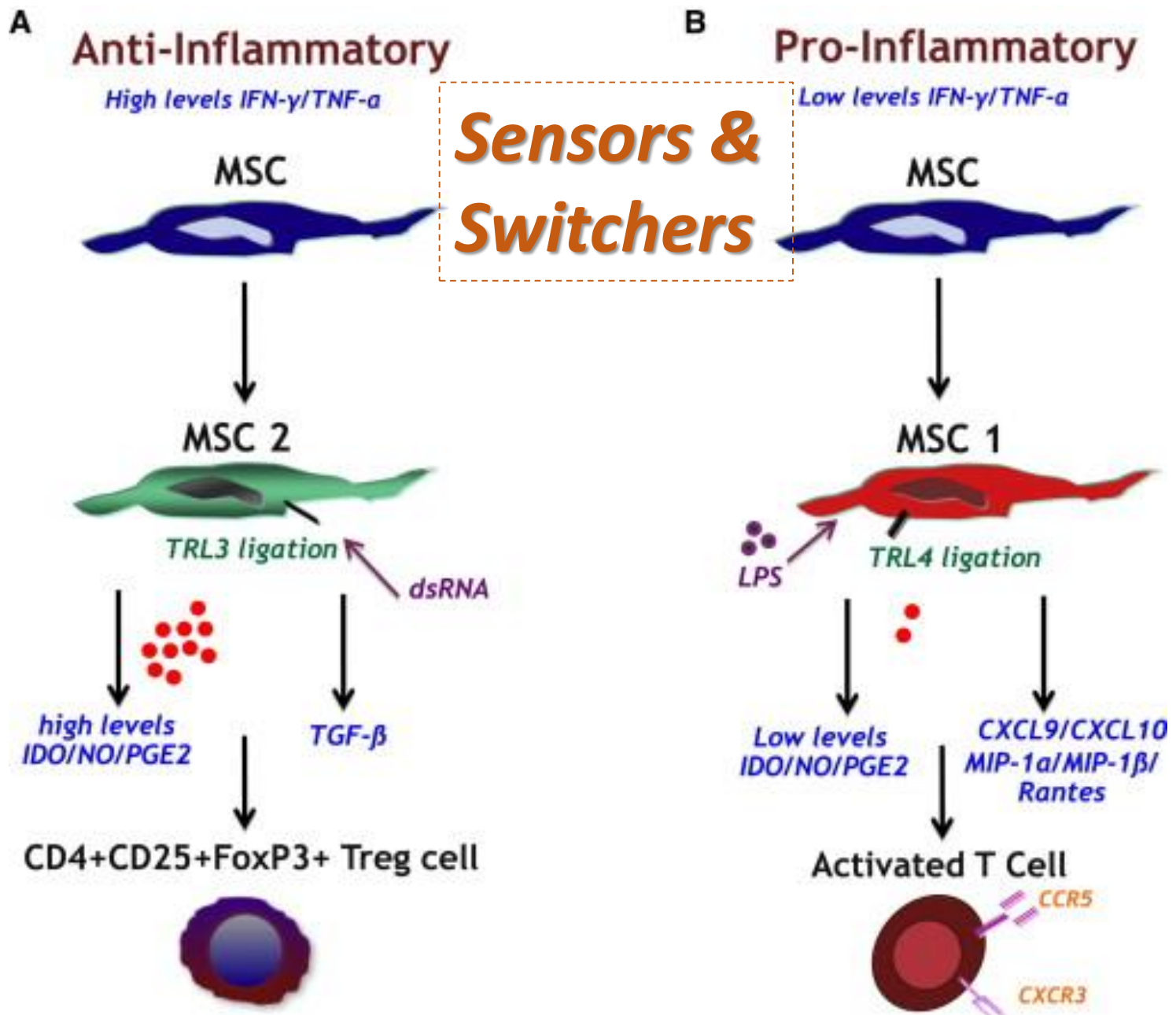
MSC-action: An Immuno-component.

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.



[M. E. Bernardo¹](#), [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 =

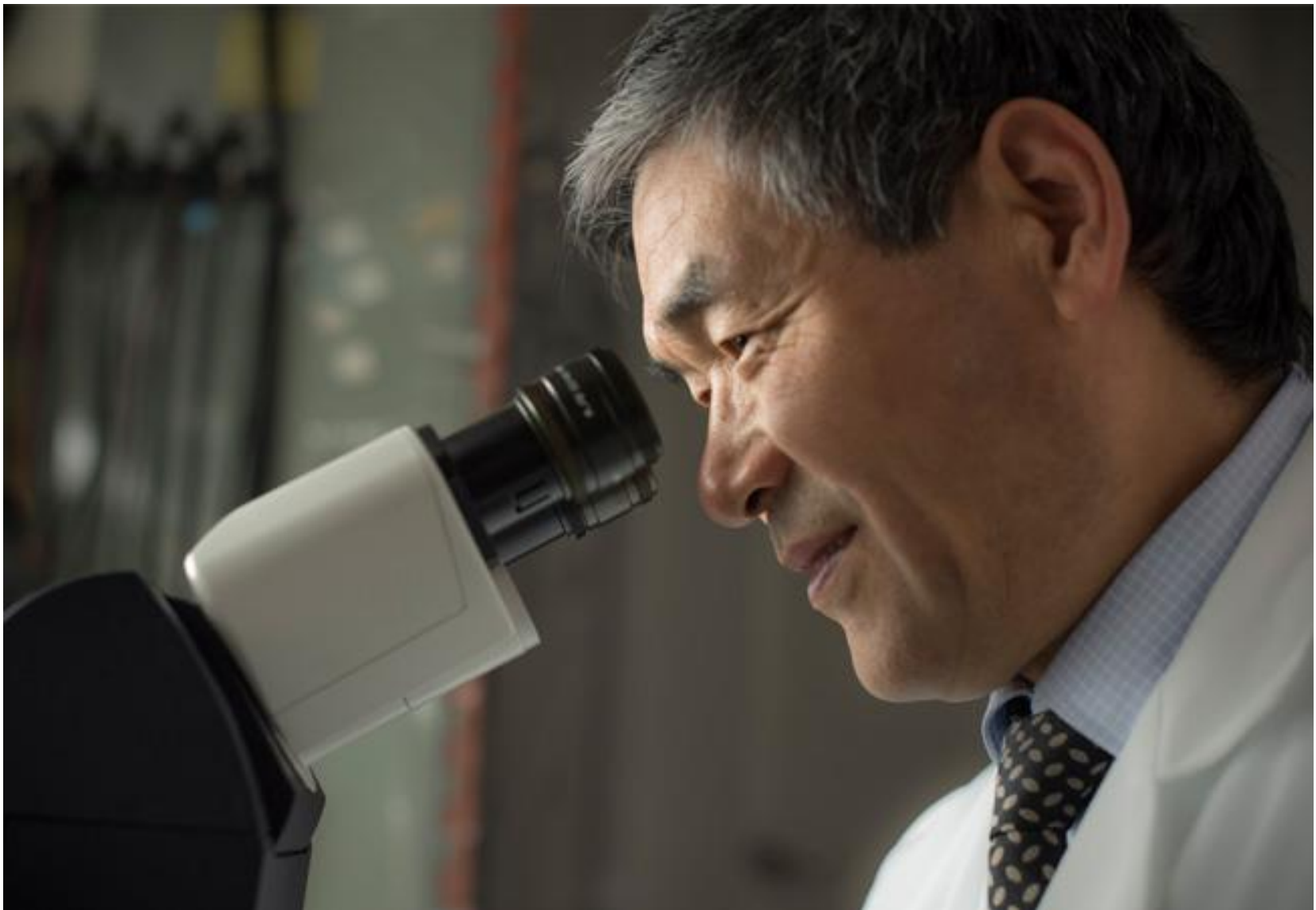
BLACK-and-BLUE MARK

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 **adipose-derived** MSCs were as efficacious as bone marrow-derived cells in reducing neuropathic pain in rats.



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 al*, *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 Report 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%.**
- **Injectations 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-1 β 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: A multi-immuno-component.

LONGTERM THERAPEUTIC EFFECTS???

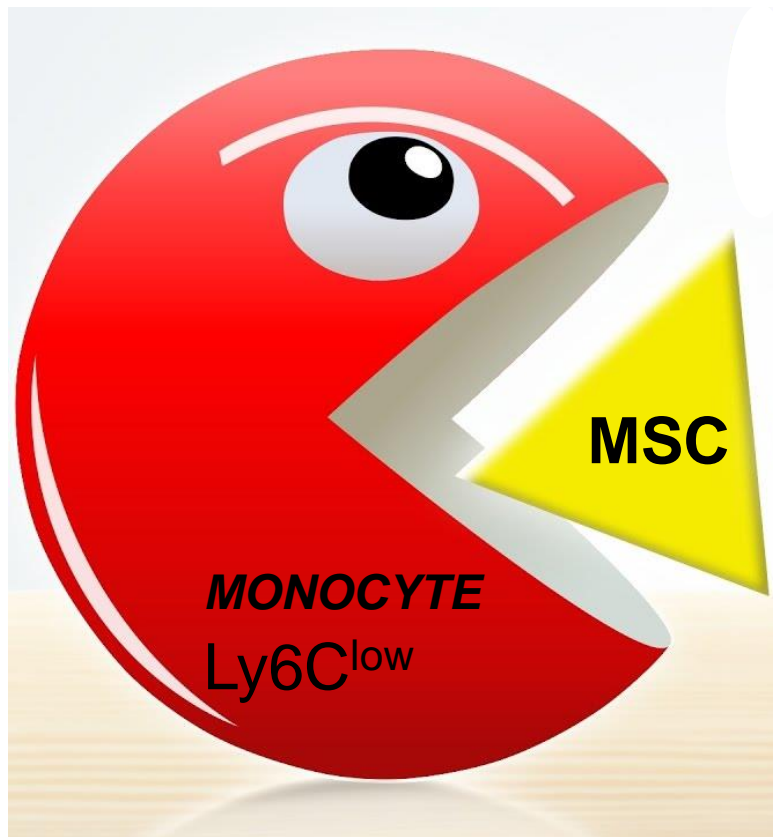
A Regenerative component.

Management of the body's innate regenerative capacity.

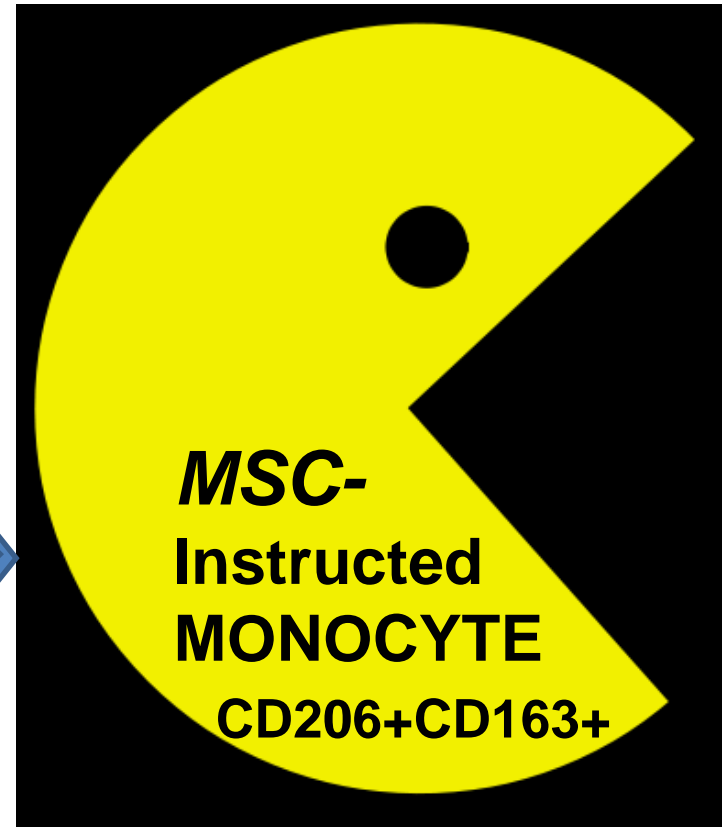
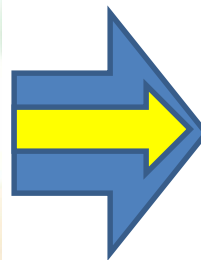
Immunomodulation by hMSCs is triggered by phagocytosis of the hMSCs by MONOCYTIC CELLS.

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



**MSC-Instructed
MONOCYTE**
CD206+CD163+



The diagram illustrates the differentiation of a T-cell into a Regulatory T-cell. On the left, a yellow Pac-Man-like shape representing an MSC-instructed Monocyte is shown against a black background. It has a black dot for an eye and an open mouth. A small red circle representing a T-cell is positioned near its mouth, with a blue starburst indicating an interaction. A large blue arrow with a red outline points from this interaction towards the right. On the right, a red, blob-like shape representing a Regulatory T-cell is shown against a white background. It has two large, white, oval eyes with black pupils. Below the red shape, the text 'REGULATORY T-CELL' is written in bold black letters, followed by the marker 'CD4+CD25^{hi}FoxP3+' in a smaller black font.

**MSC-
instructed
MONOCYTE**

T-cell

**REGULATORY
T-CELL**
CD4⁺CD25^{hi}FoxP3⁺

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 disappear within 24hrs and the cells are found in Ly6C^{low} monocytes and circulation.
- The cells stay at the injury site for a short time. Long-term therapeutic outcomes are from secondary influences.
- CD163⁺ acMSCs to become 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??

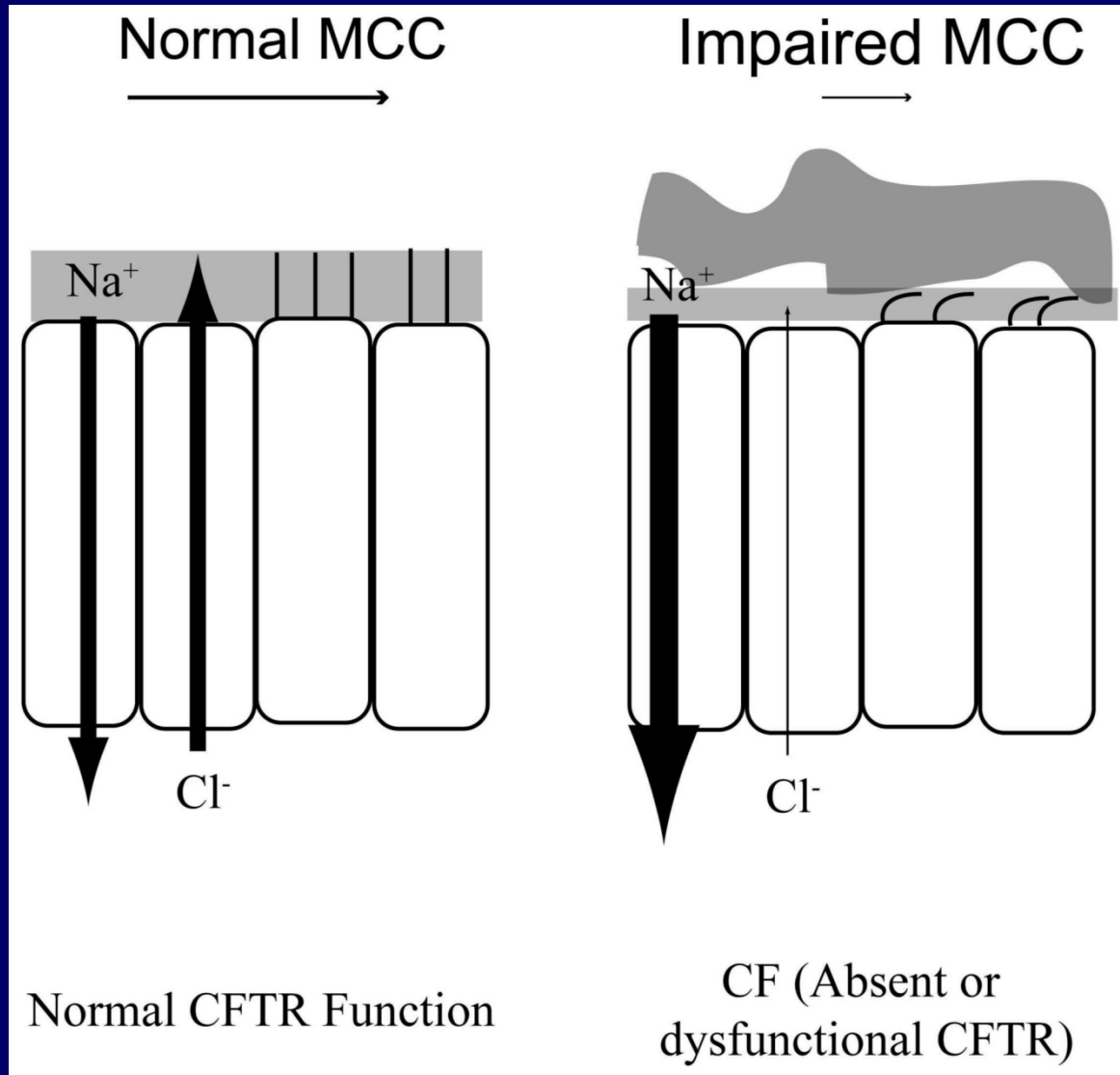
Tracey Bonfeild, PhD



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



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

Deepa Lakshminarayana

Menstrual stem cell banking is a new service that allows women to collect and store their own menstrual blood stem cells for future use. These cells can be used to treat many conditions, including heart disease, diabetes, and Parkinson's disease. The service is being launched in the city soon.

THE PROCESS

Once you have decided to proceed, you will receive a collection kit. You will use this kit to collect your menstrual blood stem cells. The process is simple and painless.

The collection kit includes a small vial and a collection tube. You will use the vial to collect your menstrual blood stem cells. The collection tube is used to collect your menstrual blood. The process is simple and painless.

Menstrual blood can save a life

research Syed Akbar

Menstrual blood stem cells (MSCs) are a type of stem cell that can be used to treat many conditions, including heart disease, diabetes, and Parkinson's disease. These cells are found in menstrual blood and can be collected and stored for future use.

The process of collecting and storing MSCs is simple and painless. Women can collect their own MSCs using a collection kit. The cells are then stored in a vial for future use.

Sabri Chaudhry

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



The process of collecting and storing MSCs is simple and painless. Women can collect their own MSCs using a collection kit. The cells are then stored in a vial for future use.

Menstrual stem cell banking is a new service that allows women to collect and store their own menstrual blood stem cells for future use. These cells can be used to treat many conditions, including heart disease, diabetes, and Parkinson's disease.



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

Treatment in 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*.

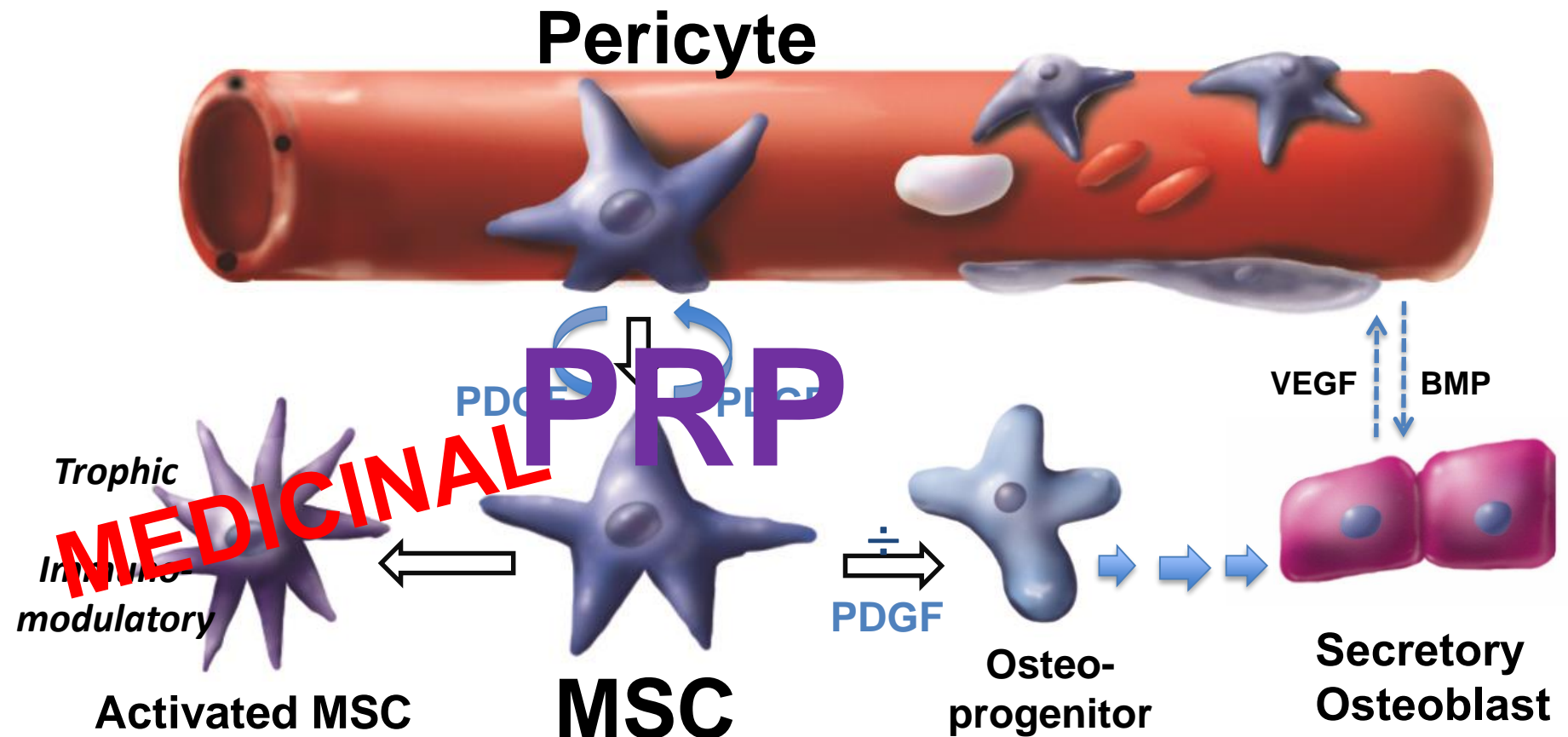
MSCs as site-regulated multi-drug delivery vehicles.

MSCs as **DRUG STORES**.

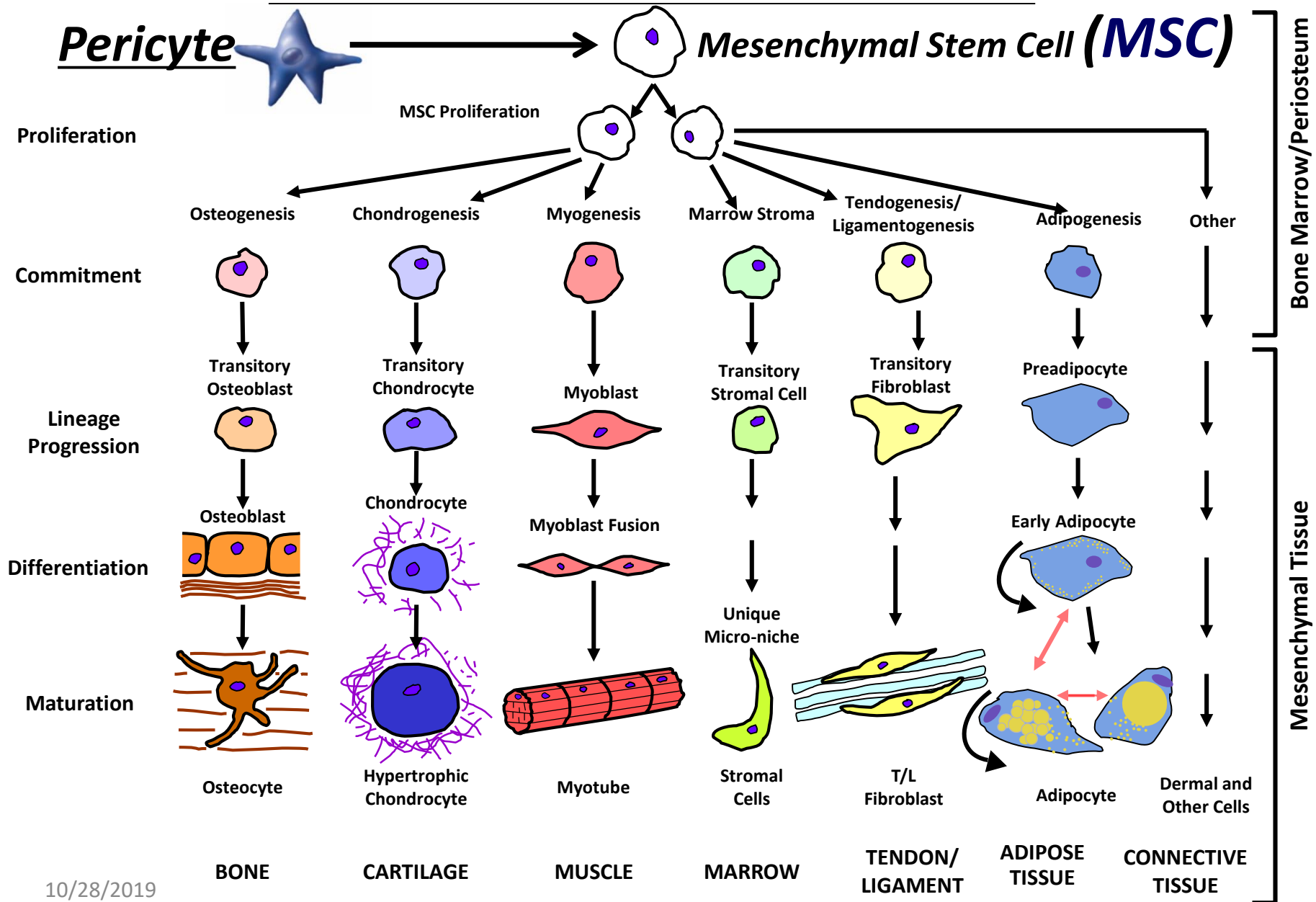
The Paramedic-ER analogy:

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*

Diego Correa



**Rodrigo Somoza,
PhD**

**Diego Correa
MD, PhD**

**Arnold I Caplan,
PhD**

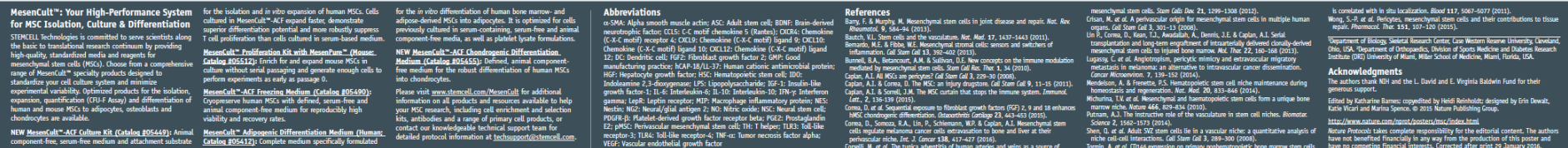
Skeletal Research
Center,
Case Western
Reserve University

Rodrigo Somoza

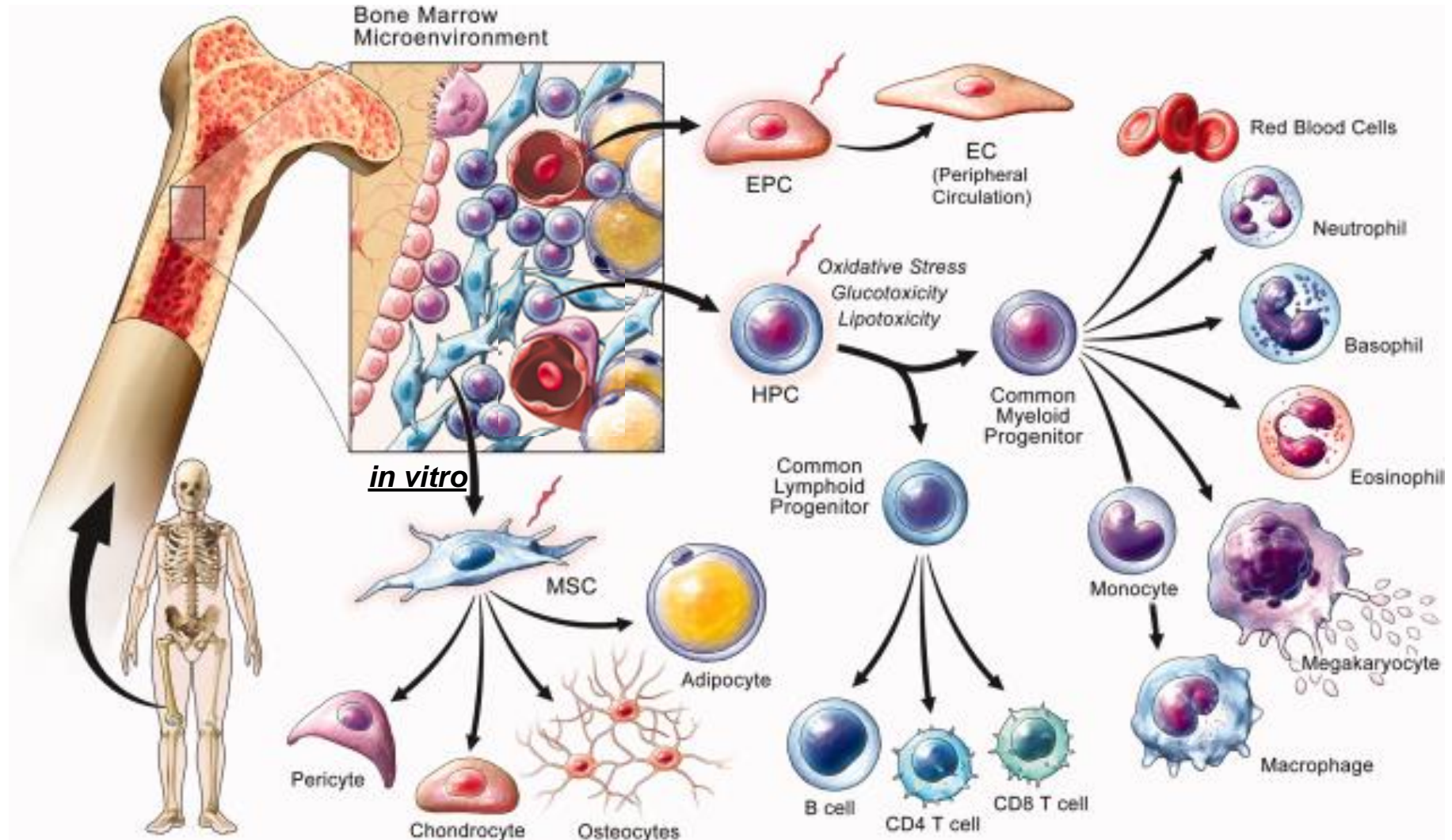


Rodrigo A Somoza¹, Diego Correa^{1,2} & Arnold I Caplan¹

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.



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



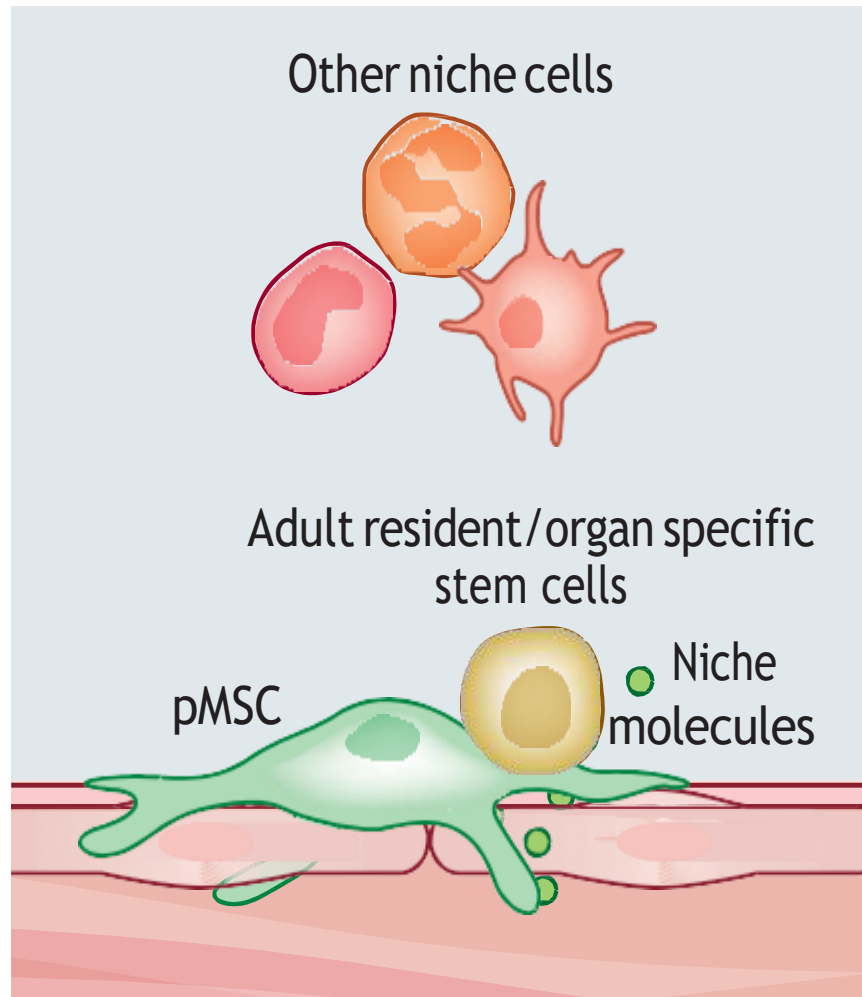
STEM CELLS

3 JAN 2018 DOI: 10.1002/stem.2751

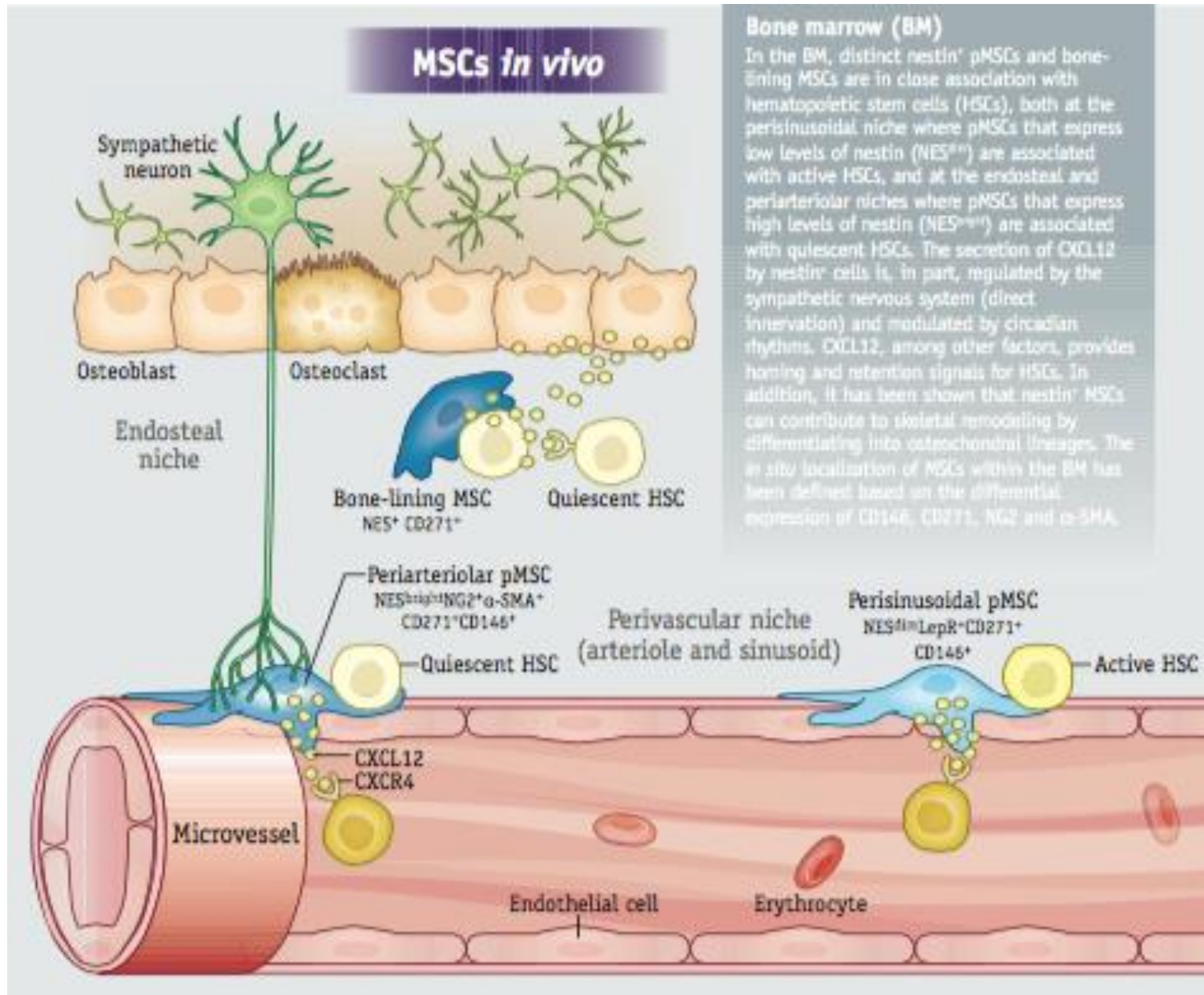
<http://onlinelibrary.wiley.com/doi/10.1002/stem.2751/full#stem2751-fig-0002>

The Universal Stem Cell Niche

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



MSCs *in vivo*: Bone marrow niche



nature protocols

Recipes for Researchers
January 2016 Vol 11 No 1

Roles for mesenchymal stem cells as medicinal signaling cells

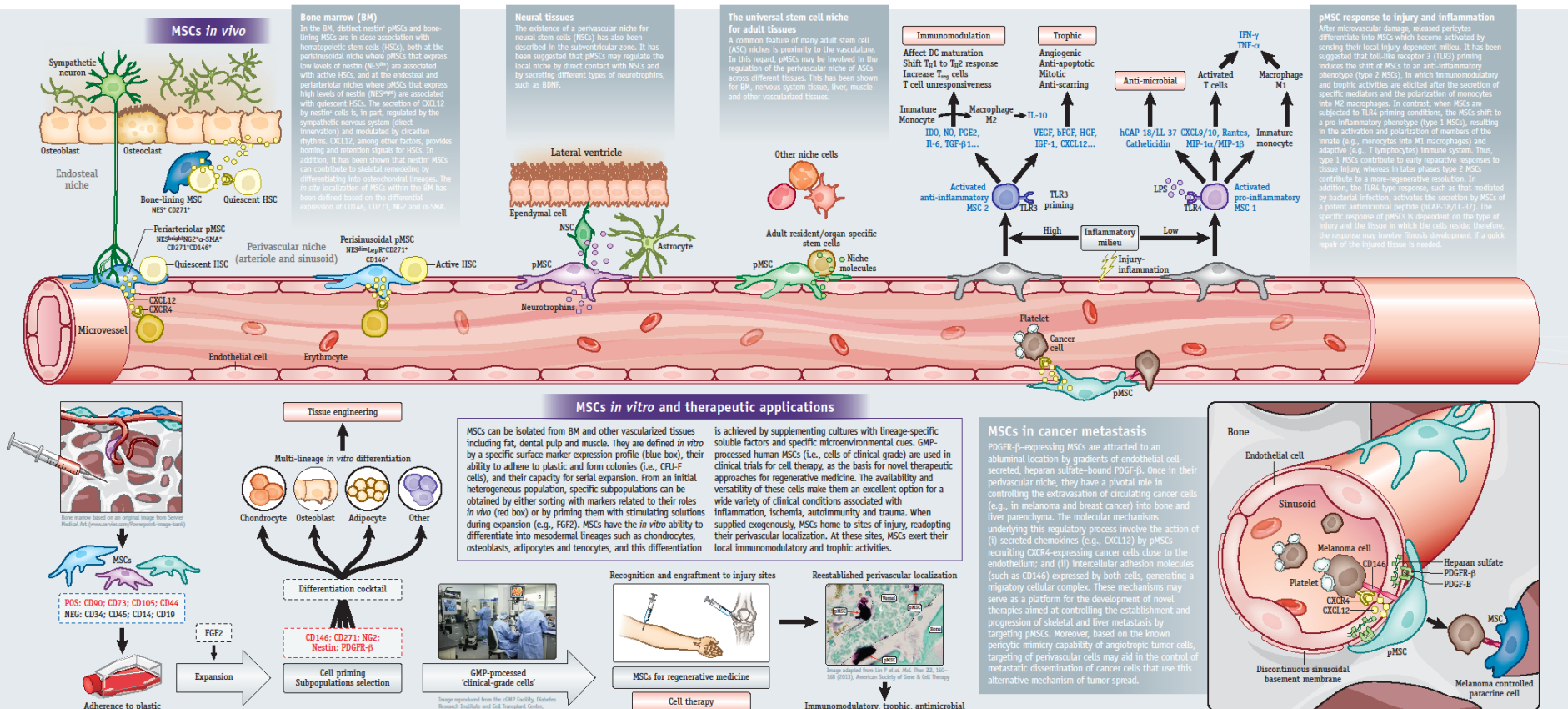
Rodrigo A Somoza¹, Diego Correa^{1,2} & Arnold I Caplan¹



Scientists Helping Scientists™ | WWW.STEMCELL.COM

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.



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.

NEW Mesencult™-ACF Culture Kit (Catalog #05449): Animal component-free, serum-free medium and attachment substrate for the isolation and *in vitro* expansion of human MSCs. Cells cultured in Mesencult™-ACF expand faster, demonstrate superior differentiation potential and more robustly express T cell proliferation than cells cultured in serum-based medium.

Mesencult™ Proliferation Kit with MesenPrime™ (Mesen): Catalog #05512) Enrich for and expand mouse MSCs in culture without serial passaging and generate enough cells to perform experiments as early as passage 0.

Mesencult™-ACF Freezing Medium (Catalog #05400): Cryopreserve human MSCs with defined, serum-free and animal component-free medium for reproducibly high viability and recovery rates.

Mesencult™ Adipogenic Differentiation Medium (Human): Catalog #05412) Complete medium specifically formulated

for the *in vitro* differentiation of human bone marrow- and adipose-derived MSCs into adipocytes. It is optimized for cells previously cultured in serum-containing, serum-free and animal component-free media, as well as platelet-rich formulations.

NEW Mesencult™-ACF Chondrogenic Differentiation Medium (Catalog #05455): Defined, animal component-free medium for the robust differentiation of human MSCs into chondrocytes.

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; C-CK: C-kit; C-CKR: C-kit receptor; C-CKR2: C-kit receptor 2; C-CKR3: C-kit receptor 3; C-CKR4: C-kit receptor 4; C-CKR5: C-kit receptor 5; C-CKR6: C-kit receptor 6; C-CKR7: C-kit receptor 7; C-CKR8: C-kit receptor 8; C-CKR9: C-kit receptor 9; C-CKR10: C-kit receptor 10; C-CKR11: C-kit receptor 11; C-CKR12: C-kit receptor 12; C-CKR13: C-kit receptor 13; C-CKR14: C-kit receptor 14; C-CKR15: C-kit receptor 15; C-CKR16: C-kit receptor 16; C-CKR17: C-kit receptor 17; C-CKR18: C-kit receptor 18; C-CKR19: C-kit receptor 19; C-CKR20: C-kit receptor 20; C-CKR21: C-kit receptor 21; C-CKR22: C-kit receptor 22; C-CKR23: C-kit receptor 23; C-CKR24: C-kit receptor 24; C-CKR25: C-kit receptor 25; C-CKR26: C-kit receptor 26; C-CKR27: C-kit receptor 27; C-CKR28: C-kit receptor 28; C-CKR29: C-kit receptor 29; C-CKR30: C-kit receptor 30; C-CKR31: C-kit receptor 31; C-CKR32: C-kit receptor 32; C-CKR33: C-kit receptor 33; C-CKR34: C-kit receptor 34; C-CKR35: C-kit receptor 35; C-CKR36: C-kit receptor 36; C-CKR37: C-kit receptor 37; C-CKR38: C-kit receptor 38; C-CKR39: C-kit receptor 39; C-CKR40: C-kit receptor 40; C-CKR41: C-kit receptor 41; C-CKR42: C-kit receptor 42; C-CKR43: C-kit receptor 43; C-CKR44: C-kit receptor 44; C-CKR45: C-kit receptor 45; C-CKR46: C-kit receptor 46; C-CKR47: C-kit receptor 47; C-CKR48: C-kit receptor 48; C-CKR49: C-kit receptor 49; C-CKR50: C-kit receptor 50; C-CKR51: C-kit receptor 51; C-CKR52: C-kit receptor 52; C-CKR53: C-kit receptor 53; C-CKR54: C-kit receptor 54; C-CKR55: C-kit receptor 55; C-CKR56: C-kit receptor 56; C-CKR57: C-kit receptor 57; C-CKR58: C-kit receptor 58; C-CKR59: C-kit receptor 59; C-CKR60: C-kit receptor 60; C-CKR61: C-kit receptor 61; C-CKR62: C-kit receptor 62; C-CKR63: C-kit receptor 63; C-CKR64: C-kit receptor 64; C-CKR65: C-kit receptor 65; C-CKR66: C-kit receptor 66; C-CKR67: C-kit receptor 67; C-CKR68: C-kit receptor 68; C-CKR69: C-kit receptor 69; C-CKR70: C-kit receptor 70; C-CKR71: C-kit receptor 71; C-CKR72: C-kit receptor 72; C-CKR73: C-kit receptor 73; C-CKR74: C-kit receptor 74; C-CKR75: C-kit receptor 75; C-CKR76: C-kit receptor 76; C-CKR77: C-kit receptor 77; C-CKR78: C-kit receptor 78; C-CKR79: C-kit receptor 79; C-CKR80: C-kit receptor 80; C-CKR81: C-kit receptor 81; C-CKR82: C-kit receptor 82; C-CKR83: C-kit receptor 83; C-CKR84: C-kit receptor 84; C-CKR85: C-kit receptor 85; C-CKR86: C-kit receptor 86; C-CKR87: C-kit receptor 87; C-CKR88: C-kit receptor 88; C-CKR89: C-kit receptor 89; C-CKR90: C-kit receptor 90; C-CKR91: C-kit receptor 91; C-CKR92: C-kit receptor 92; C-CKR93: C-kit receptor 93; C-CKR94: C-kit receptor 94; C-CKR95: C-kit receptor 95; C-CKR96: C-kit receptor 96; C-CKR97: C-kit receptor 97; C-CKR98: C-kit receptor 98; C-CKR99: C-kit receptor 99; C-CKR100: C-kit receptor 100; C-CKR101: C-kit receptor 101; C-CKR102: C-kit receptor 102; C-CKR103: C-kit receptor 103; C-CKR104: C-kit receptor 104; C-CKR105: C-kit receptor 105; C-CKR106: C-kit receptor 106; C-CKR107: C-kit receptor 107; C-CKR108: C-kit receptor 108; C-CKR109: C-kit receptor 109; C-CKR110: C-kit receptor 110; C-CKR111: C-kit receptor 111; C-CKR112: C-kit receptor 112; C-CKR113: C-kit receptor 113; C-CKR114: C-kit receptor 114; C-CKR115: C-kit receptor 115; C-CKR116: C-kit receptor 116; C-CKR117: C-kit receptor 117; C-CKR118: C-kit receptor 118; C-CKR119: C-kit receptor 119; C-CKR120: C-kit receptor 120; C-CKR121: C-kit receptor 121; C-CKR122: C-kit receptor 122; C-CKR123: C-kit receptor 123; C-CKR124: C-kit receptor 124; C-CKR125: C-kit receptor 125; C-CKR126: C-kit receptor 126; C-CKR127: C-kit receptor 127; C-CKR128: C-kit receptor 128; C-CKR129: C-kit receptor 129; C-CKR130: C-kit receptor 130; C-CKR131: C-kit receptor 131; C-CKR132: C-kit receptor 132; C-CKR133: C-kit receptor 133; C-CKR134: C-kit receptor 134; C-CKR135: C-kit receptor 135; C-CKR136: C-kit receptor 136; C-CKR137: C-kit receptor 137; C-CKR138: C-kit receptor 138; C-CKR139: C-kit receptor 139; C-CKR140: C-kit receptor 140; C-CKR141: C-kit receptor 141; C-CKR142: C-kit receptor 142; C-CKR143: C-kit receptor 143; C-CKR144: C-kit receptor 144; C-CKR145: C-kit receptor 145; C-CKR146: C-kit receptor 146; C-CKR147: C-kit receptor 147; C-CKR148: C-kit receptor 148; C-CKR149: C-kit receptor 149; C-CKR150: C-kit receptor 150; C-CKR151: C-kit receptor 151; C-CKR152: C-kit receptor 152; C-CKR153: C-kit receptor 153; C-CKR154: C-kit receptor 154; C-CKR155: C-kit receptor 155; C-CKR156: C-kit receptor 156; C-CKR157: C-kit receptor 157; C-CKR158: C-kit receptor 158; C-CKR159: C-kit receptor 159; C-CKR160: C-kit receptor 160; C-CKR161: C-kit receptor 161; C-CKR162: C-kit receptor 162; C-CKR163: C-kit receptor 163; C-CKR164: C-kit receptor 164; C-CKR165: C-kit receptor 165; C-CKR166: C-kit receptor 166; C-CKR167: C-kit receptor 167; C-CKR168: C-kit receptor 168; C-CKR169: C-kit receptor 169; C-CKR170: C-kit receptor 170; C-CKR171: C-kit receptor 171; C-CKR172: C-kit receptor 172; C-CKR173: C-kit receptor 173; C-CKR174: C-kit receptor 174; C-CKR175: C-kit receptor 175; C-CKR176: C-kit receptor 176; C-CKR177: C-kit receptor 177; C-CKR178: C-kit receptor 178; C-CKR179: C-kit receptor 179; C-CKR180: C-kit receptor 180; C-CKR181: C-kit receptor 181; C-CKR182: C-kit receptor 182; C-CKR183: C-kit receptor 183; C-CKR184: C-kit receptor 184; C-CKR185: C-kit receptor 185; C-CKR186: C-kit receptor 186; C-CKR187: C-kit receptor 187; C-CKR188: C-kit receptor 188; C-CKR189: C-kit receptor 189; C-CKR190: C-kit receptor 190; C-CKR191: C-kit receptor 191; C-CKR192: C-kit receptor 192; C-CKR193: C-kit receptor 193; C-CKR194: C-kit receptor 194; C-CKR195: C-kit receptor 195; C-CKR196: C-kit receptor 196; C-CKR197: C-kit receptor 197; C-CKR198: C-kit receptor 198; C-CKR199: C-kit receptor 199; C-CKR200: C-kit receptor 200; C-CKR201: C-kit receptor 201; C-CKR202: C-kit receptor 202; C-CKR203: C-kit receptor 203; C-CKR204: C-kit receptor 204; C-CKR205: C-kit receptor 205; C-CKR206: C-kit receptor 206; C-CKR207: C-kit receptor 207; C-CKR208: C-kit receptor 208; C-CKR209: C-kit receptor 209; C-CKR210: C-kit receptor 210; C-CKR211: C-kit receptor 211; C-CKR212: C-kit receptor 212; C-CKR213: C-kit receptor 213; C-CKR214: C-kit receptor 214; C-CKR215: C-kit receptor 215; C-CKR216: C-kit receptor 216; C-CKR217: C-kit receptor 217; C-CKR218: C-kit receptor 218; C-CKR219: C-kit receptor 219; C-CKR220: C-kit receptor 220; C-CKR221: C-kit receptor 221; C-CKR222: C-kit receptor 222; C-CKR223: C-kit receptor 223; C-CKR224: C-kit receptor 224; C-CKR225: C-kit receptor 225; C-CKR226: C-kit receptor 226; C-CKR227: C-kit receptor 227; C-CKR228: C-kit receptor 228; C-CKR229: C-kit receptor 229; C-CKR230: C-kit receptor 230; C-CKR231: C-kit receptor 231; C-CKR232: C-kit receptor 232; C-CKR233: C-kit receptor 233; C-CKR234: C-kit receptor 234; C-CKR235: C-kit receptor 235; C-CKR236: C-kit receptor 236; C-CKR237: C-kit receptor 237; C-CKR238: C-kit receptor 238; C-CKR239: C-kit receptor 239; C-CKR240: C-kit receptor 240; C-CKR241: C-kit receptor 241; C-CKR242: C-kit receptor 242; C-CKR243: C-kit receptor 243; C-CKR244: C-kit receptor 244; C-CKR245: C-kit receptor 245; C-CKR246: C-kit receptor 246; C-CKR247: C-kit receptor 247; C-CKR248: C-kit receptor 248; C-CKR249: C-kit receptor 249; C-CKR250: C-kit receptor 250; C-CKR251: C-kit receptor 251; C-CKR252: C-kit receptor 252; C-CKR253: C-kit receptor 253; C-CKR254: C-kit receptor 254; C-CKR255: C-kit receptor 255; C-CKR256: C-kit receptor 256; C-CKR257: C-kit receptor 257; C-CKR258: C-kit receptor 258; C-CKR259: C-kit receptor 259; C-CKR260: C-kit receptor 260; C-CKR261: C-kit receptor 261; C-CKR262: C-kit receptor 262; C-CKR263: C-kit receptor 263; C-CKR264: C-kit receptor 264; C-CKR265: C-kit receptor 265; C-CKR266: C-kit receptor 266; C-CKR267: C-kit receptor 267; C-CKR268: C-kit receptor 268; C-CKR269: C-kit receptor 269; C-CKR270: C-kit receptor 270; C-CKR271: C-kit receptor 271; C-CKR272: C-kit receptor 272; C-CKR273: C-kit receptor 273; C-CKR274: C-kit receptor 274; C-CKR275: C-kit receptor 275; C-CKR276: C-kit receptor 276; C-CKR277: C-kit receptor 277; C-CKR278: C-kit receptor 278; C-CKR279: C-kit receptor 279; C-CKR280: C-kit receptor 280; C-CKR281: C-kit receptor 281; C-CKR282: C-kit receptor 282; C-CKR283: C-kit receptor 283; C-CKR284: C-kit receptor 284; C-CKR285: C-kit receptor 285; C-CKR286: C-kit receptor 286; C-CKR287: C-kit receptor 287; C-CKR288: C-kit receptor 288; C-CKR289: C-kit receptor 289; C-CKR290: C-kit receptor 290; C-CKR291: C-kit receptor 291; C-CKR292: C-kit receptor 292; C-CKR293: C-kit receptor 293; C-CKR294: C-kit receptor 294; C-CKR295: C-kit receptor 295; C-CKR296: C-kit receptor 296; C-CKR297: C-kit receptor 297; C-CKR298: C-kit receptor 298; C-CKR299: C-kit receptor 299; C-CKR300: C-kit receptor 300; C-CKR301: C-kit receptor 301; C-CKR302: C-kit receptor 302; C-CKR303: C-kit receptor 303; C-CKR304: C-kit receptor 304; C-CKR305: C-kit receptor 305; C-CKR306: C-kit receptor 306; C-CKR307: C-kit receptor 307; C-CKR308: C-kit receptor 308; C-CKR309: C-kit receptor 309; C-CKR310: C-kit receptor 310; C-CKR311: C-kit receptor 311; C-CKR312: C-kit receptor 312; C-CKR313: C-kit receptor 313; C-CKR314: C-kit receptor 314; C-CKR315: C-kit receptor 315; C-CKR316: C-kit receptor 316; C-CKR317: C-kit receptor 317; C-CKR318: C-kit receptor 318; C-CKR319: C-kit receptor 319; C-CKR320: C-kit receptor 320; C-CKR321: C-kit receptor 321; C-CKR322: C-kit receptor 322; C-CKR323: C-kit receptor 323; C-CKR324: C-kit receptor 324; C-CKR325: C-kit receptor 325; C-CKR326: C-kit receptor 326; C-CKR327: C-kit receptor 327; C-CKR328: C-kit receptor 328; C-CKR329: C-kit receptor 329; C-CKR330: C-kit receptor 330; C-CKR331: C-kit receptor 331; C-CKR332: C-kit receptor 332; C-CKR333: C-kit receptor 333; C-CKR334: C-kit receptor 334; C-CKR335: C-kit receptor 335; C-CKR336: C-kit receptor 336; C-CKR337: C-kit receptor 337; C-CKR338: C-kit receptor 338; C-CKR339: C-kit receptor 339; C-CKR340: C-kit receptor 340; C-CKR341: C-kit receptor 341; C-CKR342: C-kit receptor 342; C-CKR343: C-kit receptor 343; C-CKR344: C-kit receptor 344; C-CKR345: C-kit receptor 345; C-CKR346: C-kit receptor 346; C-CKR347: C-kit receptor 347; C-CKR348: C-kit receptor 348; C-CKR349: C-kit receptor 349; C-CKR350: C-kit receptor 350; C-CKR351: C-kit receptor 351; C-CKR352: C-kit receptor 352; C-CKR353: C-kit receptor 353; C-CKR354: C-kit receptor 354; C-CKR355: C-kit receptor 355; C-CKR356: C-kit receptor 356; C-CKR357: C-kit receptor 357; C-CKR358: C-kit receptor 358; C-CKR359: C-kit receptor 359; C-CKR360: C-kit receptor 360; C-CKR361: C-kit receptor 361; C-CKR362: C-kit receptor 362; C-CKR363: C-kit receptor 363; C-CKR364: C-kit receptor 364; C-CKR365: C-kit receptor 365; C-CKR366: C-kit receptor 366; C-CKR367: C-kit receptor 367; C-CKR368: C-kit receptor 368; C-CKR369: C-kit receptor 369; C-CKR370: C-kit receptor 370; C-CKR371: C-kit receptor 371; C-CKR372: C-kit receptor 372; C-CKR373: C-kit receptor 373; C-CKR374: C-kit receptor 374; C-CKR375: C-kit receptor 375; C-CKR376: C-kit receptor 376; C-CKR377: C-kit receptor 377; C-CKR378: C-kit receptor 378; C-CKR379: C-kit receptor 379; C-CKR380: C-kit receptor 380; C-CKR381: C-kit receptor 381; C-CKR382: C-kit receptor 382; C-CKR383: C-kit receptor 383; C-CKR384: C-kit receptor 384; C-CKR385: C-kit receptor 385; C-CKR386: C-kit receptor 386; C-CKR387: C-kit receptor 387; C-CKR388: C-kit receptor 388; C-CKR389: C-kit receptor 389; C-CKR390: C-kit receptor 390; C-CKR391: C-kit receptor 391; C-CKR392: C-kit receptor 392; C-CKR393: C-kit receptor 393; C-CKR394: C-kit receptor 394; C-CKR395: C-kit receptor 395; C-CKR396: C-kit receptor 396; C-CKR397: C-kit receptor 397; C-CKR398: C-kit receptor 398; C-CKR399: C-kit receptor 399; C-CKR400: C-kit receptor 400; C-CKR401: C-kit receptor 401; C-CKR402: C-kit receptor 402; C-CKR403: C-kit receptor 403; C-CKR404: C-kit receptor 404; C-CKR405: C-kit receptor 405; C-CKR406: C-kit receptor 406; C-CKR407: C-kit receptor 407; C-CKR408: C-kit receptor 408; C-CKR409: C-kit receptor 409; C-CKR410: C-kit receptor 410; C-CKR411: C-kit receptor 411; C-CKR412: C-kit receptor 412; C-CKR413: C-kit receptor 413; C-CKR414: C-kit receptor 414; C-CKR415: C-kit receptor 415; C-CKR416: C-kit receptor 416; C-CKR417: C-kit receptor 417; C-CKR418: C-kit receptor 418; C-CKR419: C-kit receptor 419; C-CKR420: C-kit receptor 420; C-CKR421: C-kit receptor 421; C-CKR422: C-kit receptor 422; C-CKR423: C-kit receptor 423; C-CKR424: C-kit receptor 424; C-CKR425: C-kit receptor 425; C-CKR426: C-kit receptor 426; C-CKR427: C-kit receptor 427; C-CKR428: C-kit receptor 428; C-CKR429: C-kit receptor 429; C-CKR430: C-kit receptor 430; C-CKR431: C-kit receptor 431; C-CKR432: C-kit receptor 432; C-CKR433: C-kit receptor 433; C-CKR434: C-kit receptor 434; C-CKR435: C-kit receptor 435; C-CKR436: C-kit receptor 436; C-CKR437: C-kit receptor 437; C-CKR438: C-kit receptor 438; C-CKR439: C-kit receptor 439; C-CKR440: C-kit receptor 440; C-CKR441: C-kit receptor 441; C-CKR442: C-kit receptor 442; C-CKR443: C-kit receptor 443; C-CKR444: C-kit receptor 444; C-CKR445: C-kit receptor 445; C-CKR446: C-kit receptor 446; C-CKR447: C-kit receptor 447; C-CKR448: C-kit receptor 448; C-CKR449: C-kit receptor 449; C-CKR450: C-kit receptor 450; C-CKR451: C-kit receptor 451; C-CKR452: C-kit receptor 452; C-CKR453: C-kit receptor 453; C-CKR454: C-kit receptor 454; C-CKR455: C-kit receptor 455; C-CKR456: C-kit receptor 456; C-CKR457: C-kit receptor 457; C-CKR458: C-kit receptor 458; C-CKR459: C-kit receptor 459; C-CKR460: C-kit receptor 460; C-CKR461: C-kit receptor 461; C-CKR462: C-kit receptor 462; C-CKR463: C-kit receptor 463; C-CKR464: C-kit receptor 464; C-CKR465: C-kit receptor 465; C-CKR466: C-kit receptor 466; C-CKR467: C-kit receptor 467; C-CKR468: C-kit receptor 468; C-CKR469: C-kit receptor 469; C-CKR470: C-kit receptor 470; C-CKR471: C-kit receptor 471; C-CKR472: C-kit receptor 472; C-CKR473: C-kit receptor 473; C-CKR474: C-kit receptor 474; C-CKR475: C-kit receptor 475; C-CKR476: C-kit receptor 476; C-CKR477: C-kit receptor 477; C-CKR478: C-kit receptor 478; C-CKR479: C-kit receptor 479; C-CKR480: C-kit receptor 480; C-CKR481: C-kit receptor 481; C-CKR482: C-kit receptor 482; C-CKR483: C-kit receptor 483; C-CKR484: C-kit receptor 484; C-CKR485: C-kit receptor 485; C-CKR486: C-kit receptor 486; C-CKR487: C-kit receptor 487; C-CKR488: C-kit receptor 488; C-CKR489: C-kit receptor 489; C-CKR490: C-kit receptor 490; C-CKR491: C-kit receptor 491; C-CKR492: C-kit receptor 492; C-CKR493: C-kit receptor 493; C-CKR494: C-kit receptor 494; C-CKR495: C-kit receptor 495; C-CKR496: C-kit receptor 496; C-CKR497: C-kit receptor 497; C-CKR498: C-kit receptor 498; C-CKR499: C-kit receptor 499; C-CKR500: C-kit receptor 500; C-CKR501: C-kit receptor 501; C-CKR502: C-kit receptor 502; C-CKR503: C-kit receptor 503; C-CKR504: C-kit receptor 504; C-CKR505: C-kit receptor 505; C-CKR506: C-kit receptor 506; C-CKR507: C-kit receptor 507; C-CKR508: C-kit receptor 508; C-CKR509: C-kit receptor 509; C-CKR510: C-kit receptor 510; C-CKR511: C-kit receptor 511; C-CKR512: C-kit receptor 512; C-CKR513: C-kit receptor 513; C-CKR514: C-kit receptor 514; C-CKR515: C-kit receptor 515; C-CKR516: C-kit receptor 516; C-CKR517: C-kit receptor 517; C-CKR518: C-kit receptor 518; C-CKR519: C-kit receptor 519; C-CKR520: C-kit receptor 520; C-CKR521: C-kit receptor 521; C-CKR522: C-kit receptor 522; C-CKR523: C-kit receptor 523; C-CKR524: C-kit receptor 524; C-CKR525: C-kit receptor 525; C-CKR526: C-kit receptor 526; C-CKR527: C-kit receptor 527; C-CKR528: C-kit receptor 528; C-CKR529: C-kit receptor 529; C-CKR530: C-kit receptor 530; C-CKR531: C-kit receptor 531; C-CKR532: C-kit receptor 532; C-CKR533: C-kit receptor 533; C-CKR534: C-kit receptor 534; C-CKR535: C-kit receptor 535; C-CKR536: C-kit receptor 536; C-CKR537: C-kit receptor 537; C-CKR538: C-kit receptor 538; C-CKR539: C-kit receptor 539; C-CKR540: C-kit receptor 540; C-CKR541: C-kit receptor 541; C-CKR542: C-kit receptor 542; C-CKR543: C-kit receptor 543; C-CKR544: C-kit receptor 544; C-CKR545: C-kit receptor 545; C-CKR546: C-kit receptor 546; C-CKR547: C-kit receptor 547; C-CKR548: C-kit receptor 548; C-CKR549: C-kit receptor 549; C-CKR550: C-kit receptor 550; C-CKR551: C-kit receptor 551; C-CKR552: C-kit receptor 552; C-CKR553: C-kit receptor 553; C-CKR554: C-kit receptor 554; C-CKR555: C-kit receptor 555; C-CKR556: C-kit receptor 556; C-CKR557: C-kit receptor 557; C-CKR558: C-kit receptor 558; C-CKR559: C-kit receptor 559; C-CKR560: C-kit receptor 560; C-CKR561: C-kit receptor 561; C-CKR562: C-kit receptor 562; C-CKR563: C-kit receptor 563; C-CKR564: C-kit receptor 564; C-CKR565: C-kit receptor 565; C-CKR566: C-kit receptor 566; C-CKR567: C-kit receptor 567; C-CKR568: C-kit receptor 568; C-CKR569: C-kit receptor 569; C-CKR570: C-kit receptor 570; C-CKR571: C-kit receptor 571; C-CKR572: C-kit receptor 572; C-CKR573: C-kit receptor 573; C-CKR574: C-kit receptor 574; C-CKR575: C-kit receptor 575; C-CKR576: C-kit receptor 576; C-CKR577: C-kit receptor 577; C-CKR578: C-kit receptor 578; C-CKR579: C-kit receptor 579; C-CKR580: C-kit receptor 580; C-CKR581: C-kit receptor 581; C-CKR582: C-kit receptor 582; C-CKR583: C-kit receptor 583; C-CKR584: C-kit receptor 584; C-CKR585: C-kit receptor 585; C-CKR586: C-kit receptor 586; C-CKR587: C-kit receptor 587; C-CKR588: C-kit receptor 588; C-CKR589: C-kit receptor 589; C-CKR590: C-kit receptor 590; C-CKR591: C-kit receptor 591; C-CKR592: C-kit receptor 592; C-CKR593: C-kit receptor 593; C-CKR594: C-kit receptor 594; C-CKR595: C-kit receptor 595; C-CKR596: C-kit receptor 596; C-CKR597: C-kit receptor 597; C-CKR598: C-kit receptor 598; C-CKR599: C-kit receptor 599; C-CKR600: C-kit receptor 600; C-CKR601: C-kit receptor 601; C-CKR602: C-kit receptor 602; C-CKR603: C-kit receptor 603; C-CKR604: C-kit receptor 604; C-CKR605: C-kit receptor 605; C-CKR606: C-kit receptor 606; C-CKR607: C-kit receptor 607; C-CKR608: C-kit receptor 608; C-CKR609: C-kit receptor 609; C-CKR610: C-kit receptor 610; C-CKR611: C-kit receptor 611; C-CKR612: C-kit receptor 612; C-CKR613: C-kit receptor 613; C-CKR614: C-kit receptor 614; C-CKR615: C-kit receptor 615; C-CKR616: C-kit receptor 616; C-CKR617: C-kit receptor 617; C-CKR618: C-kit receptor 618; C-CKR619: C-kit receptor 619; C-CKR620: C-kit receptor 620; C-CKR621: C-kit receptor 621; C-CKR622: C-kit receptor 622; C-CKR623: C-kit receptor 623; C-CKR624: C-kit receptor 624; C-CKR625: C-kit receptor 625; C-CKR626: C-kit receptor 626; C-CKR627: C-kit receptor 627; C-CKR628: C-kit receptor 628; C-CKR629: C-kit receptor 629; C-CKR630: C-kit receptor 630; C-CKR631: C-kit receptor 631; C-CKR632: C-kit receptor 632; C-CKR633: C-kit receptor 633; C-CKR634: C-kit receptor 634; C-CKR635: C-kit receptor 635; C-CKR636: C-kit receptor 636; C-CKR637: C-kit receptor 637; C-CKR638: C-kit receptor 638; C-CKR639: C-kit receptor 639; C-CKR640: C-kit receptor 640; C-CKR641: C-kit receptor 641; C-CKR642: C-kit receptor 642; C-CKR643: C-kit receptor 643; C-CKR644: C-kit receptor 644; C-CKR645: C-kit receptor 645; C-CKR646: C-kit receptor 646; C-CKR647: C-kit receptor 647; C-CKR648: C-kit receptor 648; C-CKR649: C-kit receptor 649; C-CKR650: C-kit receptor 650; C-CKR651: C-kit receptor 651; C-CKR652: C-kit receptor 652; C-CKR653: C-kit receptor 653; C-CKR654: C-kit receptor 654; C-CKR655: C-kit receptor 655; C-CKR656: C-kit receptor 656; C-CKR657: C-kit receptor 657; C-CKR658: C-kit receptor 658; C-CKR659: C-kit receptor 659; C-CKR660: C-kit receptor 660; C-CKR661: C-kit receptor 661; C-CKR662: C-kit receptor 662; C-CKR663: C-kit receptor 663; C-CKR664: C-kit receptor 664; C-CKR665: C-kit receptor 665; C-CKR666: C-kit receptor 666; C-CKR667: C-kit receptor 667; C-CKR668: C-kit receptor 668; C-CKR669: C-kit receptor 669; C-CKR670: C-kit receptor 670; C-CKR671: C-kit receptor 671; C-CKR672: C-kit receptor 672; C-CKR673: C-kit receptor 673; C-CKR674: C-kit receptor 674; C-CKR675: C-kit receptor 675; C-CKR676: C-kit receptor 676; C-CKR677: C-kit receptor 677; C-CKR678

MSCs MANAGE YOUR REGENERATIVE POTENTIAL

The CAPLAN FORECAST:

**The MSC story will change the
way medicine is practiced!!**

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

19th Annual

**CELL-BASED THERAPIES
& TISSUE ENGINEERING**

CTTE

**SHORT
COURSE**



CWRU

2020

May 12-14, 2020

<http://caslabs.case.edu/cttecourse/>

CELL-BASED THERAPY:

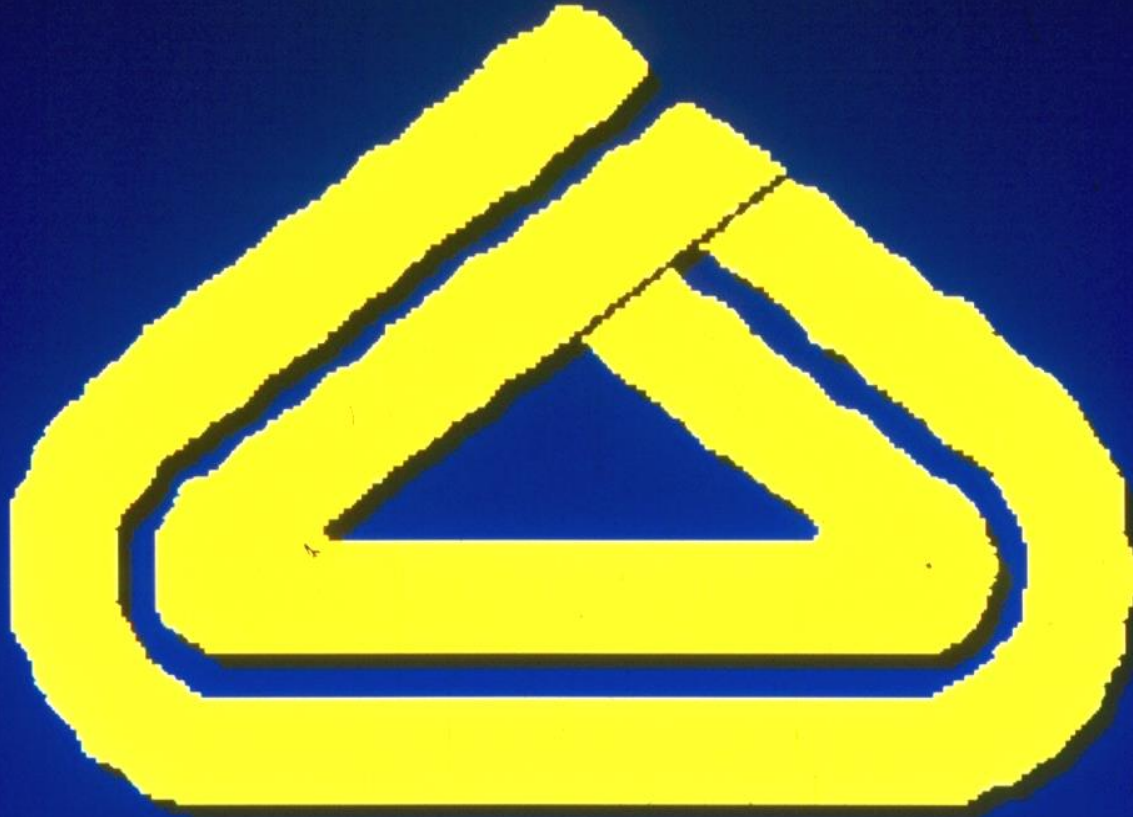
Where are we?



“This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”

W Churchill, 10 November 1942

Supported by



National Institutes of Health



College of Arts and Sciences

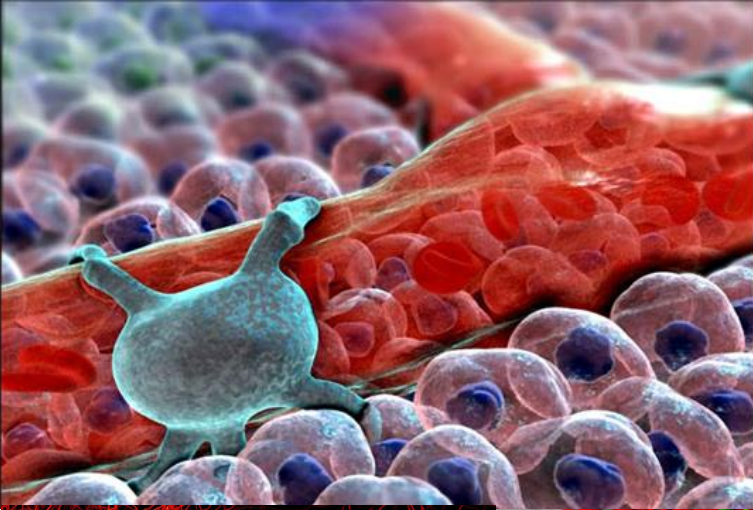
Skeletal Research Center

Cleveland, Ohio



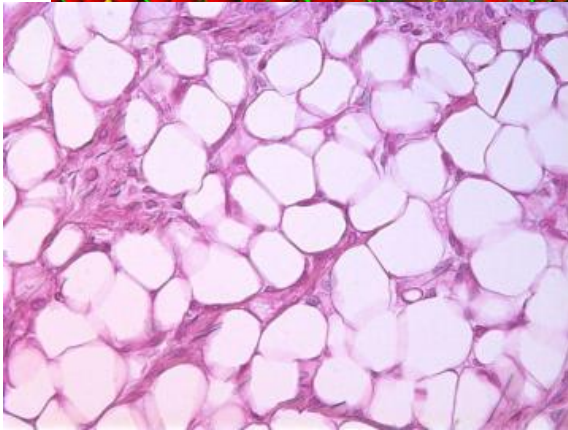
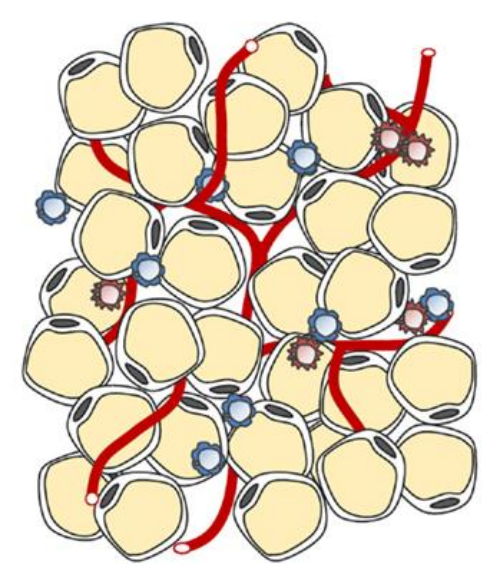
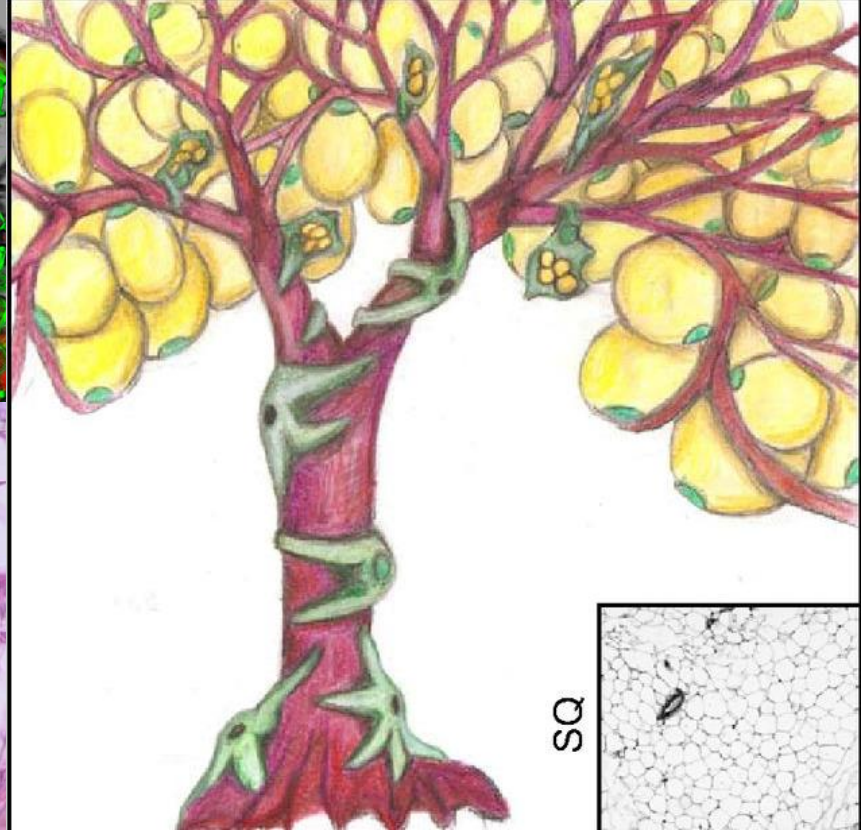
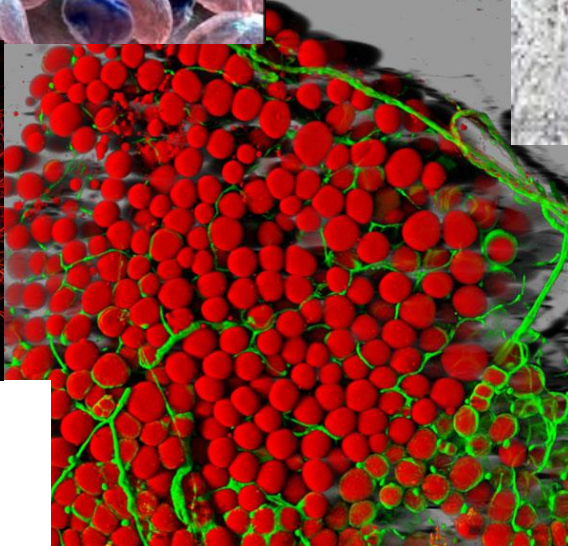
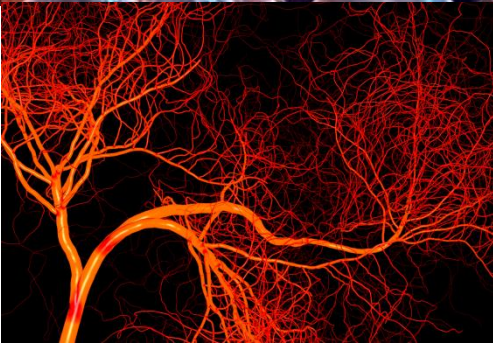
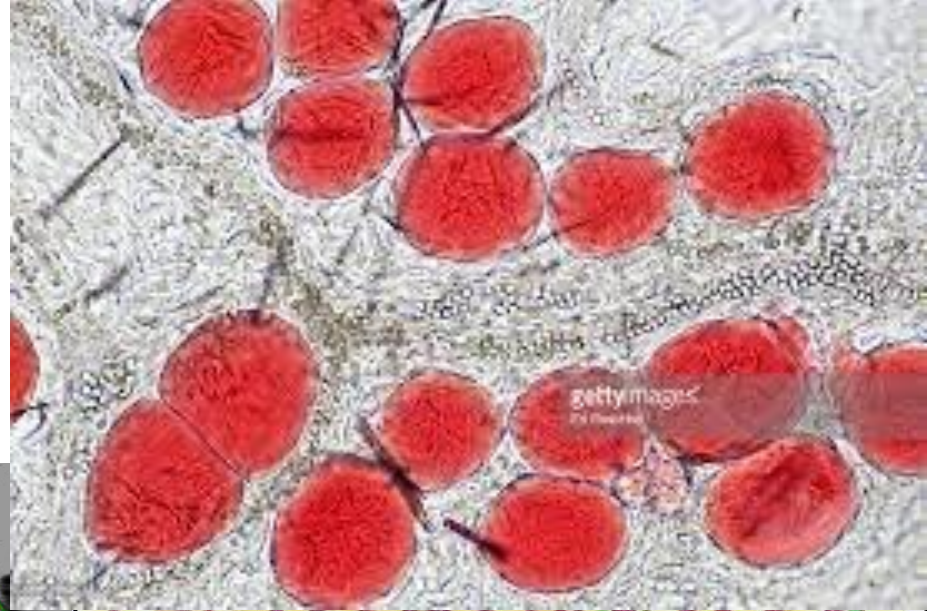
The Businesses of Regenerative Medicine





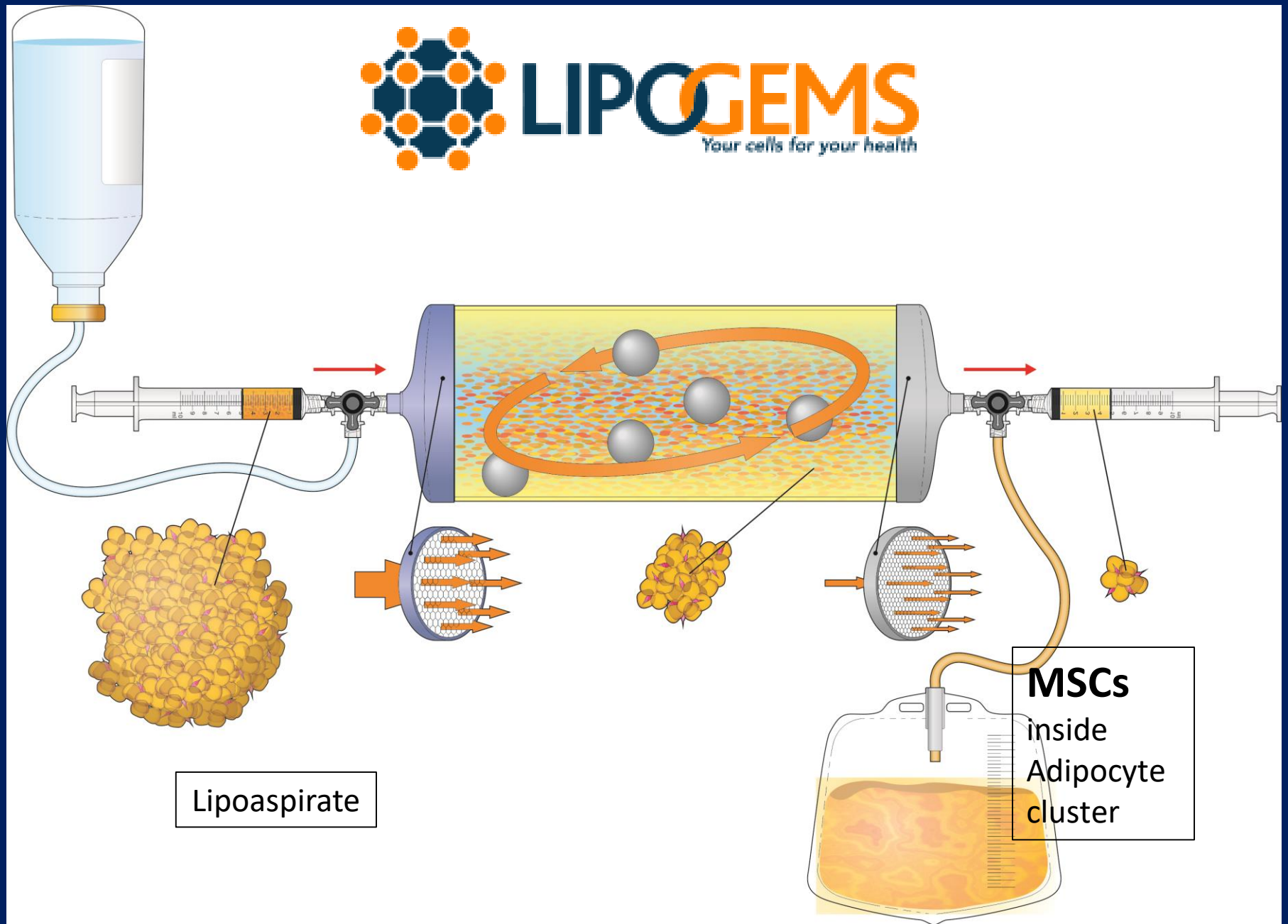
FAT

300-500 fold
more MSCs
than marrow



SQ

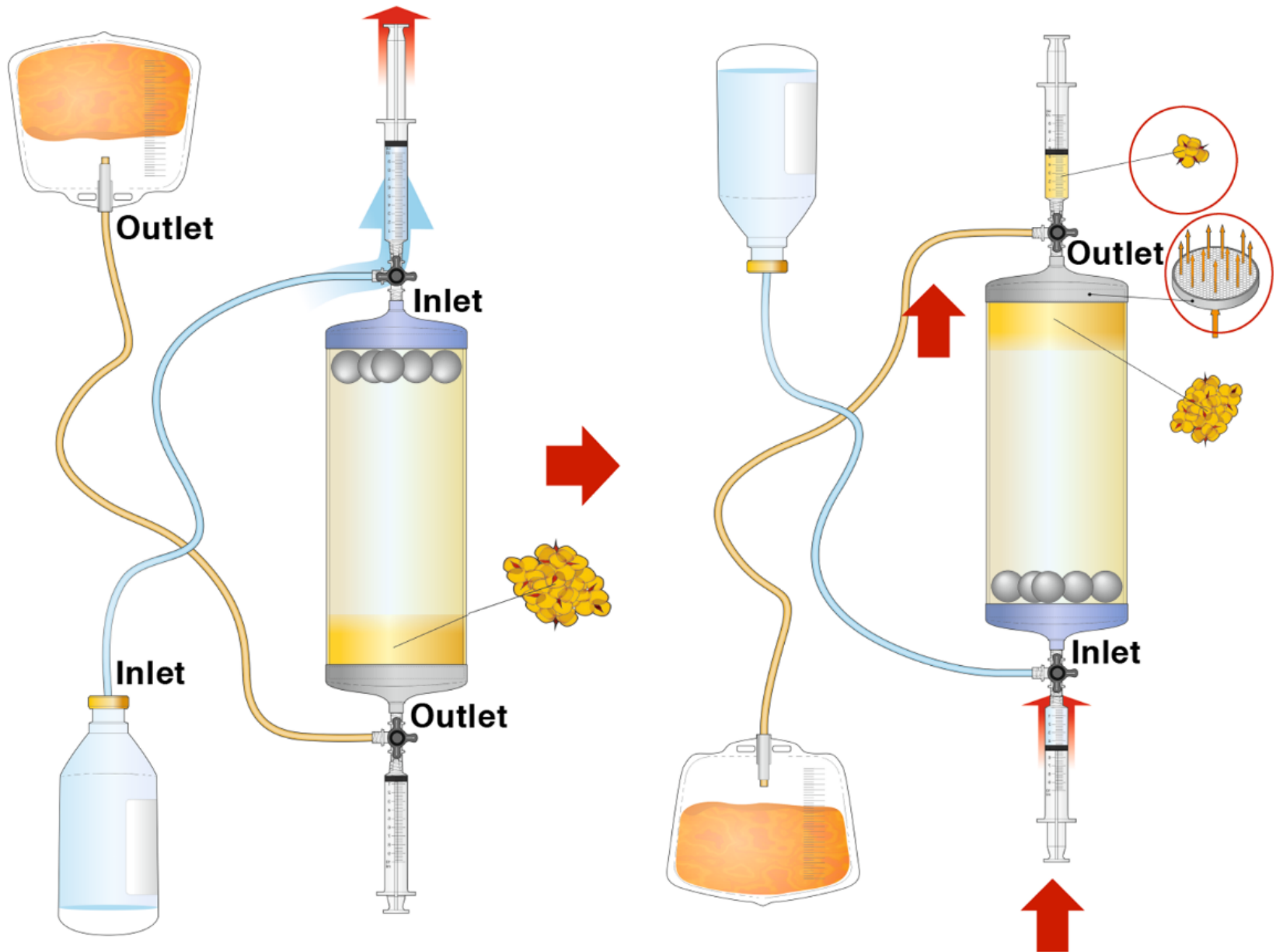




Lipoaspirate

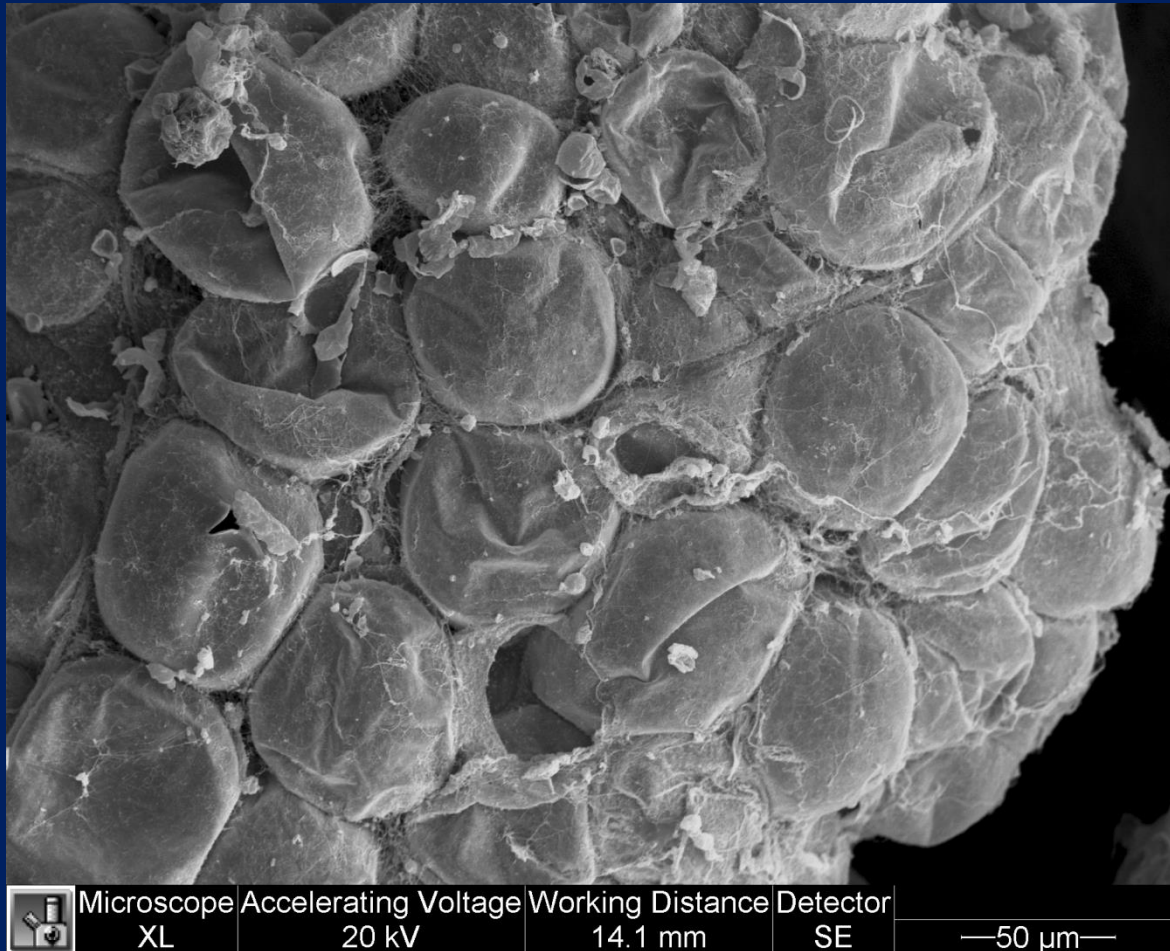
MSCs
inside
Adipocyte
cluster

Second Cluster Size Reduction and Lipogems Tissue Harvesting

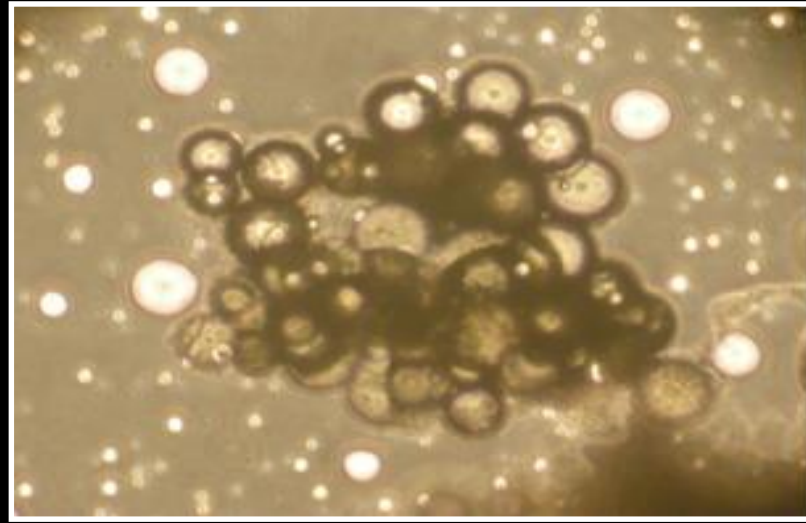


Adipose Tissue and Stem Cells

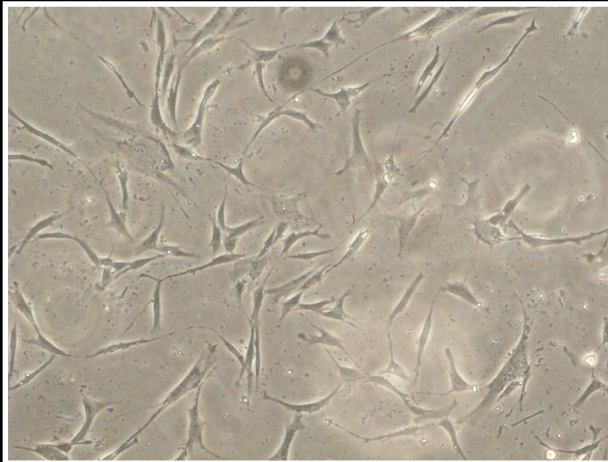
Prof. Sbarbati- University of Verona



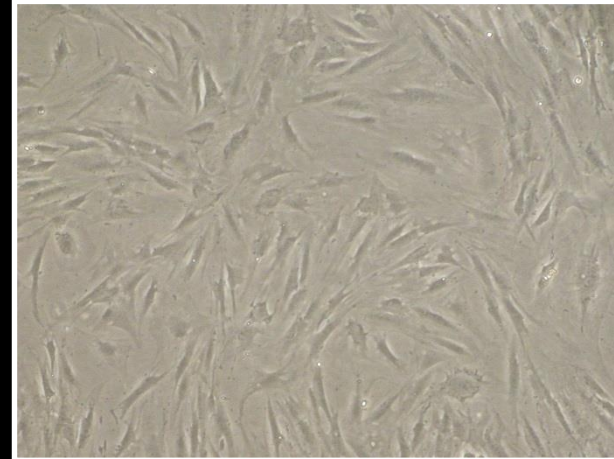
Lipogems clusters in culture:



Day 4



Day 6



Day 12