Dr Keith Laubscher
Musculoskeletal and Pain Specialist
Auckland

Dr Lucy Holtzhausen
Musculoskeletal and Sports Medicine Specialist
Auckland

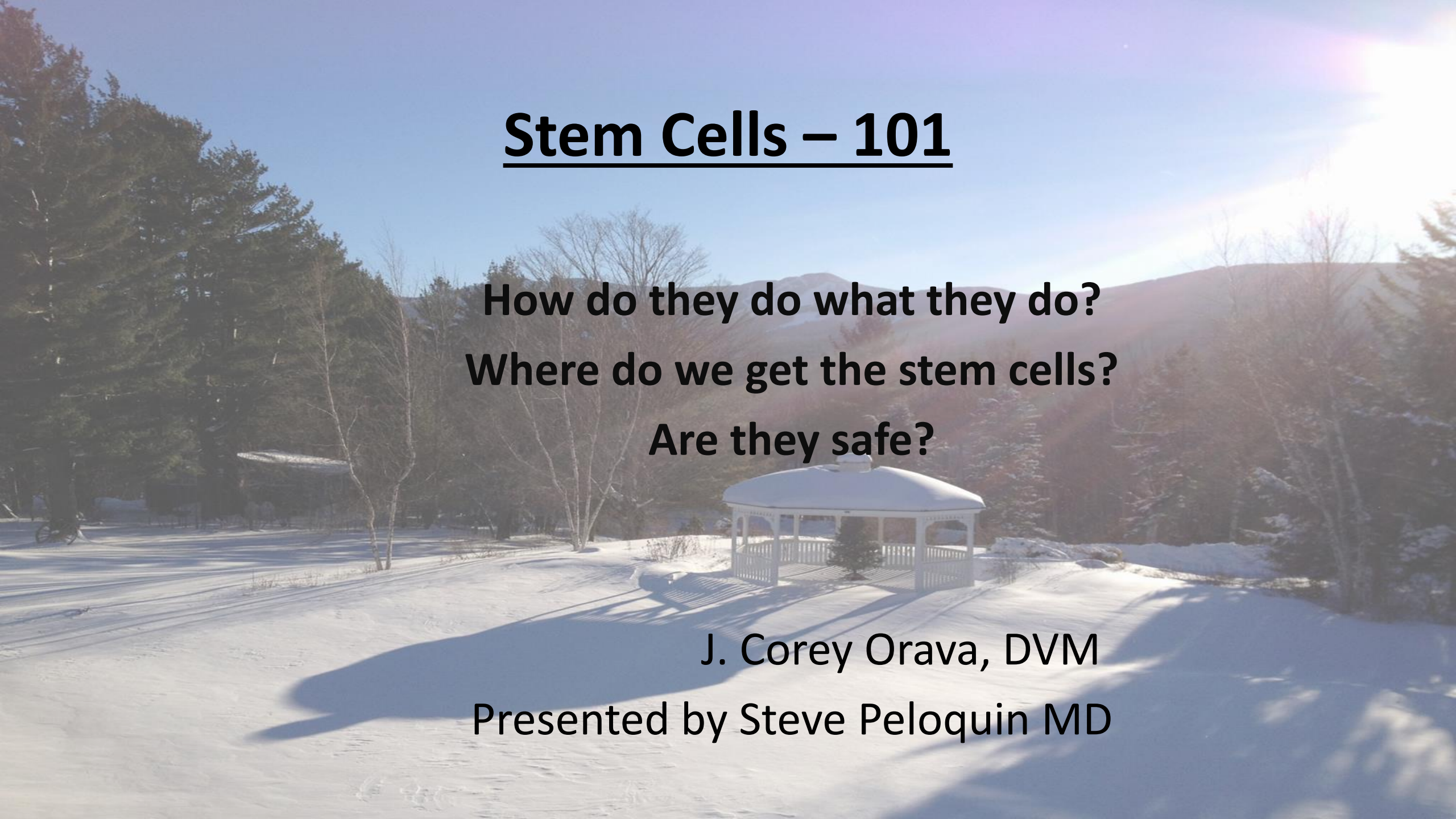
Dr Jonathan Kuttner
Musculoskeletal & Pain Specialist
Auckland

Dr Ian Wallbridge
Musculoskeletal Specialist
Rotorua

Dr Steve Peloquin
Pain Medicine/Anesthesiology
USA

Thursday, June 9, 2016 (Room 4)

8:30 - 10:30 WS #5: Musculoskeletal Medicine 1
11:00 - 13:00 WS #12: Musculoskeletal Medicine 2
14:00 - 16:00 WS #18: Musculoskeletal Medicine 3
16:30 - 18:30 WS #24: Musculoskeletal Medicine 4



Stem Cells – 101

How do they do what they do?

Where do we get the stem cells?

Are they safe?

J. Corey Orava, DVM

Presented by Steve Peloquin MD

Embryonic vs Adult Stem Cells

Embryonic

Source: early embryo
ethical dilemma

Purpose: form organism

Form Teratomas

UNPREDICTABLE

Adult

Source: all adult tissues?
No ethical dilemma

Purpose: 1. maintain
2. repair

No evidence of forming teratomas

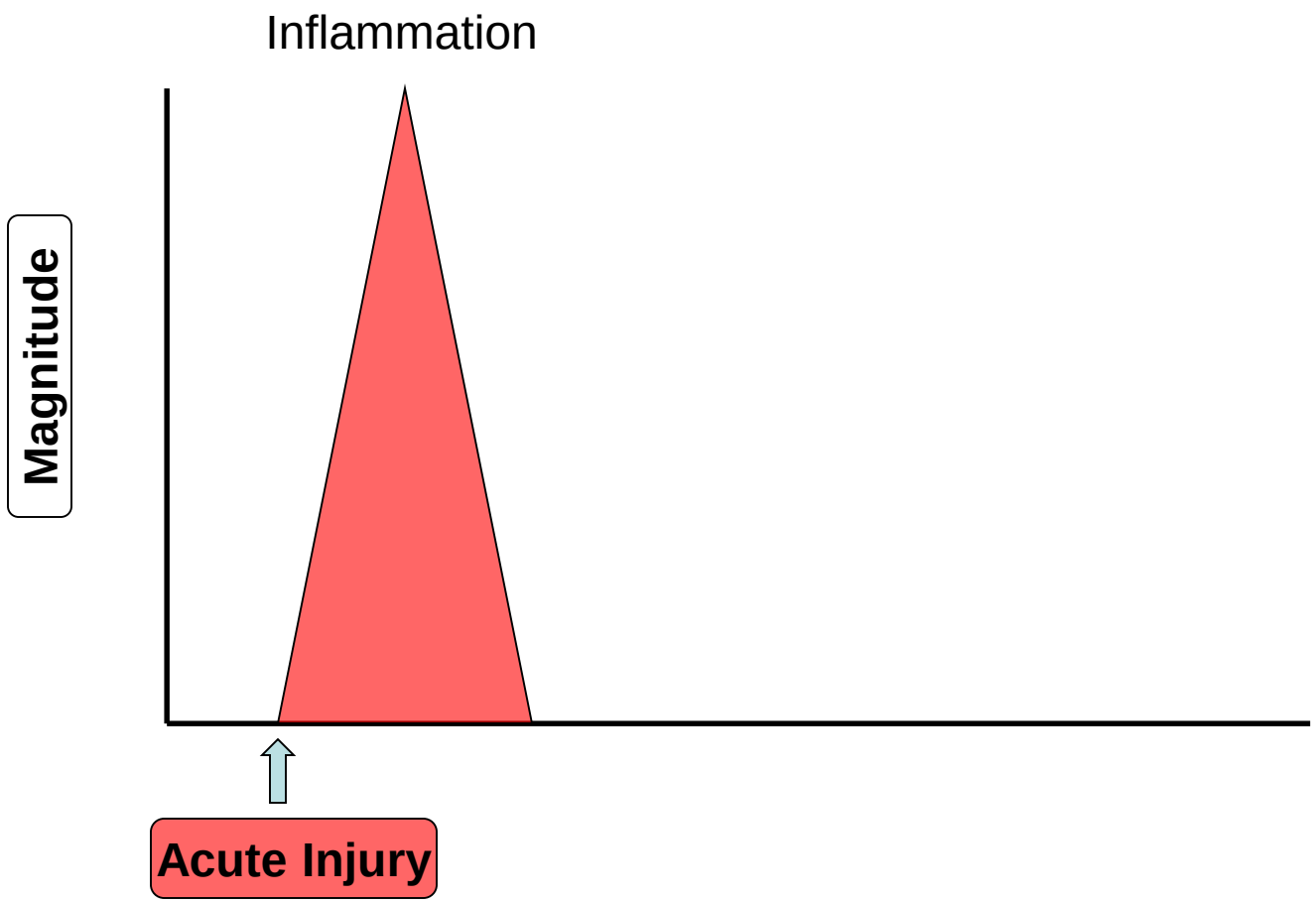
SAFE!

Damage

Repair

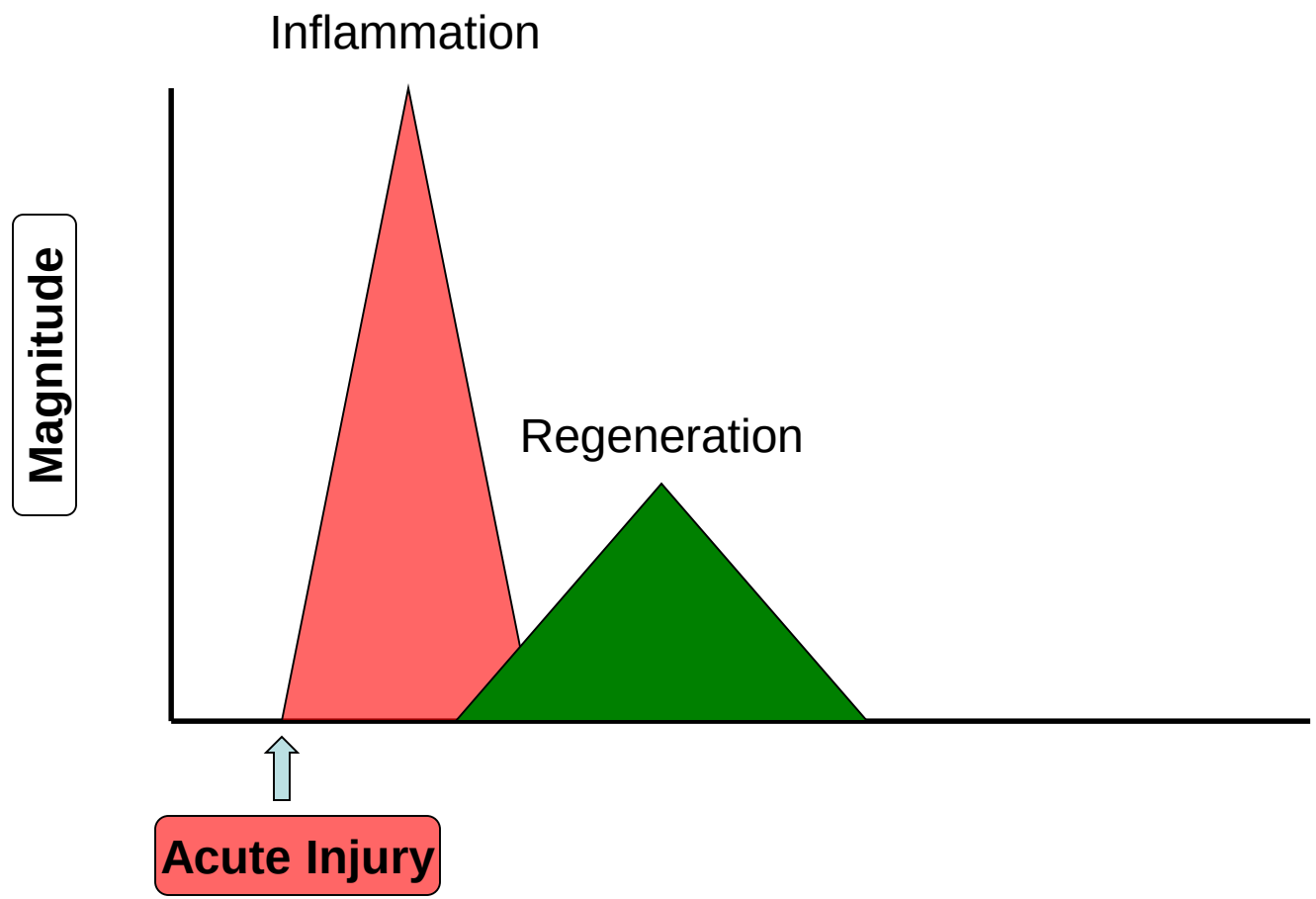
Regeneration

Repair Casade
w/o Regenerative Cells



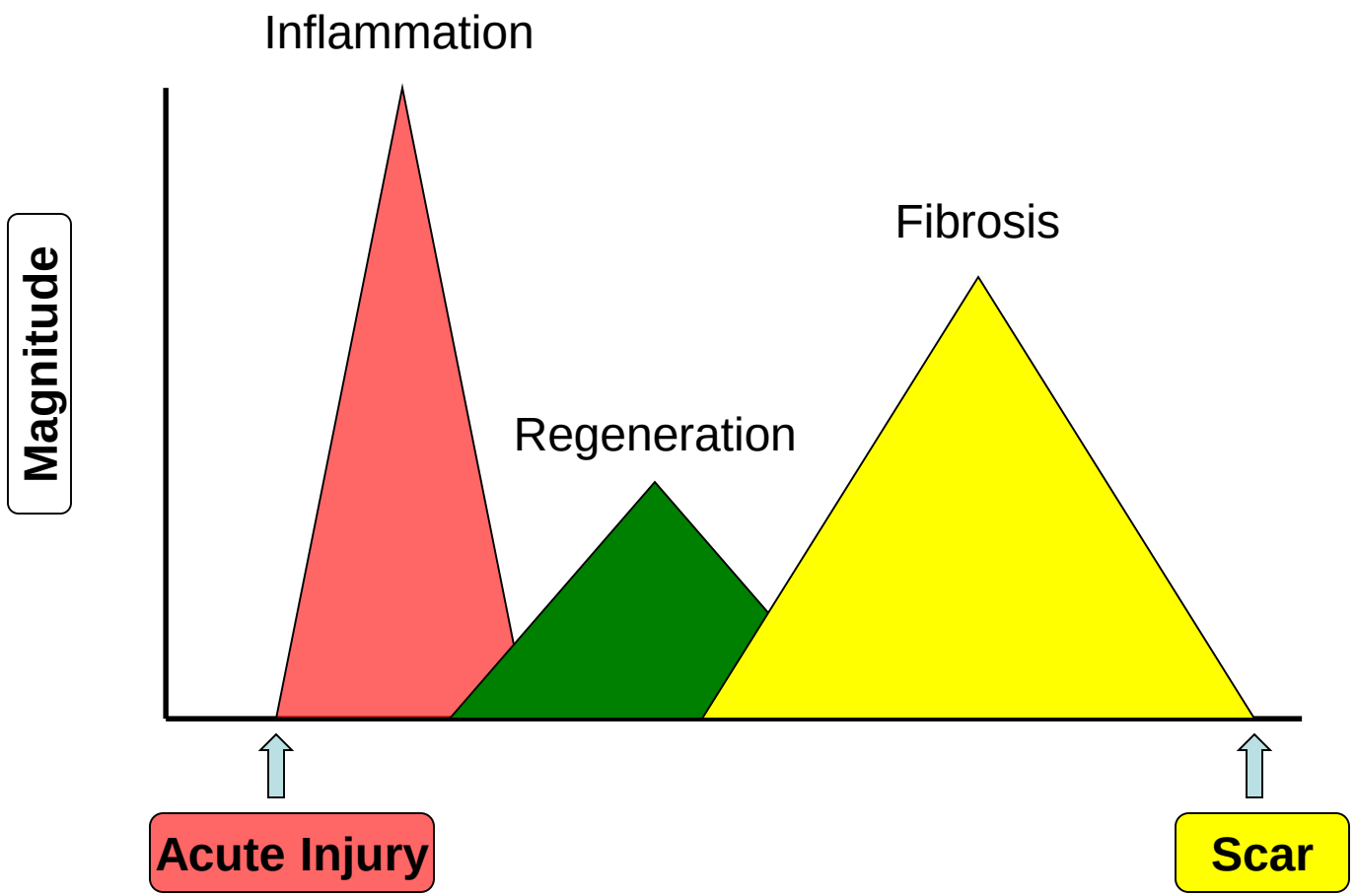
Adapted from: Arnold Caplan, PhD
Case Western Reserve University

Repair Casade
w/o Regenerative Cells



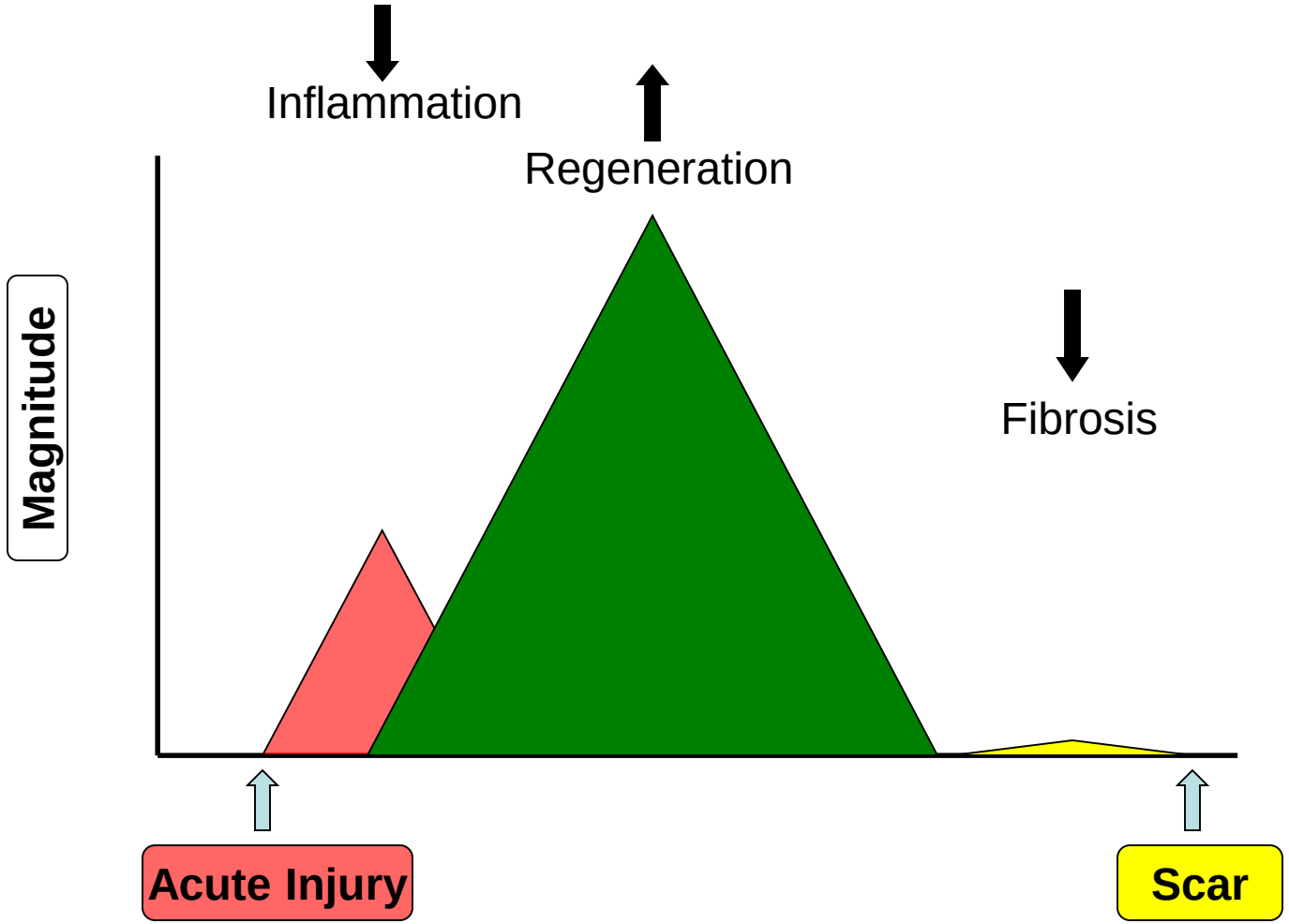
Adapted from: Arnold Caplan, PhD
Case Western Reserve University

Repair Casade w/o Regenerative Cells



Adapted from: Arnold Caplan, PhD
Case Western Reserve University

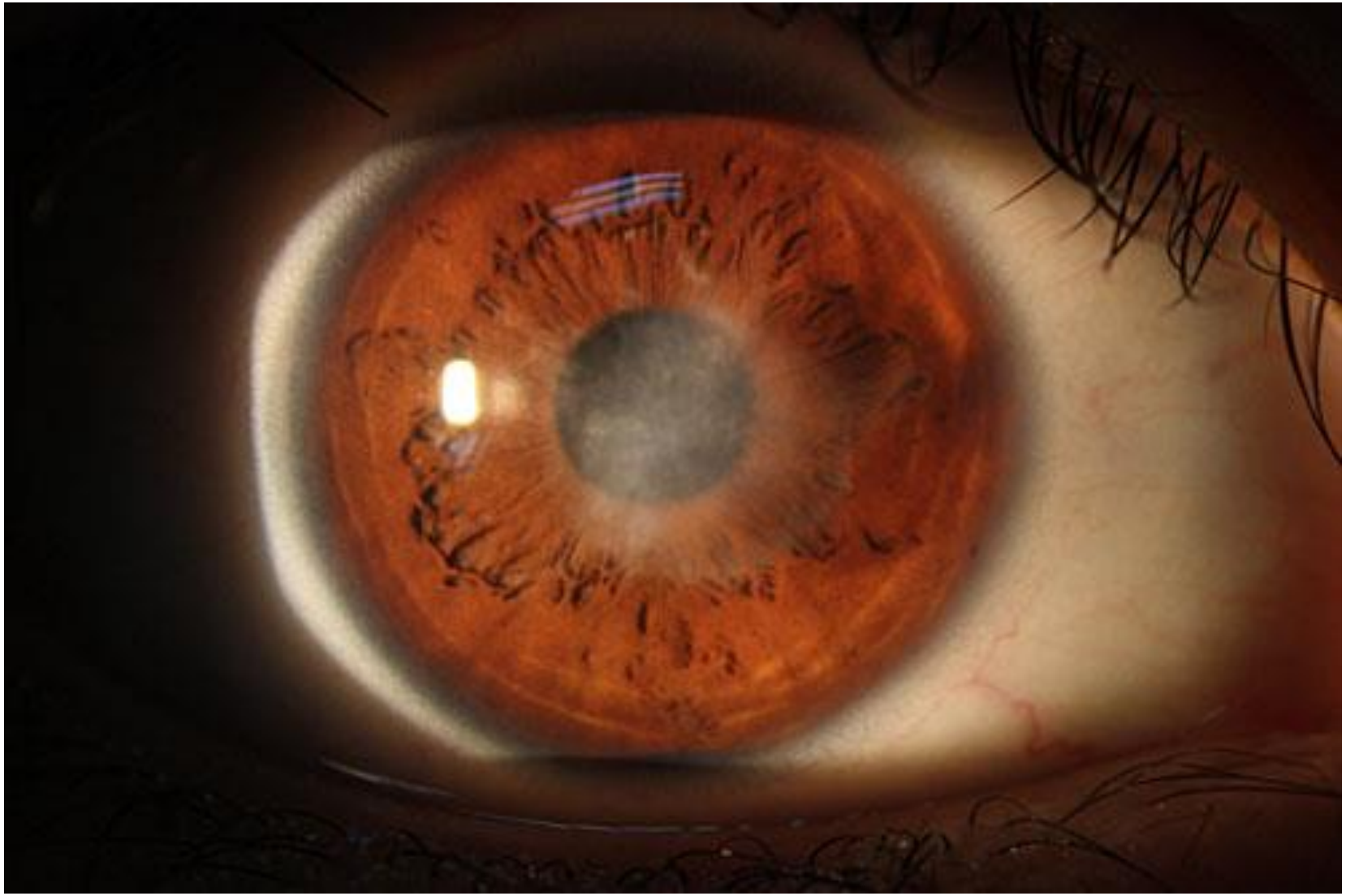
Regeneration >> Repair



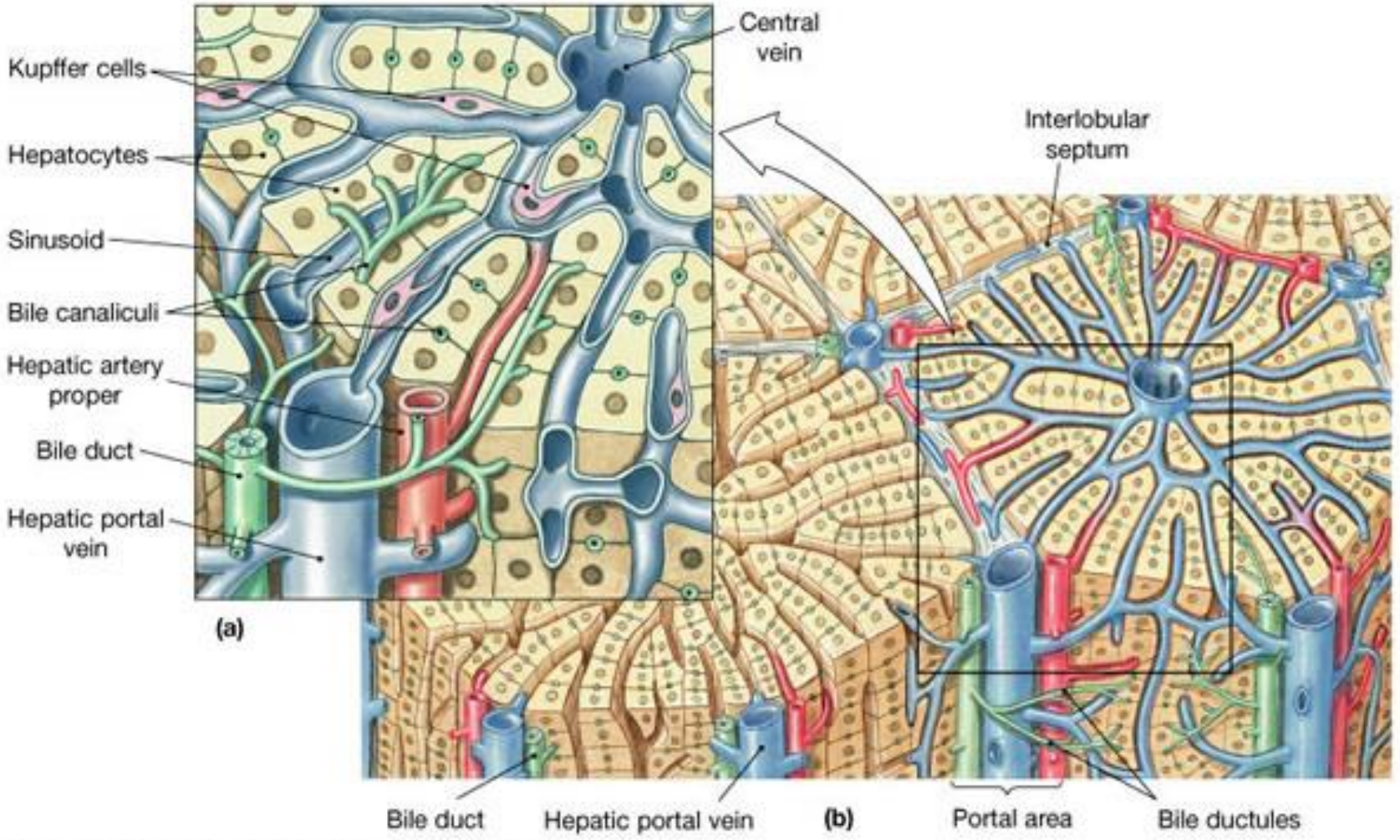
Adapted from: Arnold Caplan, PhD
Case Western Reserve University

Scar - Skin

Scar - Cornea



Scar – Liver…



A Rose By Any Other Name

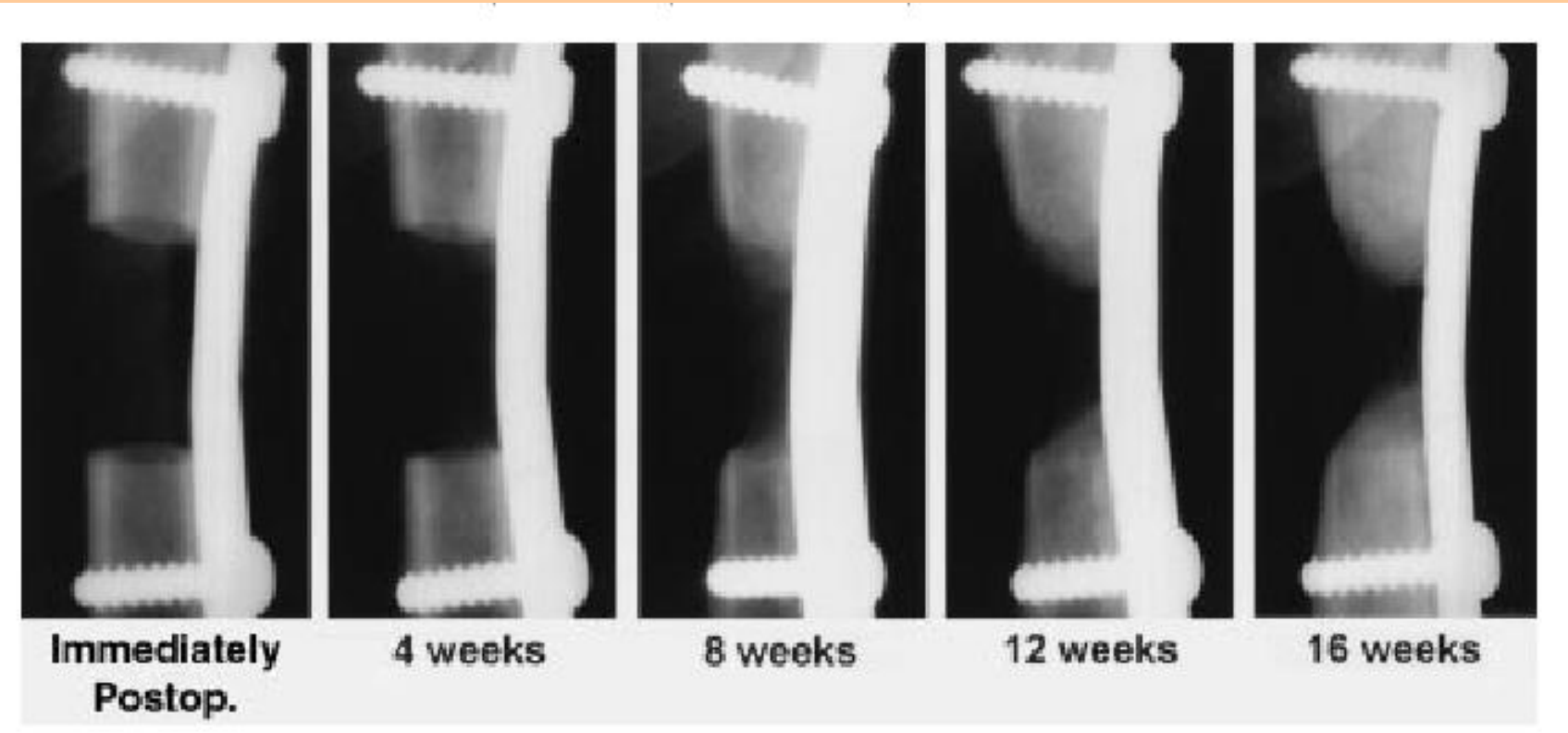
Stem cells aka…

Mesenchymal stem cells
Stromal cells
Multipotent cells
Stromal vascular fraction
Nucleated cell fraction

Roles / Functions

- **Differentiate**

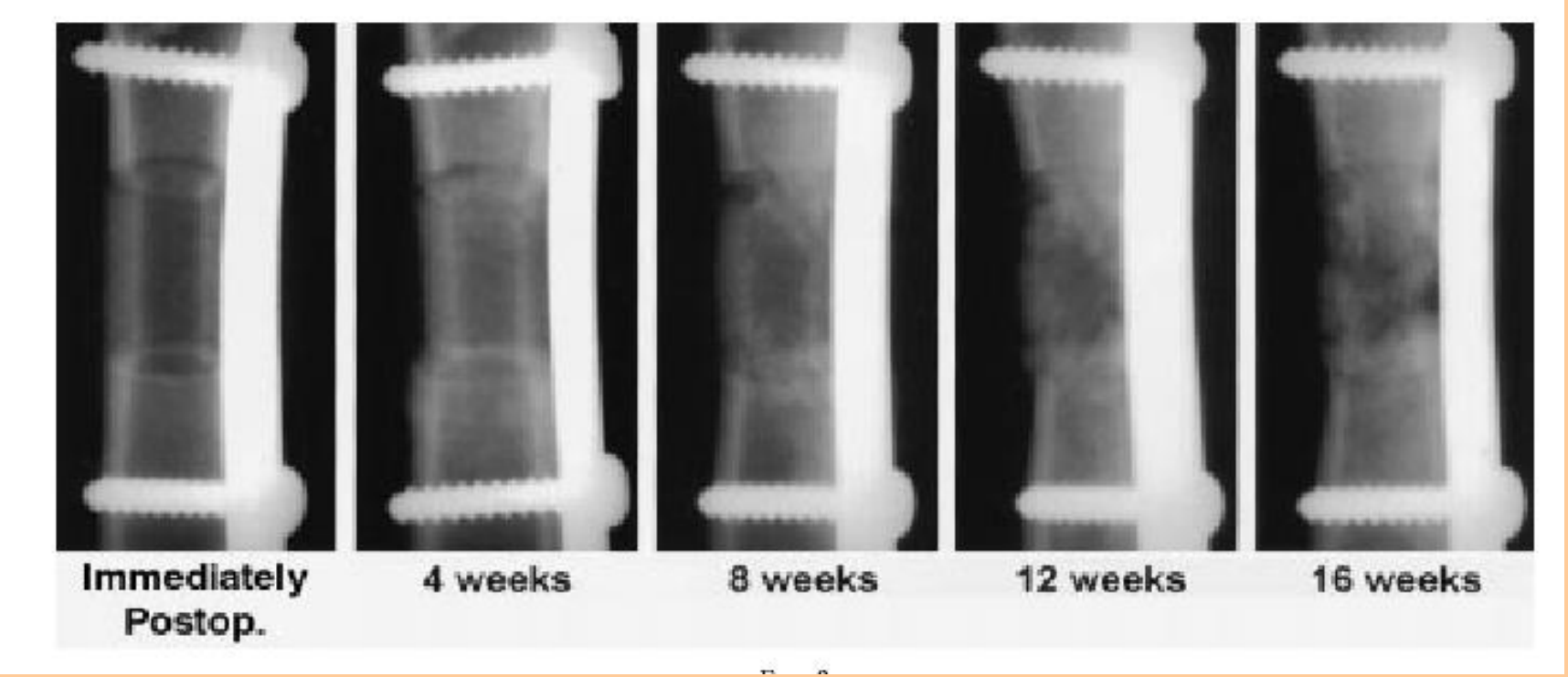
Clinical Study - Fractures



J Bone Joint Sx (1998) 80:985-996

Case Study - Fractures

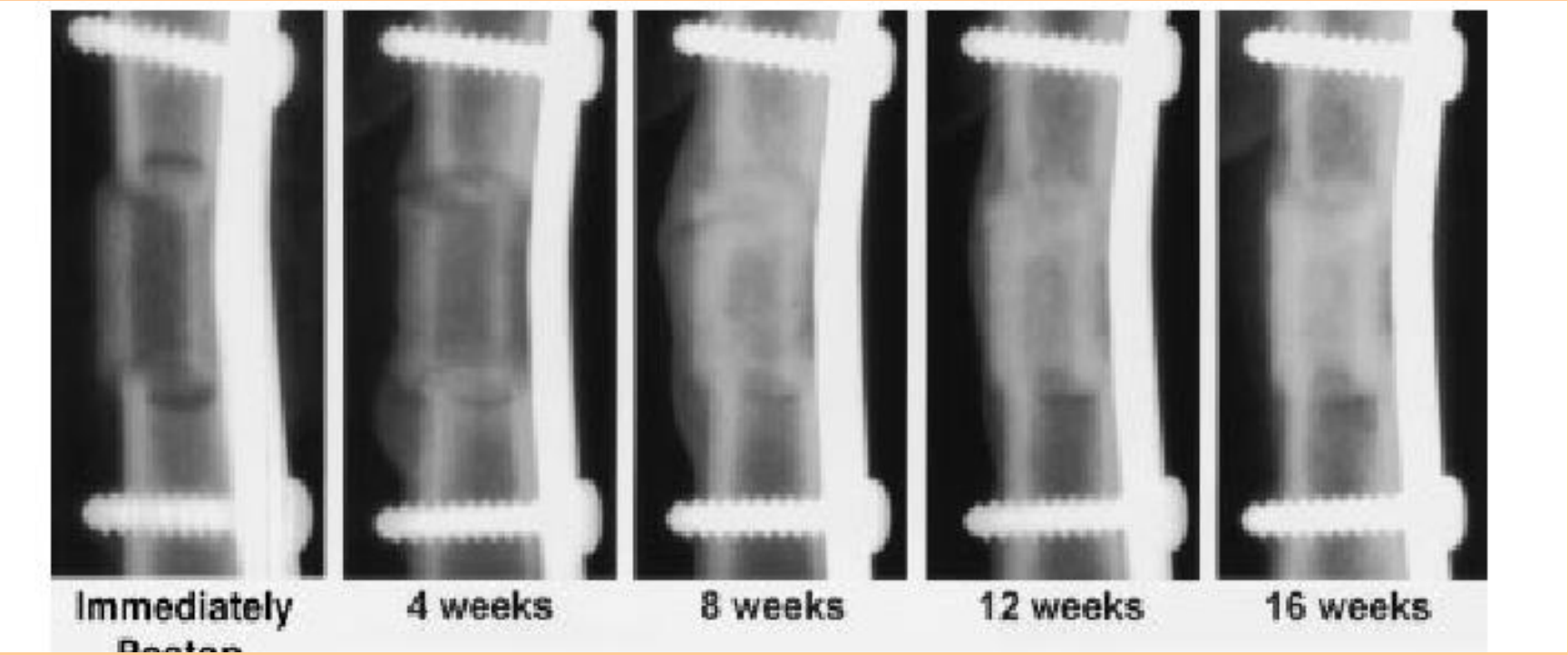
Comparison in Fracture – Implant without Stem Cells



J Bone Joint Sx (1998) 80:985-996

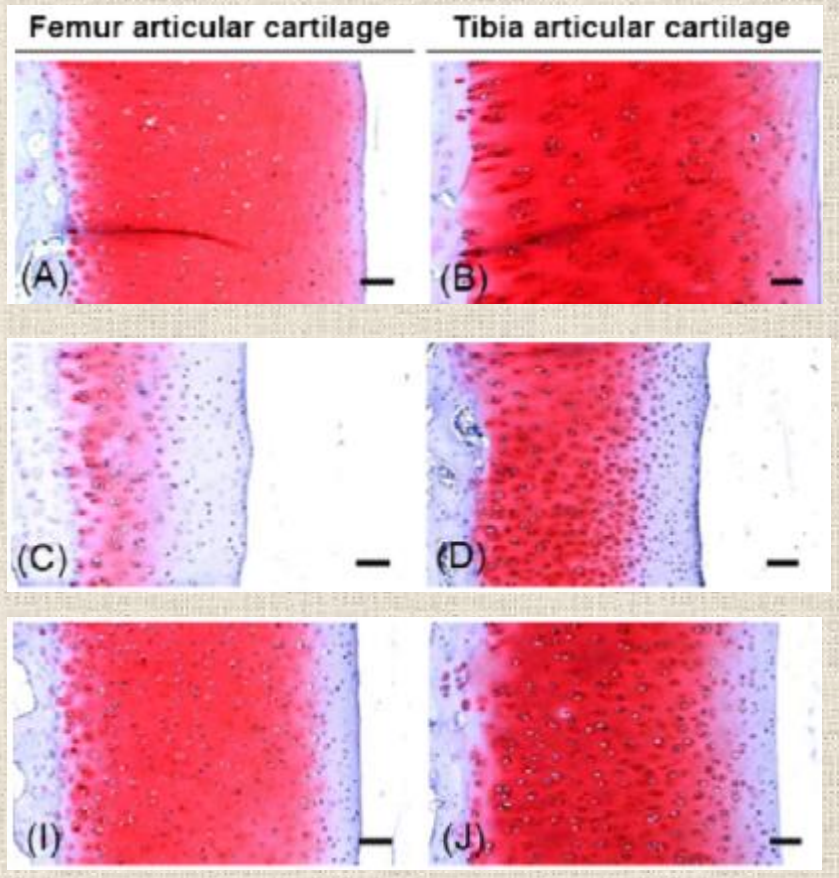
Case Study - Fractures

Comparison in Fracture – Implant with Stem Cells



J Bone Joint Sx (1998) 80:985-996

Adipose-derived mesenchymal stem cells and platelet-rich plasma synergistically ameliorate the surgical-induced osteoarthritis in Beagle dogs



J Orthopedic Research & Surgery (2016) 11:9

Stem Cell Therapy in a Caprine Model of Osteoarthritis

J. Mary Murphy,[1] David J. Fink,[1] Ernst B. Hunziker,[2] and Frank P. Barry[1]

Arthritis & Rheumatism (2003) 48 (12) 3464-3474

- *24 goats (4 groups – 12 wks or 26 wks; 2 control, 2 treated)*
- *Surgical resection of CCL and medial meniscus*
- *Exercise to induce OA*
- *Single injection of stem cells w/ HA or HA alone*

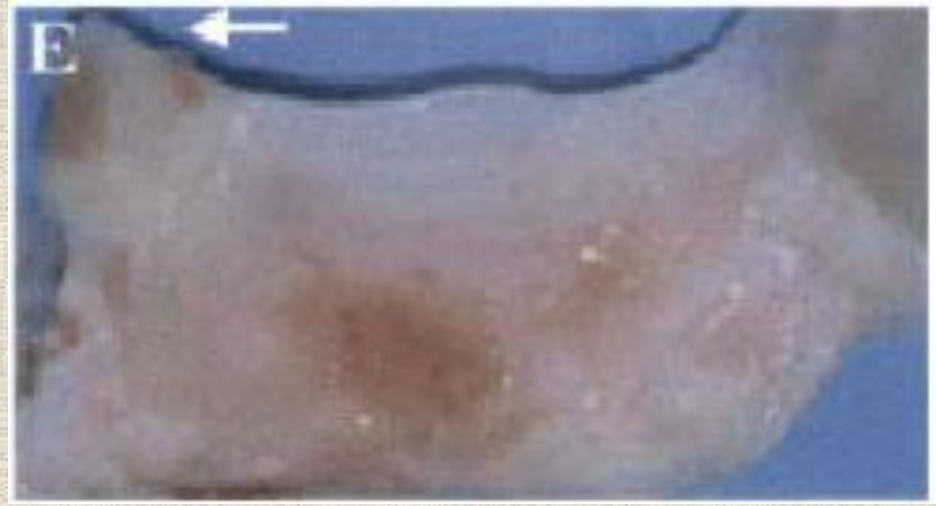
Murphy et al (2003)

Results. In cell-treated joints, there was evidence of marked regeneration of the medial meniscus, and implanted cells were detected in the newly formed tissue. Degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis were reduced in cell-treated joints compared with joints treated with vehicle alone without cells. There was no evidence of repair of the ligament in any of the joints.

Murphy et al (2003)

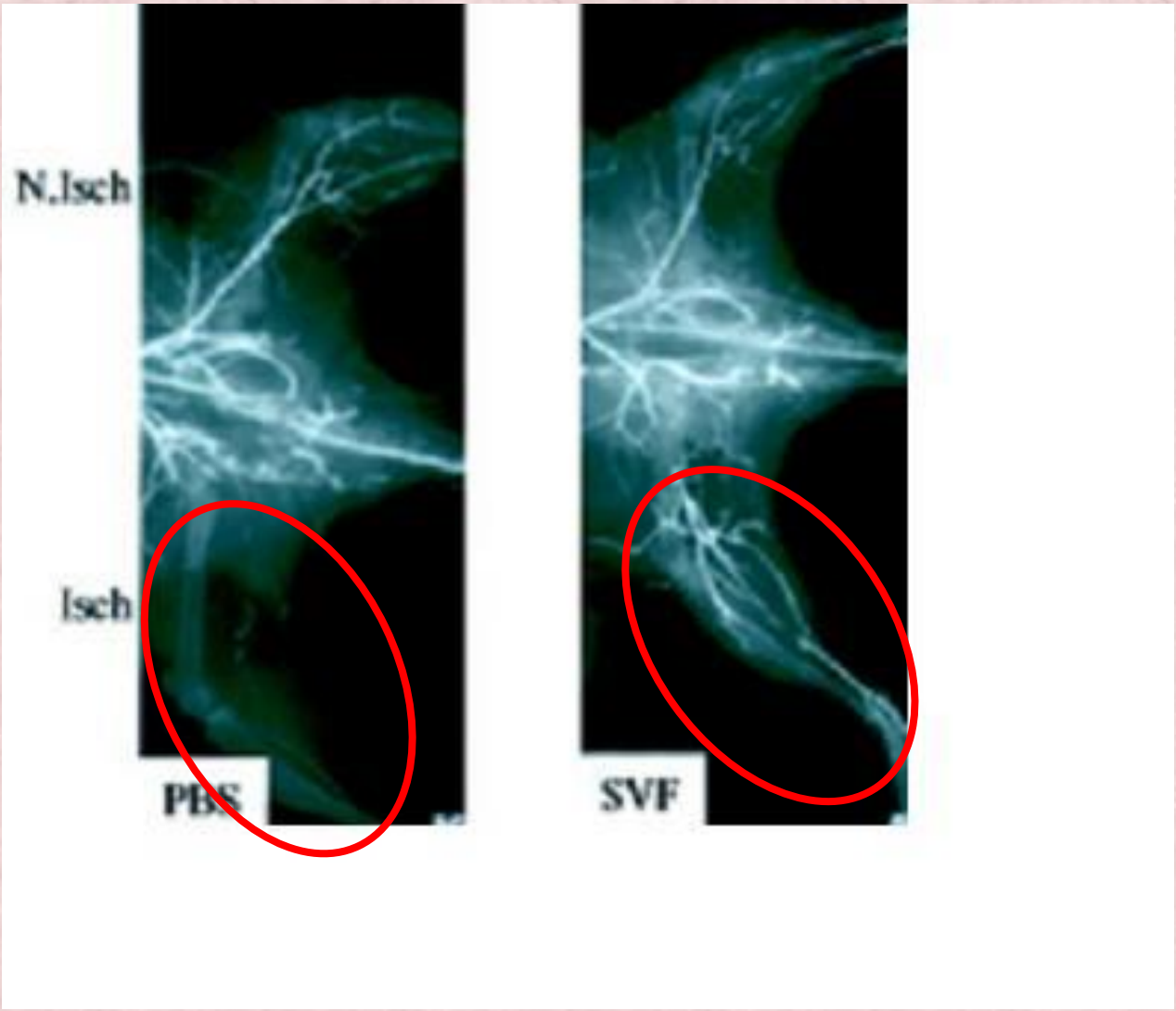
Surgically resected Meniscus

Regenerated Meniscus

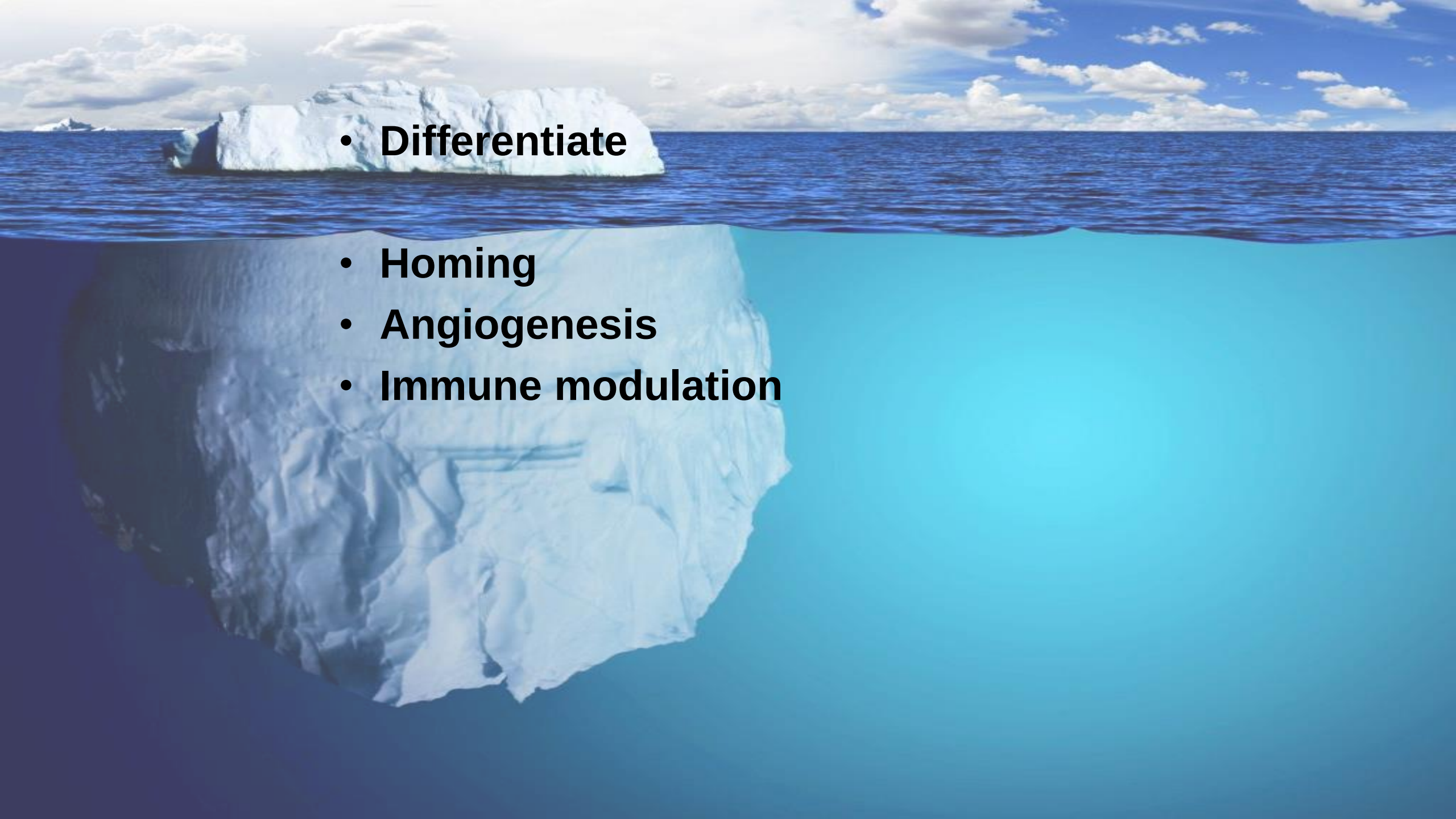


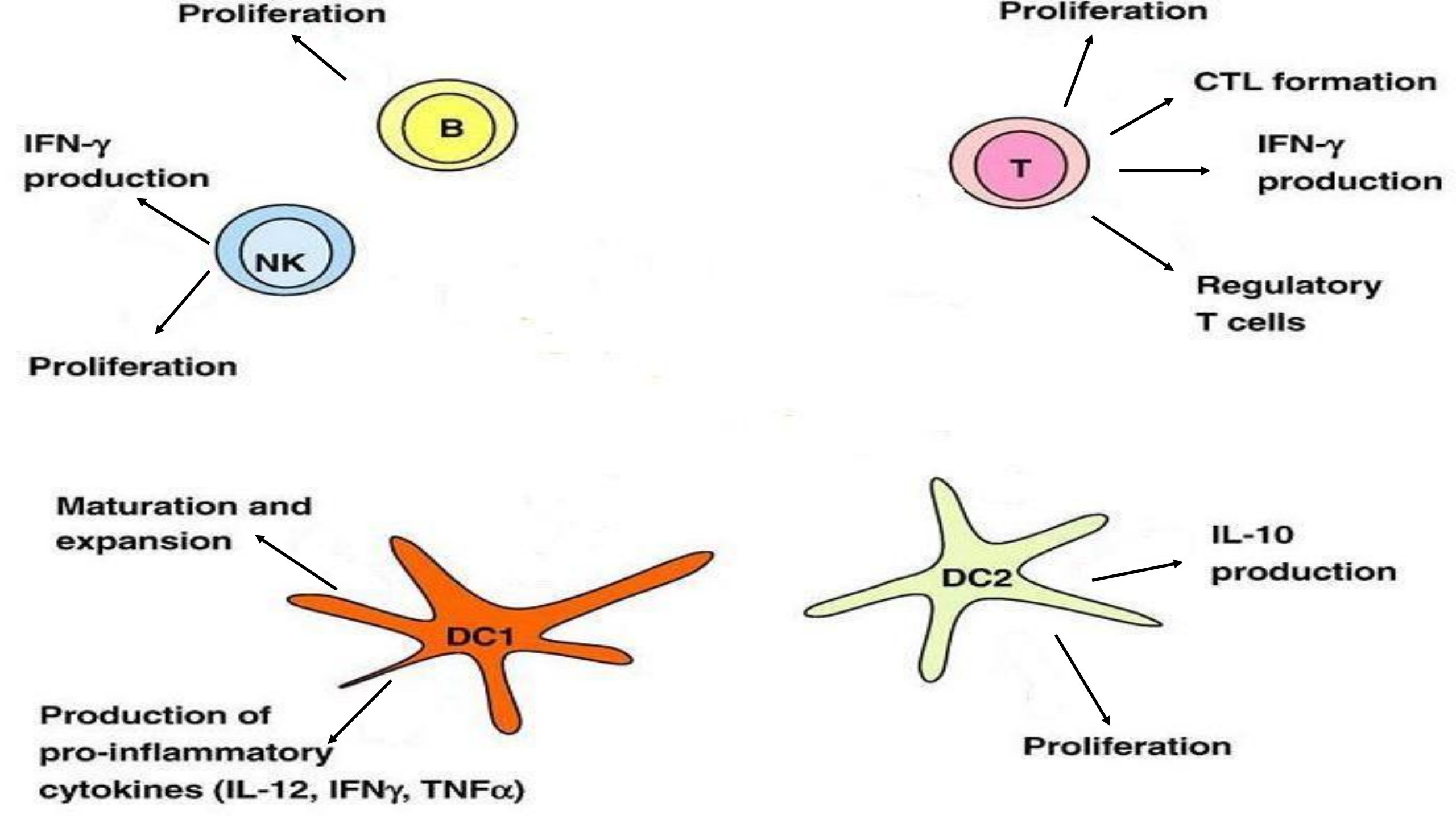

• Differentiate
• Homing
• Angiogenesis

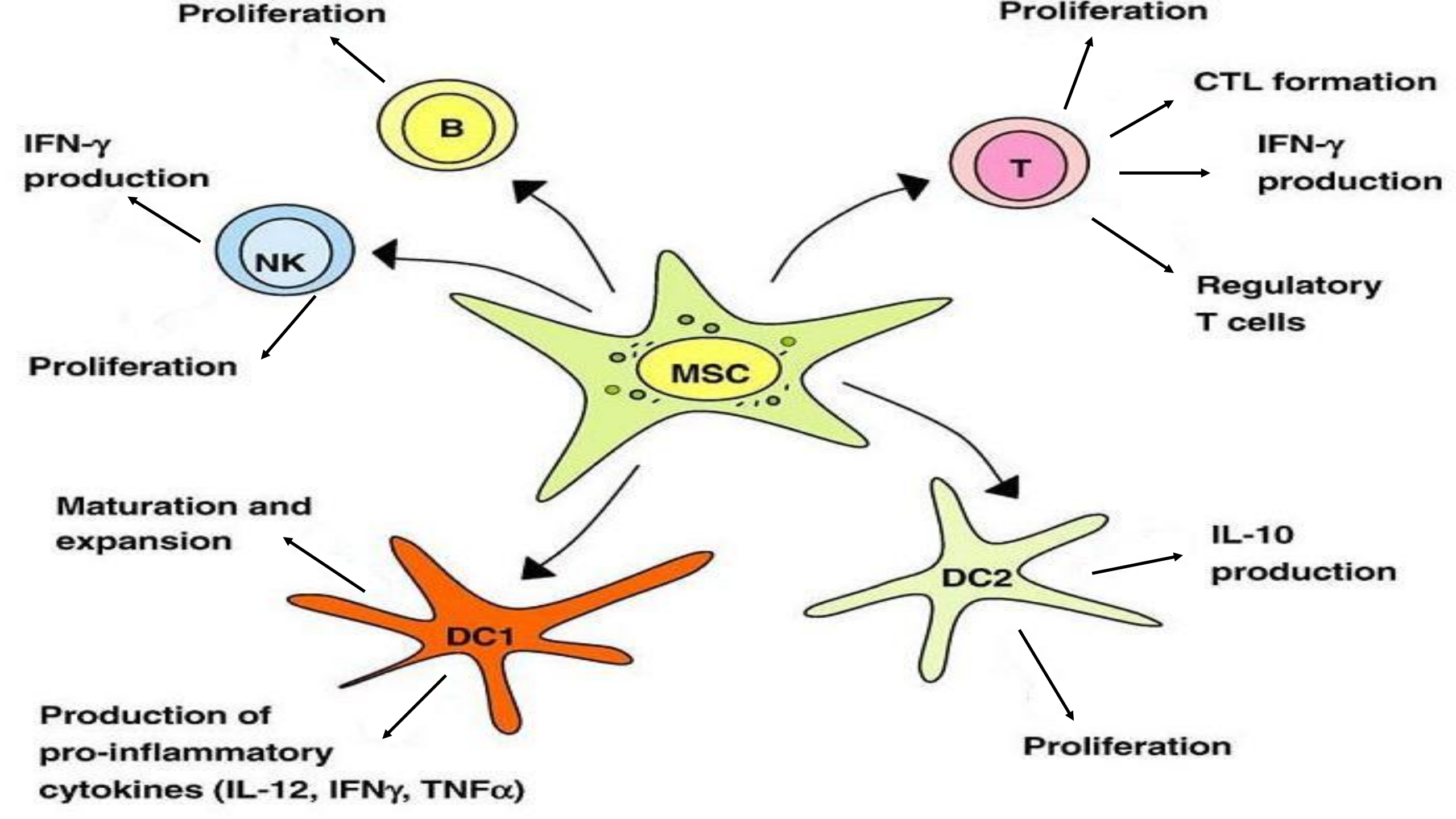
Homing & Angiogenesis

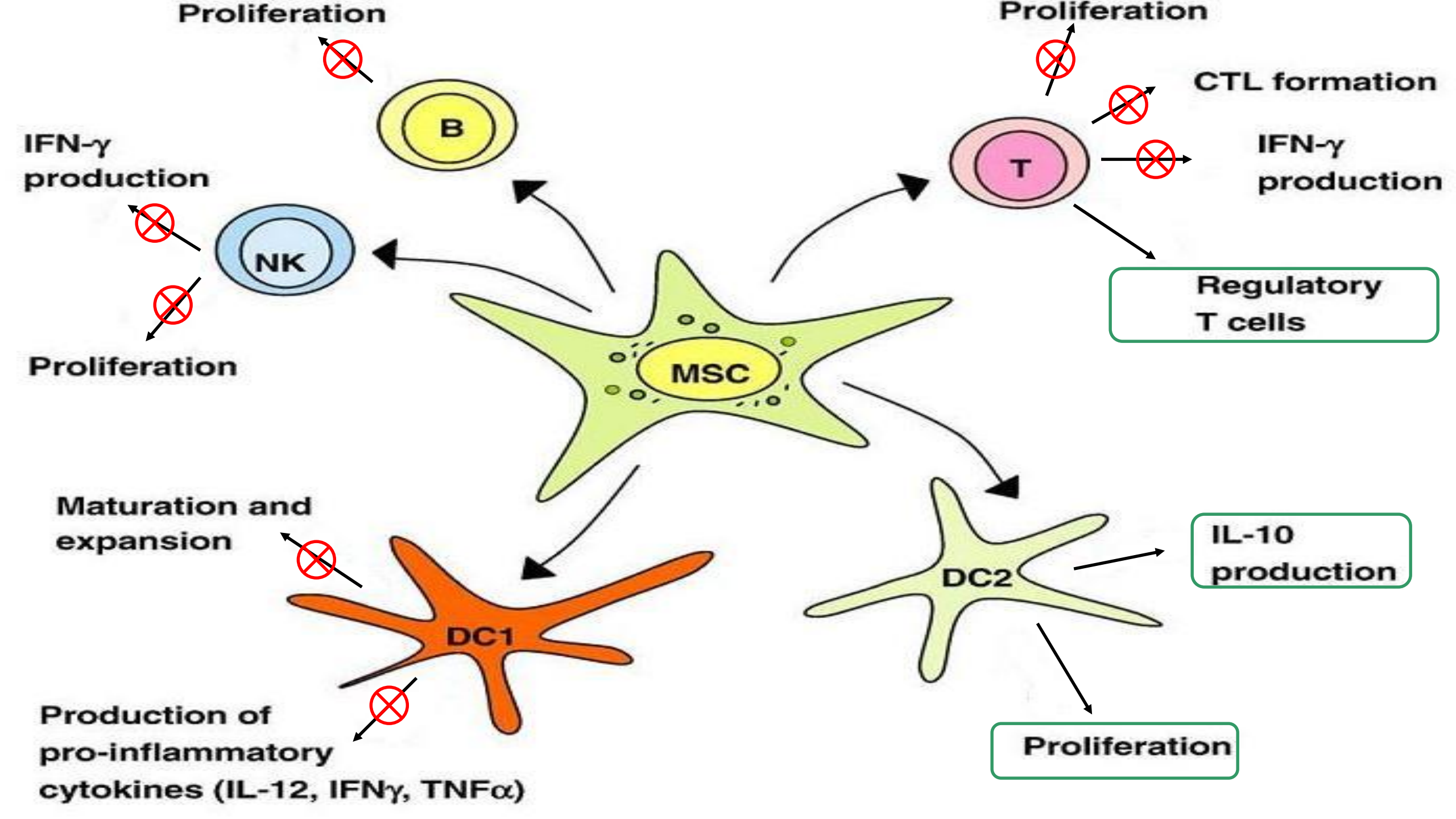


Miranville et al, *Circulation 2004;110; 349-355*


• Differentiate
• Homing
• Angiogenesis
• Immune modulation


Proliferation
B
IFN-γ
production
NK
Proliferation
Proliferation
CTL formation
T
IFN-γ
production
Regulatory
T cells
Maturation and
expansion
DC1
Production of
pro-inflammatory
cytokines (IL-12, IFNγ, TNFα)
DC2
IL-10
production
Proliferation


Proliferation
B
IFN-γ
production
NK
Proliferation
Proliferation
CTL formation
IFN-γ
production
T
Regulatory
T cells
MSC
Maturation and
expansion
DC1
Production of
pro-inflammatory
cytokines (IL-12, IFNγ, TNFα)
DC2
IL-10
production
Proliferation

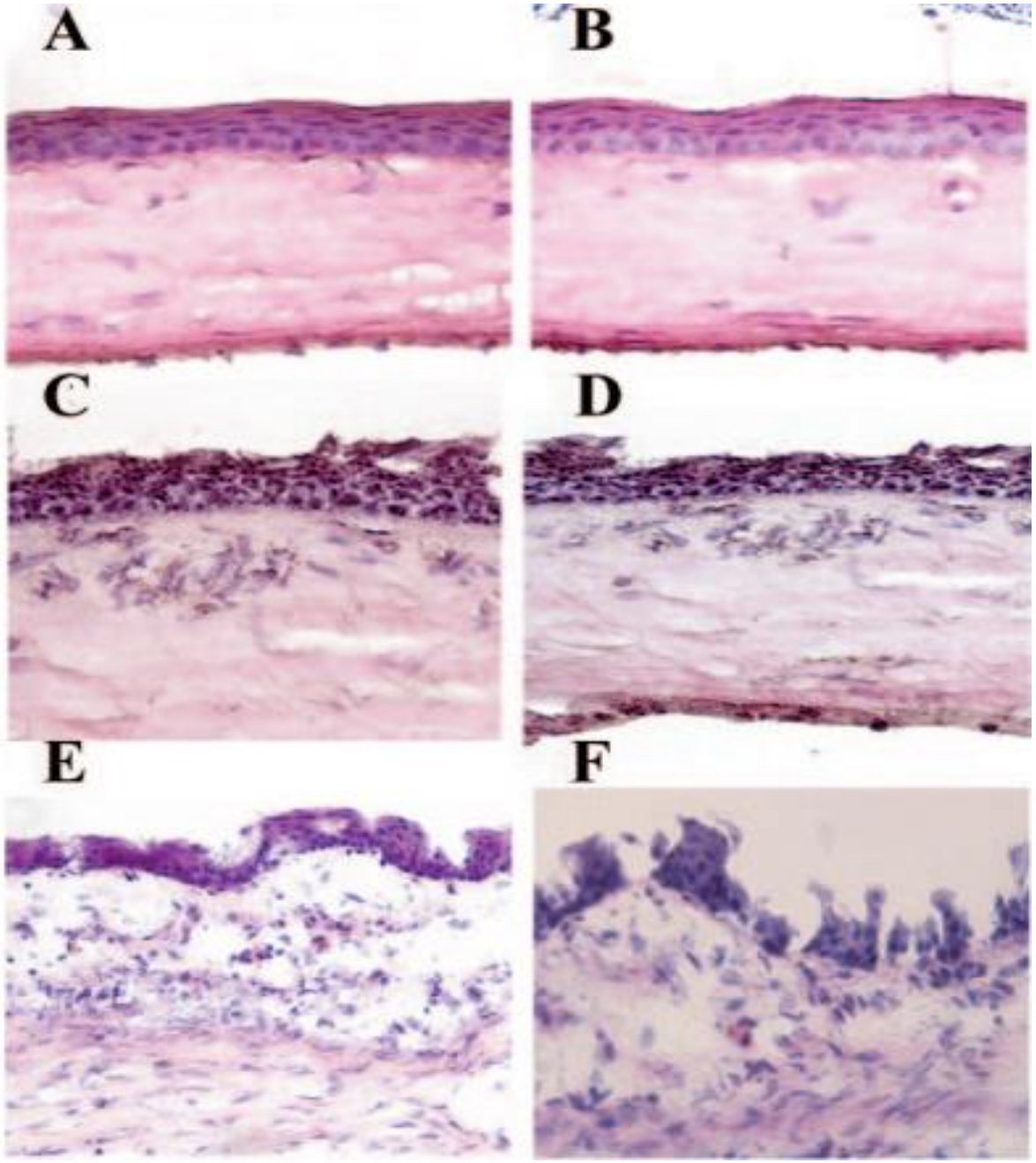

Proliferation
B
IFN-γ production
NK
Proliferation
Proliferation
CTL formation
T
IFN-γ production
Regulatory T cells
MSC
Maturation and expansion
DC1
Production of pro-inflammatory cytokines (IL-12, IFNγ, TNFα)
DC2
IL-10 production
Proliferation

Balanced immunity

Reconstruction of Chemically Burned Rat Corneal Surface by Bone Marrow–Derived Human Mesenchymal Stem Cells

YANLING MA,[a] YONGSHENG XU,[a,b] ZHIFENG XIAO,[a] WEI YANG,[a] CHUN ZHANG,[b] E. SONG,[a] YIQIN DU,[a] LINGSONG LI[a]

Stem Cells (2006) 24: 315-321



A – BM Stem Cells

B – Limbic Stem Cells

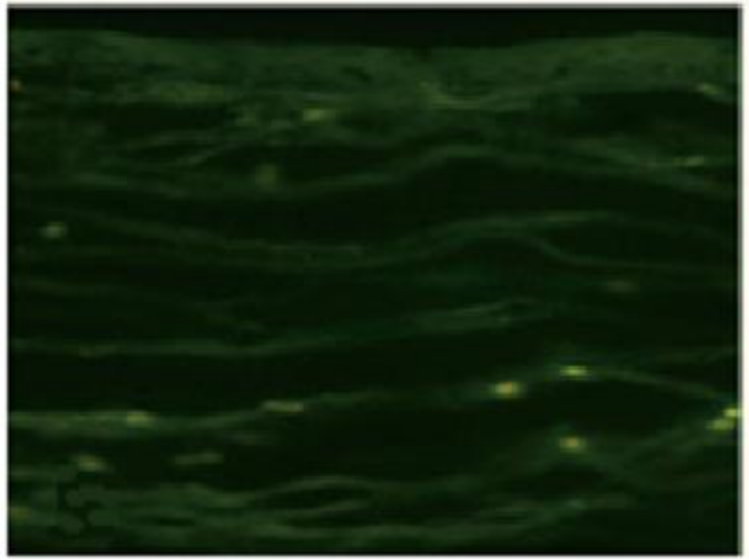
C – Fibroblasts

D – Amnion

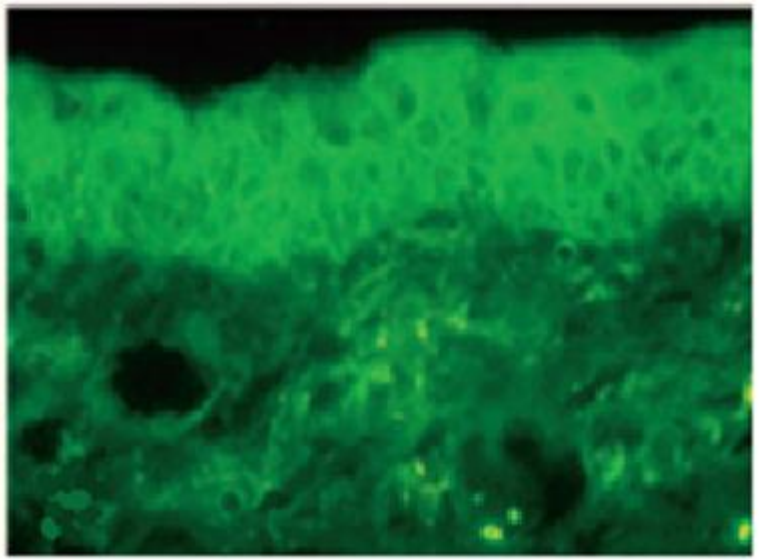
E – Dexamethasone

F - Gentamicin

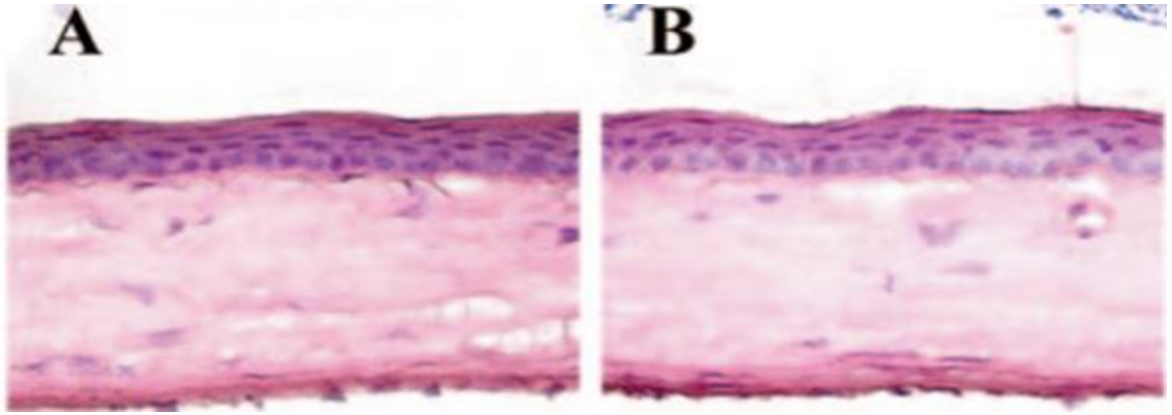
Immunofluorescence (human antibodies)



BM Stem Cells



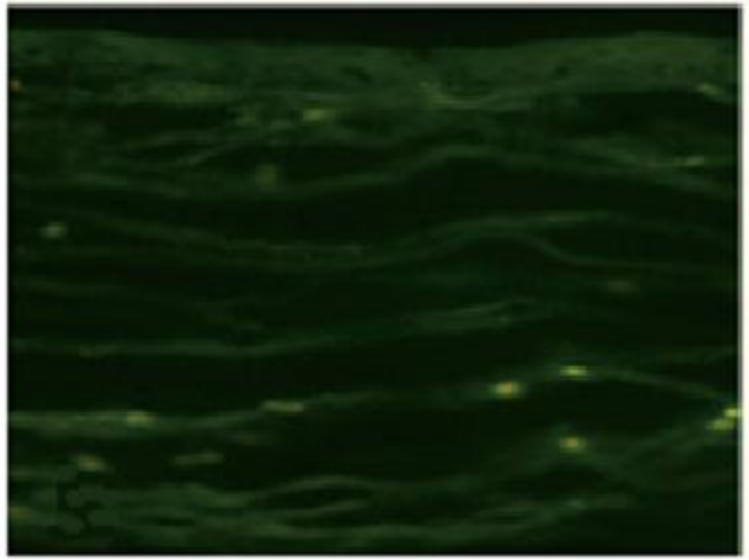
Limbic Stem Cells



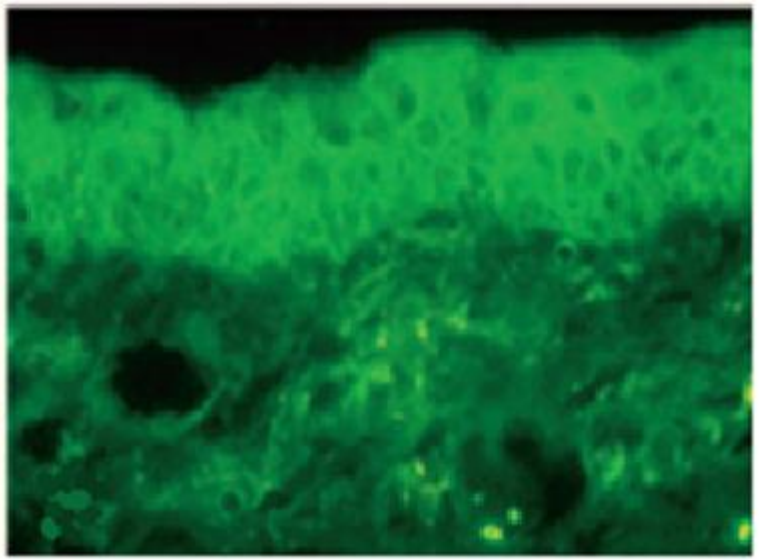
A – BM Stem Cells

B – Limbic Stem Cells

Immunofluorescence (human antibodies)



BM-MSC

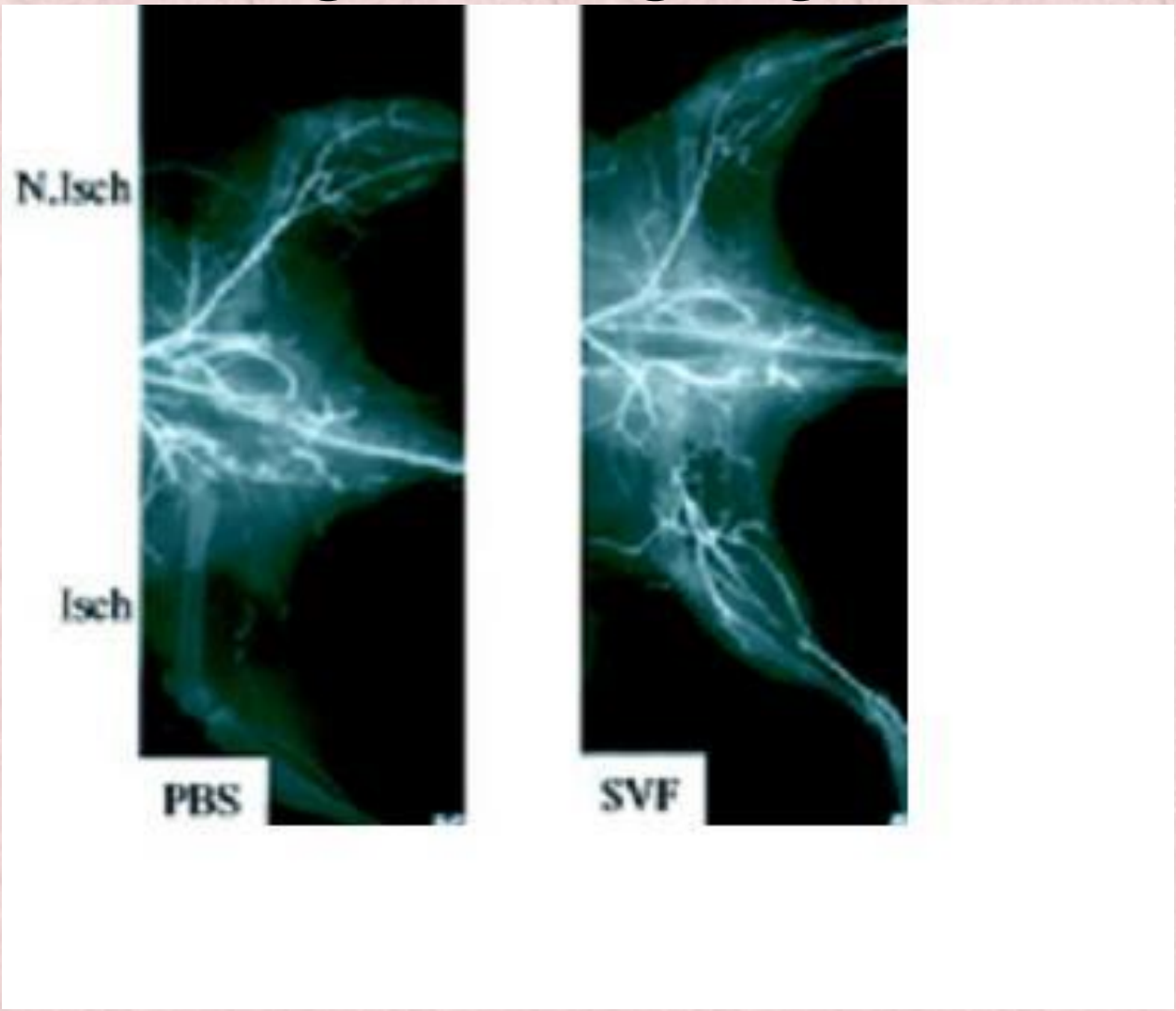


Limbic MSC

Conclusion

Therapeutic Effect Did Not Come from Epithelial Differentiation of MSCs but May Be a Result of Inhibition of Neovascularization and Inflammation

Homing & Angiogenesis



Miranville et al, *Circulation 2004;110; 349-355*

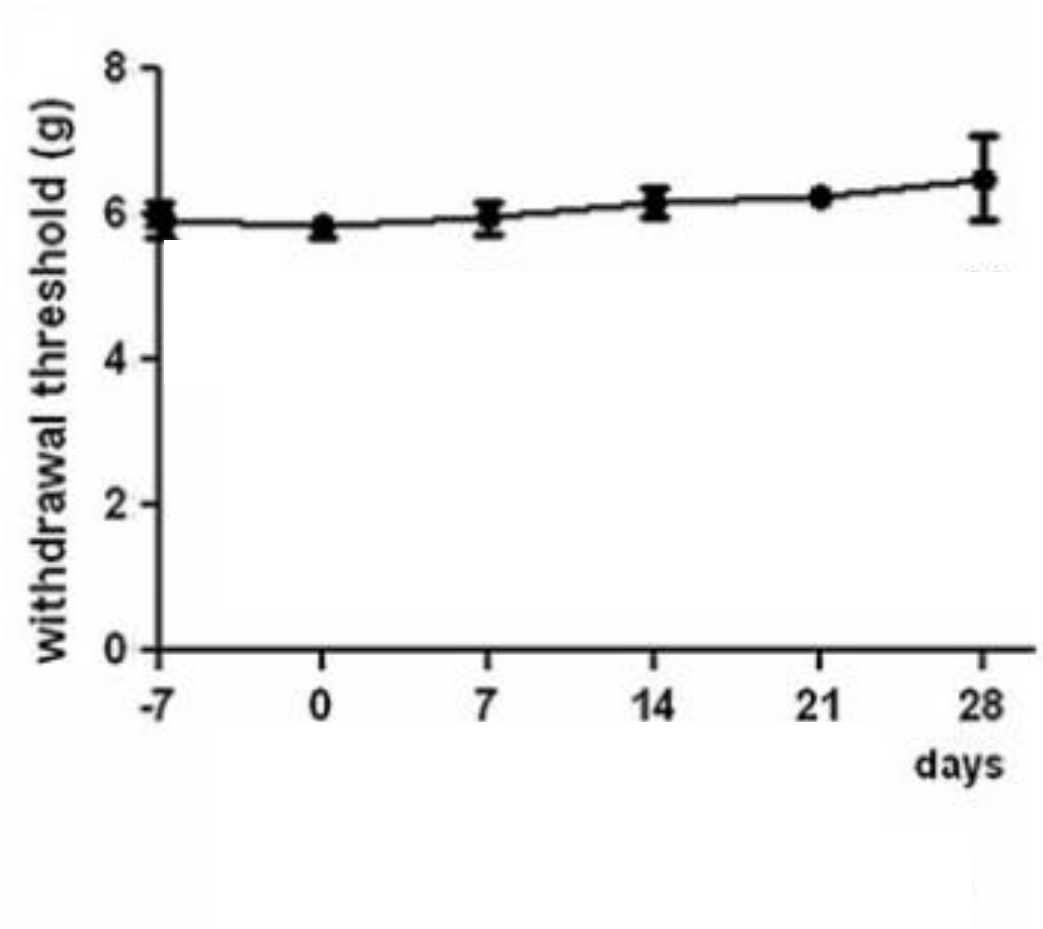

• Differentiate
• Homing
• Angiogenesis
• Immune modulation
• Anti-fibrotic
• Anti-apoptotic
• Free Radical Scavenger
• Exosomes
• Organelle transfer
• Block Pain

STEM CELLS AND DEVELOPMENT

ORIGINAL RESEARCH REPORT

Systemic Administration of Human Adipose-Derived Stem Cells Reverts Nociceptive Hypersensitivity in an Experimental Model of Neuropathy

Paola Sacerdote,[1] Stefania Niada,[2,3] Silvia Franchi,[1] Elena Arrigoni,[2] Alice Rossi,[1] Vijay Yenagi,[2] Laura de Girolamo,[3] Alberto Emilio Panerai,[1] and Anna Teresa Brini[2,3]



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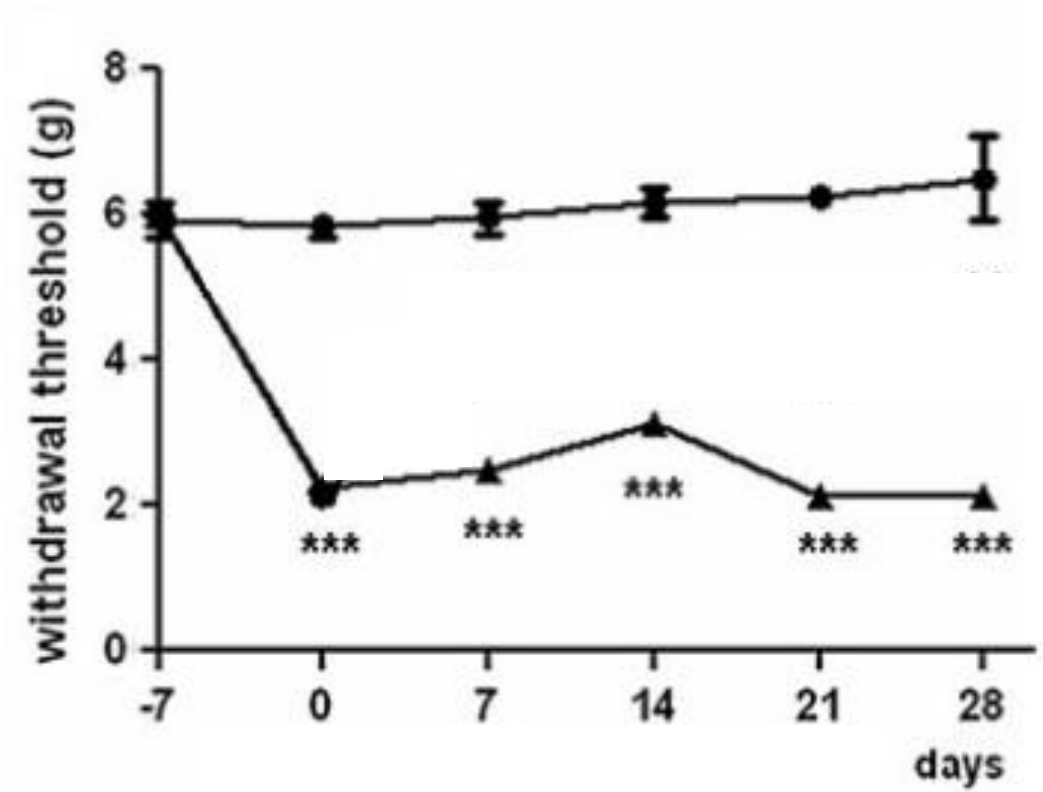

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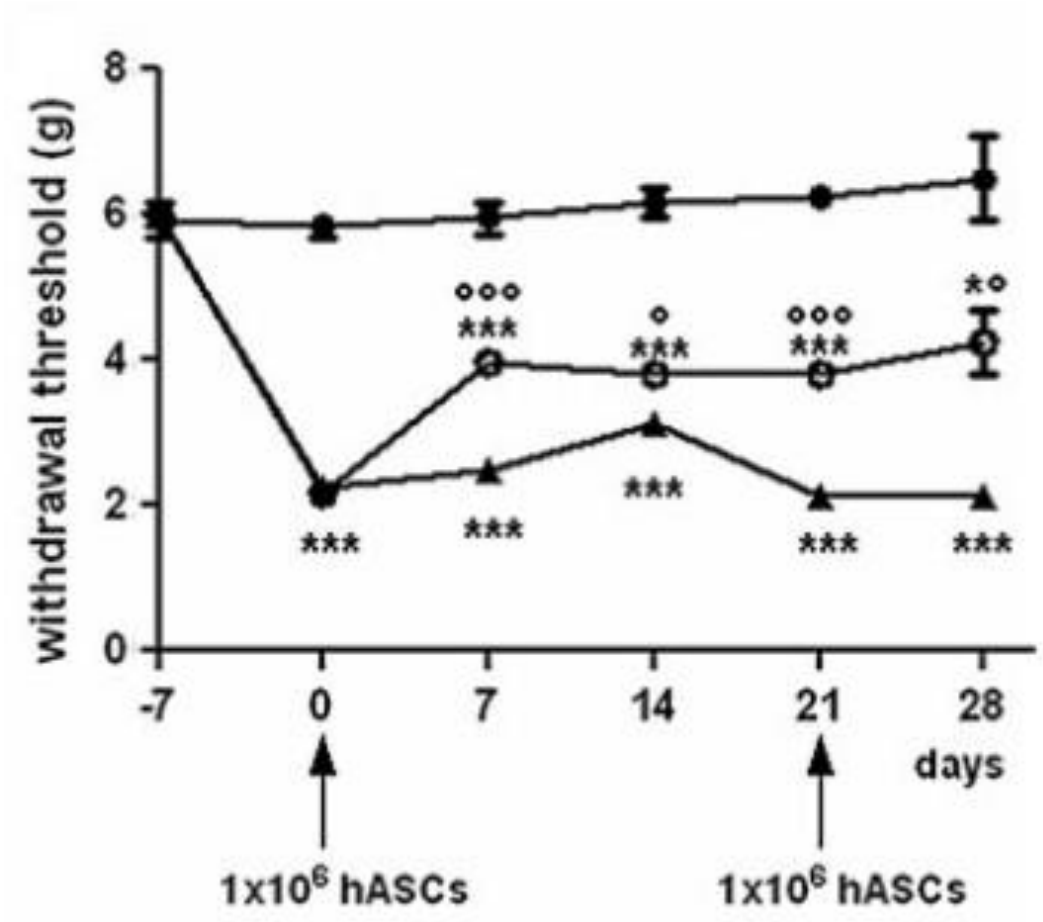
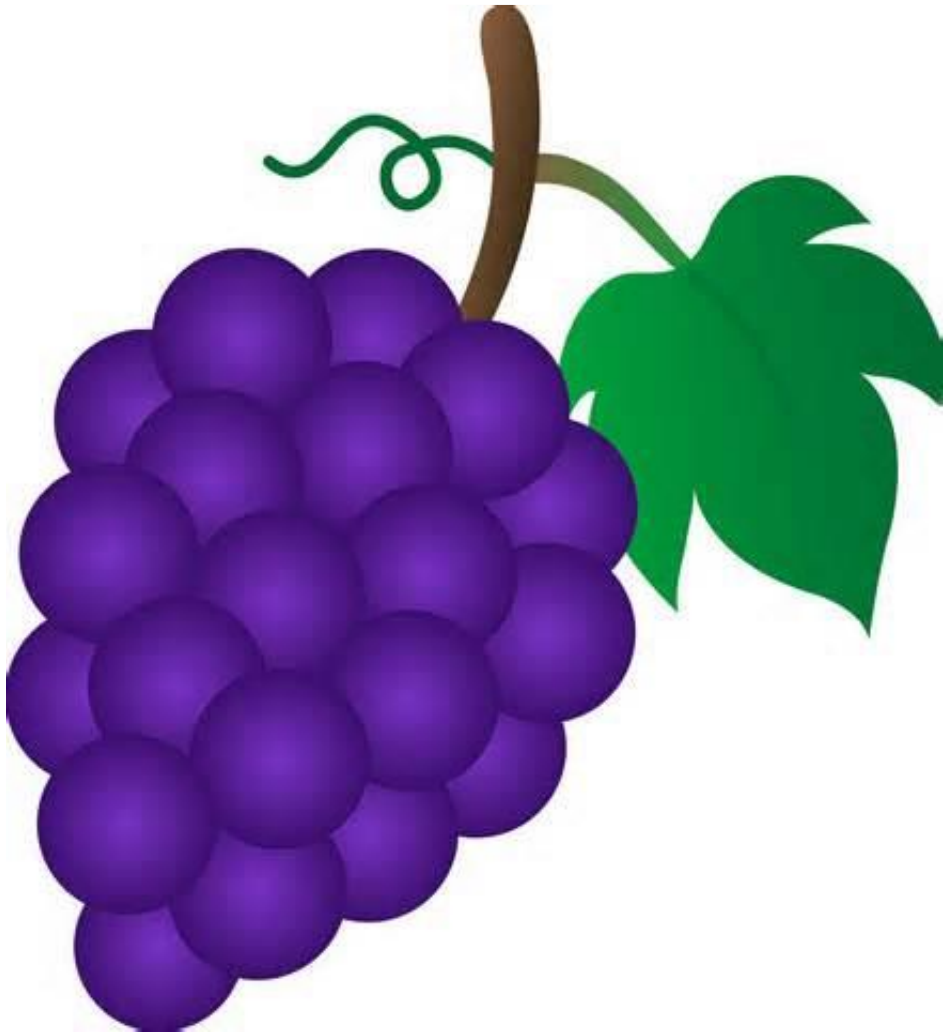
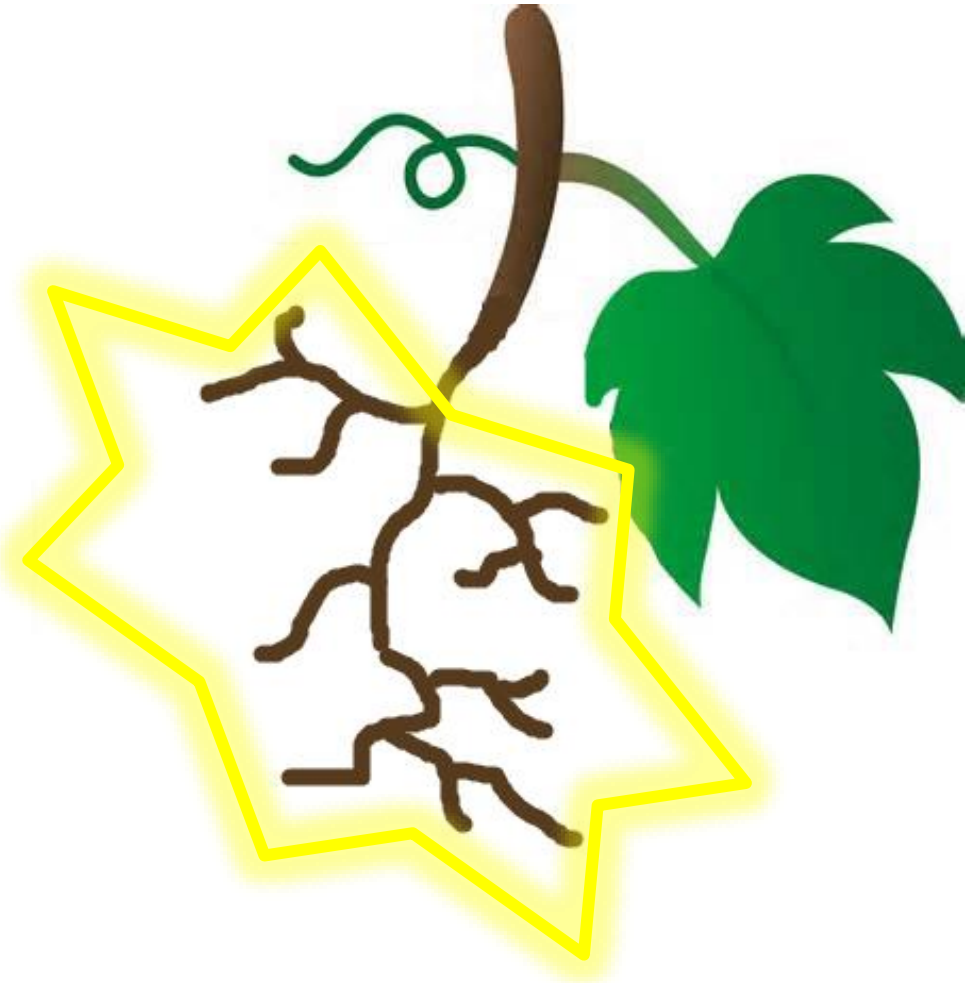



Stem Cell

Why Fat?



Why Fat?



Where Do We Find Stem Cells?

Muscle
Skin
Brain
Bone Marrow (1 in 4,224 cells) .02%
Fat (4 in 10 cells) 43%

Vidal et al, Vet Surg, 2006 & 2007

Are Stem Cells Safe?

Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis

Michalek, J, Moster R, Lukac L, Proefrock K, Petrasovic M, Rybar J, Capkova M, Chaloupka A, Darinskas A, Kristek J, Travnik J, Jabandziev P, Cibulka M, Holek M and Jurik M

- 1128 patients
- 1 to 4 intra-articular injections of SVF (total 1856 joint injections)
- Followed up 12 – 50 months later

Czech Republic, Slovakia and Arizona
Jan 20 Epub

Cell Transplant (2015)

Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis

Michalek, J, Moster R, Lukac L, Proefrock K, Petrasovic M, Rybar J, Capkova M, Chaloupka A, Darinskas A, Kristek J, Travnik J, Jabandziev P, Cibulka M, Holek M and Jurik M

"No serious side effects, systemic infection or cancer was associated with SVF cell therapy."

"at least 50% Score improvement was documented in 91% of patients 12 months after SVF cell therapy"

Preliminary Report

Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of Osteoarthritis in the Human Knee Joint

Peter B. Fodor, MD, FACS; and Stephen G. Paulseth, PT, MS, DPT, SCS, ATC

“No infections, acute pain flares or other adverse events were reported.”

“Autologous SVF was shown to be safe and to present a new potential therapy for reduction of pain for osteoarthritis of the knee.”

Evidence Pyramid

Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials

Manoj M. Lalu[1,5], Lauralyn McIntyre[2,5]*, Christina Pugliese[5], Dean Fergusson[5], Brent W. Winston[6], John C. Marshall[7], John Granton[8], Duncan J. Stewart[3,4], for the Canadian Critical Care Trials Group

- Reviewed 36 studies that used MSCs in people
- Total of 1012 participants
- Stroke, Crohn's, heart disease, GvD, healthy volunteers
- All had Intravascular (IV, IA, IC) injections +/- other routes
- Most studies were with cultured cells, some with allogeneic

Universities of Ottawa, Calgary and Toronto
(2012) 7(10):e47559

PLOS ONE

Safety of Cell Therapy with Mesenchymal Stromal Cells (SafeCell): A Systematic Review and Meta-Analysis of Clinical Trials

Manoj M. Lalu[1,5], Lauralyn McIntyre[2,5*], Christina Pugliese[5], Dean Fergusson[5], Brent W. Winston[6], John C. Marshall[7], John Granton[8], Duncan J. Stewart[3,4], for the Canadian Critical Care Trials Group

- NO association between “acute infusional toxicity, organ system complications, infection, death or malignancy”
- “MSC therapy appears safe”

FDA Registered Trials

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

Study # NCT01813279 **Safety, tolerability and potential efficacy of injection of autologous adipose-derived stromal vascular fraction in the fingers of patients with systemic sclerosis: an open-label phase I trial.**

Study # NCT02276833 **Use of Autologous Adipose-Derived Stromal Vascular Fraction to Treat Osteoarthritis of the Knee**

Study # NCT02357485 **ADSC Injections for Pain Management of Osteoarthritis in the Human Knee Joint**

No serious adverse events reported in any of these trials.

What are we treating?

- Arthritis

  (knee, shoulder, back, neck…)
- Peripheral neuropathies
- Tendon/ligament injuries
- Autoimmune diseases
- Other…

Free consult with a doctor

Take Home Message

Stem cells:

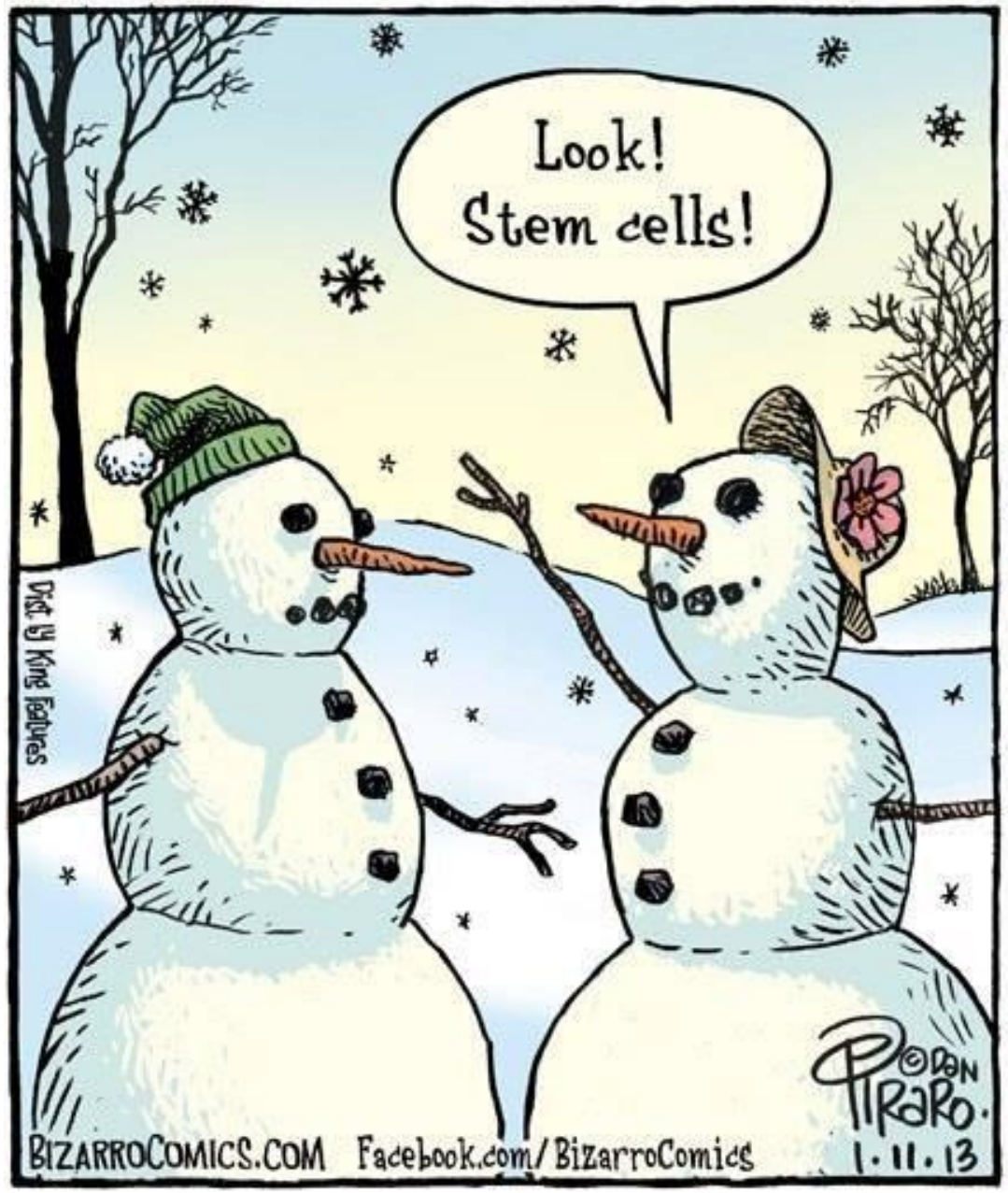
- **Act as Medical Conductors**
- **Fat is the richest source**
- **SAFE!**

Questions?

Mayo Clinic

“Regenerative medicine is a game-changing area of medicine with the potential to fully heal damaged tissues and organs, offering solutions and hope for people who have conditions that today are beyond repair.”

www.mayo.edu


Look!
Stem cells!
Dist. by King Features
BIZARROCOMICS.COM
Facebook.com/BizarroComics
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1.11.13