同济大学
TONGJI UNIVERSITY

骨髓间充质干细胞
(Bone marrow mesenchymal stem cells)

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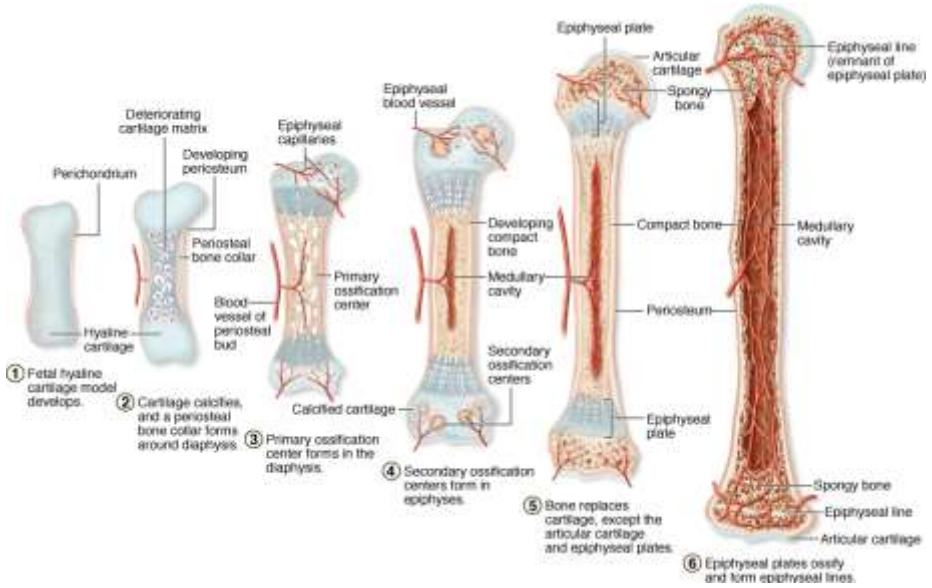
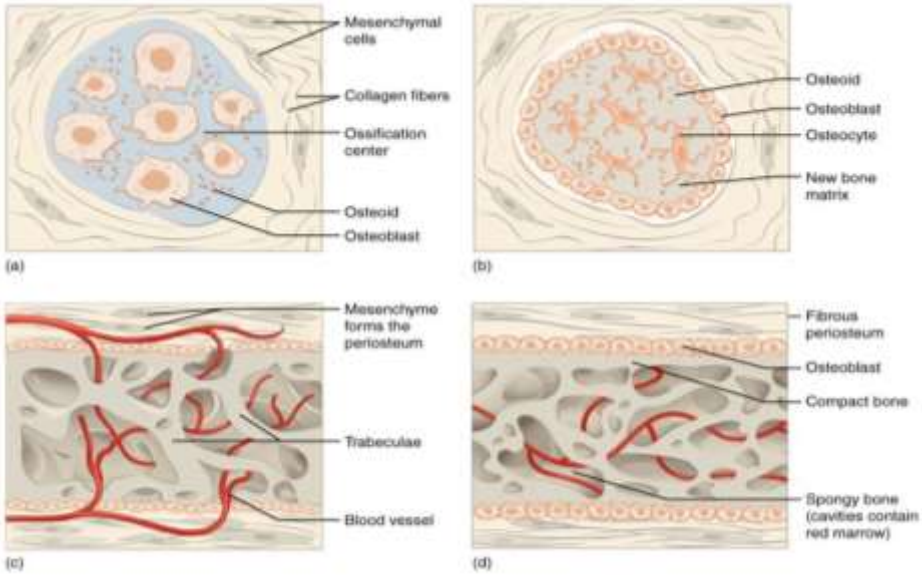
同济大学生命科学与技术学院
同济大学附属东方医院

Skeletal development

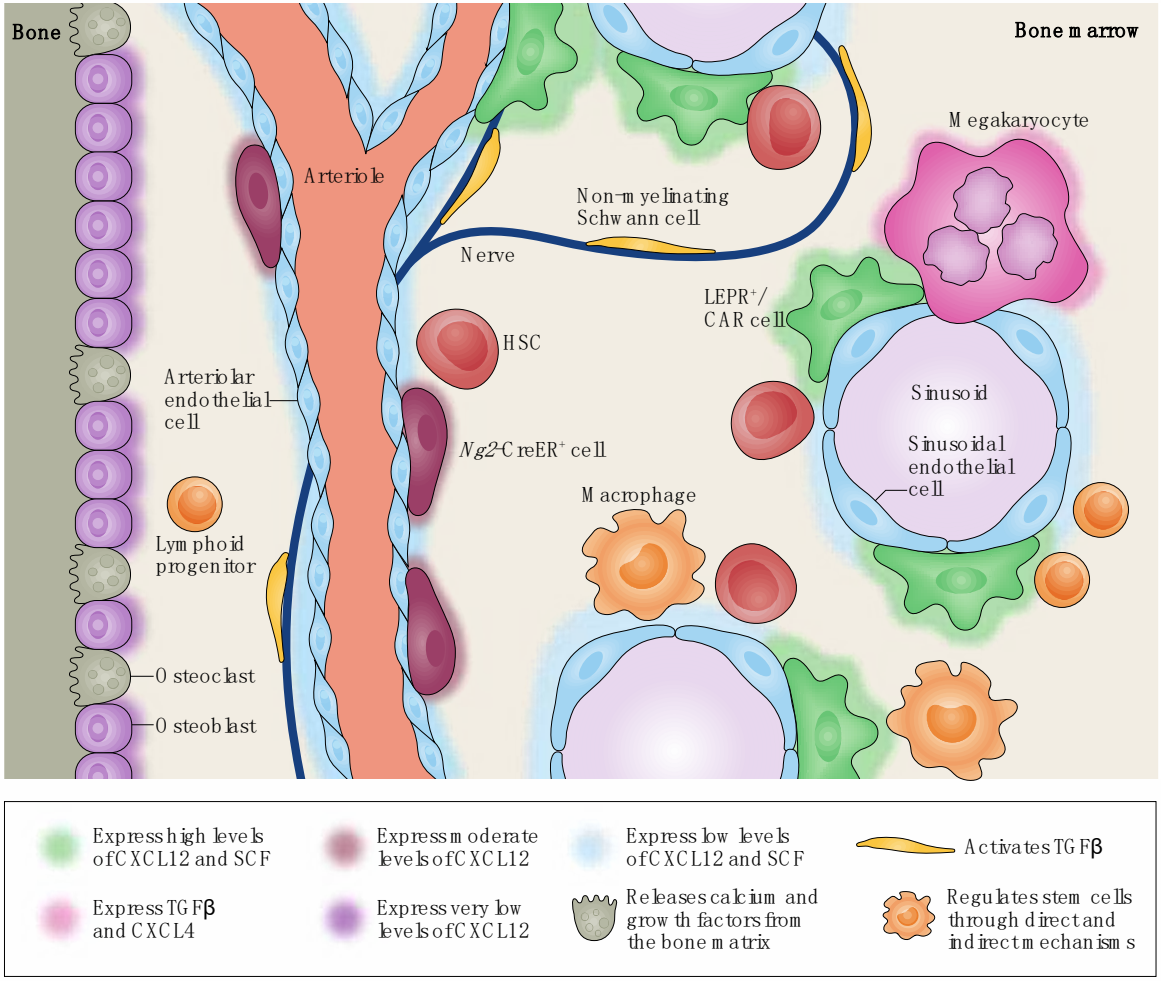




Endochondral ossification

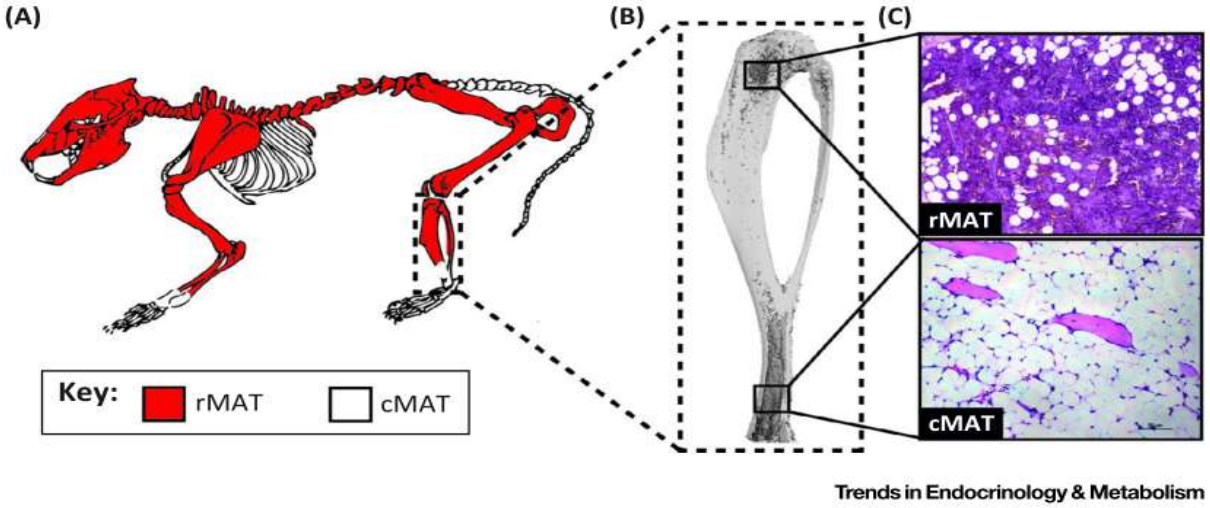
Intramembranous ossification

The bone marrow microenvironment



Crane *et al.*, Nat. Rev. Immunol., 2017

Bone marrow adipocytes



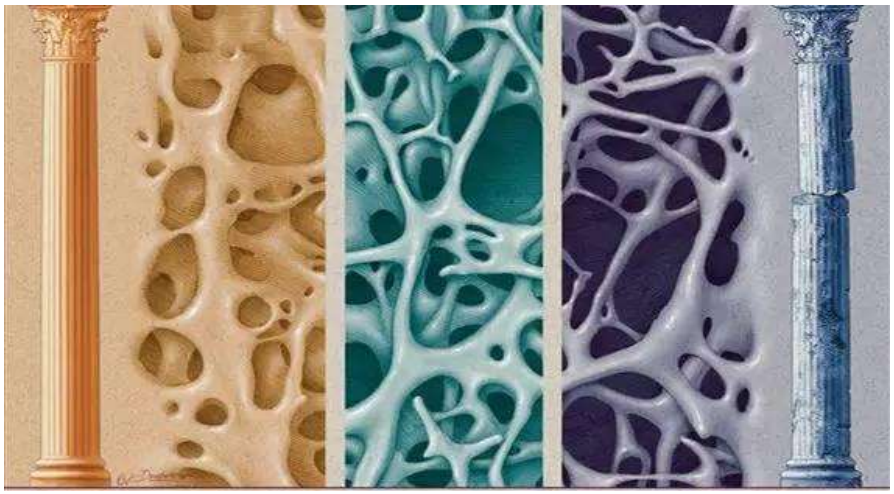
regulated Marrow Adipose Tissue (rMAT):
Inducible

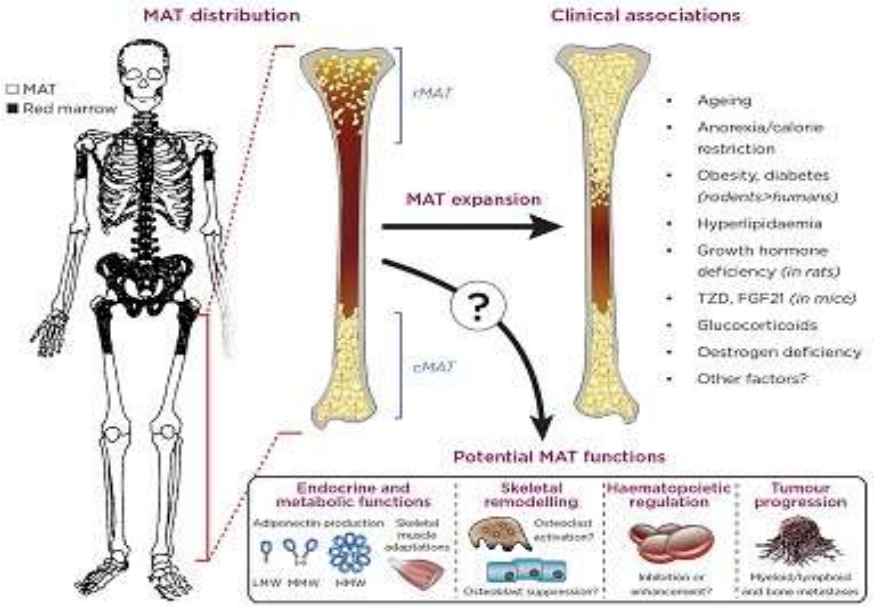
constitutive Marrow Adipose Tissue (cMAT):
Appears early in postnatal life

Scheller et al. *Trends in Endocrinology & Metabolism Tem*, 2016

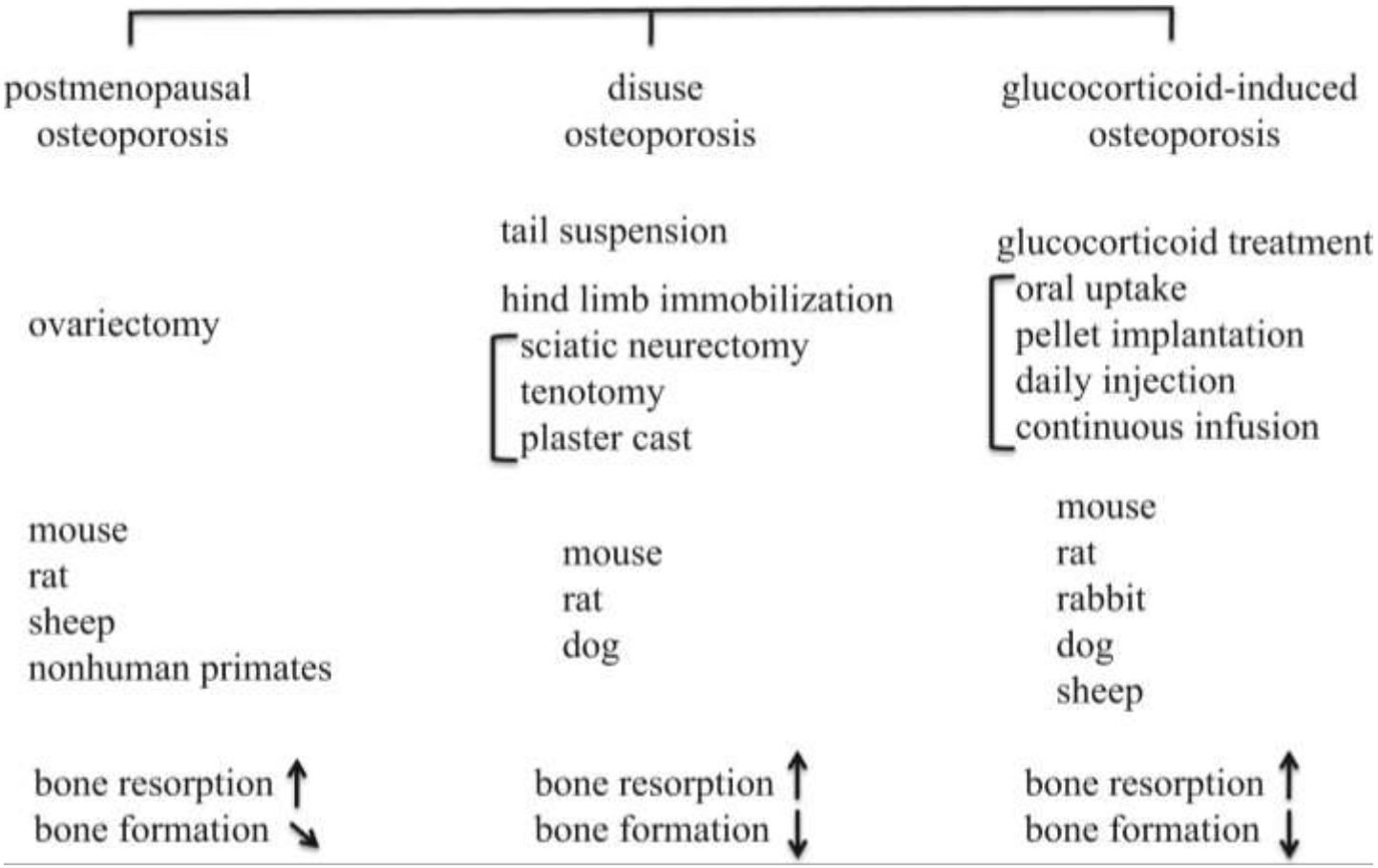
Bone aging: Osteoporosis and fatty marrow

Osteogenic activity



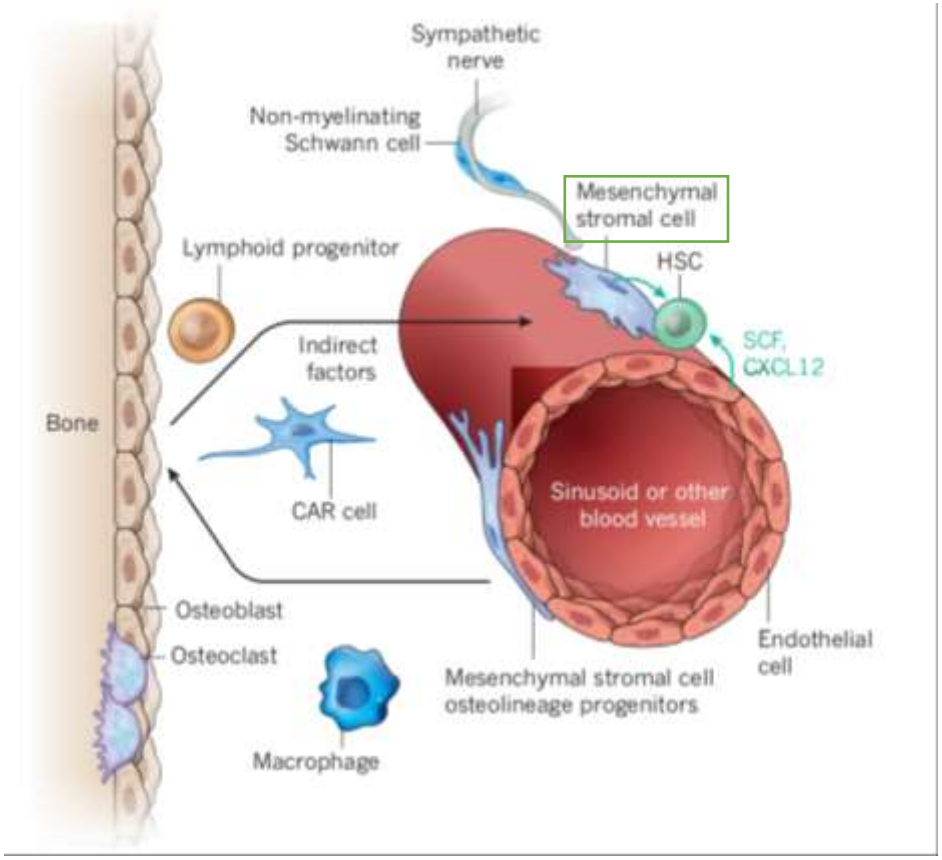


Animal models for osteoporosis



1. What is mesenchymal stem cells?

Definition of BMSC



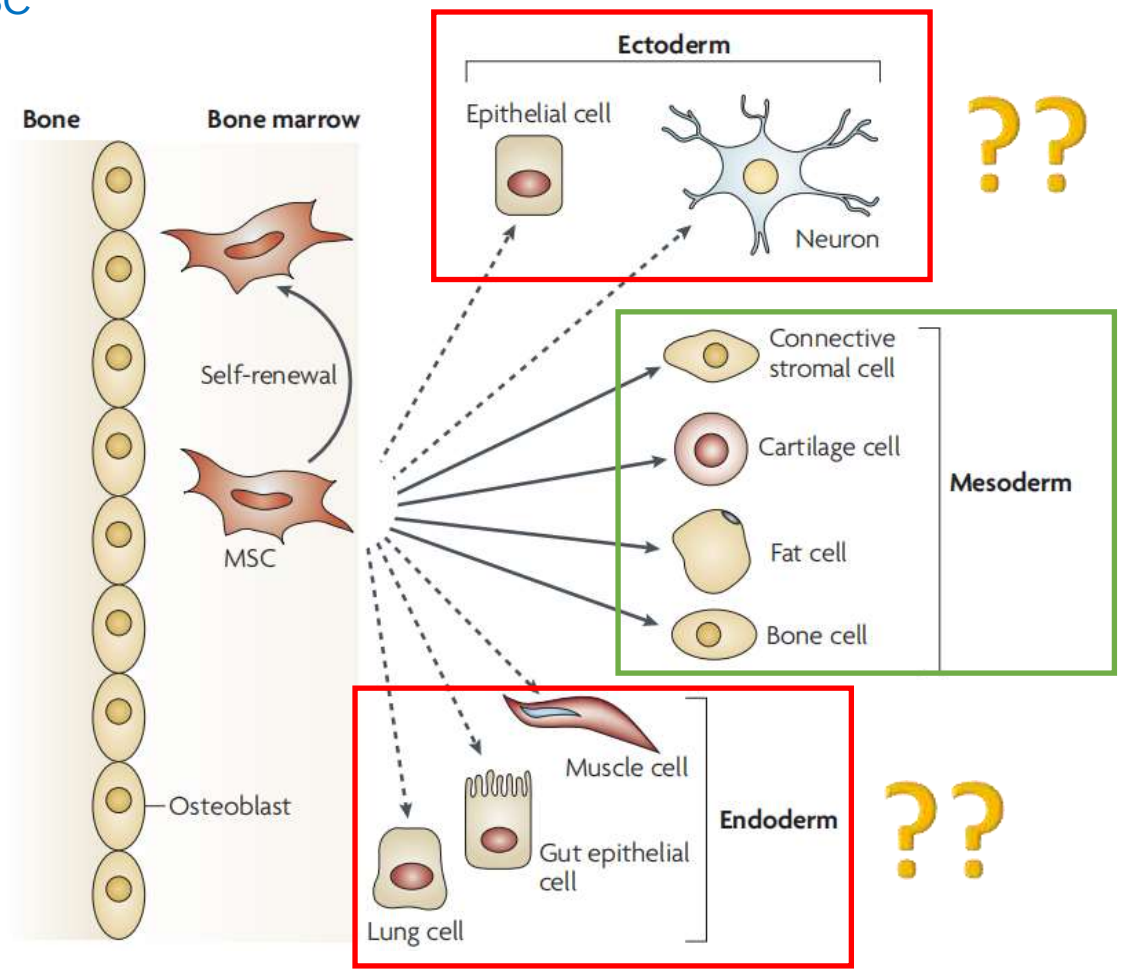
Stem cells
- Self-renewal
- Multilineage differentiation

- BMSC: Bone marrow stromal cells
- HSC: Hematopoietic stem cells

Morrison SJ, Scadden DT. *Nature*. 2014

1. What is mesenchymal stem cells?

- Definition of BMSC

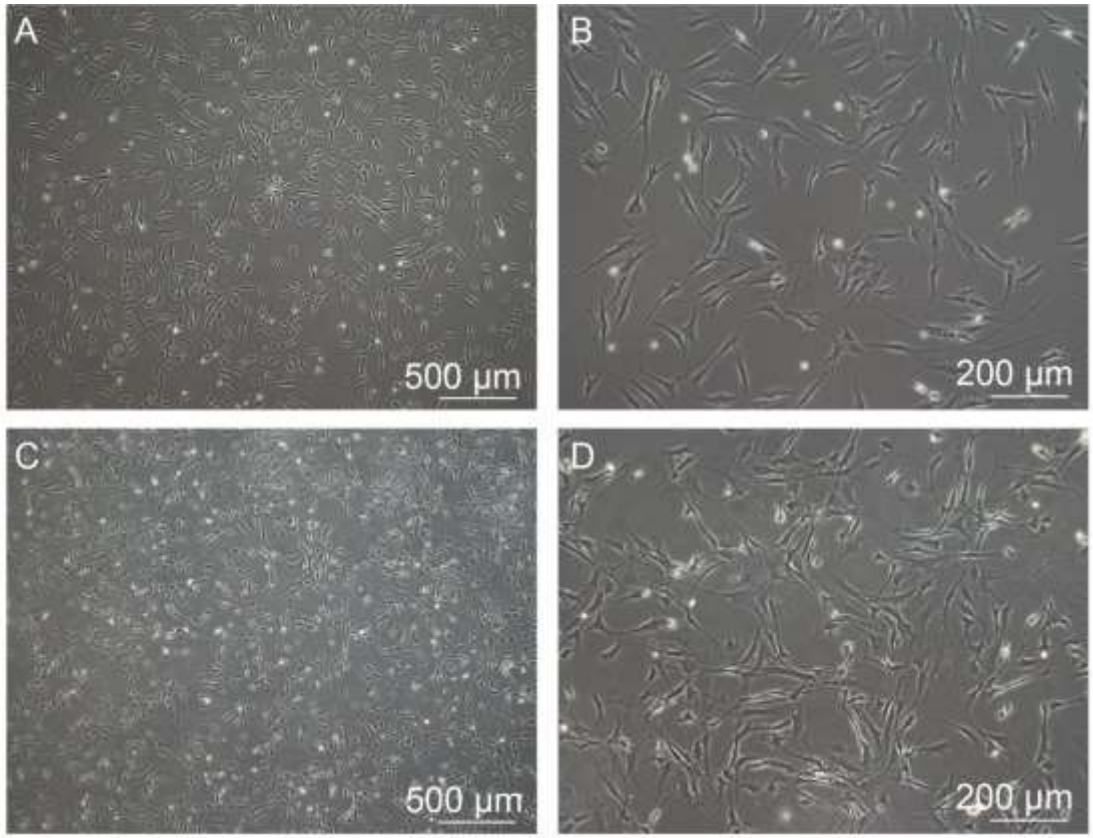


Uccelli A, Moretta L, Pistoia V. *Nat Rev Immunol*. 2008

Morphologies of mouse and human BMSCs

Human

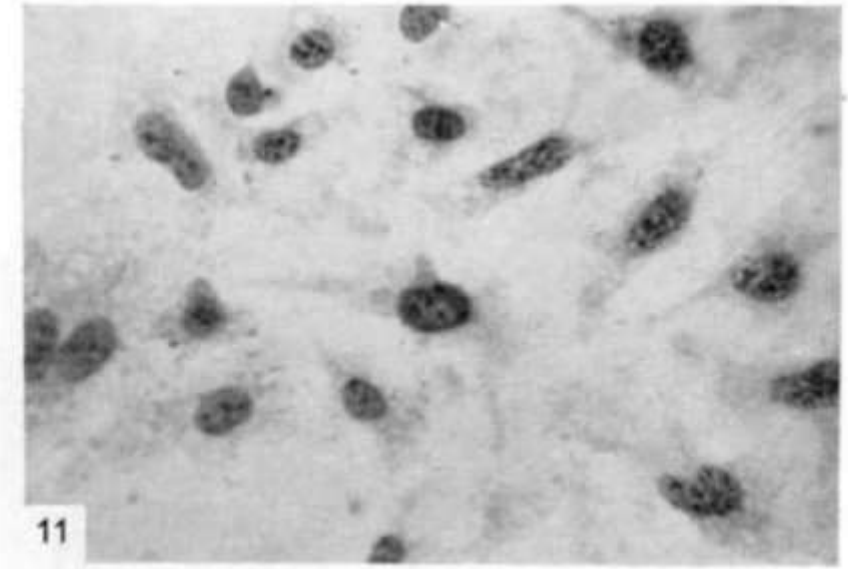
Mouse



2. History of BMSC

1966
Friedenstein
Bone marrow cells

History



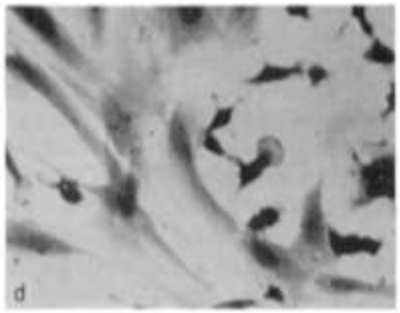
Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. *J Embryol Exp Morphol*. 1966

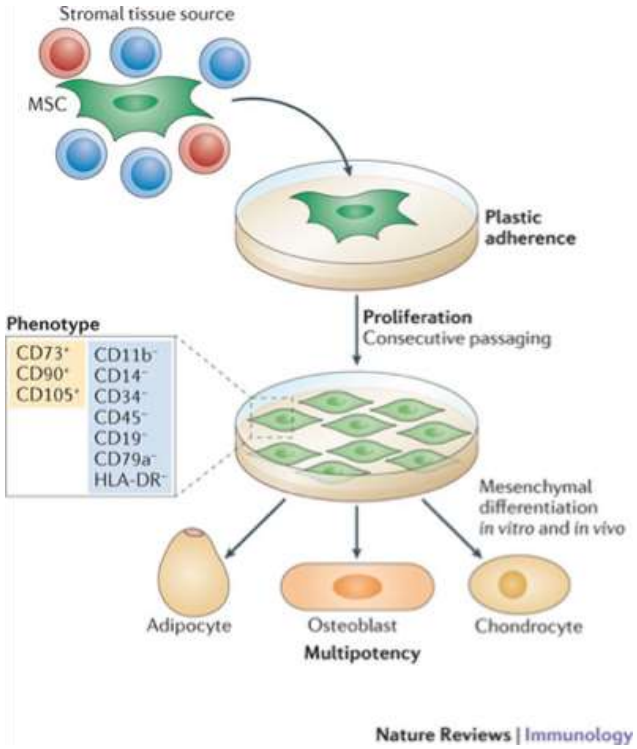
2. History of BMSC

1966
Friedenstein
Bone marrow cells

History

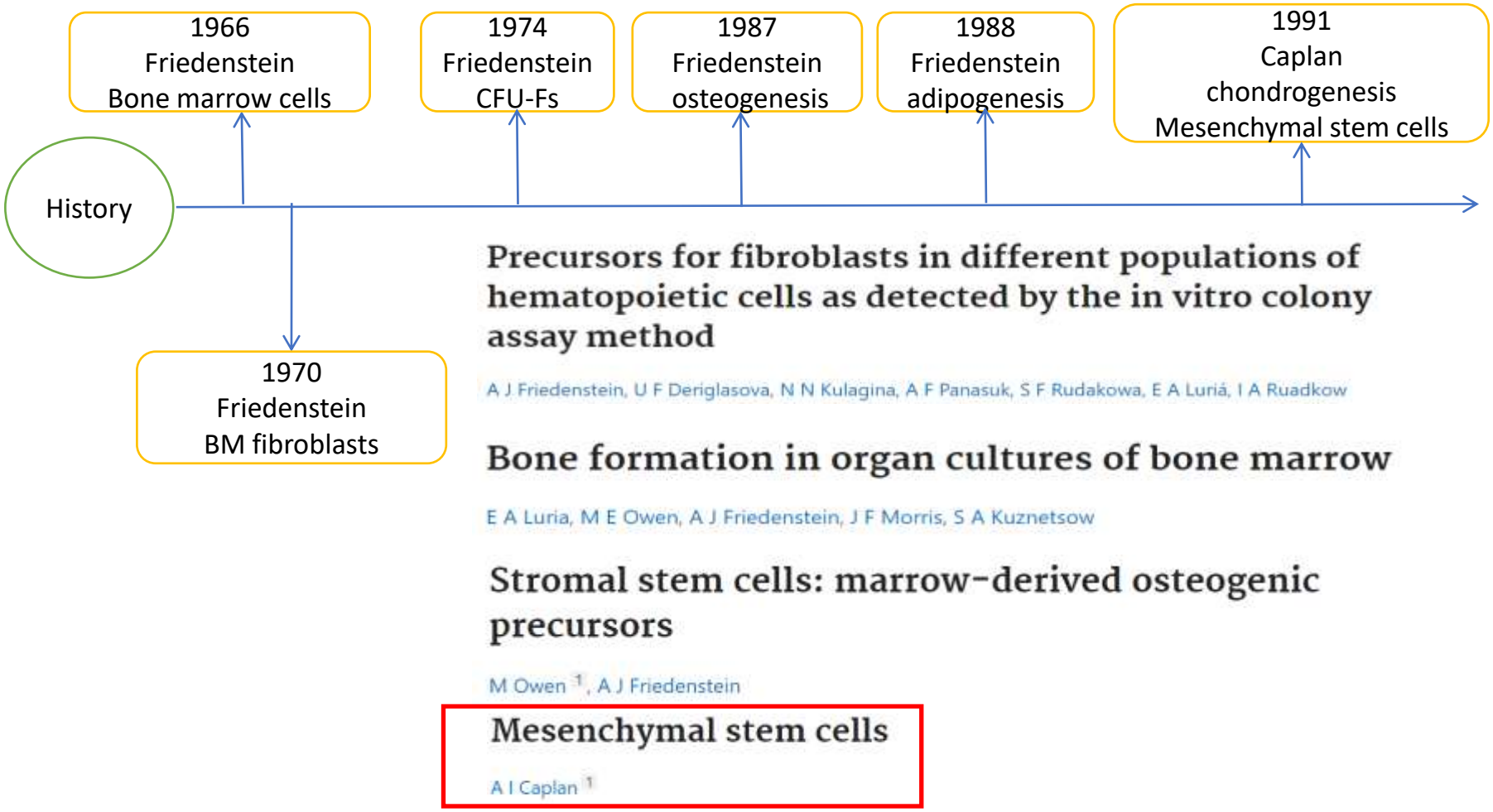
1970
Friedenstein
BM fibroblasts





Friedenstein AJ, Chailakhjan RK, Lalykina KS. *Cell Tissue Kinet*. 1970

2. History of BMSC



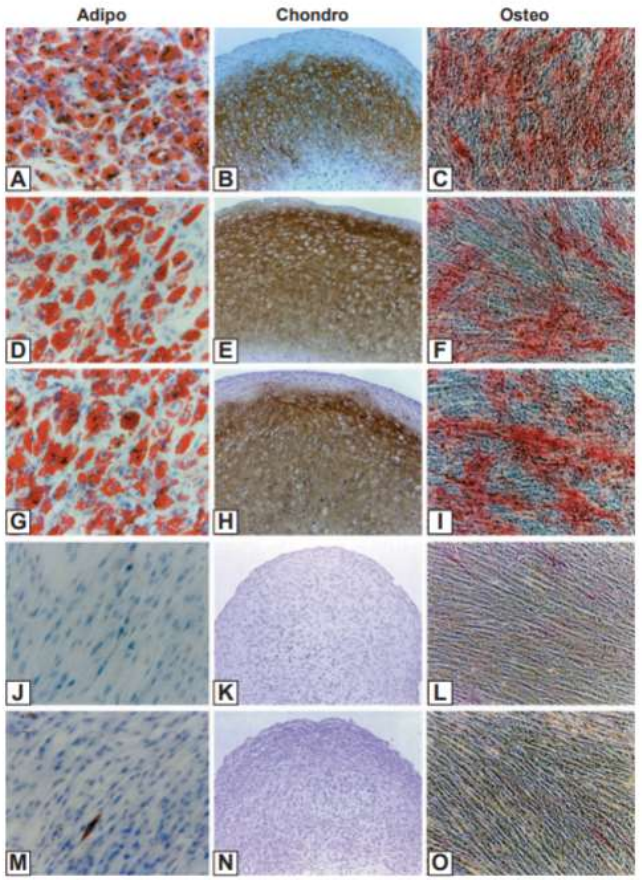
2. History of BMSC

History

1966
Friedenstein
Bone marrow cells

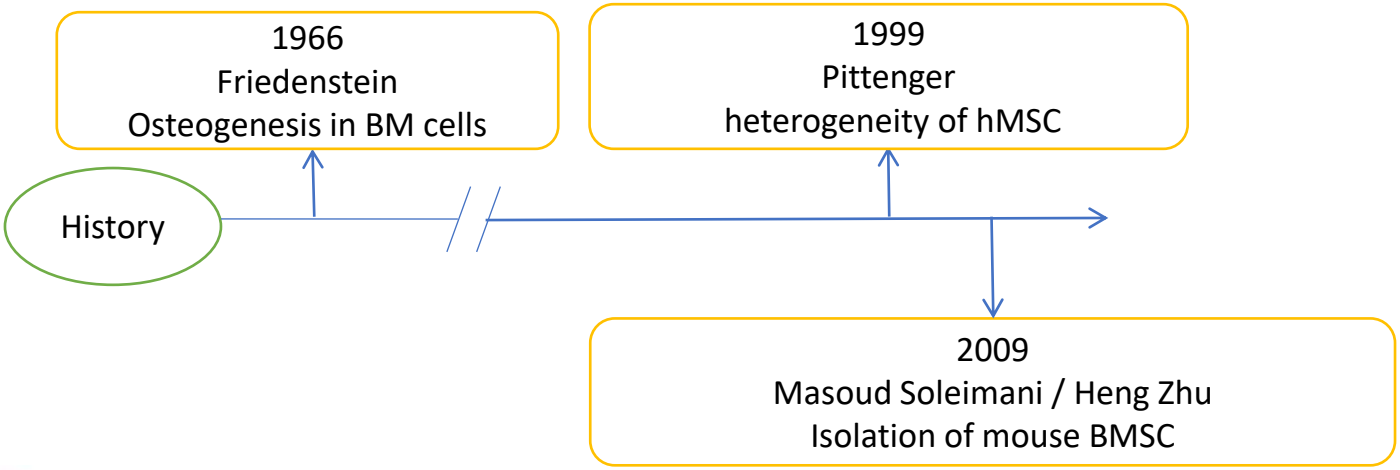
1991
Caplan
chondrogenesis

1999
Pittenger
heterogeneity of hMSC



Pittenger MF, Mackay AM, Beck SC, et al. *Science*. 1999

2. History of BMSC



PROTOCOL

A protocol for isolation and culture of mesenchymal stem cells from mouse bone marrow

Masoud Soleimani[1,4] & Samad Nadri[2–4]

Soleimani M, Nadri S. *Nat Protoc*. 2009

PROTOCOL

A protocol for isolation and culture of mesenchymal stem cells from mouse compact bone

Heng Zhu[1], Zi-Kuan Guo[2], Xiao-Xia Jiang[1], Hong Li[1], Xiao-Yan Wang[1], Hui-Yu Yao[1], Yi Zhang[1] & Ning Mao[1]

Zhu H, Guo ZK, Jiang XX, et al.*Nat Protoc*.2009

2. History of BMSC

1966
Friedenstein
Osteogenesis in BM cells

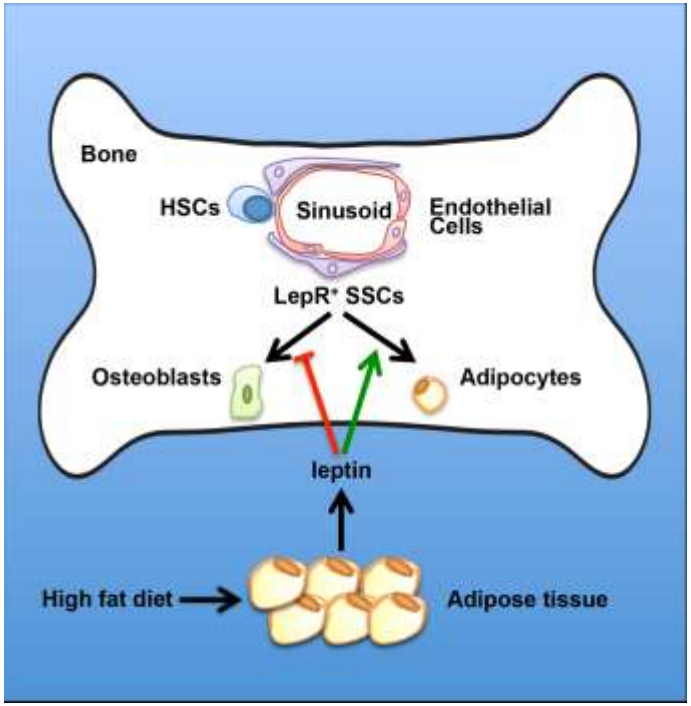
2014
Discovery of Lepr as an
in vivo marker of BMSCs

2015
Discovery of mouse
skeletal stem cells (hSSCs)

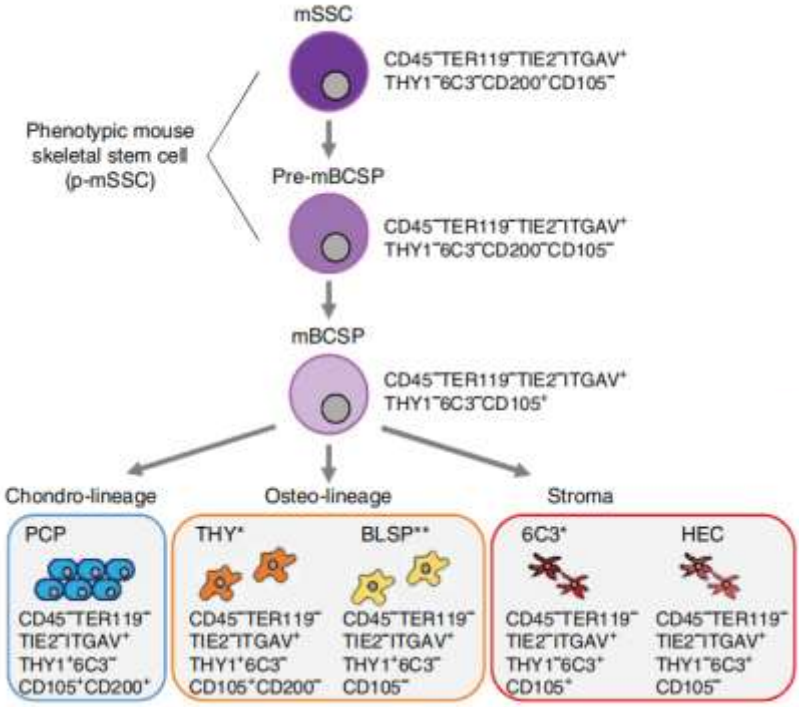
2018
Discovery of human
skeletal stem cells (hSSCs)

History

Present



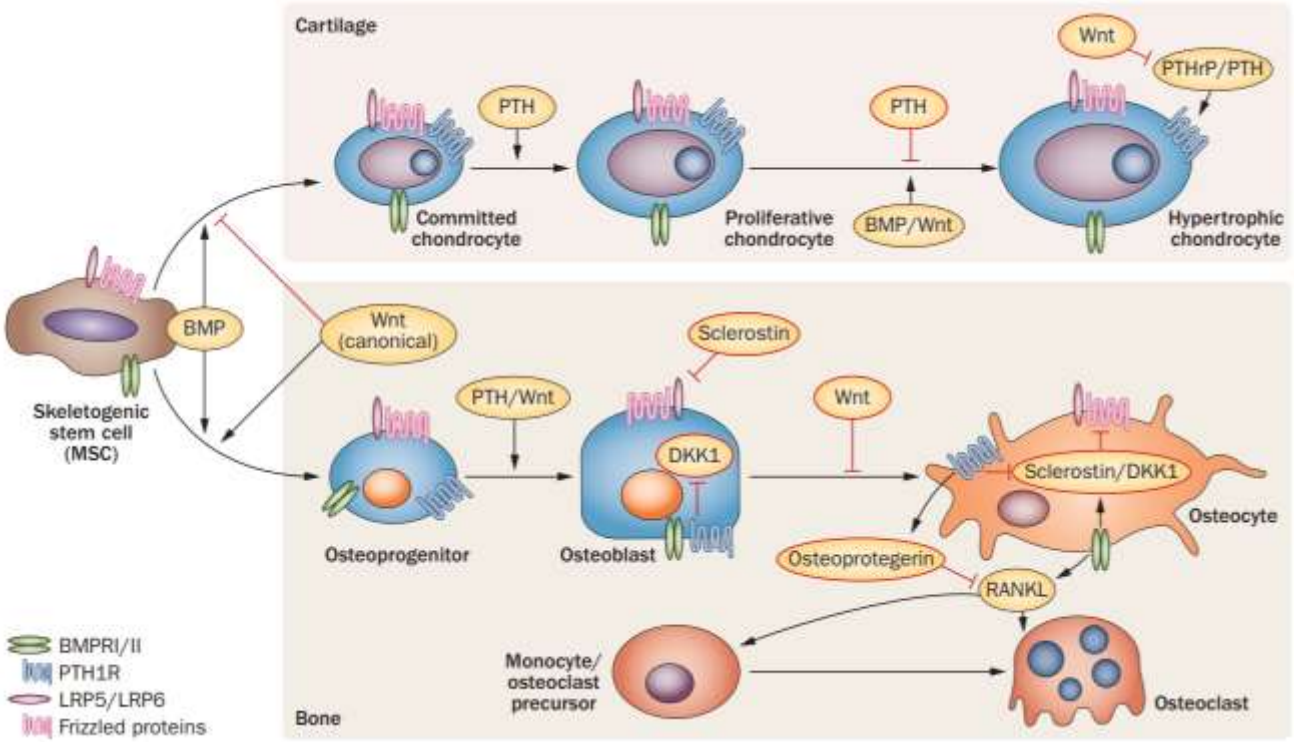
Yue et al. *Cell,* 2016



Chan et al. *Cell,* 2015, 2018

3. Function of BMSC

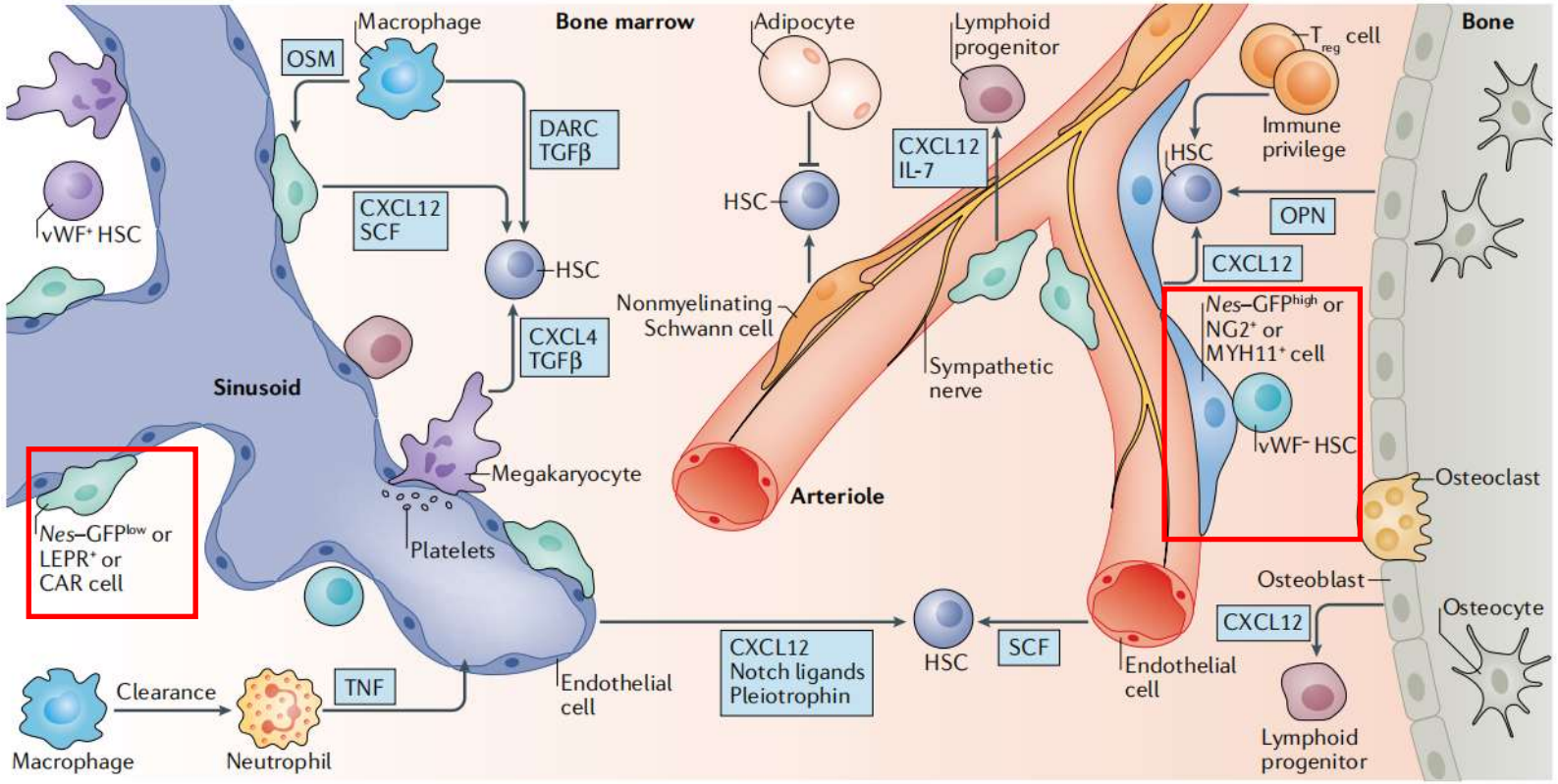
- Maintain bone homeostasis and fracture repair



Einhorn, T., Gerstenfeld, L. *Nat Rev Rheumatol*. 2015

3. Function of BMSC

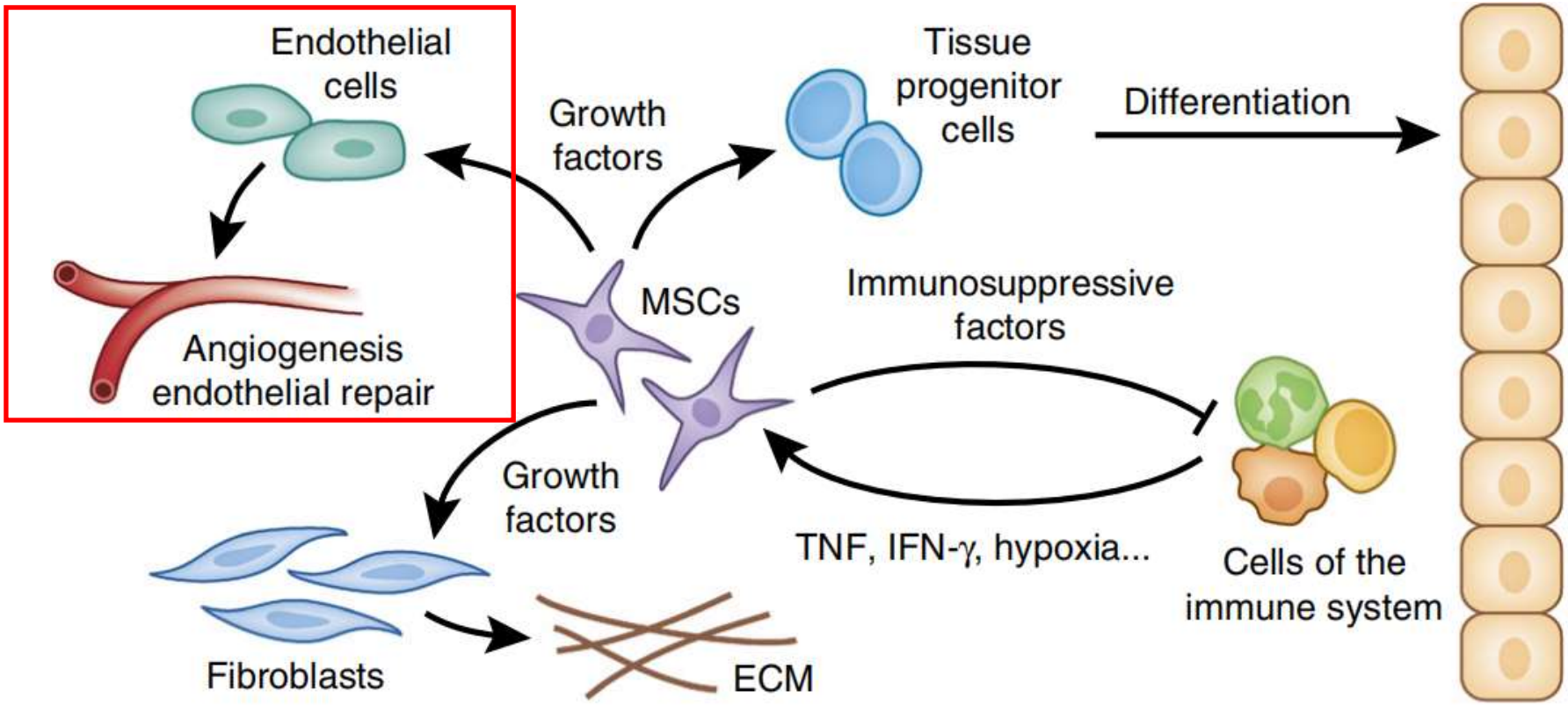
- Formation of HSC niche in the bone marrow



Pinho S, Frenette PS. *Nat Rev Mol Cell Biol*. 2019

3. Function of BMSC

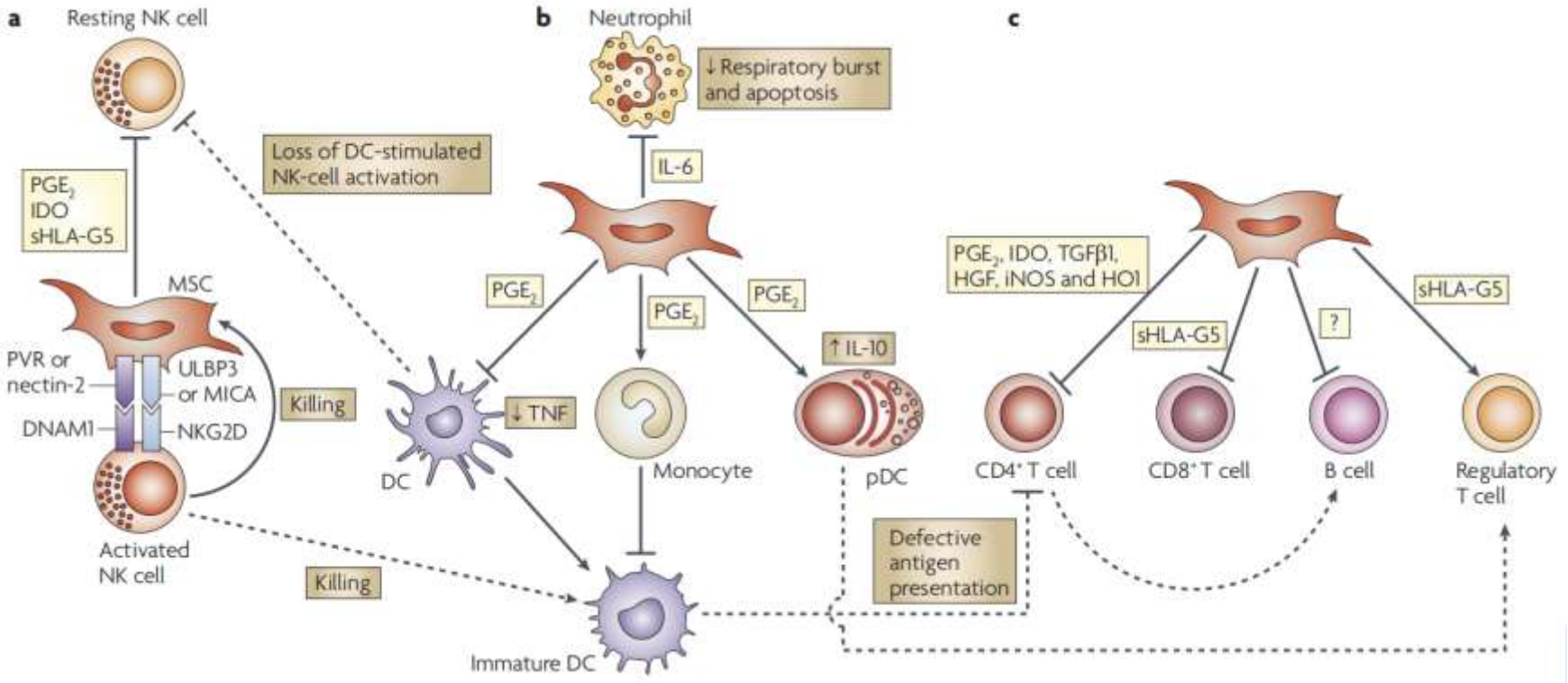
- Angiogenesis



Wang Y, Chen X, Cao W, Shi Y. *Nat Immunol*. 2014

3. Function of BMSC

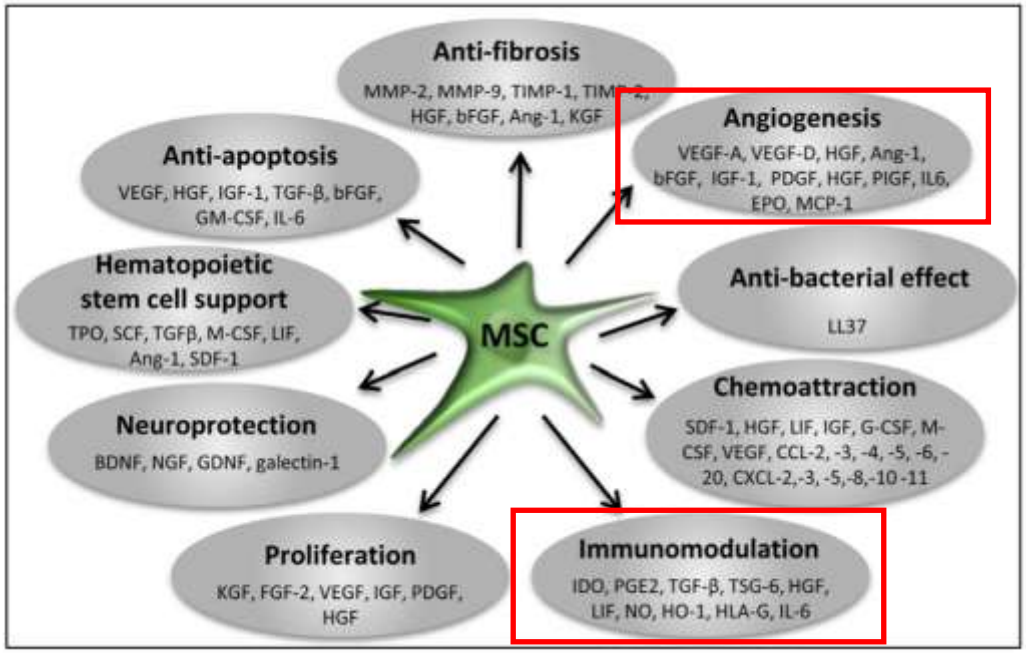
- The effects of MSCs on immune cells

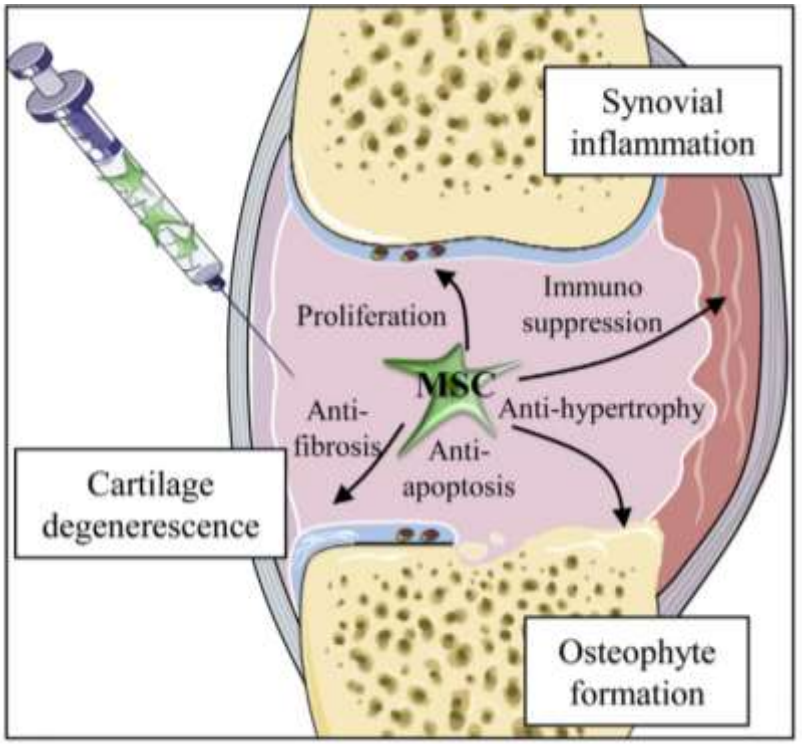


Uccelli A, Moretta L, Pistoia V. *Nat Rev Immunol*. 2008

4. Clinical application of BMSC

- Mechanisms





Maumus M, Jorgensen C, Noël D. *Biochimie*. 2013

4. Clinical applications of BMSC

Disease	Target organ	Mechanism of MSC
Myocardial infarction	Heart	Generation of new myocytes and vascular structures
Skin-graft rejection	Skin	Inhibition of T cells
Stroke	CNS	Release of trophic factors and induction of neurogenesis
Melanoma	Skin	Inhibition of tumour-specific T cells by CD8+ T cells
Acute renal failure	Kidney	Inhibition of pro-inflammatory cytokine production and induction of anti-apoptotic and trophic factors
EAE	CNS	Inhibition of myelin-specific T cells and induction of peripheral tolerance
Diabetes	Pancreas & renal glomeruli	Induction of local progenitor cells and inhibition of macrophage infiltration
Rheumatoid arthritis	Joint	Inhibition of T cells and of production of pro-inflammatory cytokines; induction of regulatory T cells
Retinal degeneration	Eye	Decreased retinal degeneration through anti-apoptotic and trophic molecules
Acute lung injury	Lung	Inhibition of production of pro-inflammatory cytokines
Acute renal failure	Kidney	Tubular-cell regeneration through IGF1 secretion
Hepatic failure	Liver	Inhibition of leukocyte invasion through the release of cytokines and chemokines

4. limitations

Advantages:

- Easy to culture and industrialize
- Low immunogenicity and tumorigenicity
- Little ethical issues

Limitations:

- Unwanted differentiation
- Potential to suppress anti-tumor immune response
- Generation of new blood vessels that may promote tumor growth and metastasis
- Undesired calcifications or ossifications
- Postoperative complications