Un esperimento è una domanda che la scienza pone alla natura, ed una misurazione è la registrazione della risposta della Natura.
(Max Planck)

# Hepatic stem cells

•Liver is an organ capable of extensive regeneration

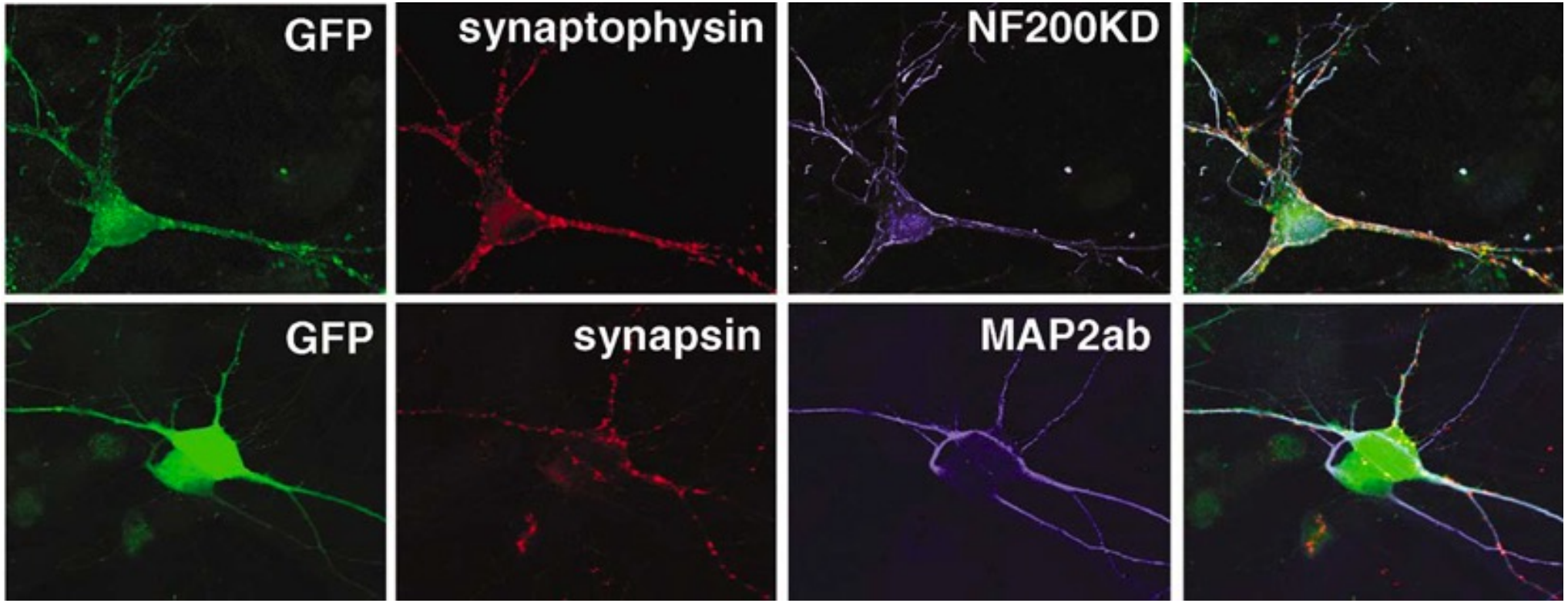
But

•The precise source of stem cells remains unclear (terminal bile ductules ?)

# Neural stem cells

- Old studies in rats and songbirds (1969)
- More recent studies in mammals: neuronal progenitors exist, are capable of extensive cell division and self renewal
- Can be obtained by differential sedimentation on a gradient
- Available markers allow only 45 fold enrichment
- Neural progenitors can migrate and home to specific sites of damage or regeneration

# Post natal neural cells




Song et al, 2002

# Skeletal muscle stem cells

- Satellite cell: mononucleated cell ensheathed under the basal lamina that surrounds multinucleated muscle fibers (1961)

- Can be activated, induced to proliferate, and contribute to intact skeletal muscle fibers even after extensive tissue doublings

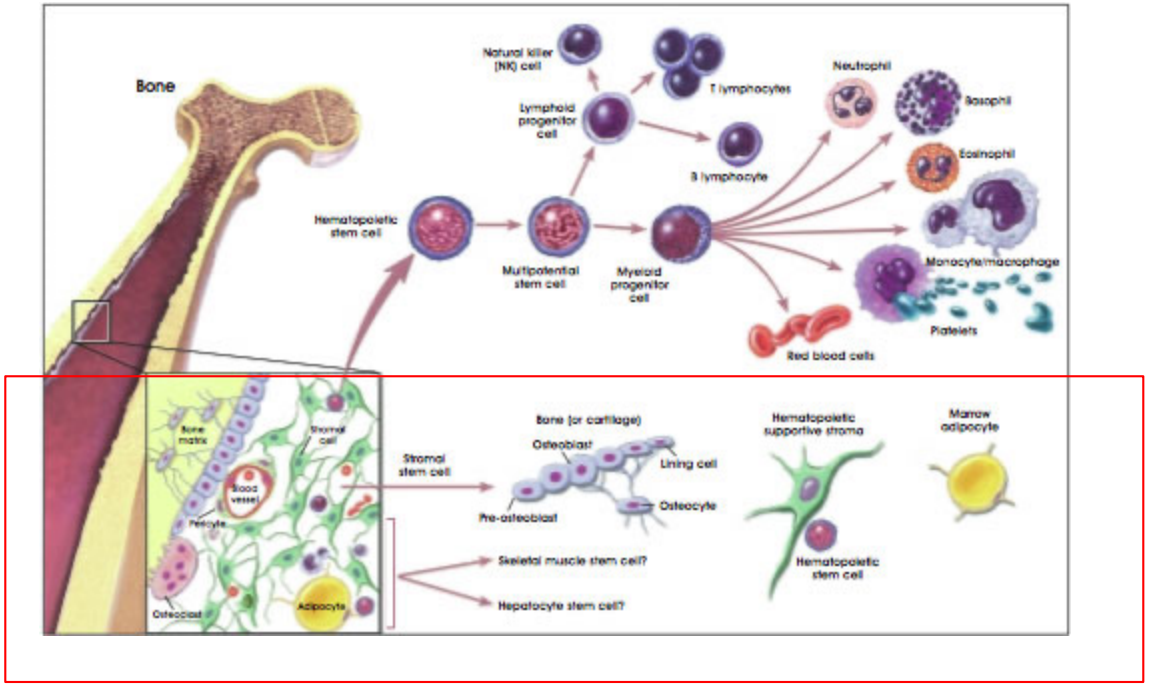
- Heterogeneous, no specific markers

- Are rapidly depleted in muscle of Duchenne patients

# Mesenchymal stem cells

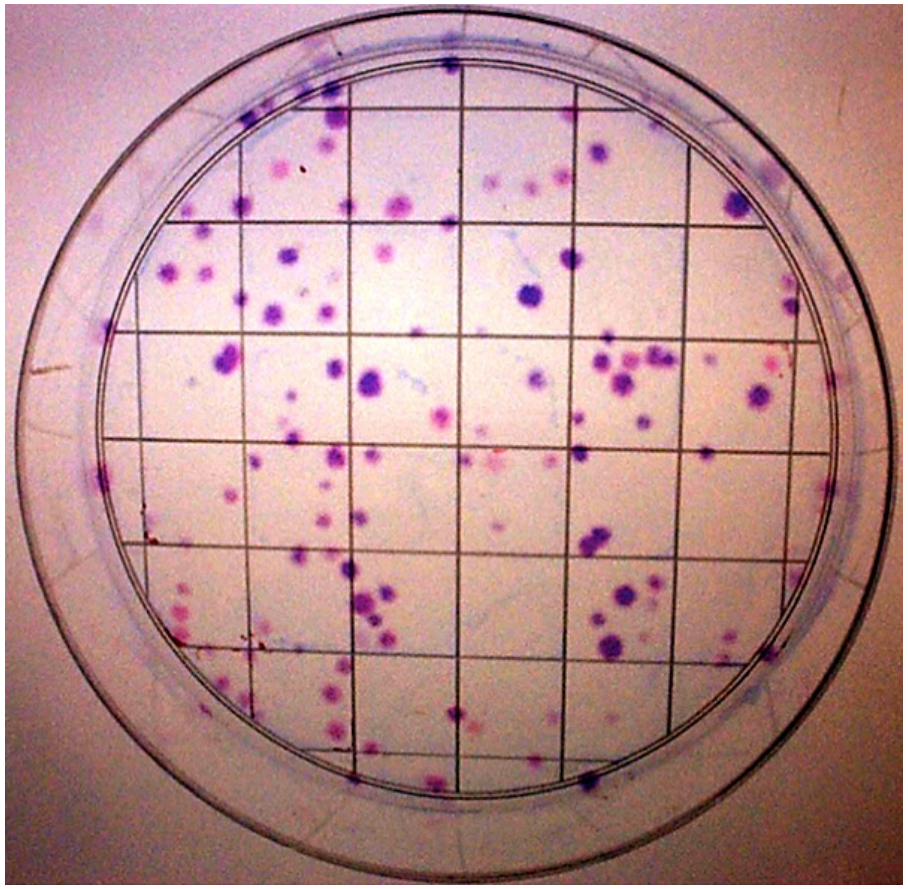
- Bone marrow-derived (non circulating fraction)
- Isolated on the basis of their adhesive properties

- Remarkable plasticity (condrocytes, osteoblasts, adipocytes, cardiac and skeletal muscle cells, neurons, astrocytes)



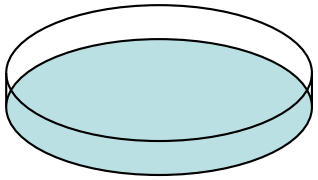
# MSC properties

Alexander
Friedenstein



In bone marrow (“fibroblasts”)
Can be isolated and amplified ex vivo
transplantable
multipotent

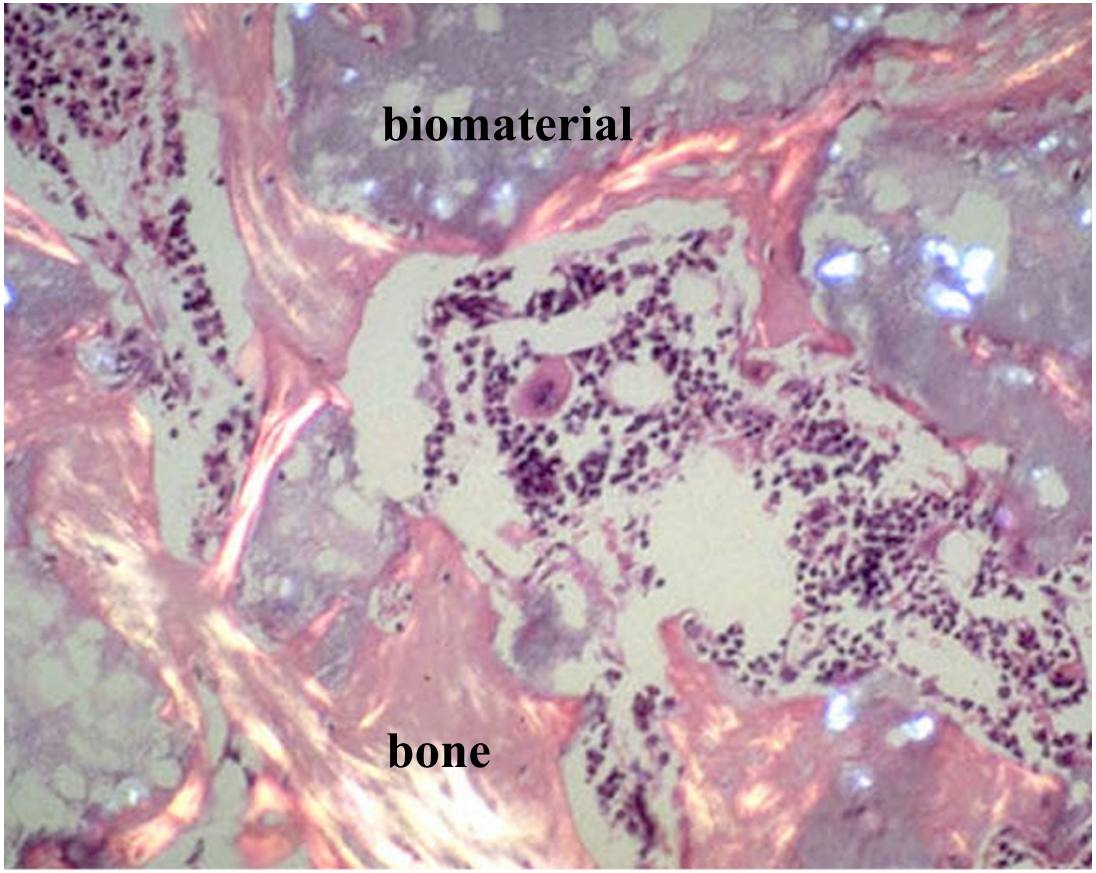
# MSC/skeletal stem cells, transplant

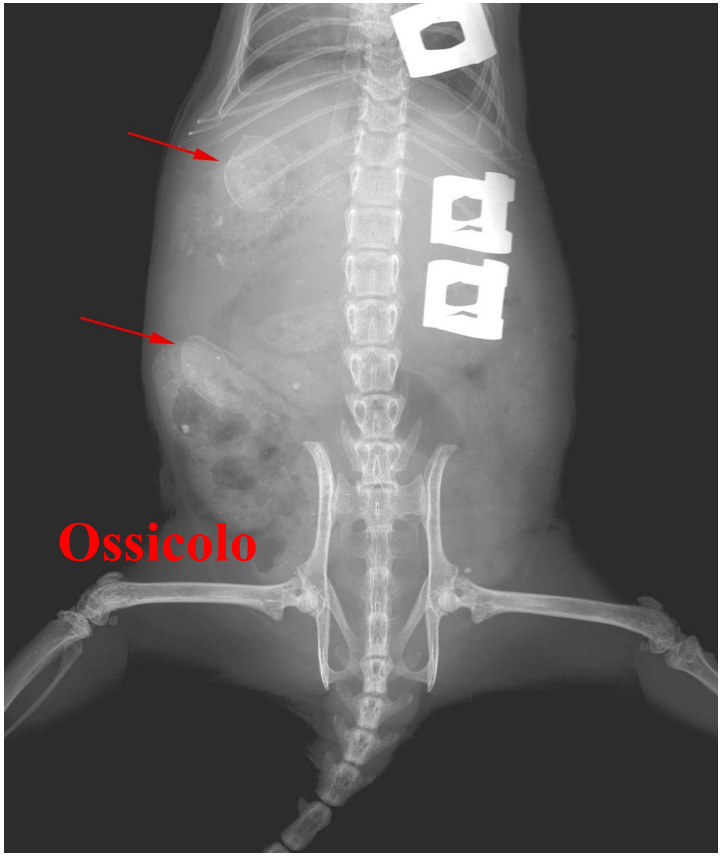


Espansion, ex vivo

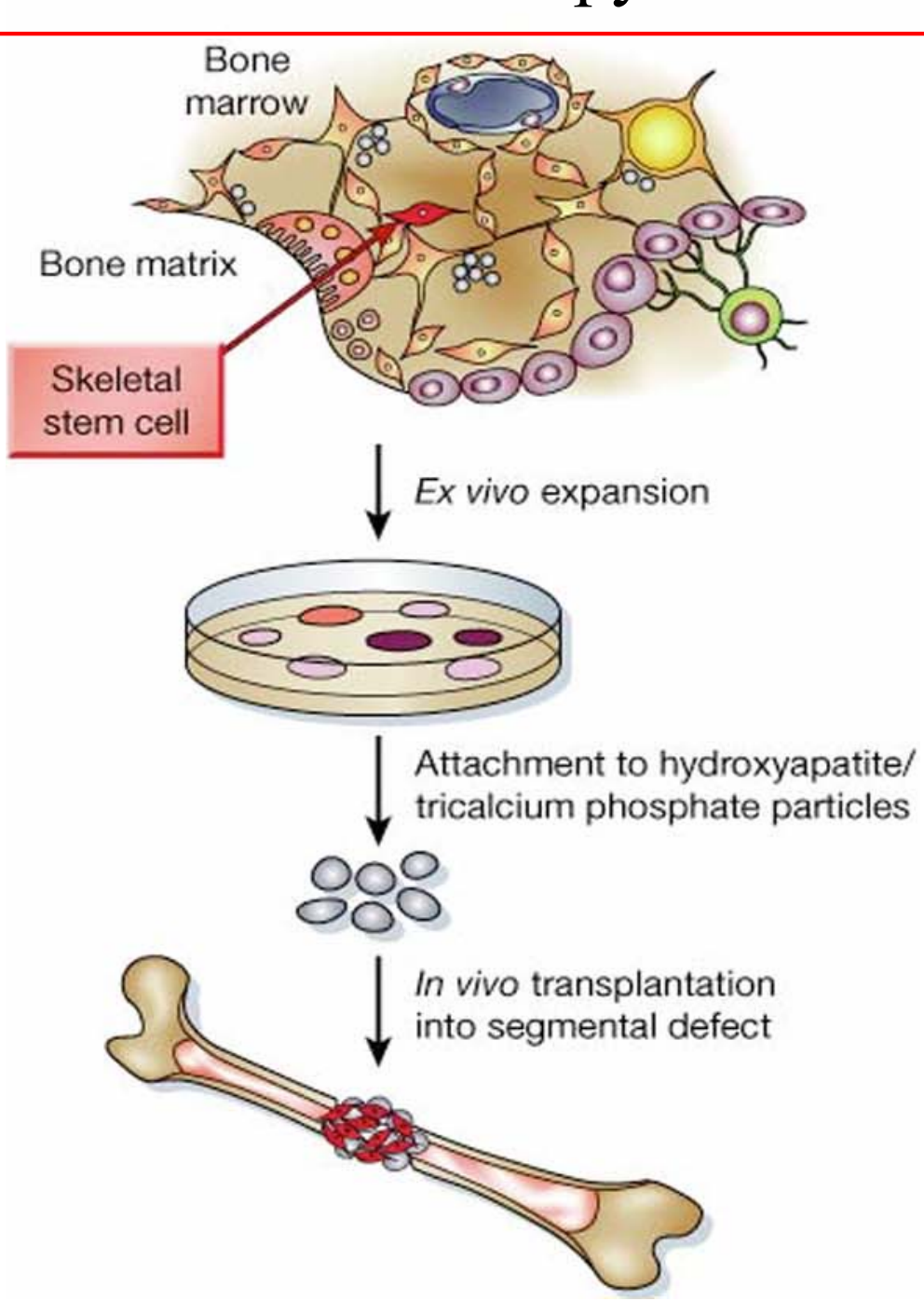
biomaterial

SCID mouse

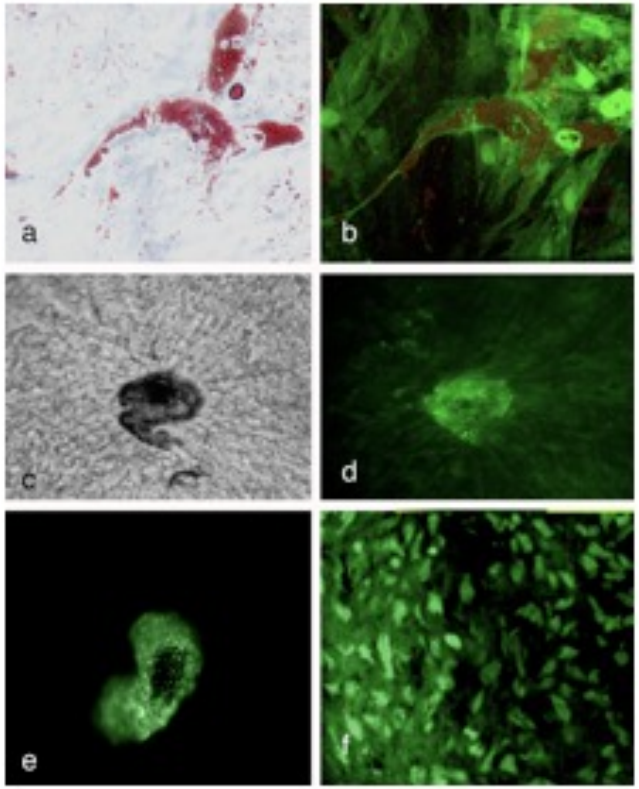


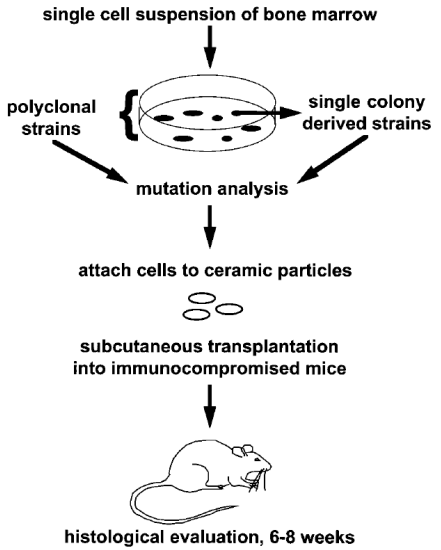



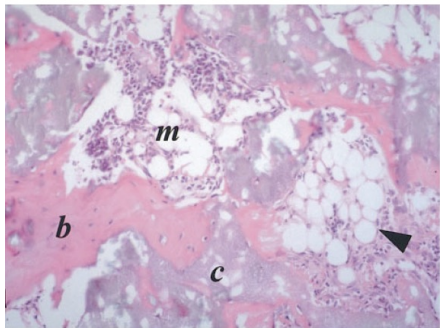
# MSC in therapy



# Mesenchymal stem cells pluripotency



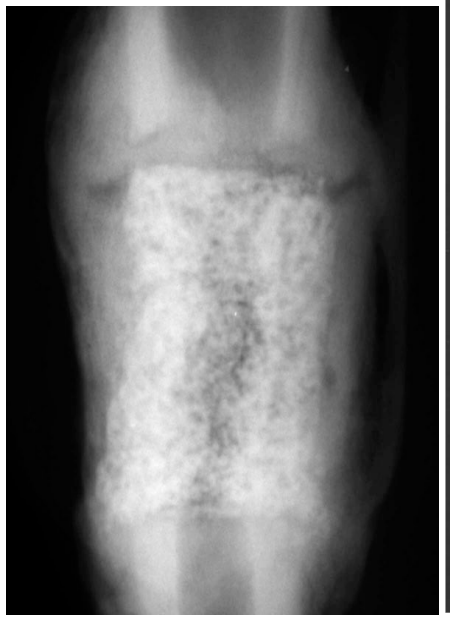

Spaces separating newly formed bony structures are occupied by hematopoietic marrow (m), in which all hematopoietic lines are detected (meg, megakaryocyte). Adipocytes are readily recognizable in the ectopic marrow (arrowheads).

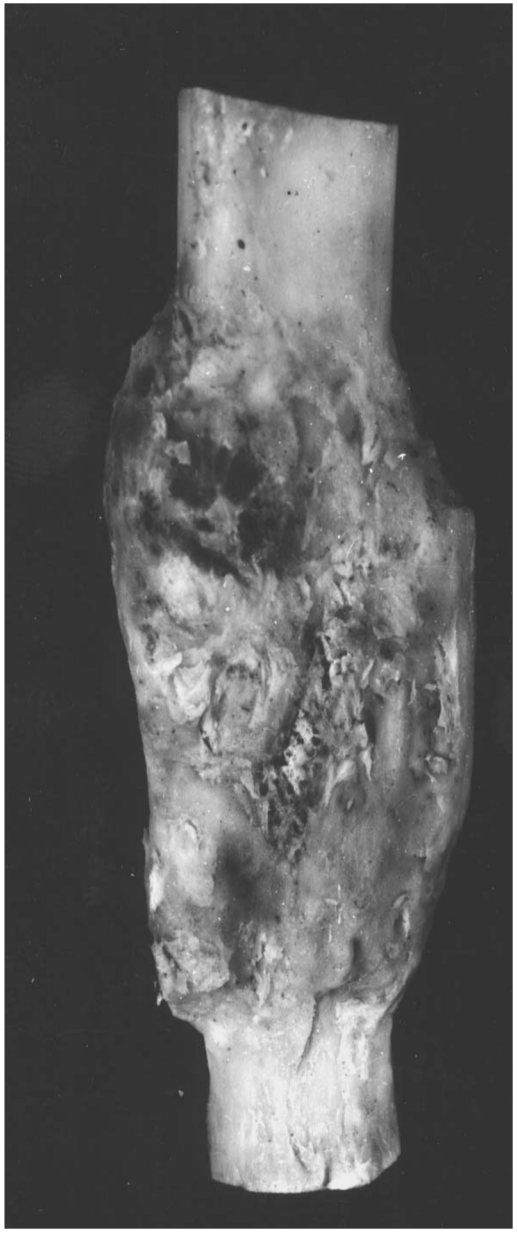
*www.bianco-lab.it*

# Animal models

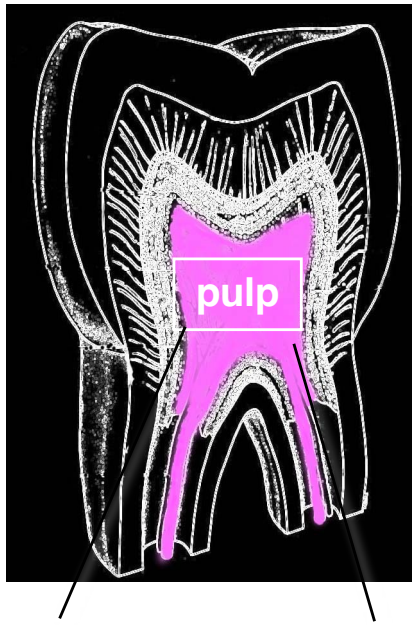
## Preclinical models

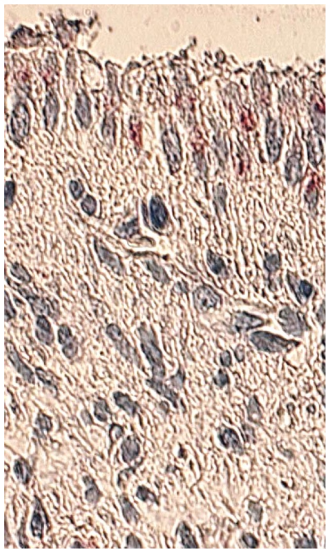
Mice
Dogs
Sheep
….

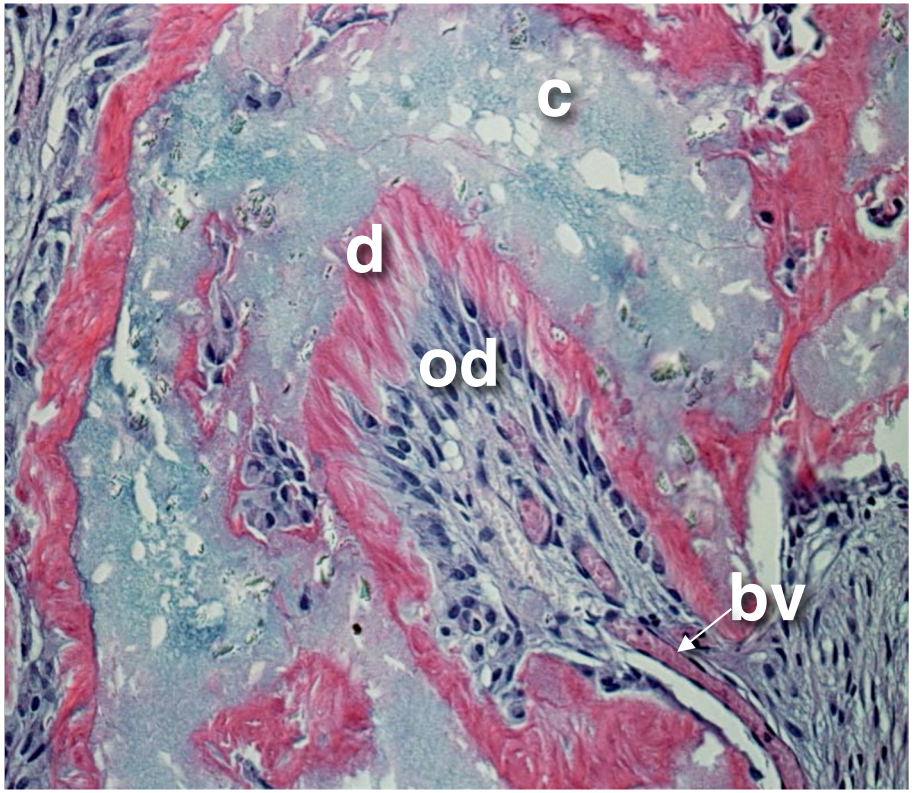


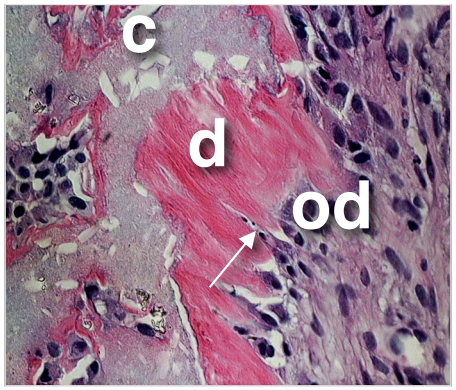


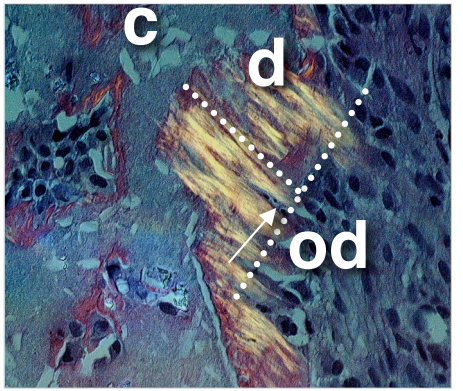
# Post natal dental stem cells






Gronthos et al., 2000

# MSC in therapy: problems

| | |
|---|---|
| purification | CD146 |
| espansion ex vivo | gmp/glp |
| | culture medium quality |
| biomaterial | |
| Way of injection | -- |

# Adult cell plasticity: an old concept - truth or not??

- Cloning experiments in amphibia (1962)
- Cloning experiments in sheep (1997)

provide evidence that the differentiated state in adult is not irreversible.

Adult genes in enucleated cell; fusions..

But more in detail? And without fusions or egg inductions?

“I have learned that the forest, humans and animals are interdependent, and if the forest is sick, then the animals will be sick, and animals will surely impact humans’ health too.”

# Original idea on adult stem cells: **self renewal and differentiation potential**

hematopoietc stem cell

blood

Satellite cell

muscle

Liver stem cell

liver

Skin stem cell

epithelium

**Plasticity** of adult stem cells: self renewal, differentiation and transdifferentiation

Bone marrow derived cells:

*Blood*
Muscle
Brain
Liver
Heart
Vascular endothelium

Muscle cell

blood

CNS cell

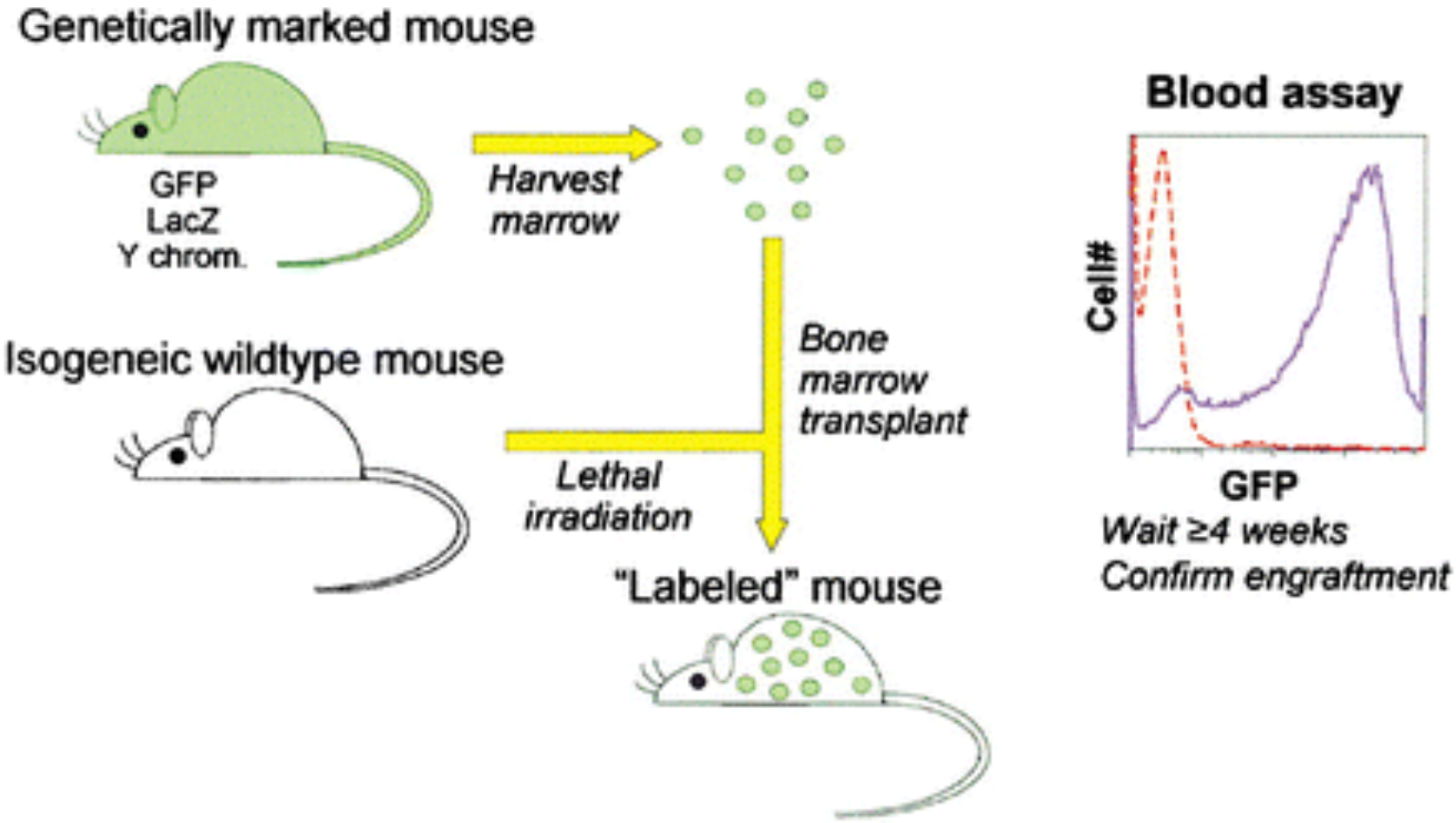
Blood
muscle

BM stromal cells (tissue injury…)

Adipocytes
Muscle
bone

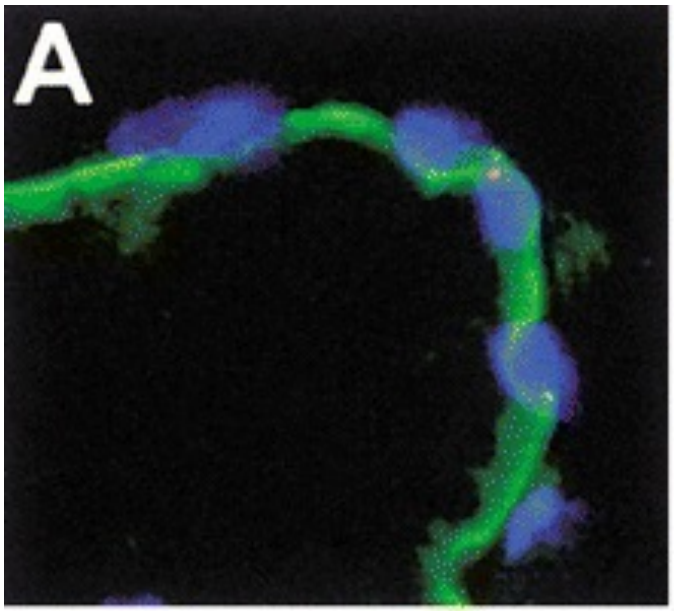
# General strategy for identifying cell fate transitions using BM-derived cells - same tissue

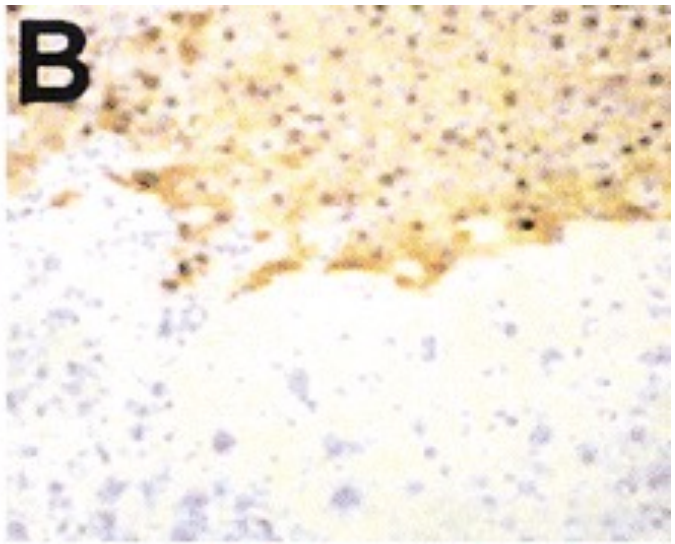
(transgenic mouse)



# Derivation of diverse tissue-specific cell types from BM-derived stem cells - different tissue

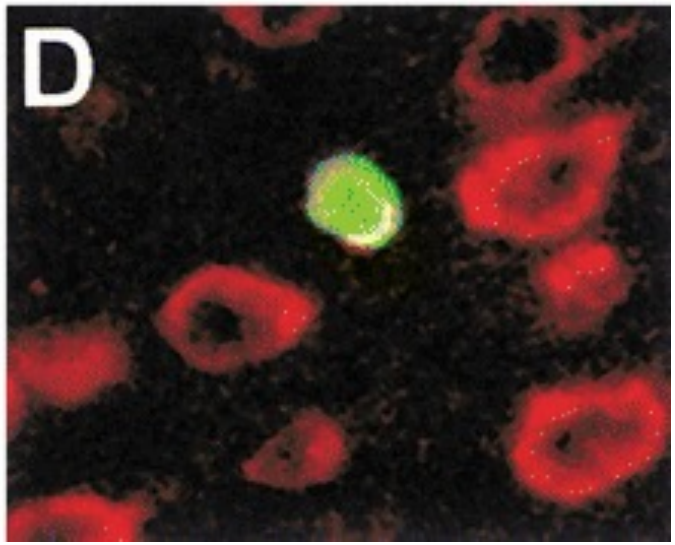
Dystrophin (green) and Y chromosome (blue) in BM-transplanted female mdx mice




FAH staining hepatocytes in FAH-/- BM-transplanted mice
30-50% of liver mass **7 months** posttransplant

Beta gal positive myocardium in a murine model of infarctum BM-transplanted (SP fraction intravascular delivery)


Neurons (red) GFP positive (green) in the cortex of a mouse intravascularly delivered with GFP +BM.

# Criteria for trans-differentiation

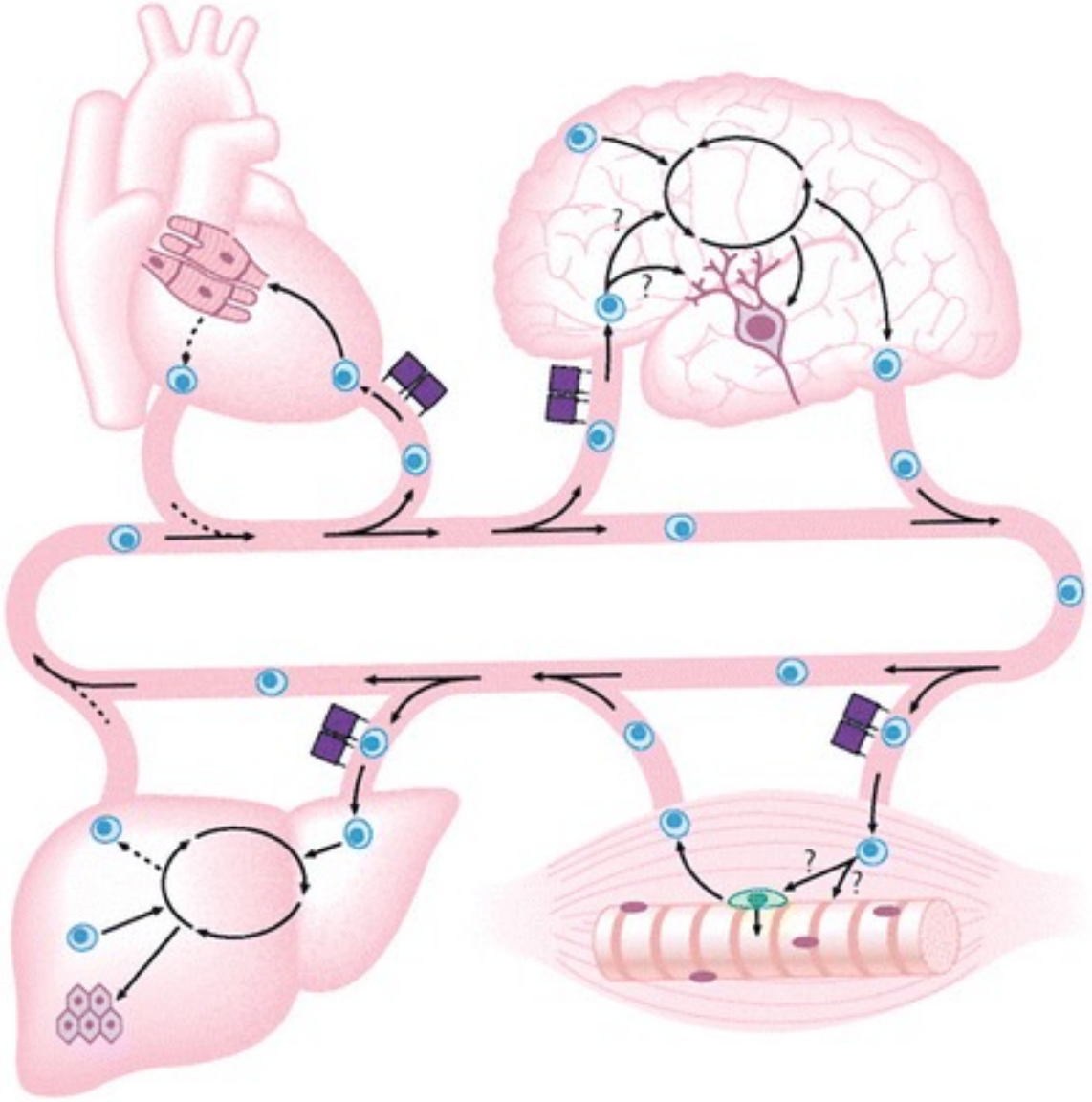
- New specific gene expression, in vitro and in vivo
- Marker of the stem cell (Y, GFP, lacZ..)
- Colocalization (confocal)
- Integration in the tissue
- Functional assay

# Stem cells

Entity or function?

*HM Blau Cell - 2001*

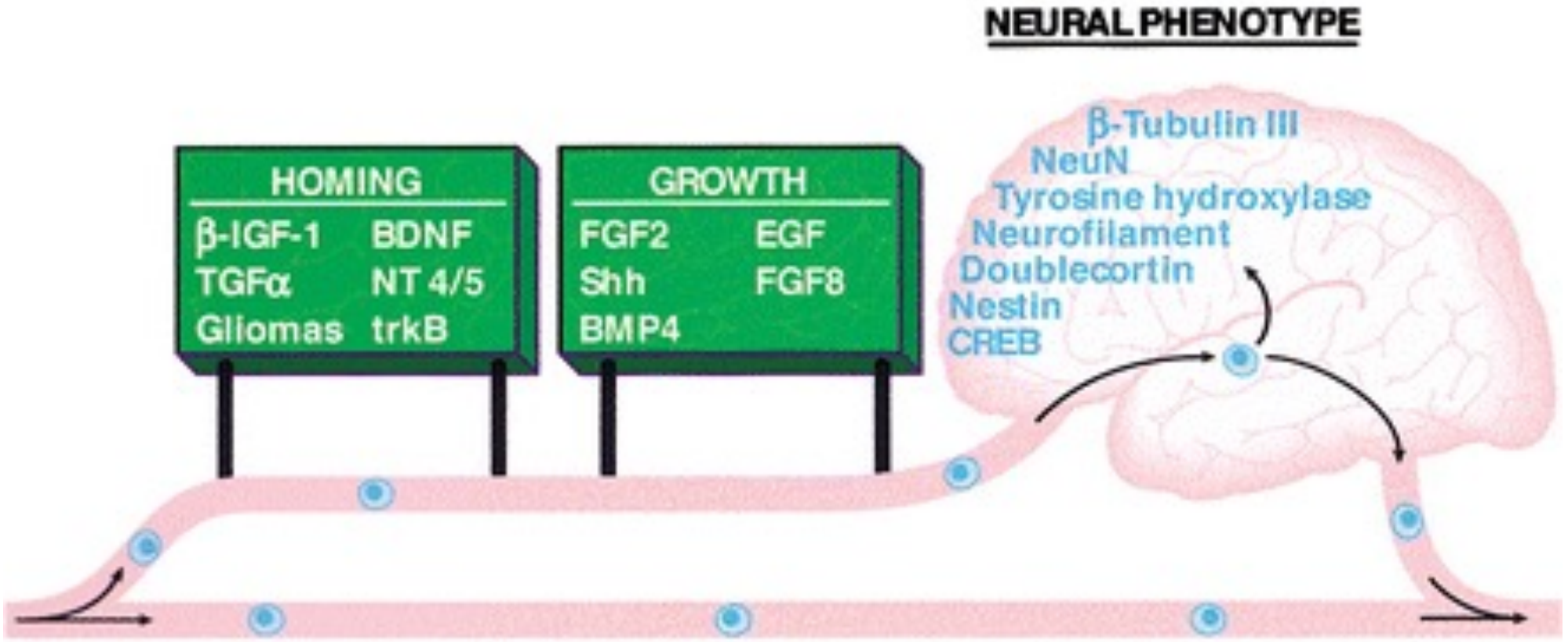
# Circulation: the highway of stem cells



•contact with surrounding cells,
•Extra-cellular matrix,
•local milieu,
•growth and differentiation factors

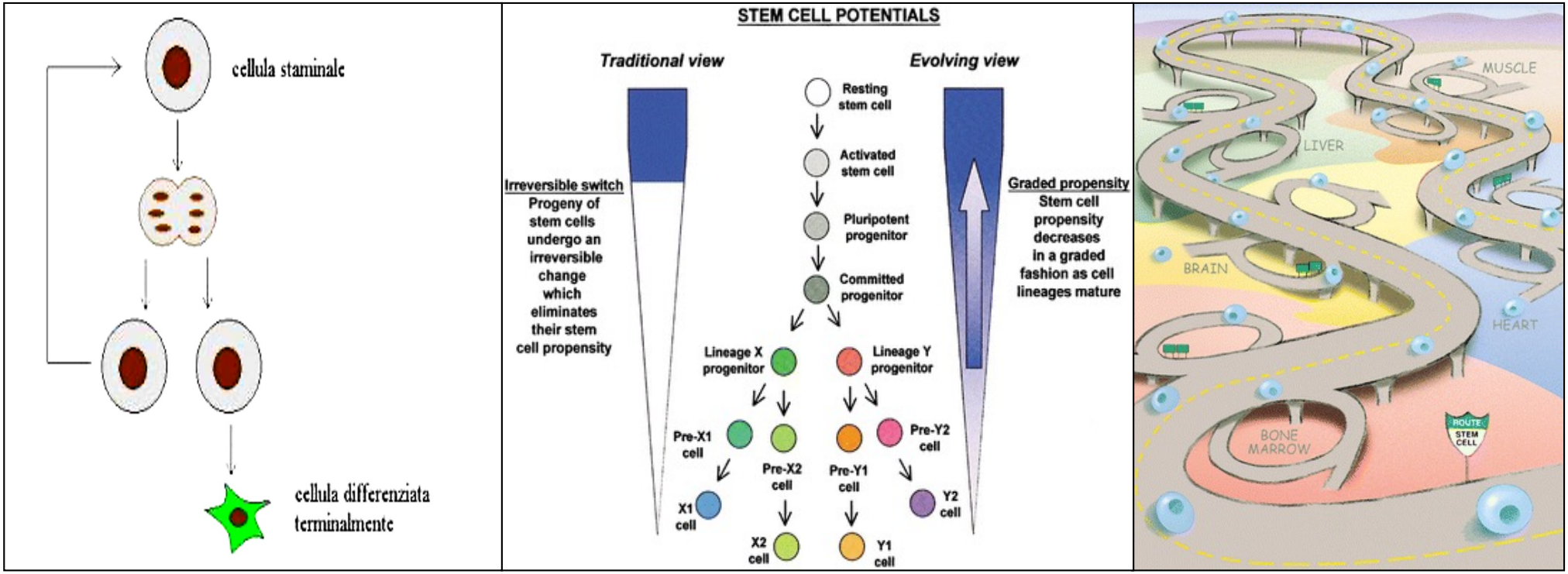
play a key role in determining stem cell function

# Factors that control trans-differentiation



# General concepts

1. 2. 3.




*HM Blau Cell - 2001*

QUESTIONS
REFERENCES