

# Transformation of lineages in fetal and adult stem cells

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# The problem

- ***Multicellularity requires specialization of cell types.***
- ***Specialized cells often lose the capacity to reproduce themselves.***
- ***When these specialized cells become exhausted or are injured, they must be replaced from unspecialized precursors.***

**STEM CELLS**

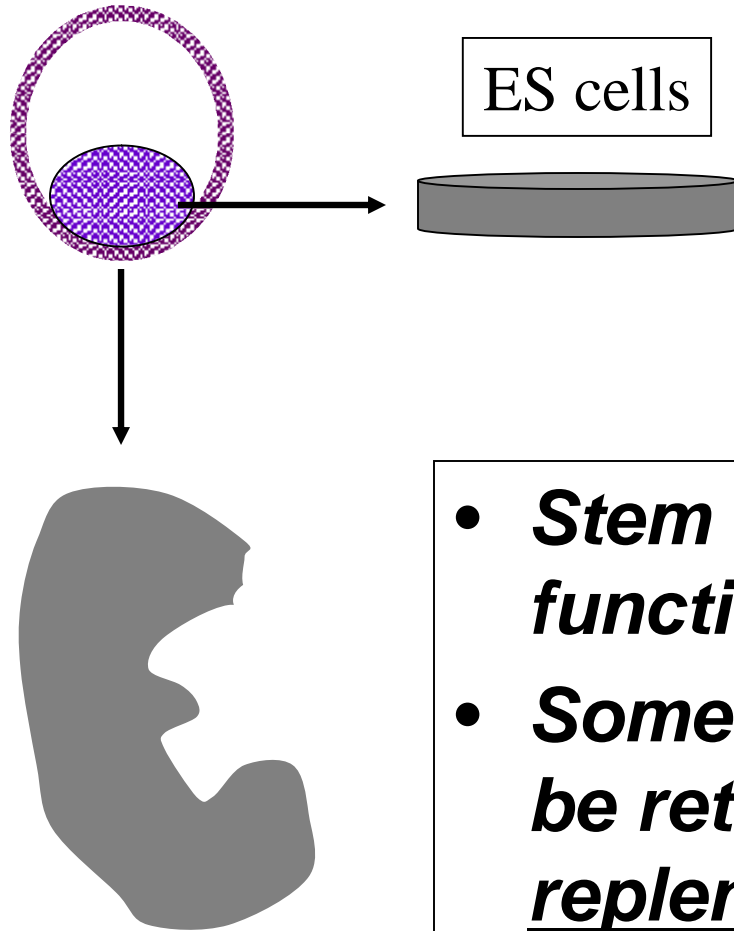
# Stem Cells

- *Are themselves **undifferentiated** but can generate specialized cells.*
- ***Self-renew** and thus maintain cell replacement potential for long periods of time.*
- ***Promise for regenerative medicine:***
  - *Manipulation of endogenous cells*
  - *Cell transplantation*
  - *Laboratory studies of development and disease*

# Sources of Stem Cells

- *Embryonic*
- *Fetal*
- *Adult*
  
- *The best source of stem cells for the study or treatment of a particular disease will likely vary depending on the tissue and/or cell type that is targeted.*

# Stem Cell Relationships



- **Embryonic**
- **Fetal**
- **Adult**

- ***Stem cells in the embryo/fetus function to generate tissues.***
- ***Some of these stem cells may be retained after birth to replenish or regenerate adult cells and tissues.***

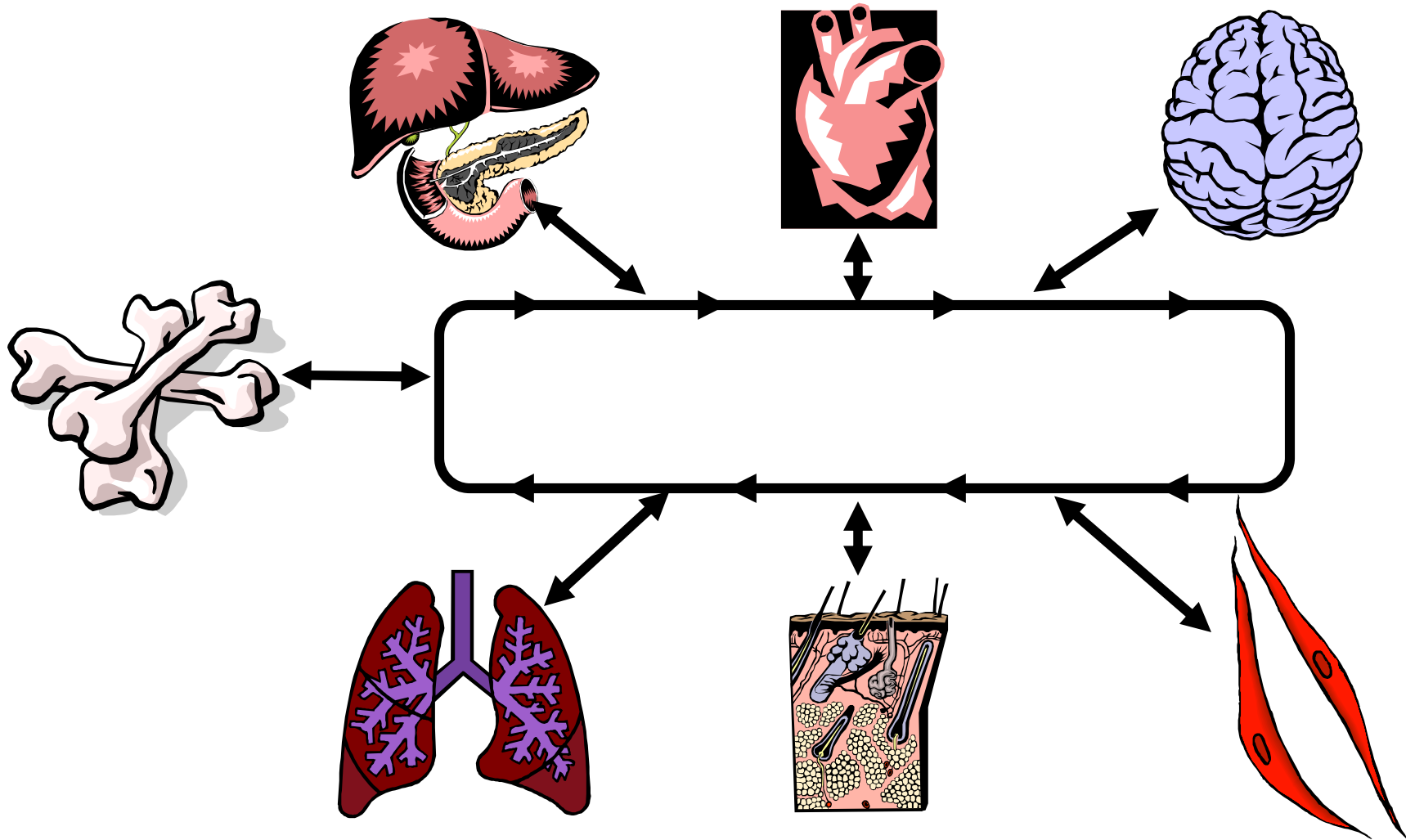
# Stem Cells in Fetal and Adult Tissues

- **Identified in *some but not all* adult tissues (best characterized for blood, muscle, brain, skin, and intestine)**
- **Are generally very *rare***
- **Can be present only *transiently***
- **Can be *difficult to expand* outside the body**
- **Give rise to a *limited subset* of cell types**

***Are tissue stem cells lineage restricted?***

# Plasticity hypothesis

All adult stem cells are roughly equivalent, and respond to environmental cues to provide necessary cell types to regenerate damaged tissues



# Reports of stem cell plasticity

**Bone marrow**



**Non-blood  
tissue**

**Blood stem cells**



**Non-blood  
tissue**

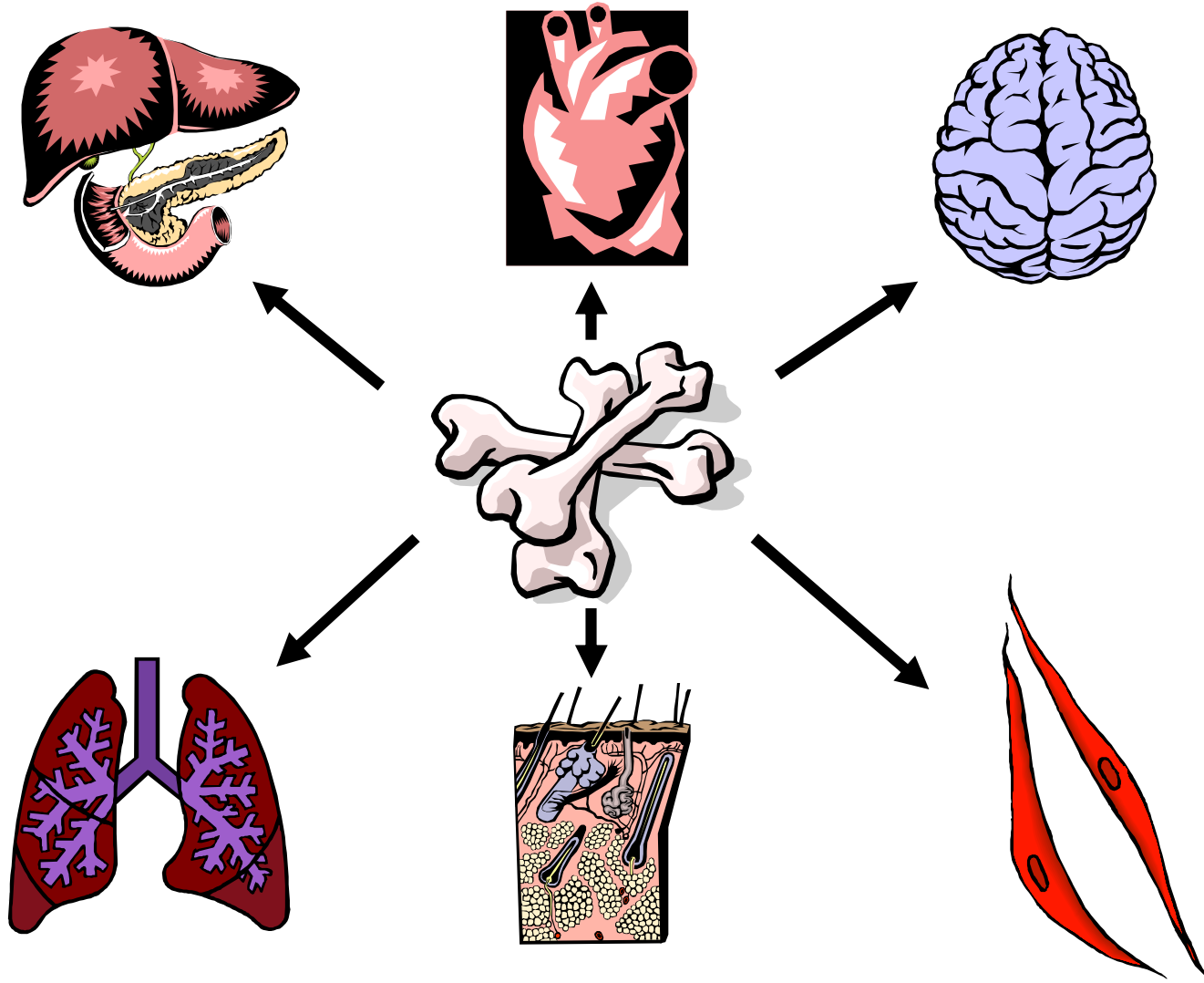
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**Non-blood  
tissue**



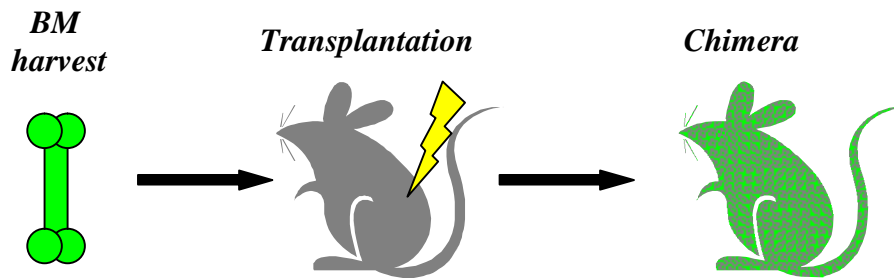
**Blood**

# Are adult stem cells tissue-restricted?

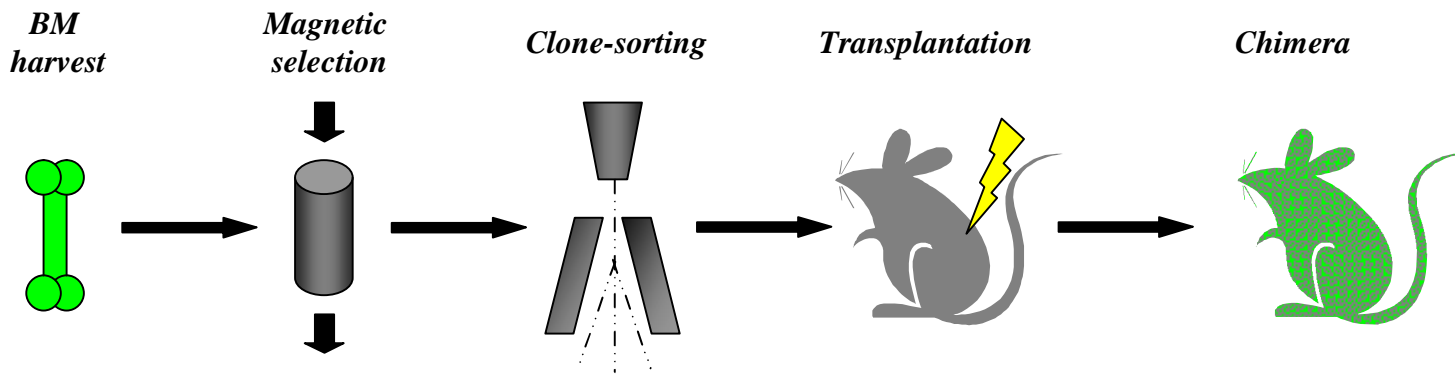


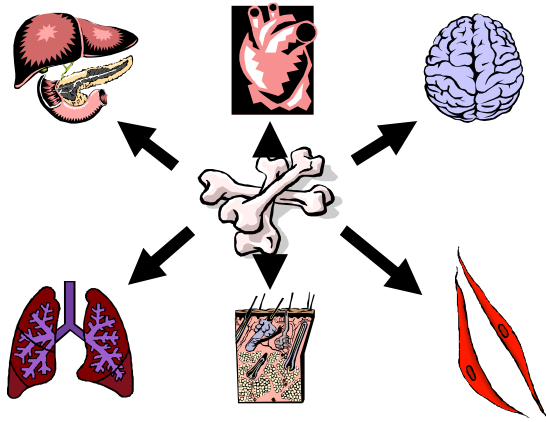
# Models for testing adult stem cell plasticity

## BM transplant



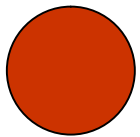
## HSC transplant



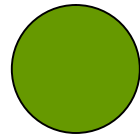
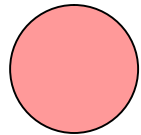
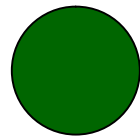
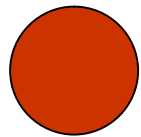


# Possible mechanisms of BM and HSC plasticity

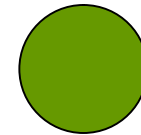
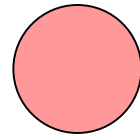
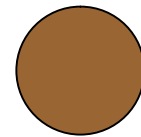
***Trans-differentiation***



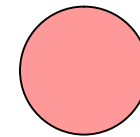
***Multiple stem/progenitor cells***



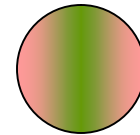
***Pluripotent stem cell***



***Cell fusion***



+



## Criteria for the demonstration of stem cell plasticity

- **Multiple cell fates/lineages derived from a SINGLE STEM CELL.**
- **Generation of FUNCTIONAL mature cells of both lineages.**
- **Occurs in the absence of CELL FUSION.**
- **ROBUST contribution to both lineages (for therapeutic application)**

# Outcomes of adult stem cell plasticity experiments

- ***Tissue contributions are generally extremely rare.***

**Non-hematopoietic cells derived from transplanted single HSC:**

Brain - 1 of  $\sim 1.3 \times 10^7$

Liver – 7 of  $\sim 5 \times 10^5$

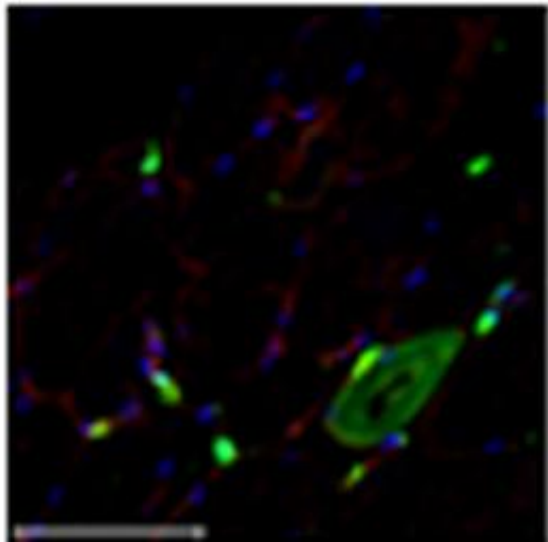
None detected in other tissues.

***Most marrow cells form blood.***

# A Comparison of Muscle Regenerative Potential

**BM**

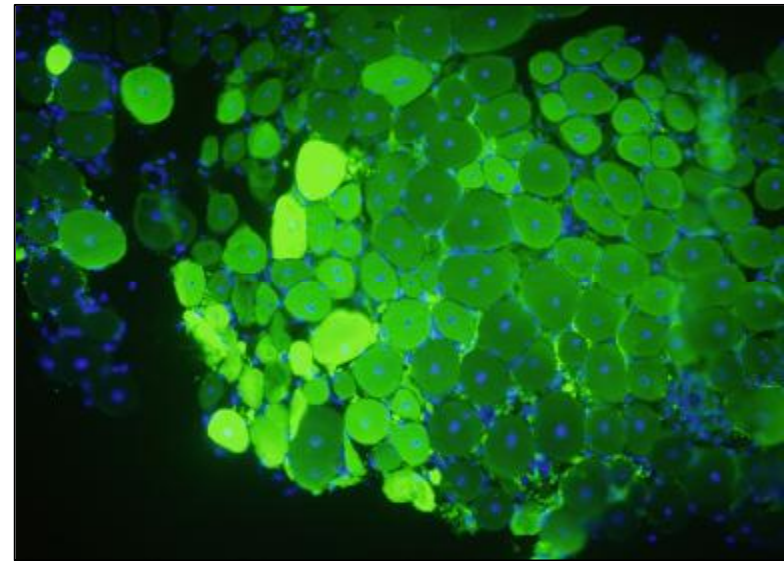
**– single myofiber**



***Do not engraft as  
muscle stem cells.***

**MuSC**

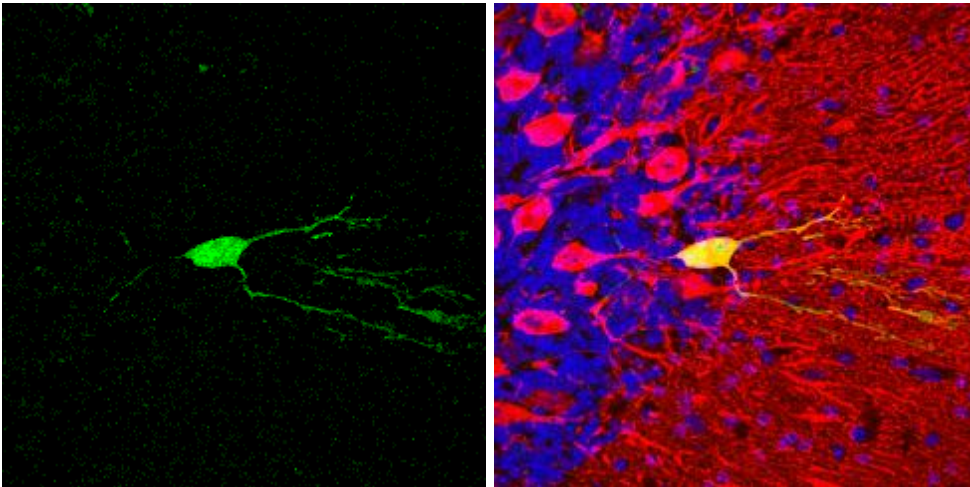
**– up to 500 myofibers**



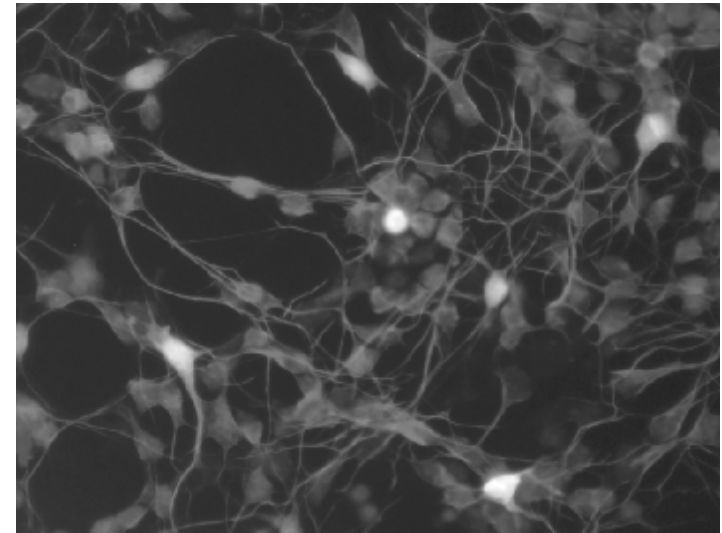
***Replenishes the muscle  
stem cell pool***

# A Comparison of Neural Differentiation Potential

*BM*  
– *single Purkinje*  
*neuron*



*ES cells*  
– *millions of*  
*motor neurons*



# Outcomes of adult stem cell plasticity experiments

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- ***They may require specific types of tissue injury.***

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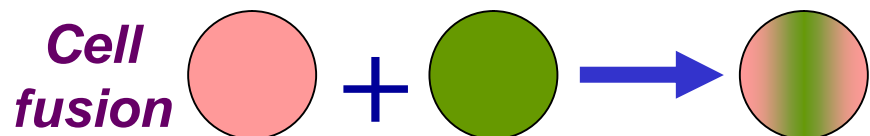
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***Most marrow cells form blood.***

- ***They may require specific types of tissue injury.***
- ***They do not always generate fully functional cells.***
- ***The mechanism involves cell fusion rather than transdifferentiation.***



# Reports of stem cell plasticity

**Bone marrow**



**Non-blood  
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**FUSION**

**Blood stem cells**



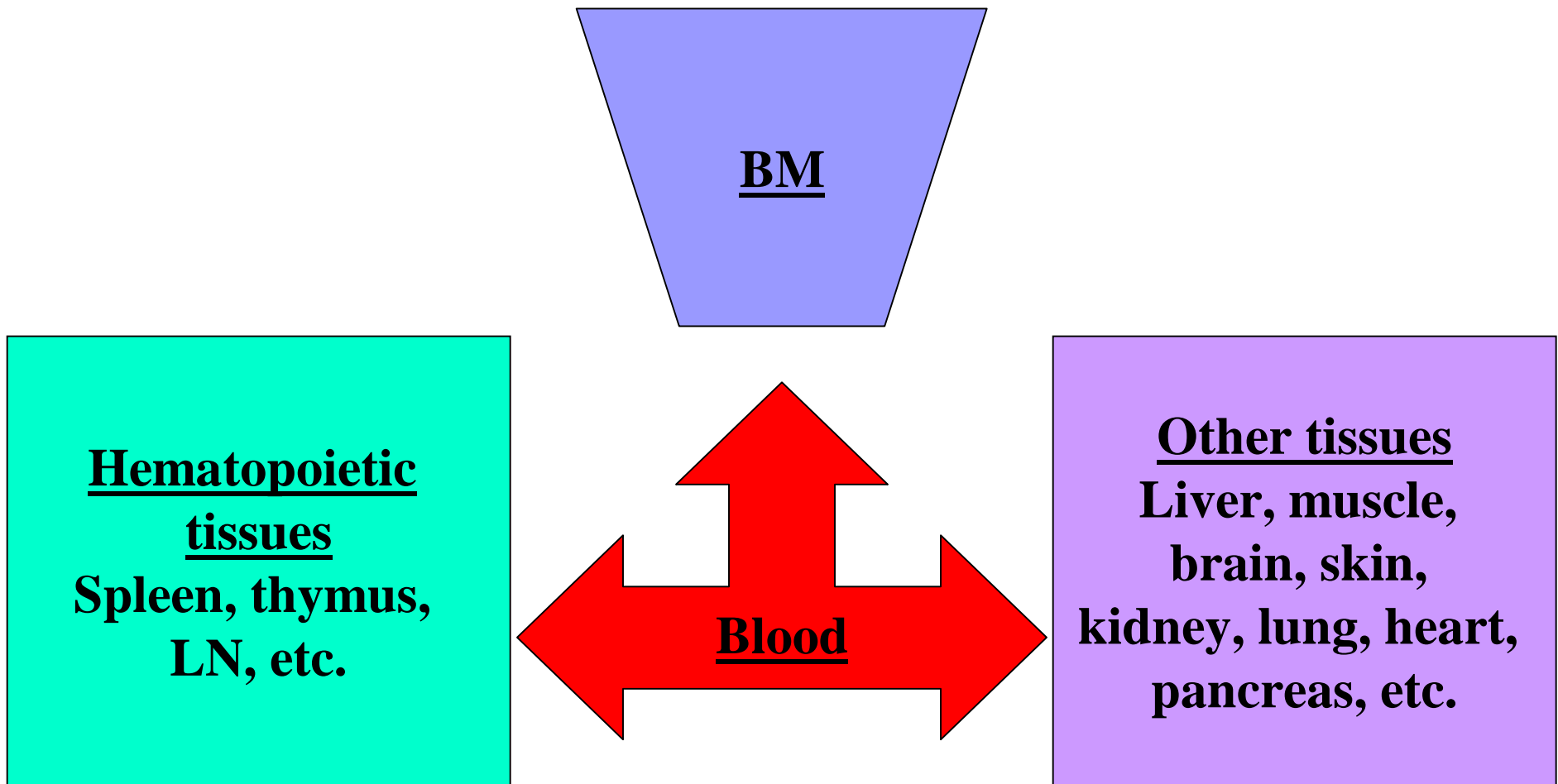
**Non-blood  
tissue**

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**Non-blood  
tissue**



**Blood**



***Circulating HSC likely contaminate many non-hematopoietic tissues and thus may confound interpretation of experiments designed to test the hematopoietic potential of these tissues.***

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**FUSION**

**Blood stem cells**



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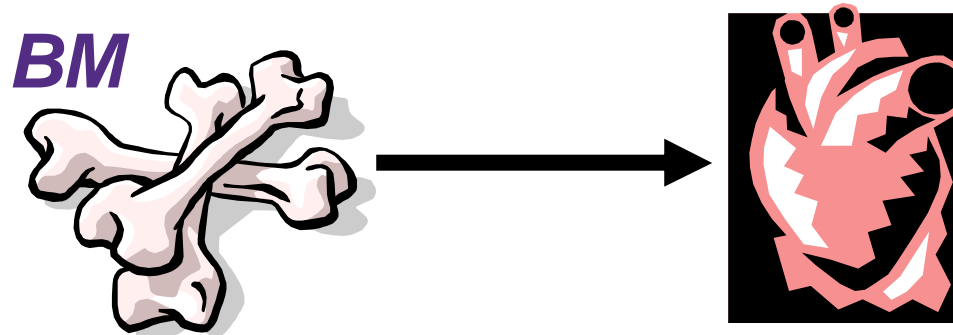
**Non-blood  
tissue**



**Blood**

**CONTAMINATION**

# Clinical trials to exploit bone marrow plasticity

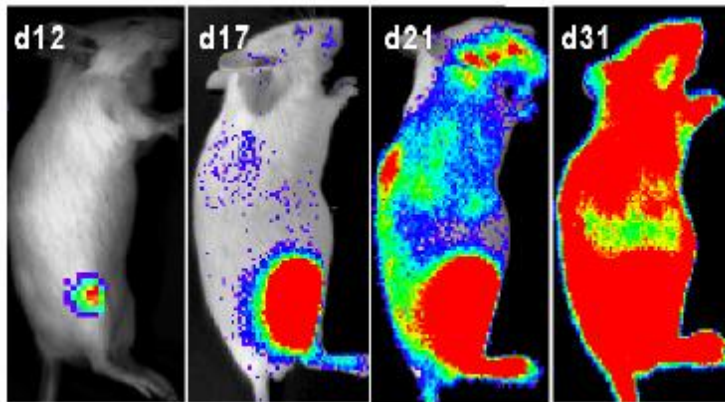


- ***BOOST, TOPCARE-CHD, ASTAMI, REPAIR-AMI***
- ***Feasible***
- ***Safe***
- ***Effective?***

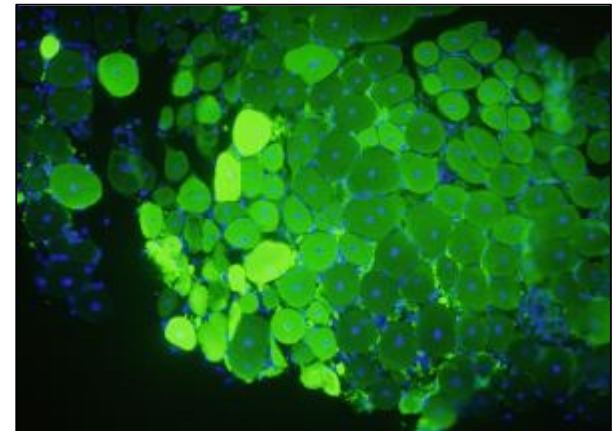
# Tissue Stem Cells

- *Where they are available, tissue stem cells can provide robust regenerative activity.*

## Blood



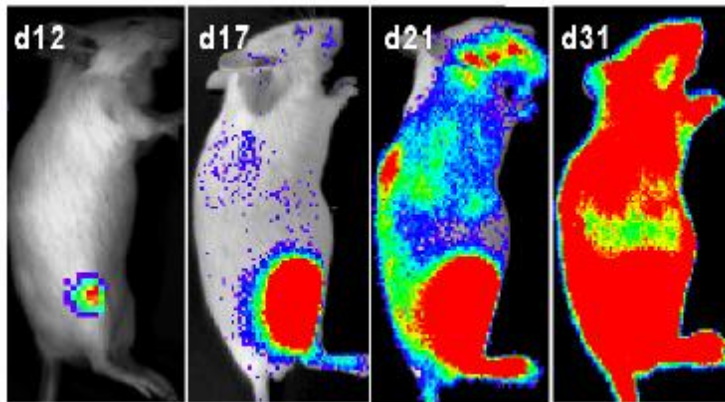
## Skeletal Muscle



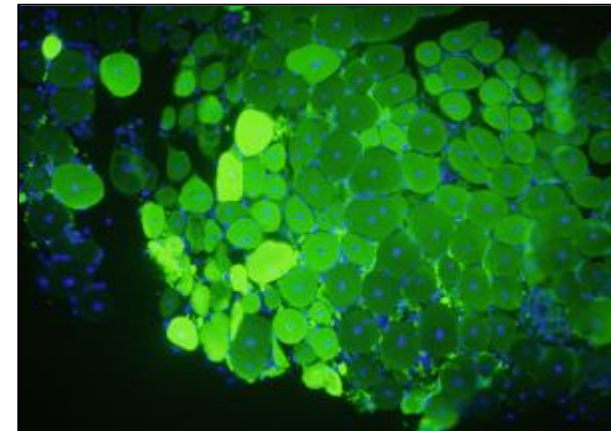
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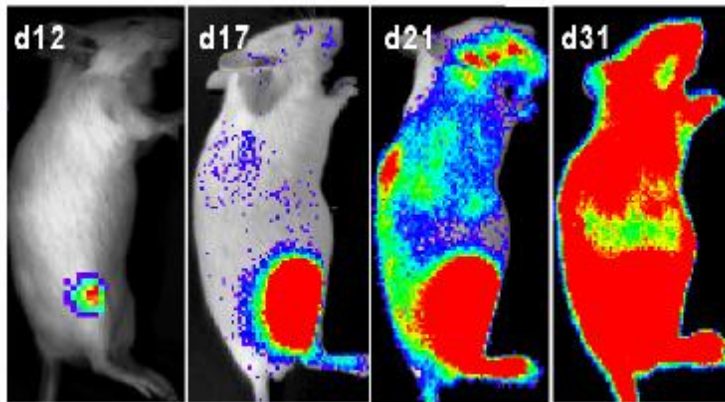


- *Such cells may not be isolatable from all adult or fetal tissues.*

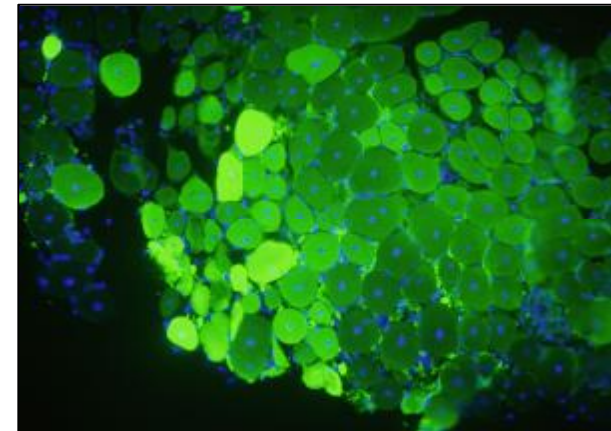
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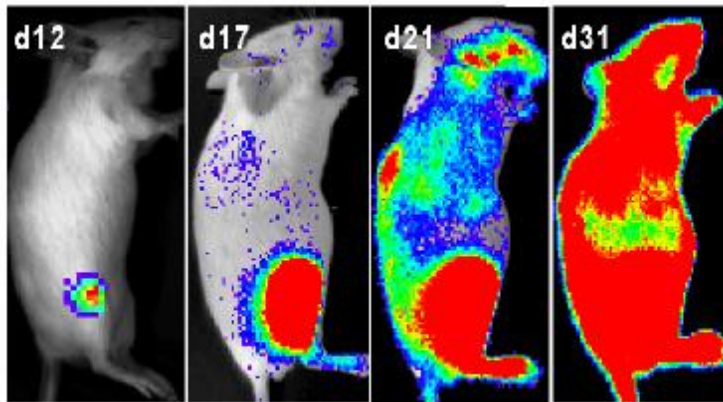
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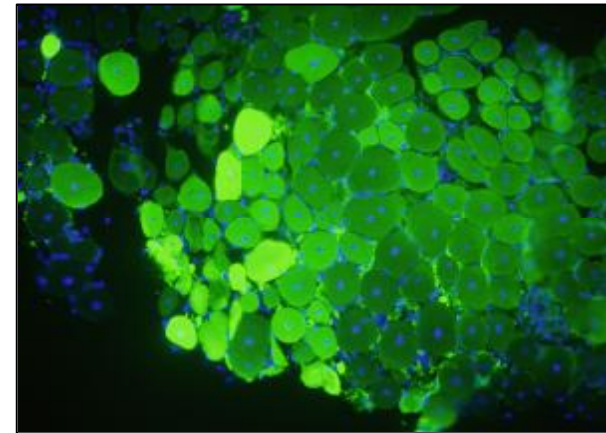
- *Such cells may not be isolatable from all adult or fetal tissues.*
- *Tissue stem cells may be very difficult to propagate or manipulate for study.*

# Tissue Stem Cells

## Blood



## Skeletal Muscle



- ***Where they are available, tissue stem cells can help to inform studies using ES cells and in particular attempts to direct ES cell differentiation.***