Stem cells:
origin and possible applications in clinical medicine

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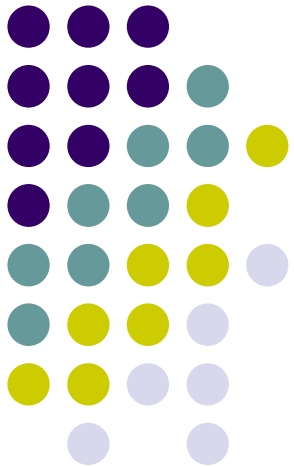
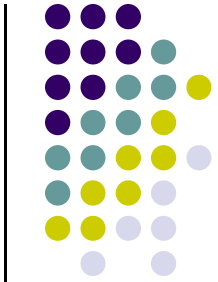
www.kuleuven.be/scil

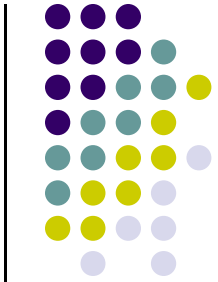


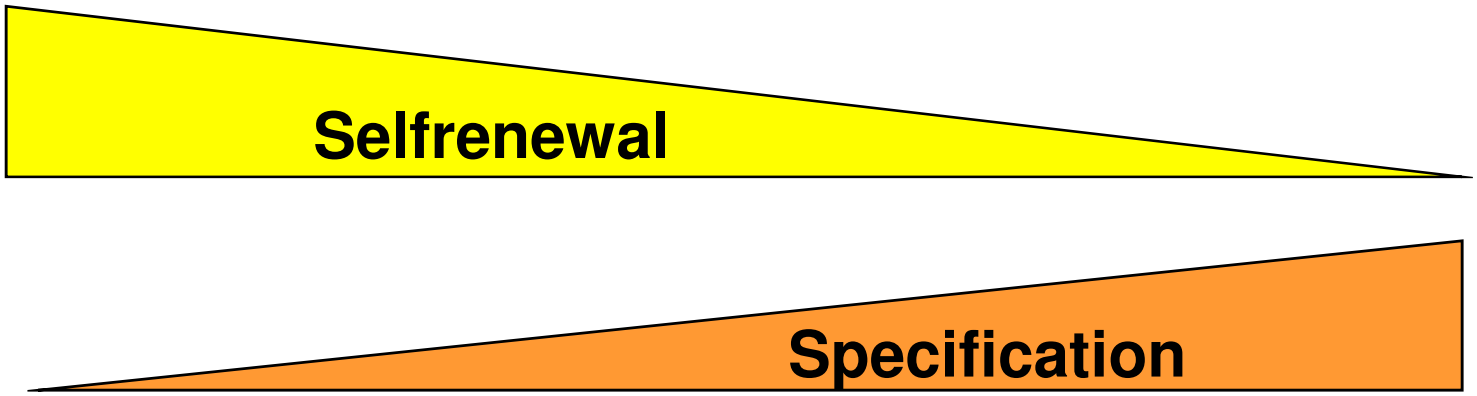
Stem cell: definition

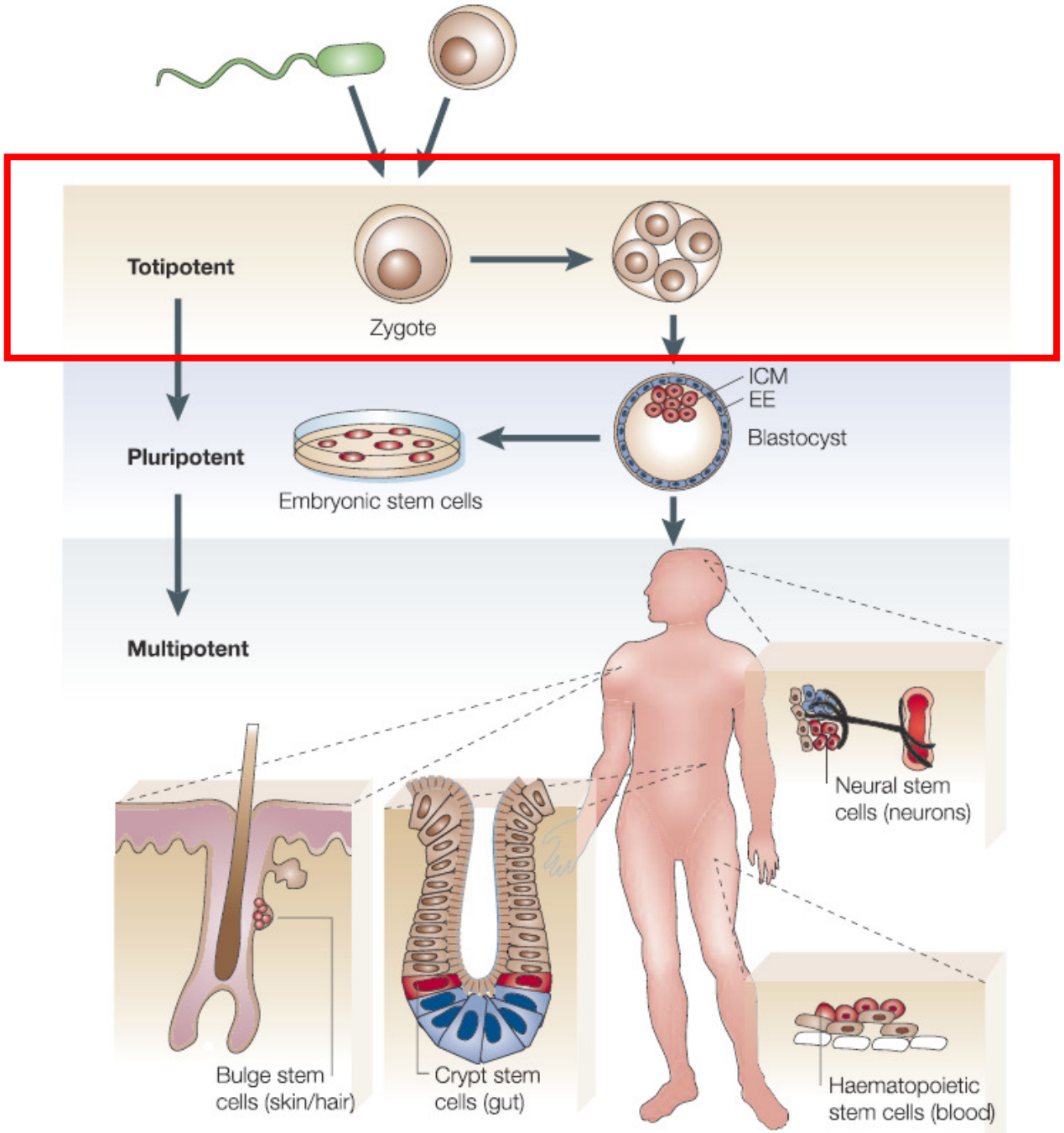


- Stem cells self-renew
- Single stem cell differentiates into multiple, functional cell types
- Stem cells functionally reconstitute a given tissue in vivo.

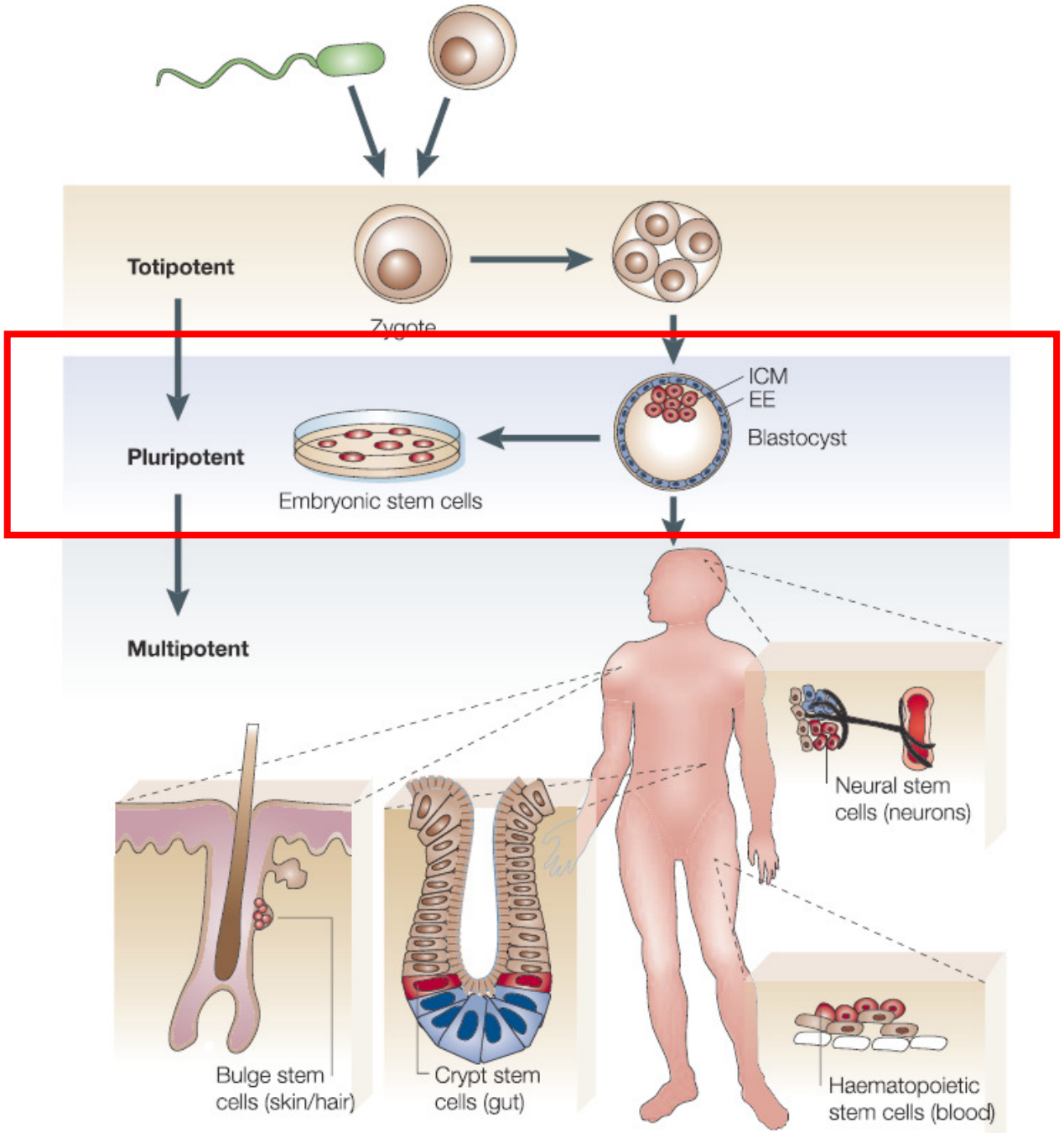
Stem Cell vs. Progenitor Cells vs. Precursor cell







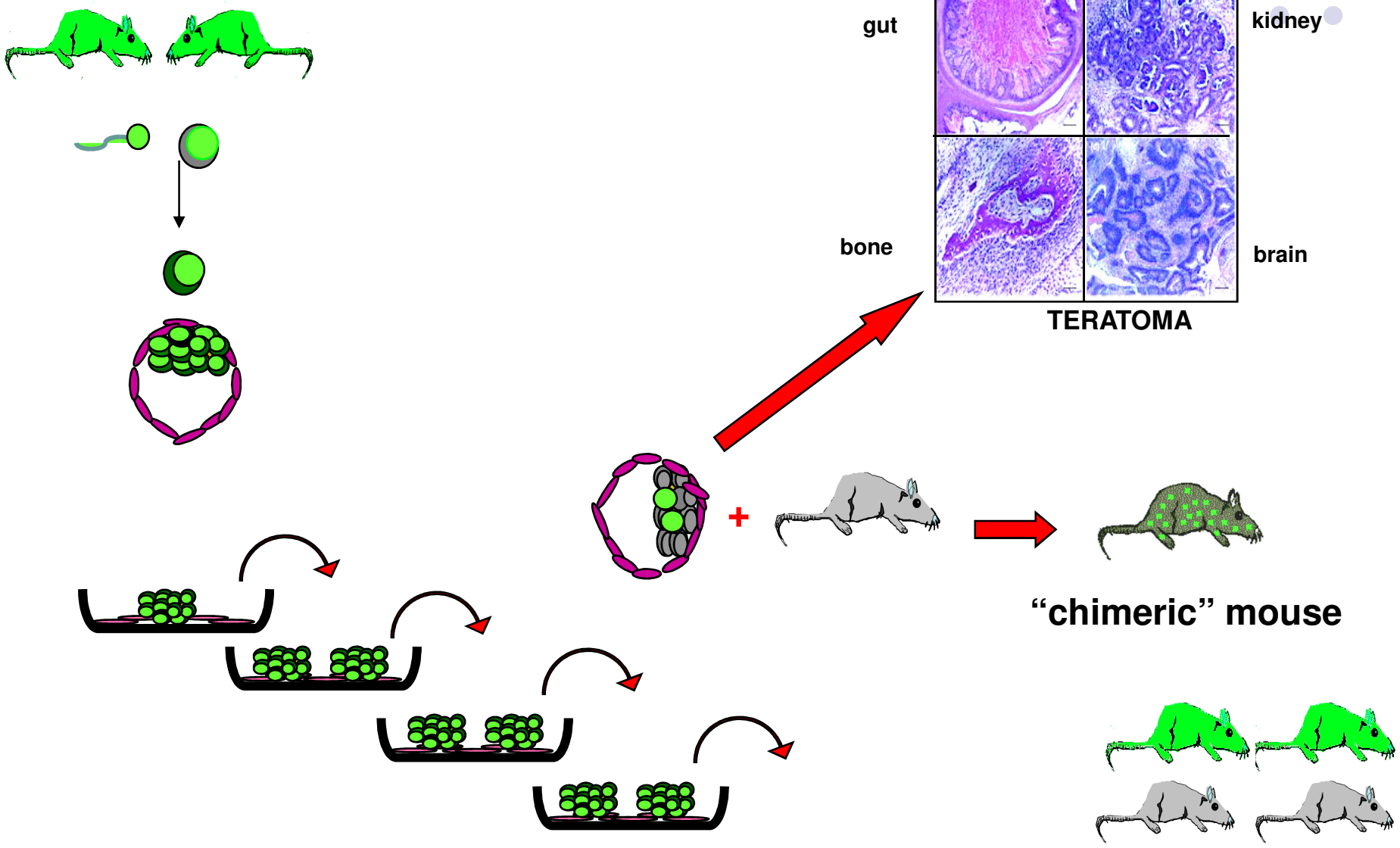
ECKFELDT, NAT REV | MOL CELL BIOL, 2005



ECKFELDT, NAT REV | MOL CELL BIOL, 2005

The quintessential stem cell: embryonic stem cells

They do not senesce and are pluripotent



Potency of embryonic stem cells

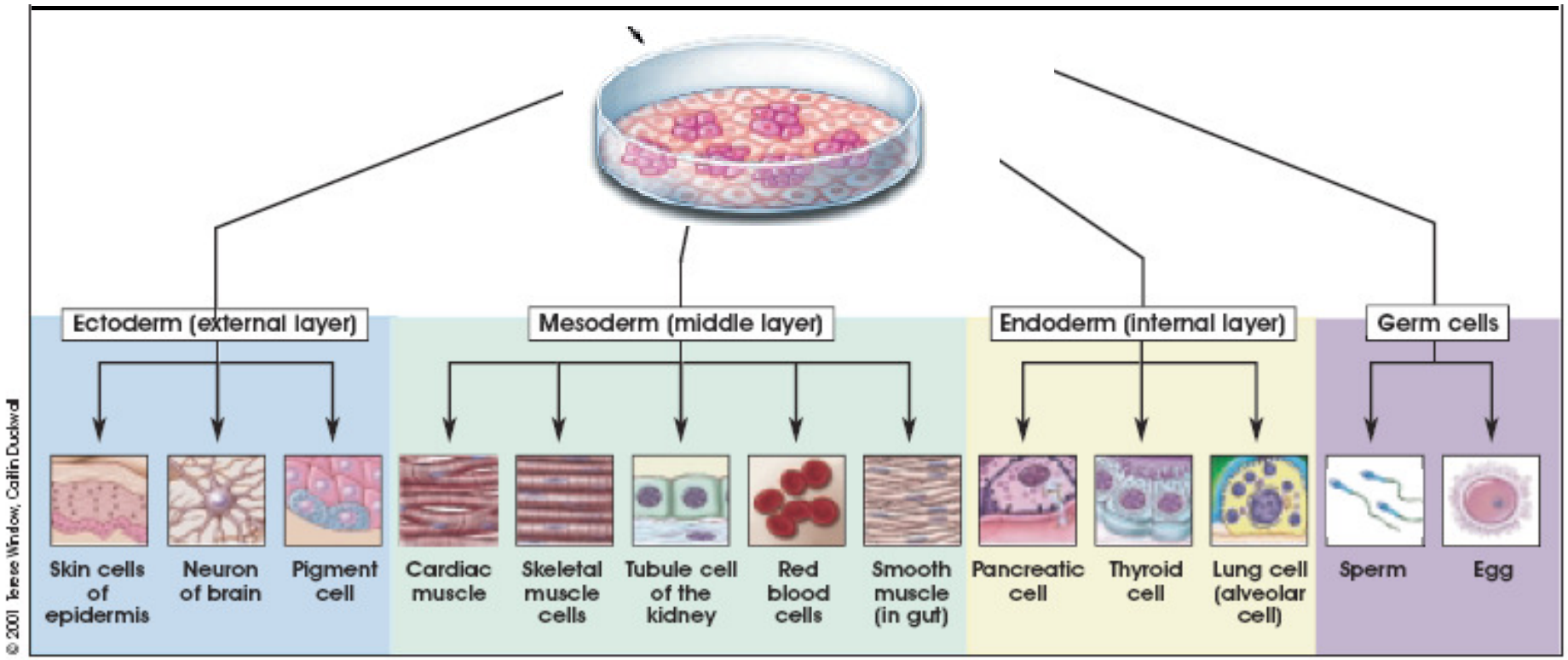
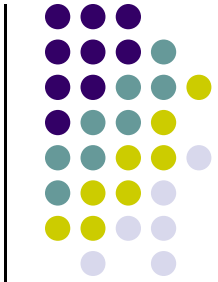


Figure 1.1. Differentiation of Human Tissues.

ADAPTED FROM NIH STEM CELL WEBSITE

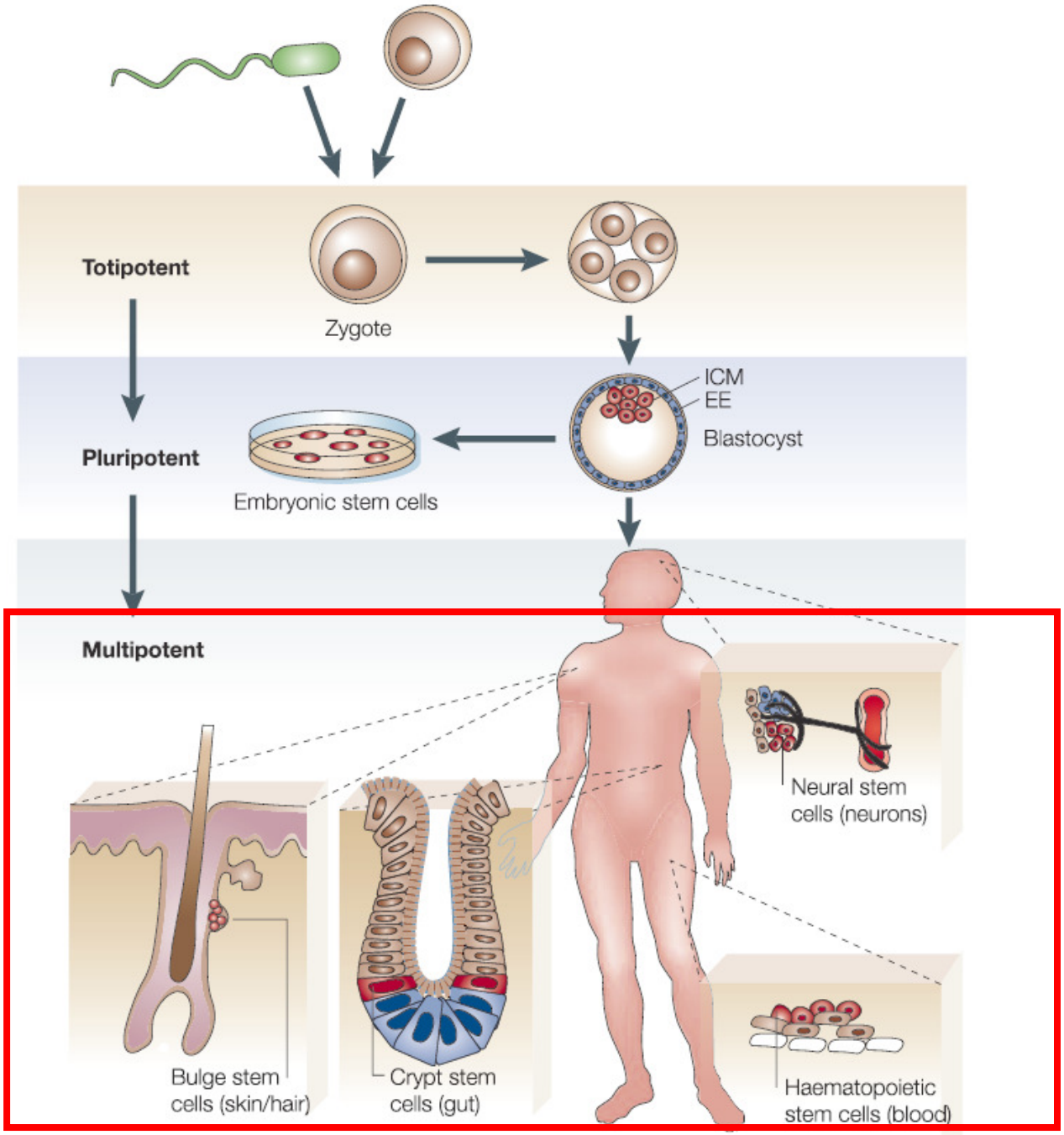
Enthusiasm surrounding embryonic stem cells



- Does not age and can differentiate to all cell types
- Thus: embryonic stem cells can heal all diseases?

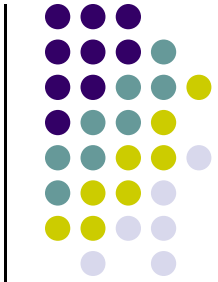
But, scientific and ethical questions surrounding ES cells

- Teratomas (non malignant tumor)
- Allogeneic (from other person)
- Need to destroy early embryos (left over after IVF)



ECKFELDT, NAT REV | MOL CELL BIOL, 2005

Adult stem cells

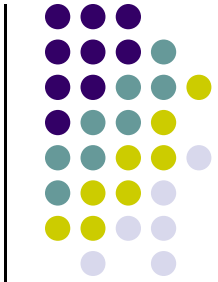


- Ages
- Differentiates in multiple cells but not all cells

Adult stem cell is only cell currently used clinically

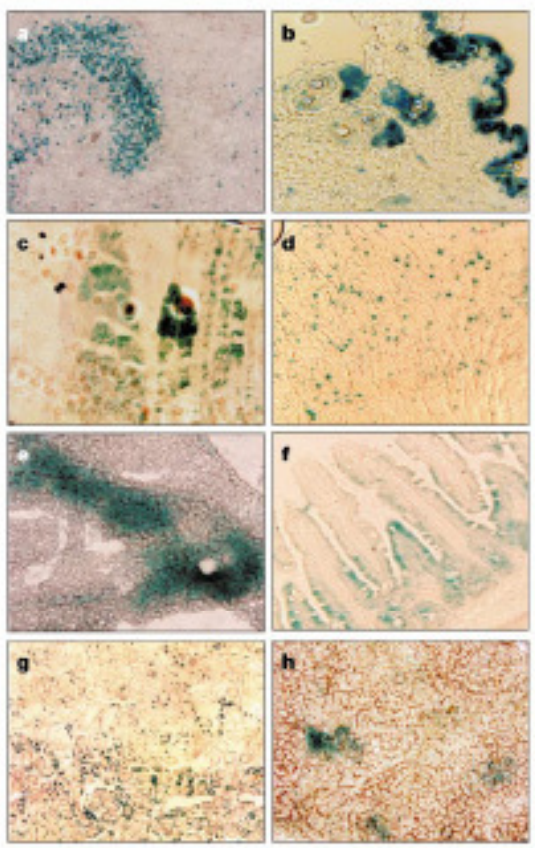
- Blood stem cell
- Skin stem cell
- cornea stem cell
- …

Can one isolate / create more potent stem cells from adult tissues?



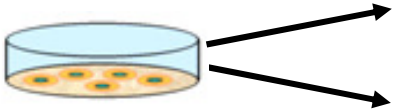
- 1958: first cloned frog
- 1997: “Dolly”
- 2002: from bone marrow, MAPC …
- 2004-8: from sperm stem cells
- 2007: from all tissues: iPS cell

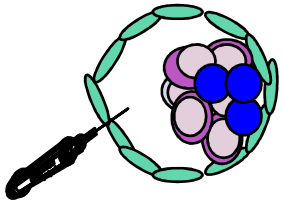
Culture isolation of more potent stem cell from bone marrow
(Multipotent Adult Progenitor Cell)



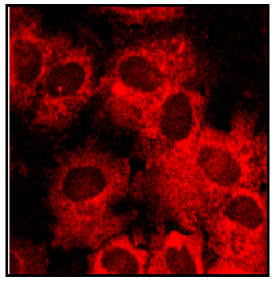
Mouse
Rat
Human

5% O_2, 6% CO_2
2% FCS
EGF, PDGF, LIF

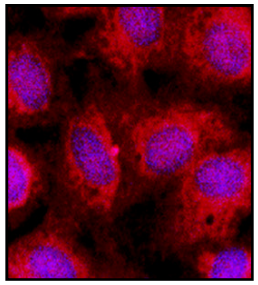




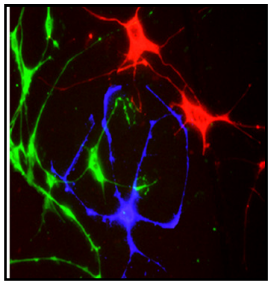
CD45-
Sca1-, Thy1-
Oct4
Telomerase+



Endothelium



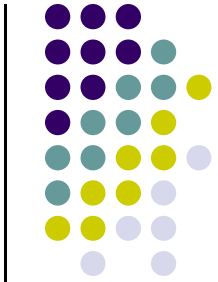
Liver cell



Astrocyte
Olio/Neuron

JIANG , NATURE 2002; JIANG PNAS 2003; QI PNAS 2003, BREYER EXP HEMATOL 2006; ZENG STEM CELLS 2006; ROSS, JCI 2006; ARANGUREN BLOOD 2006, SERAFINI J EXP MED 2007; ARANGUREN J CLIN INVEST 2008

Can one isolate / create more potent stem cells from adult tissues?



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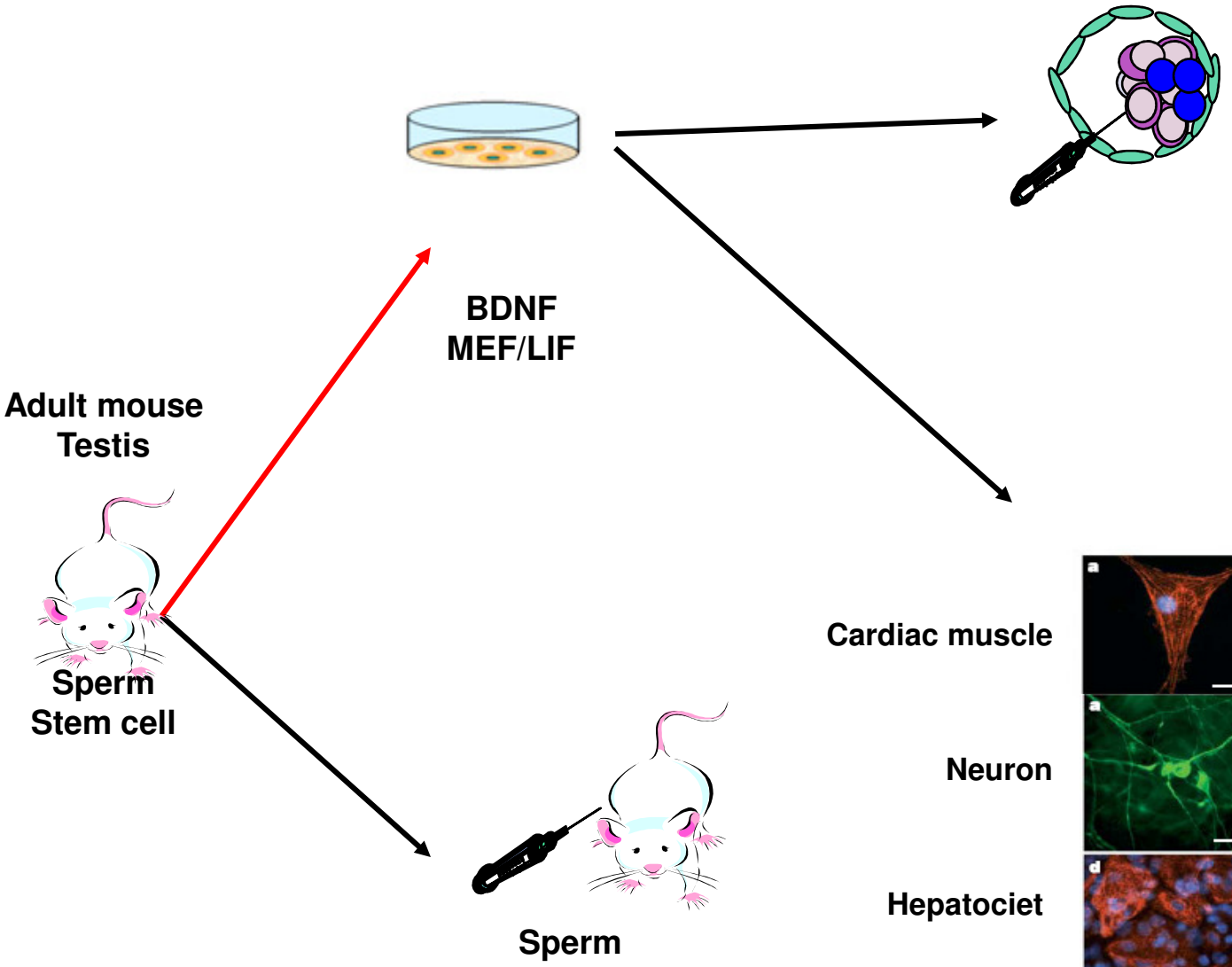
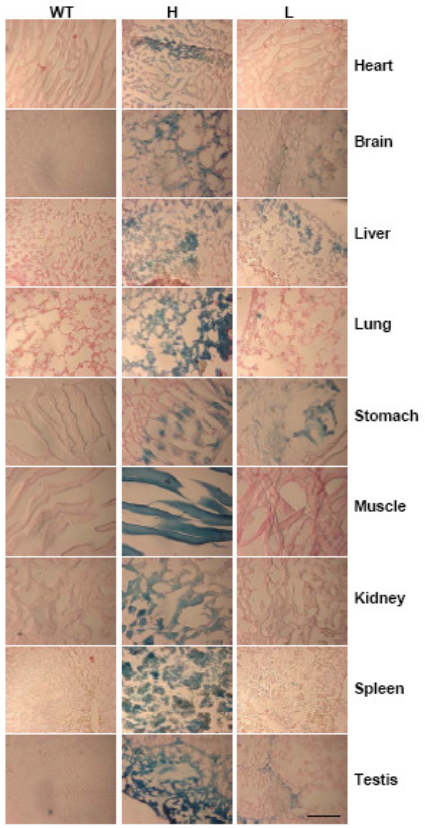
Culture isolation of more potent stem cell from sperm stem cell

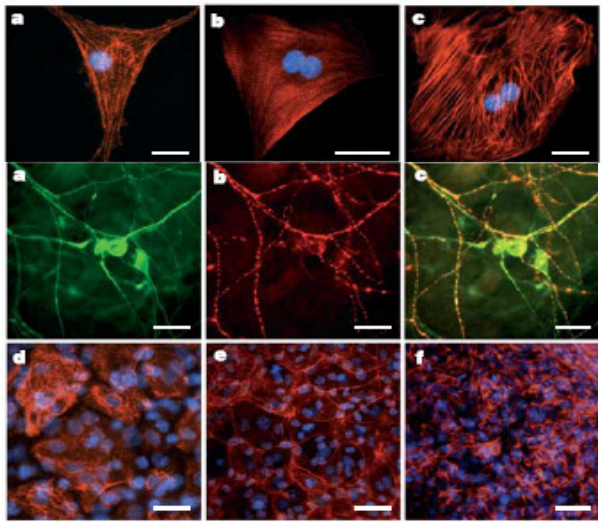




Cardiac muscle

Neuron

Hepatociet



KANATSU-SHINOHARA & COLLEAGUES 2004; GUAN & COLLEAGUES 2006; RAFII & COLLEAGUES 2007; CONRAD ET AL 2008; KOSACK ET AL 2008

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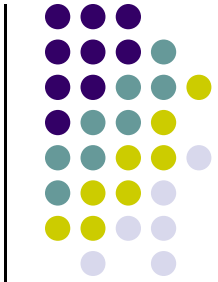

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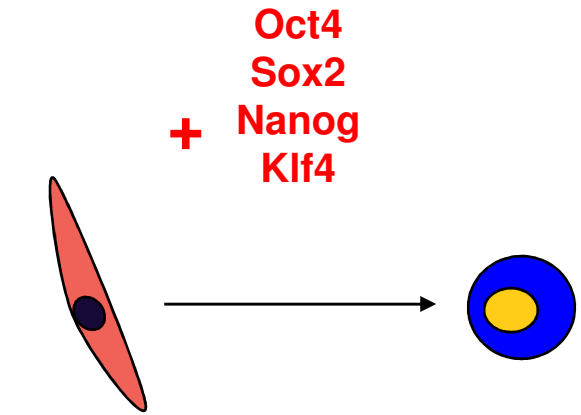
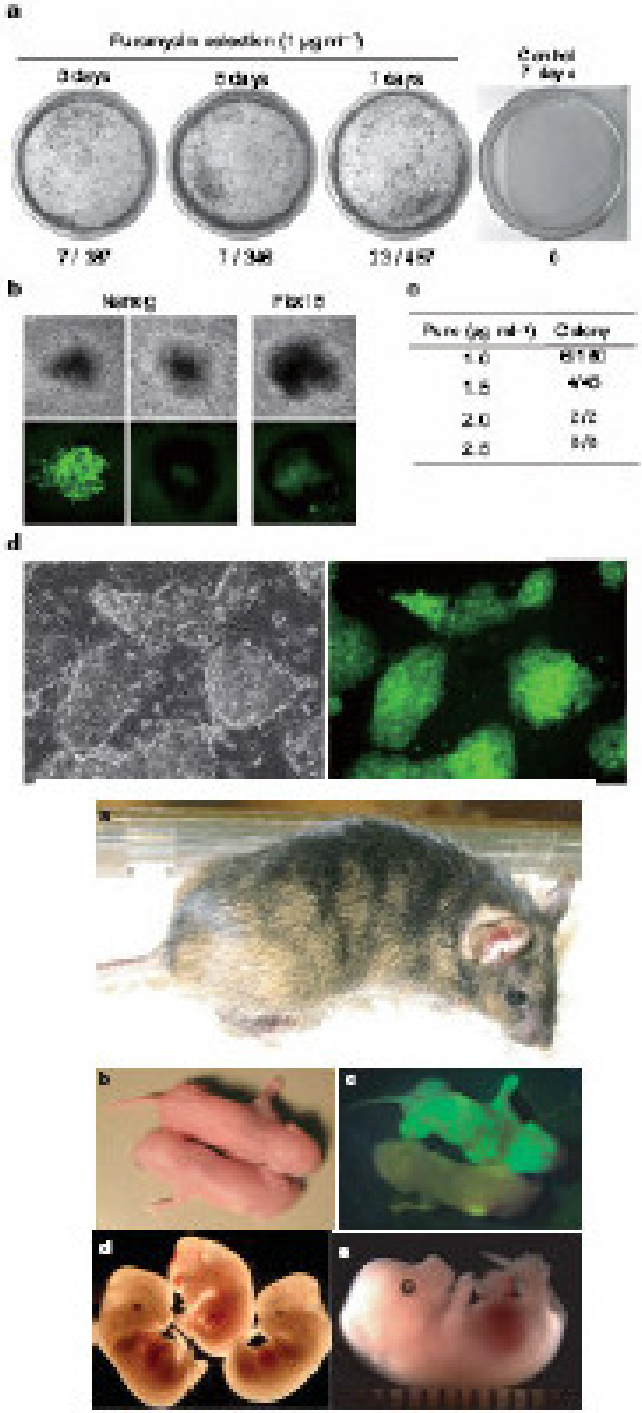
Embryonic stem cell-like cells created from an adult fibroblast



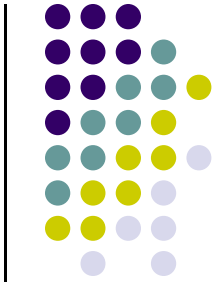
Fibroblast
Keratinocyte
Liver cell
B-cell,
all cells?

iPS cell



YAMANAKA AND COLLEAGUES 2007
THOMSON AND COLLEAGUES 2007

Enthusiasm because of “more potent” adult stem cells isolated from postnatal tissues

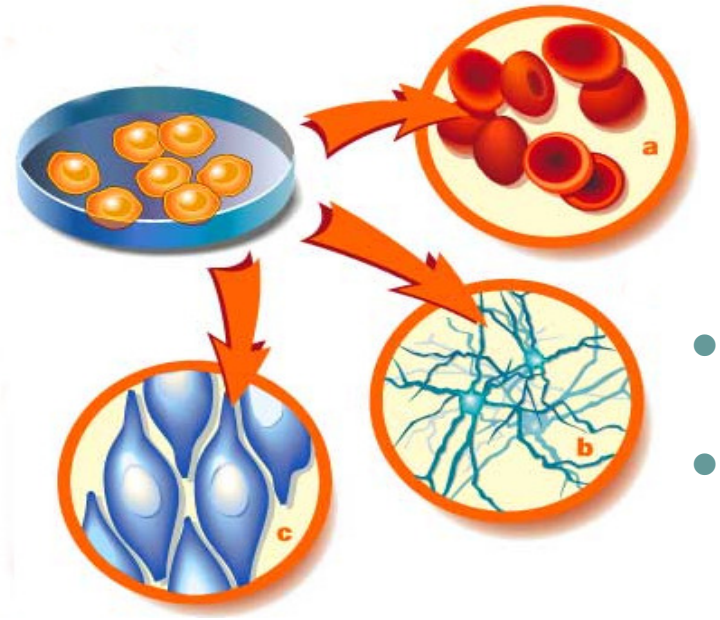


- Does not age and differentiates in most (all) tissues
- More potent adult stem cells can be used to treat “all” diseases?
- May be used in autologous manner?
- No ethical concerns

But, much work to be done to evaluate the extent of potency of these more potent cells generated from adult tissues

The promise of stem cell research

Stem cells

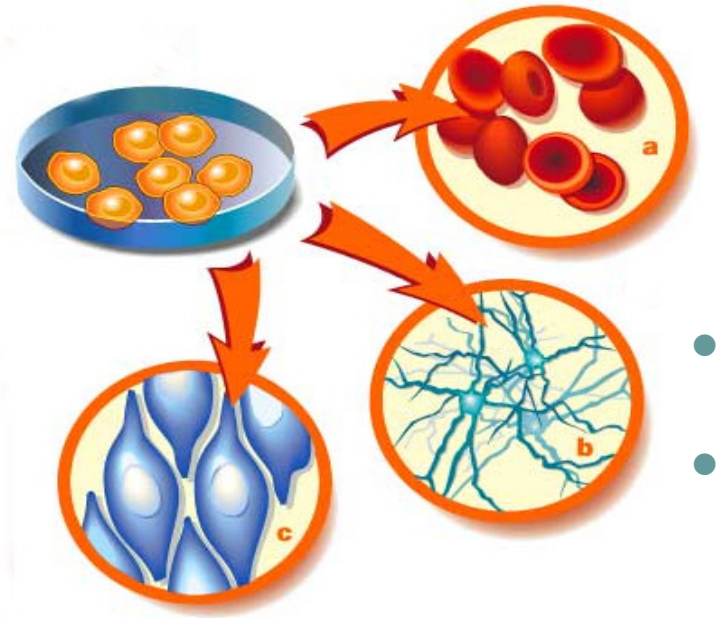


- Understanding development
- Drug discovery
- Use to test drug toxicity
- Study disease

- Cell therapy
- Tissue engineering

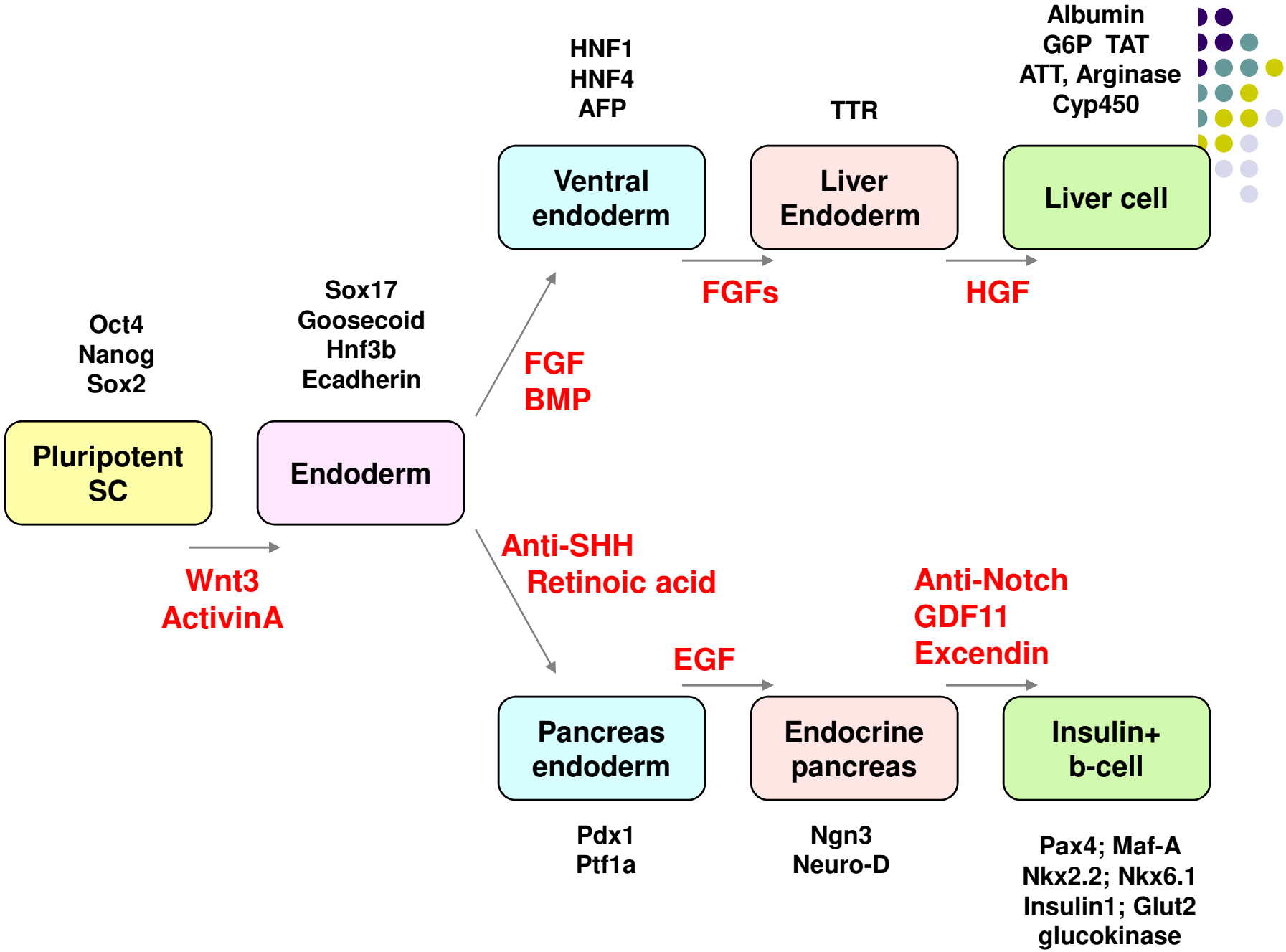
The promise of stem cell research

Stem cells

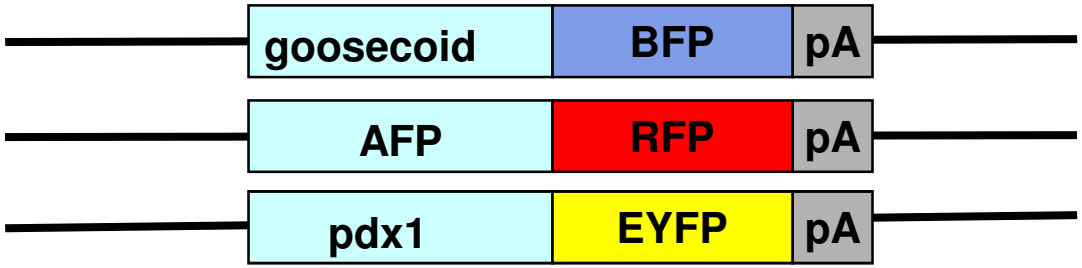


- **Understanding development**
- **Drug discovery**
- Use to test drug toxicity
- Study disease

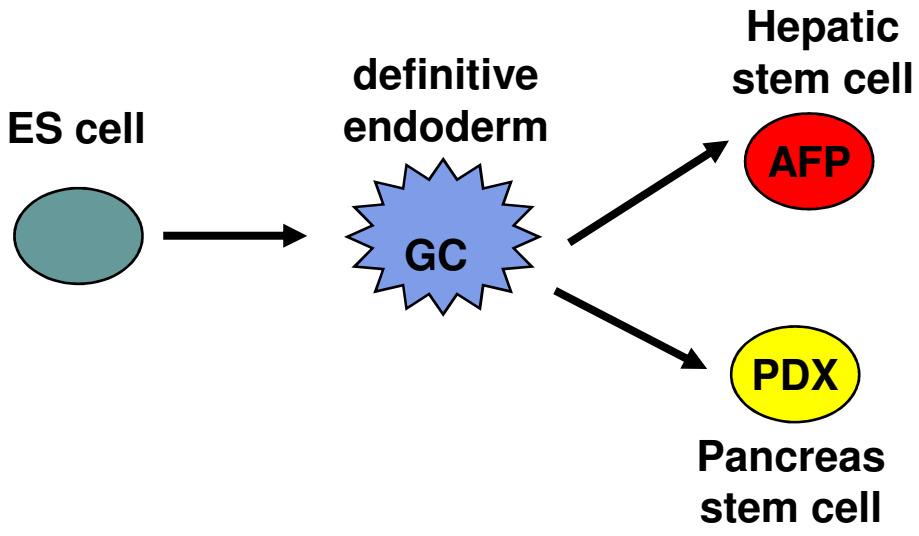
- Cell therapy
- Tissue engineering


Albumin
G6P TAT
ATT, Arginase
Cyp450
HNF1
HNF4
AFP
TTR
Ventral endoderm
Liver Endoderm
Liver cell
FGFs
HGF
Oct4
Nanog
Sox2
Sox17
Goosecoid
Hnf3b
Ecadherin
FGF
BMP
Pluripotent SC
Endoderm
Anti-SHH
Retinoic acid
Wnt3
ActivinA
EGF
Anti-Notch
GDF11
Excendin
Pancreas endoderm
Endocrine pancreas
Insulin+ b-cell
Pdx1
Ptf1a
Ngn3
Neuro-D
Pax4; Maf-A
Nkx2.2; Nkx6.1
Insulin1; Glut2
glucokinase

Introduce reporter genes: possible to do high throughput screens



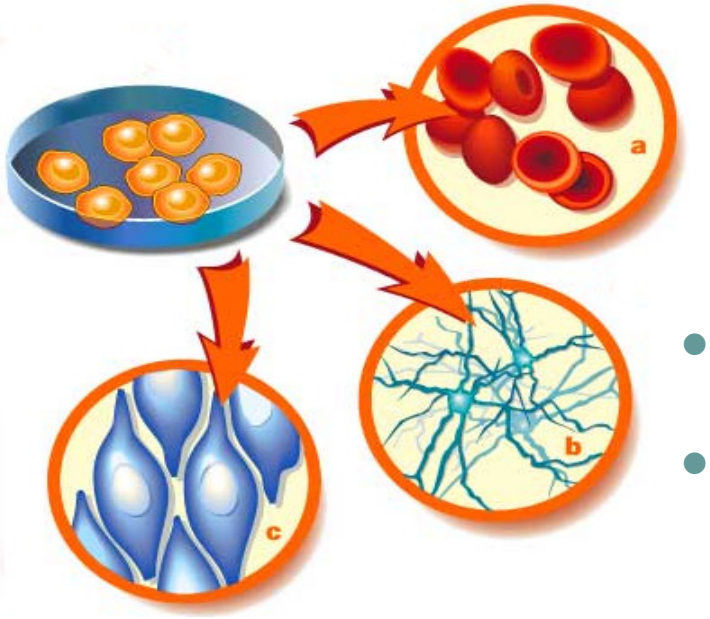
Protein library
miRNA library
Small molecule library



The promise of stem cell research

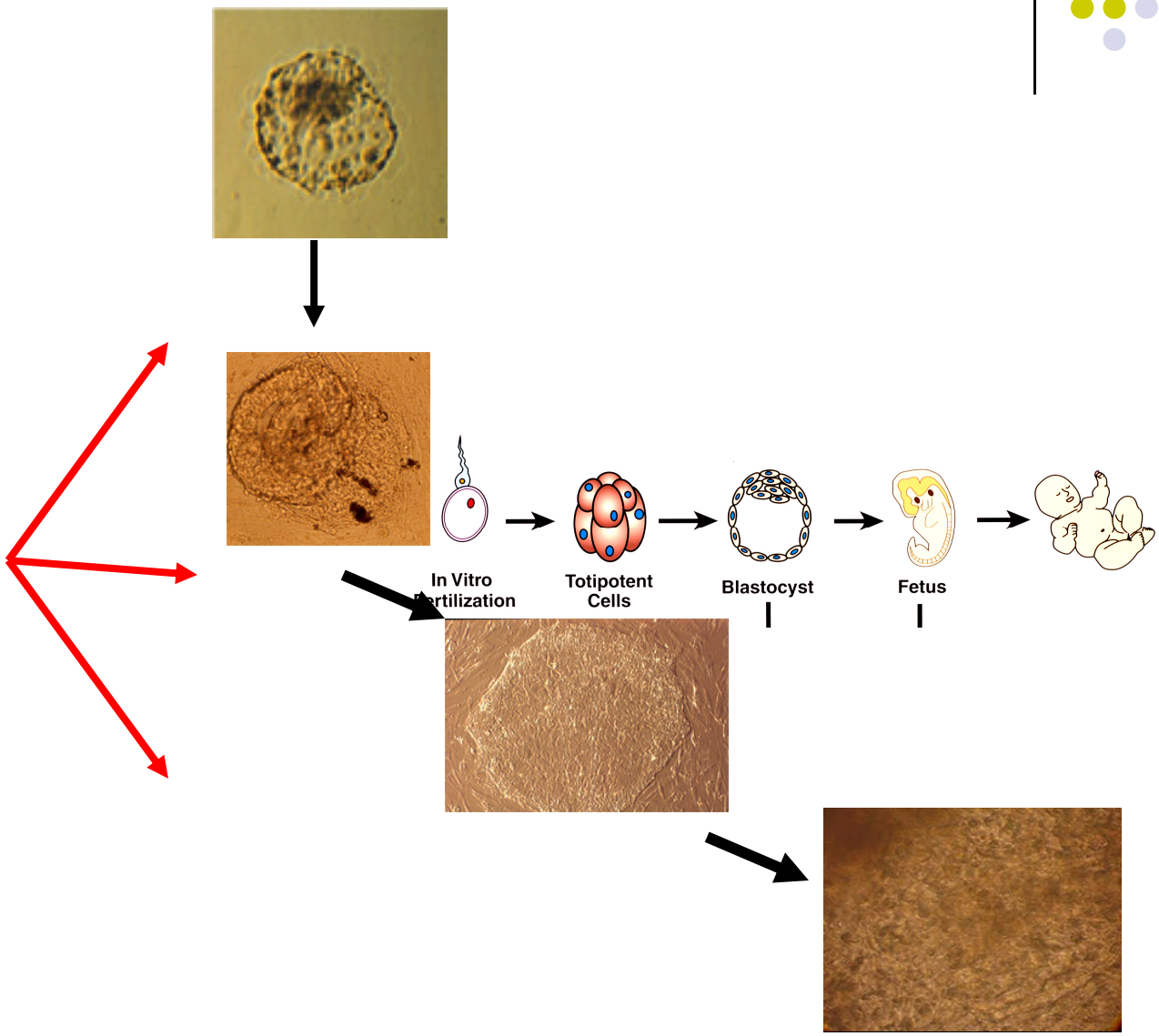
Stem cells

- Understanding development
- Drug discovery
- **Use to test drug toxicity**
- Study disease

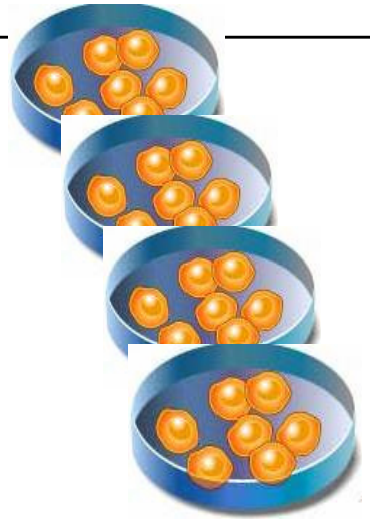


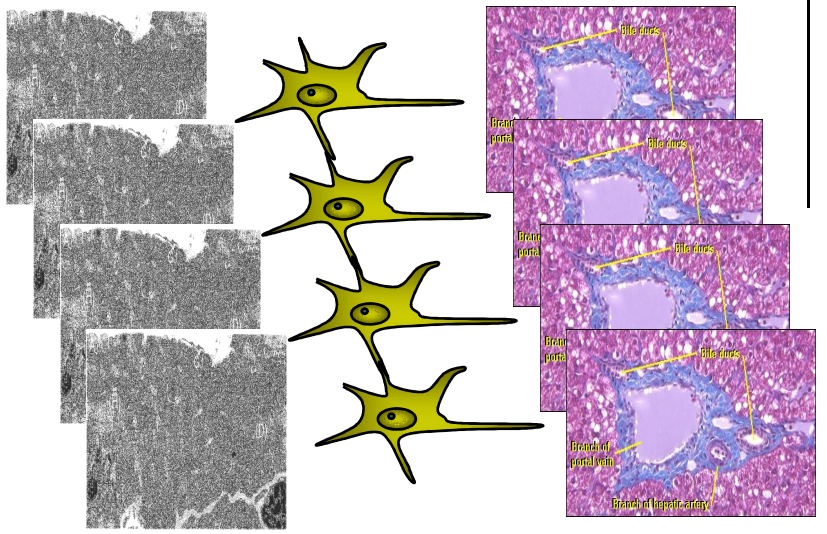
- Cell therapy
- Tissue engineering

Effect of drugs on early developing embryo



Stem cells from
X human donors with
different SNIP profile





Liver cells, neural cells and cardiac muscle from X human donors with different SNIP profile

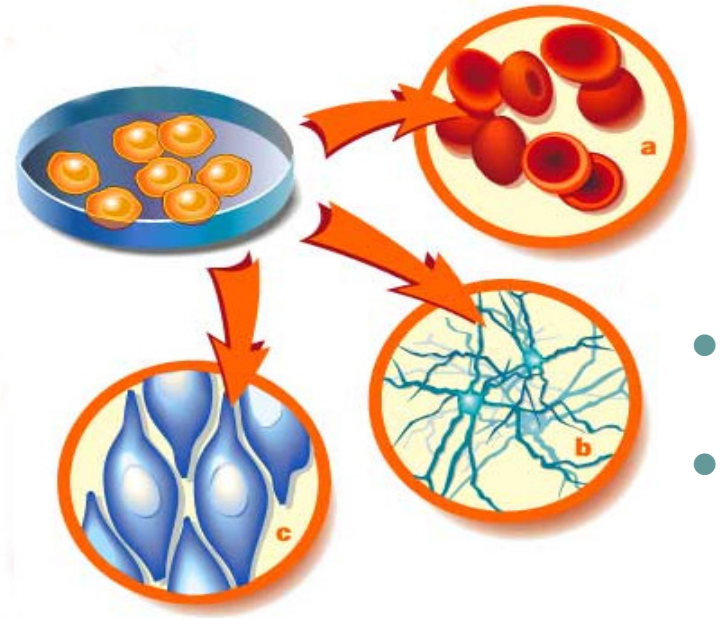
High throughput screen for toxicity

Phase I/II studies

The promise of stem cell research

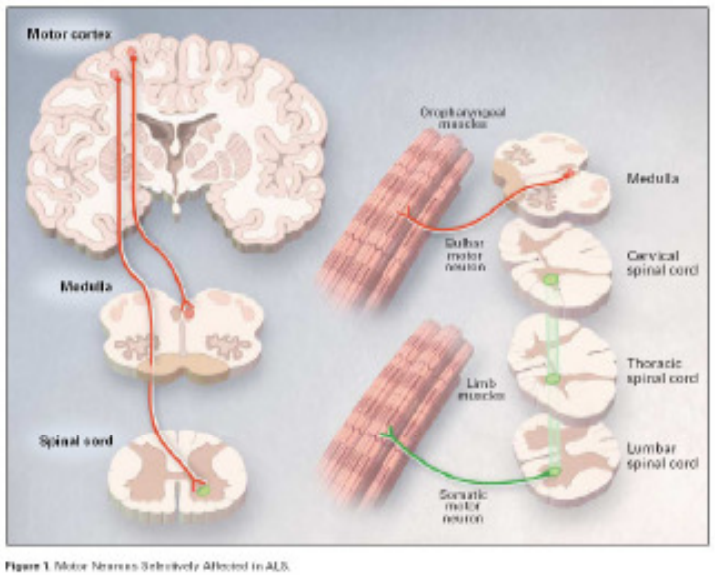
Stem cells

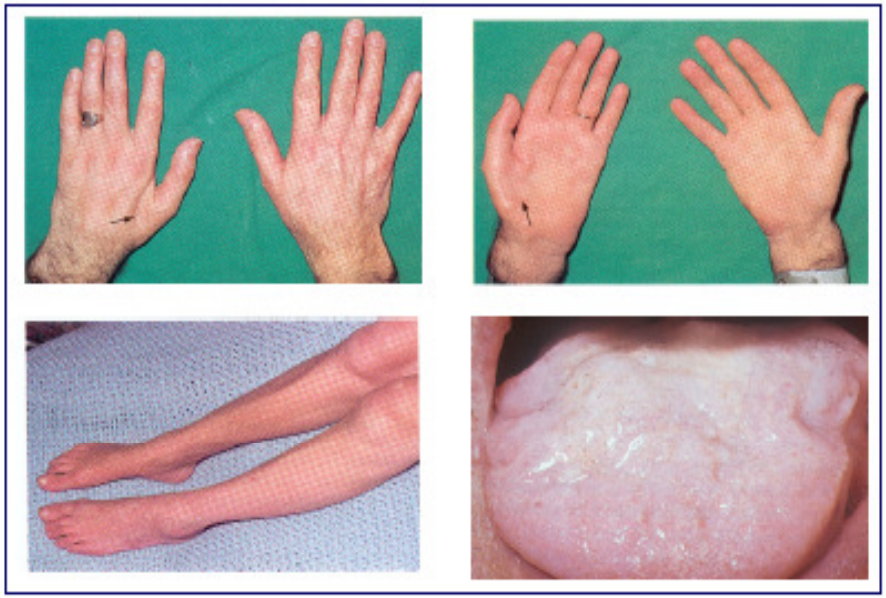
- Understanding development
- Drug discovery
- Use to test drug toxicity
- **Study disease**



- Cell therapy
- Tissue engineering

Amyotrophe Lateraal Sclerosis (ALS)

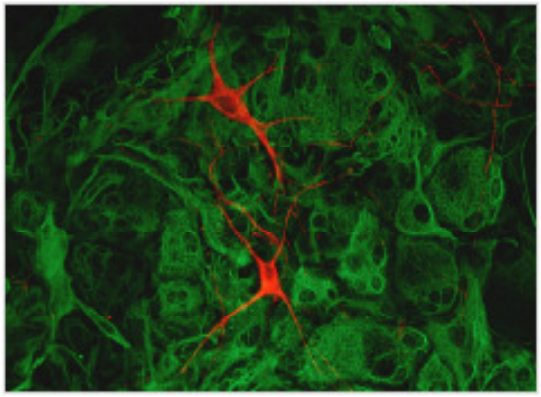


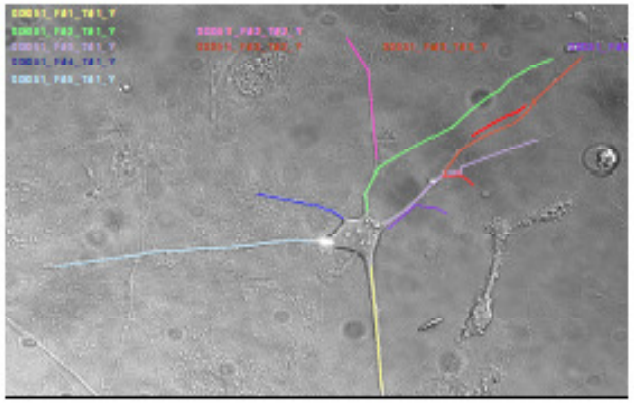


In 90% of patients genetic cause not known

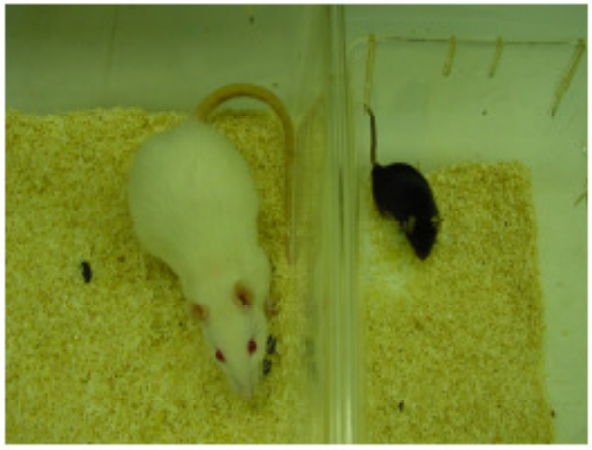
Courtesy Dr W Robberecht

Amyotrophic Lateral Sclerosis (ALS)





In vitro neural cells from mice, rats



Transgenic mice or rats

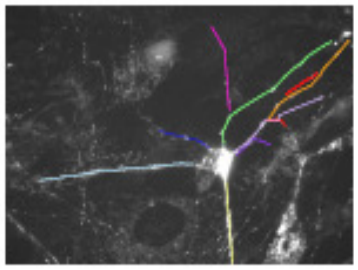
Zebrafish

Courtesy Dr W Robberecht

ESC-like cells (iPSC) from patients with ALS:

Fibroblast +
Oct4, Sox2, Klf4, cMyc

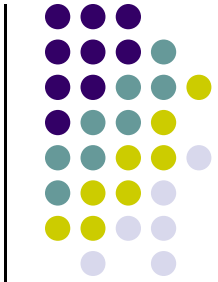
iPSC with ALS defect



Human neurons and glial cells with ALS defect

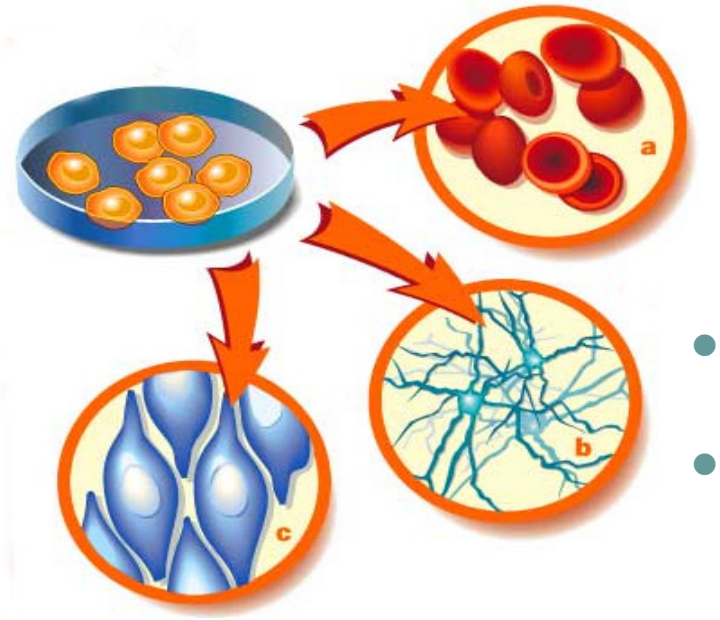
Evaluate mechanism of disease
Develop therapies

Promise of stem cells



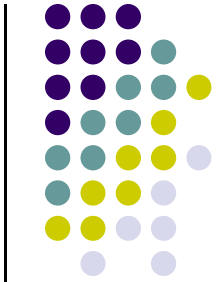
Stem cells

- Understanding development
- Drug discovery
- Used to test drug toxicity
- Study disease



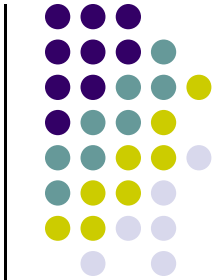
- **Cell therapy**
- **Tissue engineering**

Stem cells and regenerative medicine



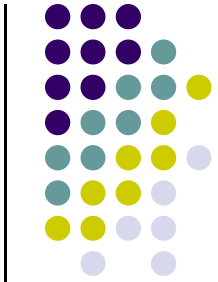
- Tissue replacement
  - Stem cell progeny infusion
  - Tissue engineering
- Trophic effects inducing endogenous repair
- Anti-inflammatory and immunosuppressive effects

Diabetes



- Loss of insulin producing ccells (type >type II)
- Immunological basis for type I
- Therapy with insulin; but this is palliation, and not a cure
- Cure with pancreas (or islet?) transplantation; but
  - Insufficient donors
  - Immune complications
- Despite therapy with insulin, vascular complications

Stem cells and regenerative medicine



- Tissue replacement
  - Stem cell progeny infusion
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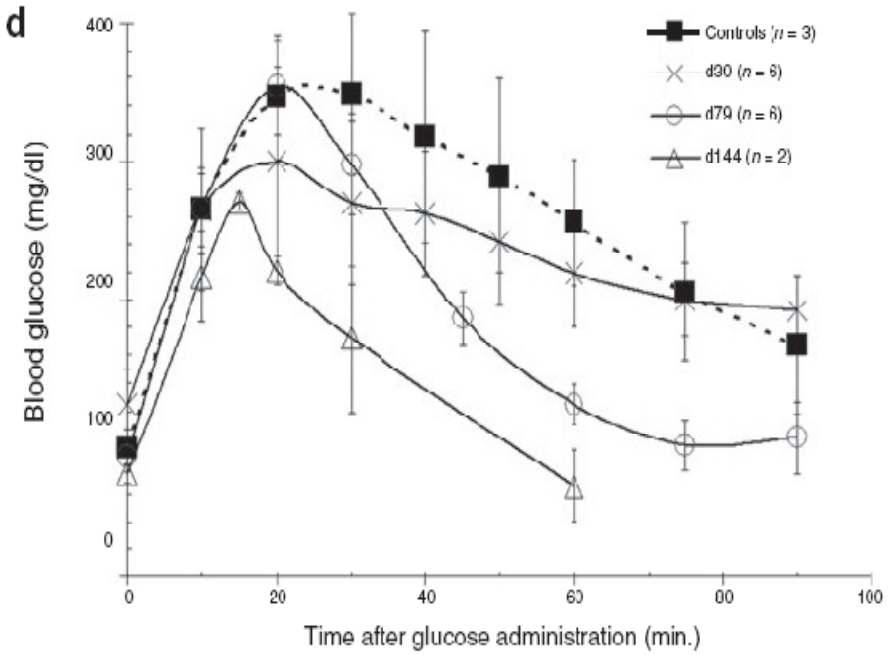
- Trophic effects inducing endogenous repair
- Anti-inflammatory and immunosuppressive effects

Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells

Kevin A D'Amour, Anne G Bang, Susan Eliazer, Olivia G Kelly, Alan D Agulnick, Nora G Smart, Mark A Moorman, Evert Kroon, Melissa K Carpenter & Emmanuel E Baetge

Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*

Evert Kroon, Laura A Martinson, Kuniko Kadoya, Anne G Bang, Olivia G Kelly, Susan Eliazer, Holly Young, Mike Richardson, Nora G Smart, Justine Cunningham, Alan D Agulnick, Kevin A D'Amour, Melissa K Carpenter, Emmanuel E Baetge



Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells

Kevin A D'Amour, Anne G Bang, Susan Eliazer, Olivia G Kelly, Alan D Agulnick, Nora G Smart, Mark A Moorman, Evert Kroon, Melissa K Carpenter & Emmanuel E Baetge

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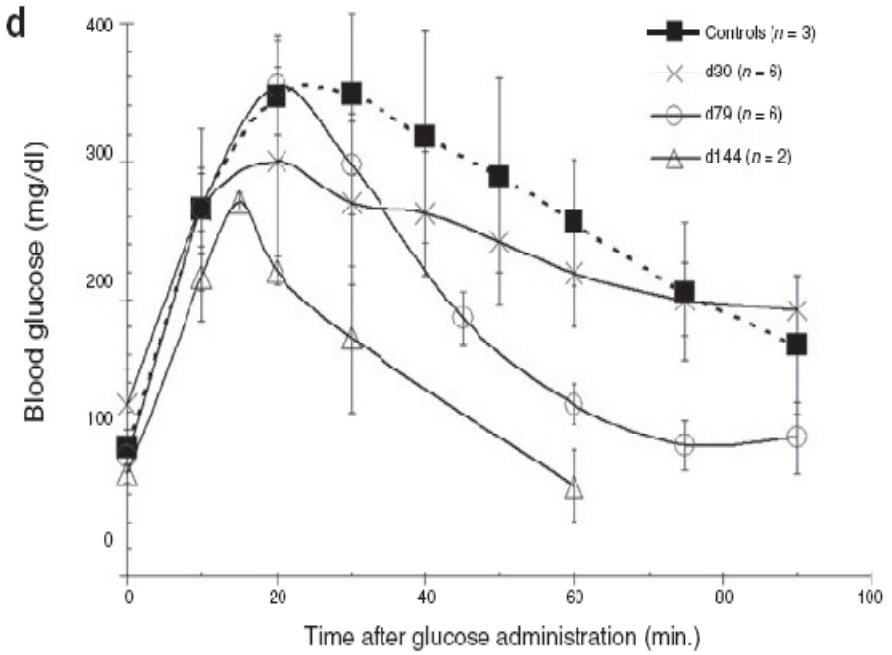
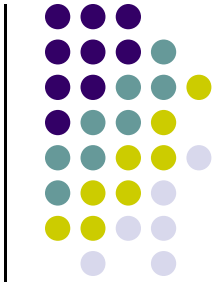
But also tumor (teratomas)

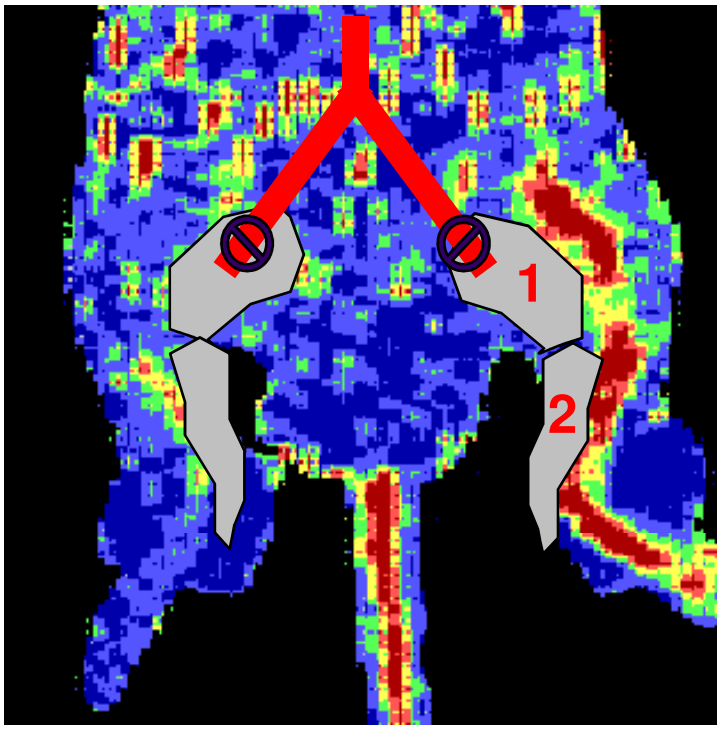


Diabetes



- Despite therapy with insulin, vascular complications
  - Cell transplantation to regenerate vessels
  - Trophic effects vs. Cell replacement

Model and Treatment Scheme



Transplant 1 million mouse, or human MAPC In C57BL/6 mice or BalbC Nude mice

1. **Laser Doppler for 21 days**

2. **Swim endurance till 21**
   Treadmill test till d21

3. **Histology**

   a. **Fibrosis, necrosis, regeneration**
   b. **Vascularity**
   c. **Contribution to arteries, capillaries and skeletal muscle**

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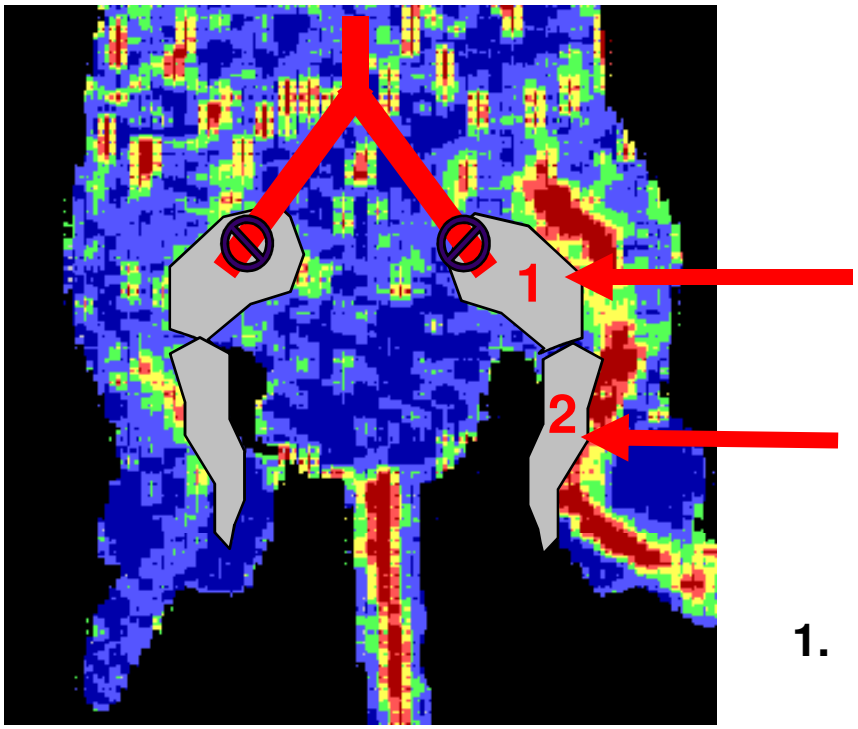
Model and Treatment Scheme



Transplant 1 million mouse, or human MAPC In C57BL/6 mice or BalbC Nude mice

In some studies

- **Mouse BM cells**
- **Human AC133 EPC**
- **EC/SMC committed mMAPC**

1. **Laser Doppler for 21 days**
2. **Swim endurance till 21**
   Treadmill test till d21
3. **Histology**
   a. **Fibrosis, necrosis, regeneration**
   b. **Vascularity**
   c. **Contribution to arteries, capillaries and skeletal muscle**

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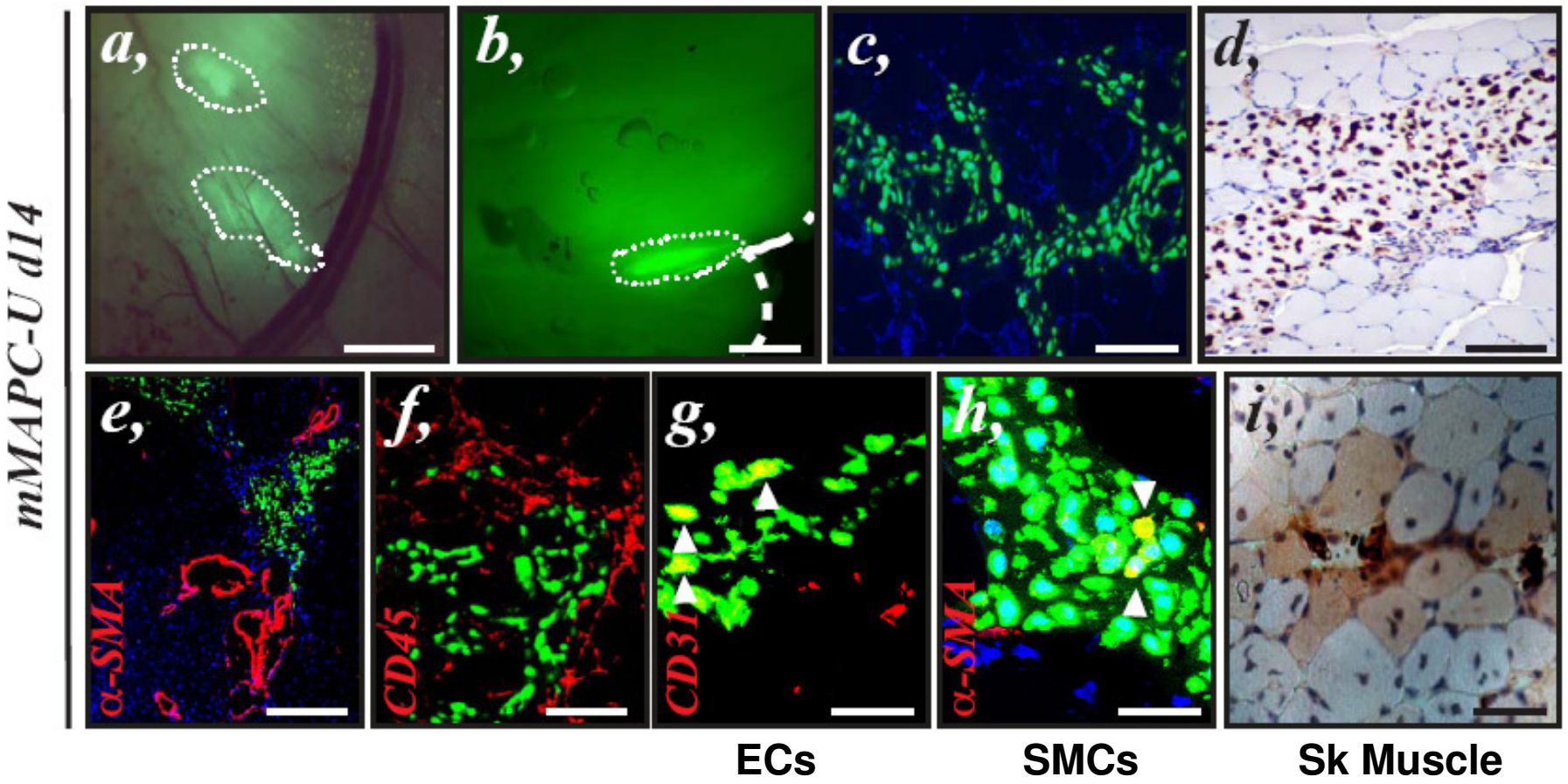
Mouse MAPC engraft, and differentiate (in part) to SMC, EC and Sk. muscle cells



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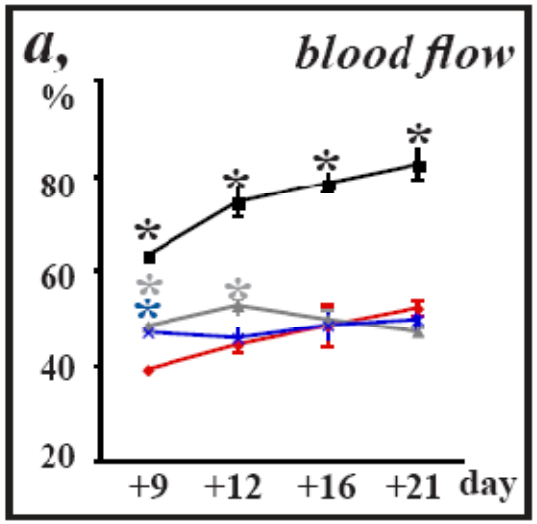
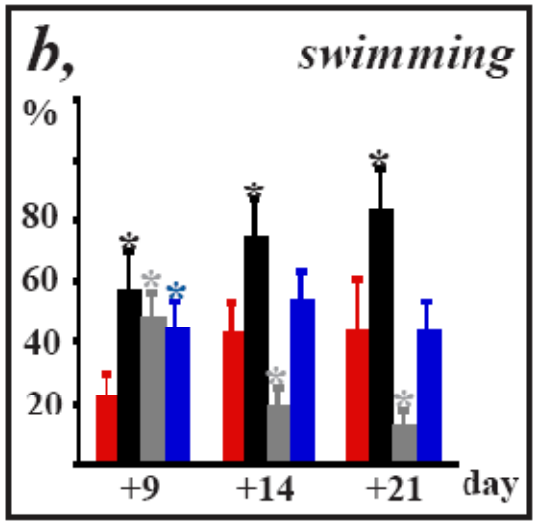
Significant functional improvement





c, clinical status

	toe necrosis	sudden death	
vehicle	5/15	0/15	
mMAPC-U	0/15	0/15	
mBMC	11/16	2/16	
mMAPC-VP	5/17	0/17	

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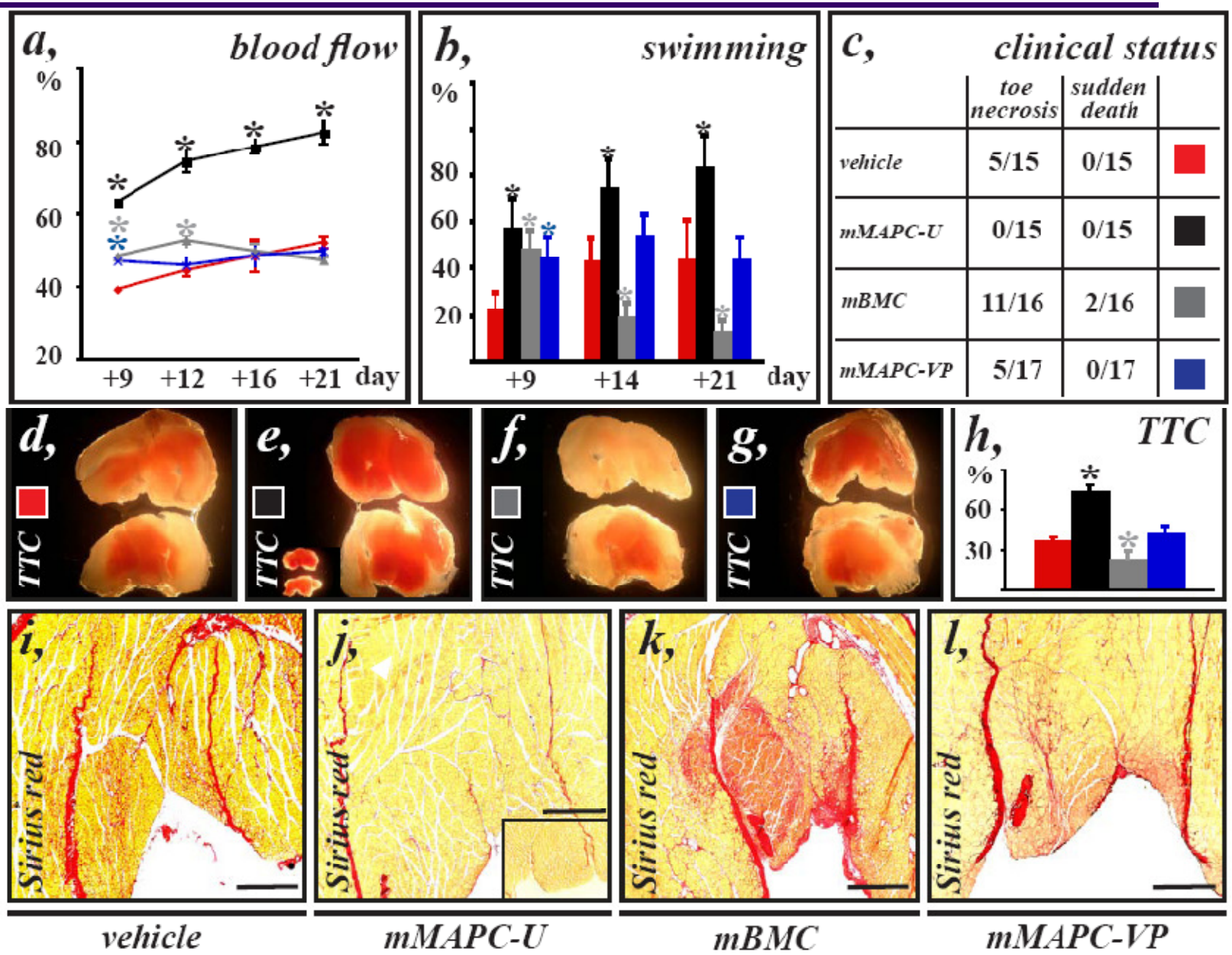
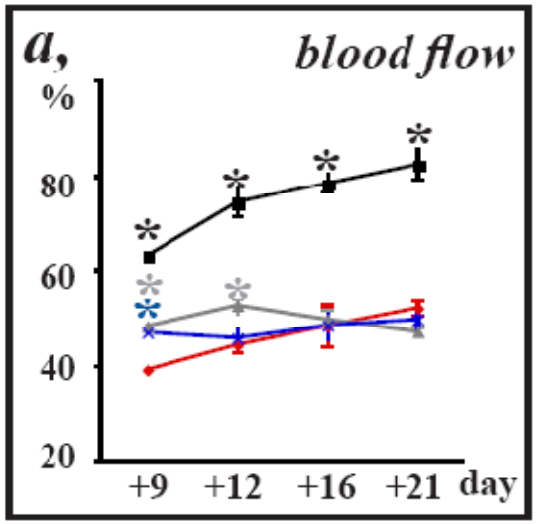
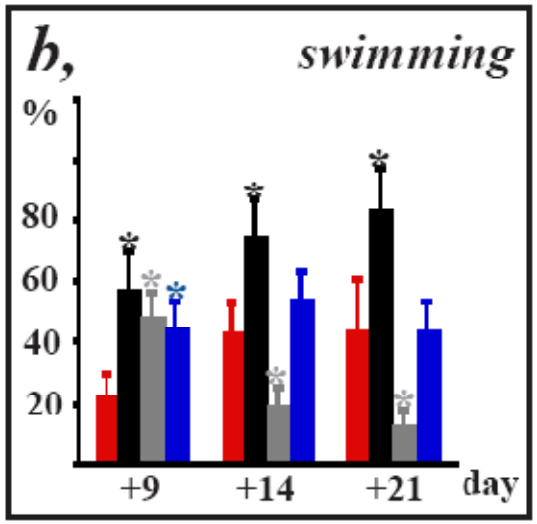
Significant functional improvement and almost complete lack of fibrosis in MAPC treated ischemic limb



MAPC suppress necrosis and fibrosis and significantly enhance muscle regeneration in acute ischemia model





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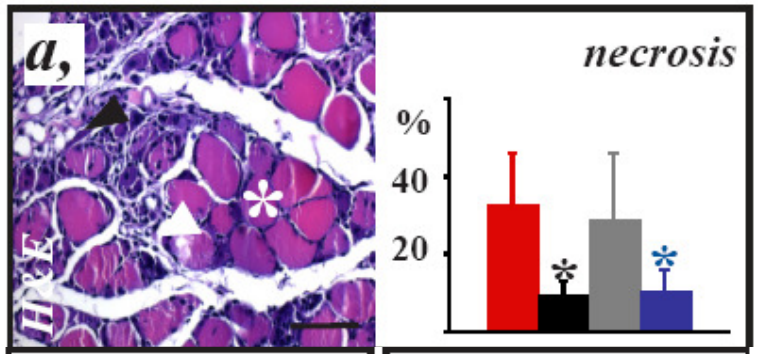
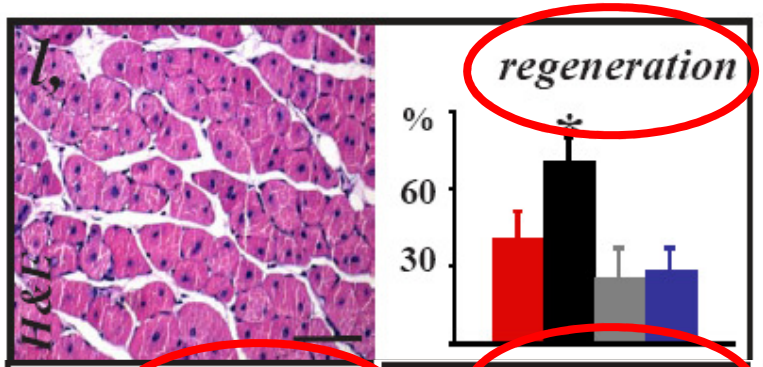
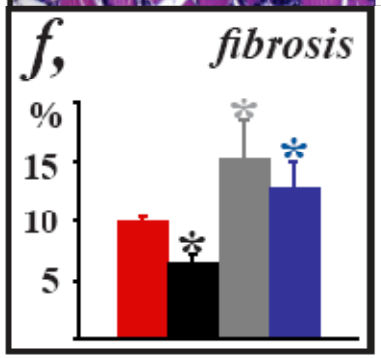
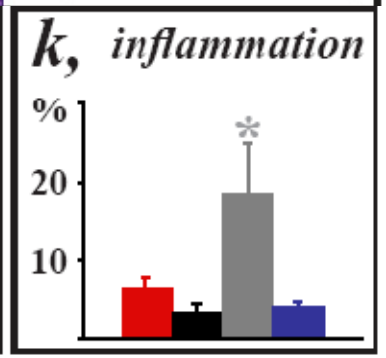
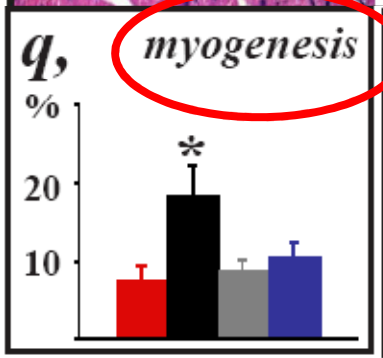
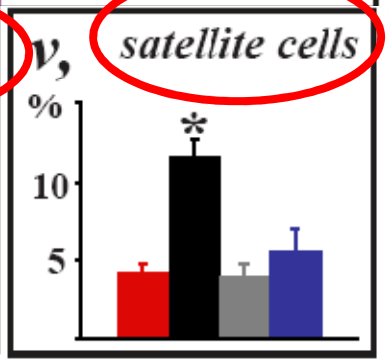


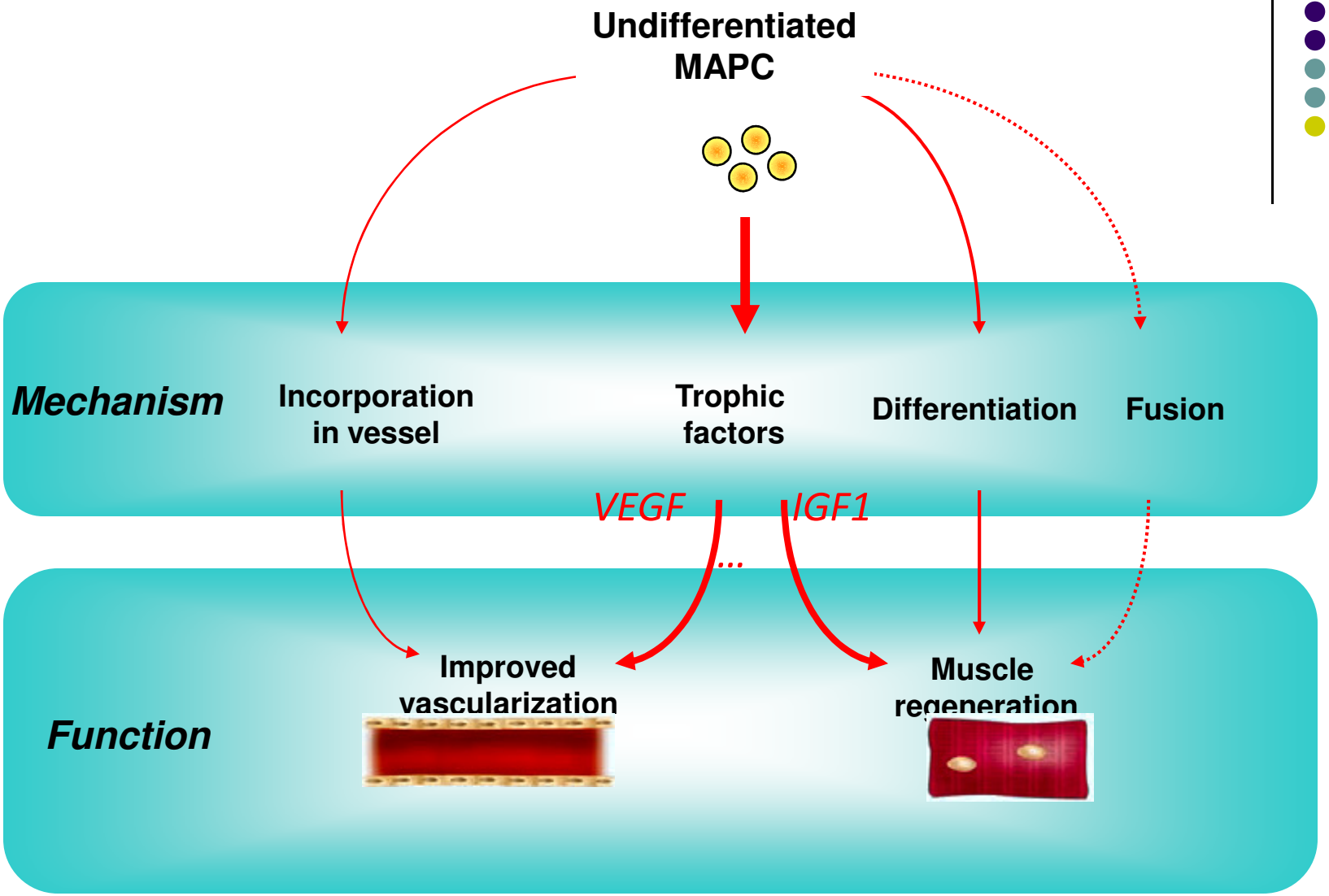






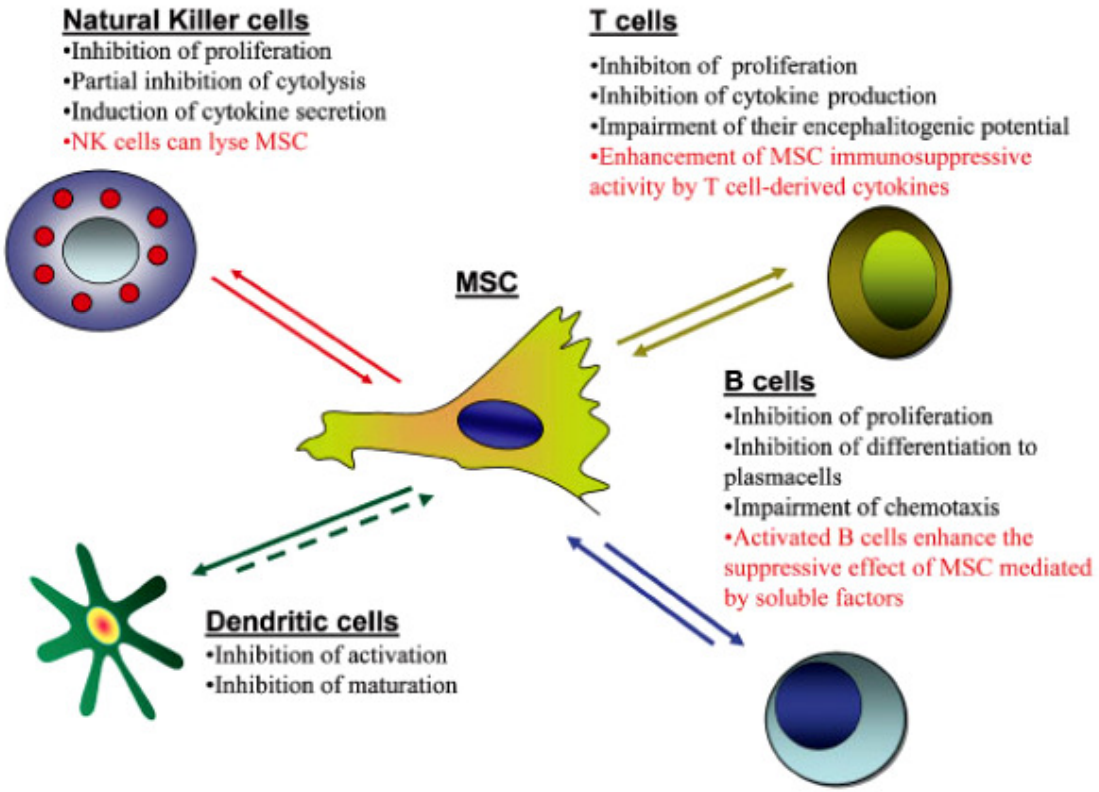






ADAPTED FROM DIMMELER, ZEIHER, AND SCHNEIDER, JCI 2005

MSC/MAPC/… are immunomodulatory

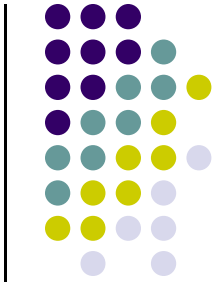


Use (allegeneic cells) to

1. **Decrease GVHD**
2. **Decrease organ rejection**
3. **Treat immune disorders**
   1. **Crohn's disease**
   2. **Type I diabetes**
   3. **Scleroderma, …**

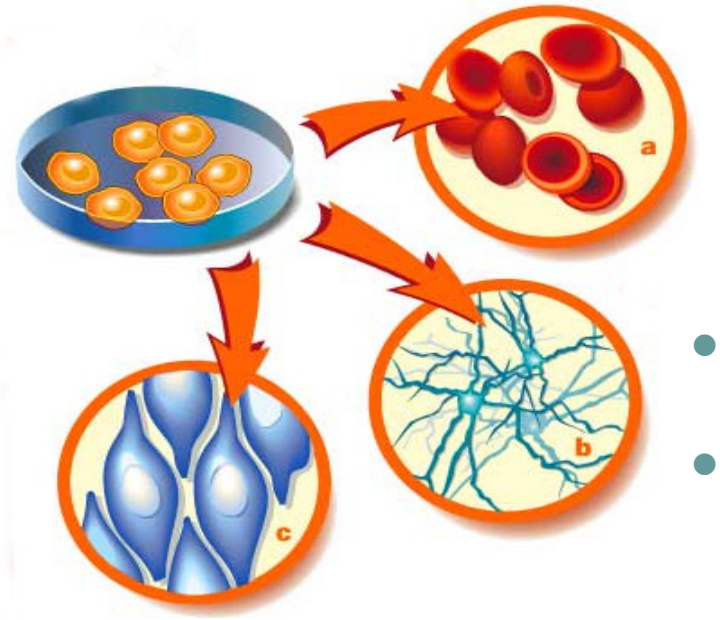
UCCELLI ET AL, EUR J IMMUNOL, 2006

Promise of stem cells



Stem cells

- Understanding development
- Drug discovery
- Used to test drug toxicity
- Study disease



- Cell therapy
- Tissue engineering

UNIVERSITY of MINNESOTA

KU LEUVEN

FWO VLAANDEREN
Fonds Wetenschappelijk Onderzoek
Research Foundation – Flanders

iwt

Athersys inc.

STROKEMAP
Multipotent Adult Progenitor Cells to treat Stroke

Juvenile Diabetes Research Foundation International
dedicated to finding a cure

National Institutes of Health
The Nation's Medical Research Agency

Verfaillie lab

Collaborators

Stem Cell Isolation/Characterization

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Ben Kidder
Antonio Lo Nigro
Masayuki Oki
Valerie Roobrouck
Fernando Ulloa

Wei Shou Hu
Minoru Ko
Yves Moreau
Shin-Ichi Nishikawa
Tim O'Brien

Hepatic/Pancreatic Differentiation

Miguel Barajas
Bipasha Bose
Qing Cai
Anukith Kuma
Karen Pauwelyn
Pau Sancho-Bru
Philip Roelandt
Kartik Subramanian

Rita Devos
Johan Fevery
Bernhard Hering
Wei Shou Hu
Chamtal Mathieu
Frederik Nevens
Tania Roskams
Michael Ott

Vascular Differentiation

Aernout Luttun
Jeff Ross
Valerie roobrouck
Abisheck Sohni

Peter Carmeliet
Steve Ekker
Paul Tranquillo
Jay Zhang

Immunology

An Billiau
Stefaan VanGool