Stem and Progenitor Cell Biology - an introduction

Berlin, June 27, 2004

m.alison@imperial.ac.uk

- Properties of adult stem cells
- Plasticity
- Disease:
    1) metaplasia
    2) fibrosis
    3) cancer

Organ-specific stem cells

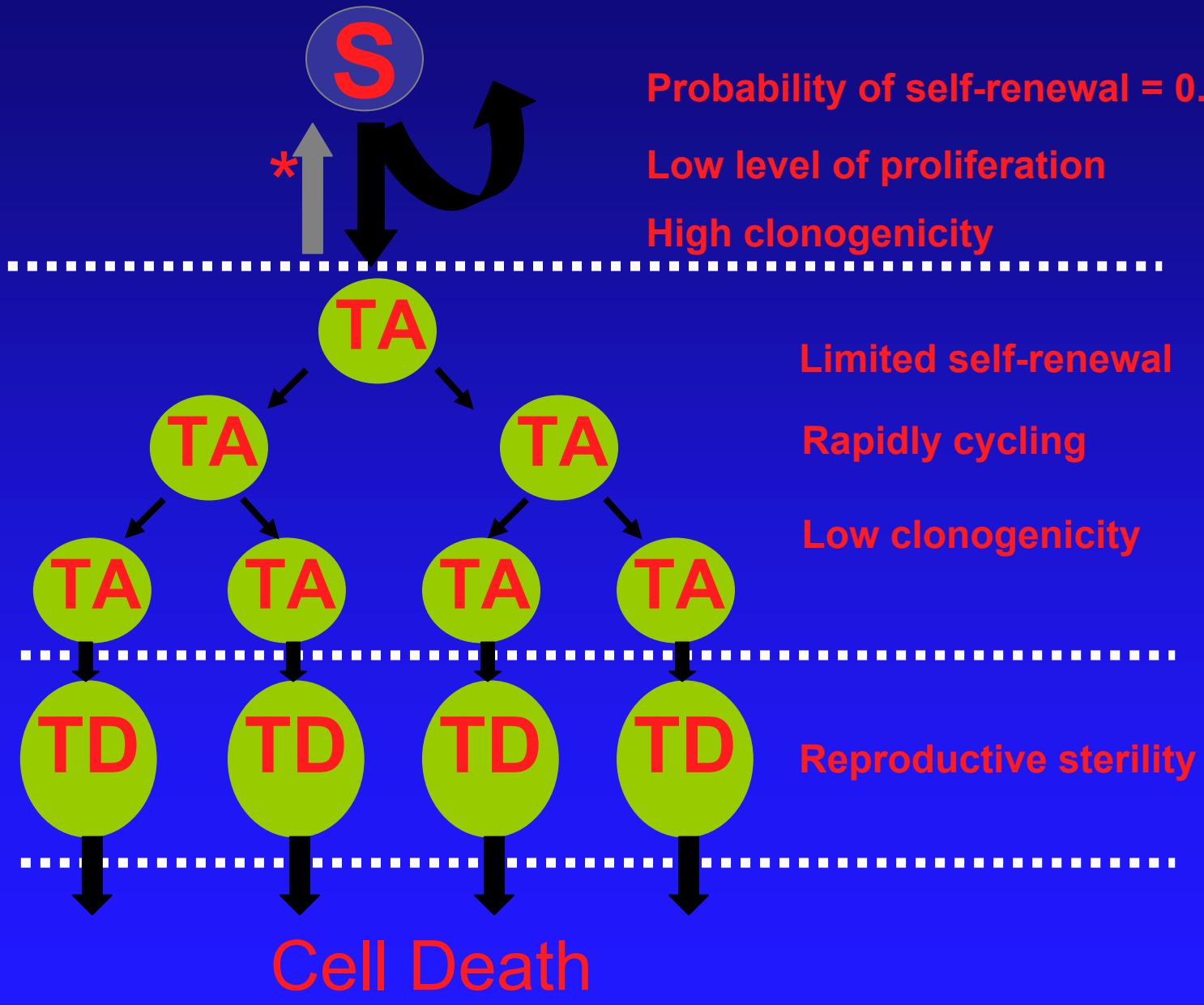
Journal of Pathology
J Pathol 2002; **197**: 419–423.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/path.1187

Review Article

An introduction to stem cells

Malcolm R. Alison[1,2]*, Richard Poulsom[1], Stuart Forbes[3] and Nicholas A. Wright[1]

Adult Tissue-Specific Stem Cells



Probability of self-renewal = 0.5

Low level of proliferation

High clonogenicity

Limited self-renewal

Rapidly cycling

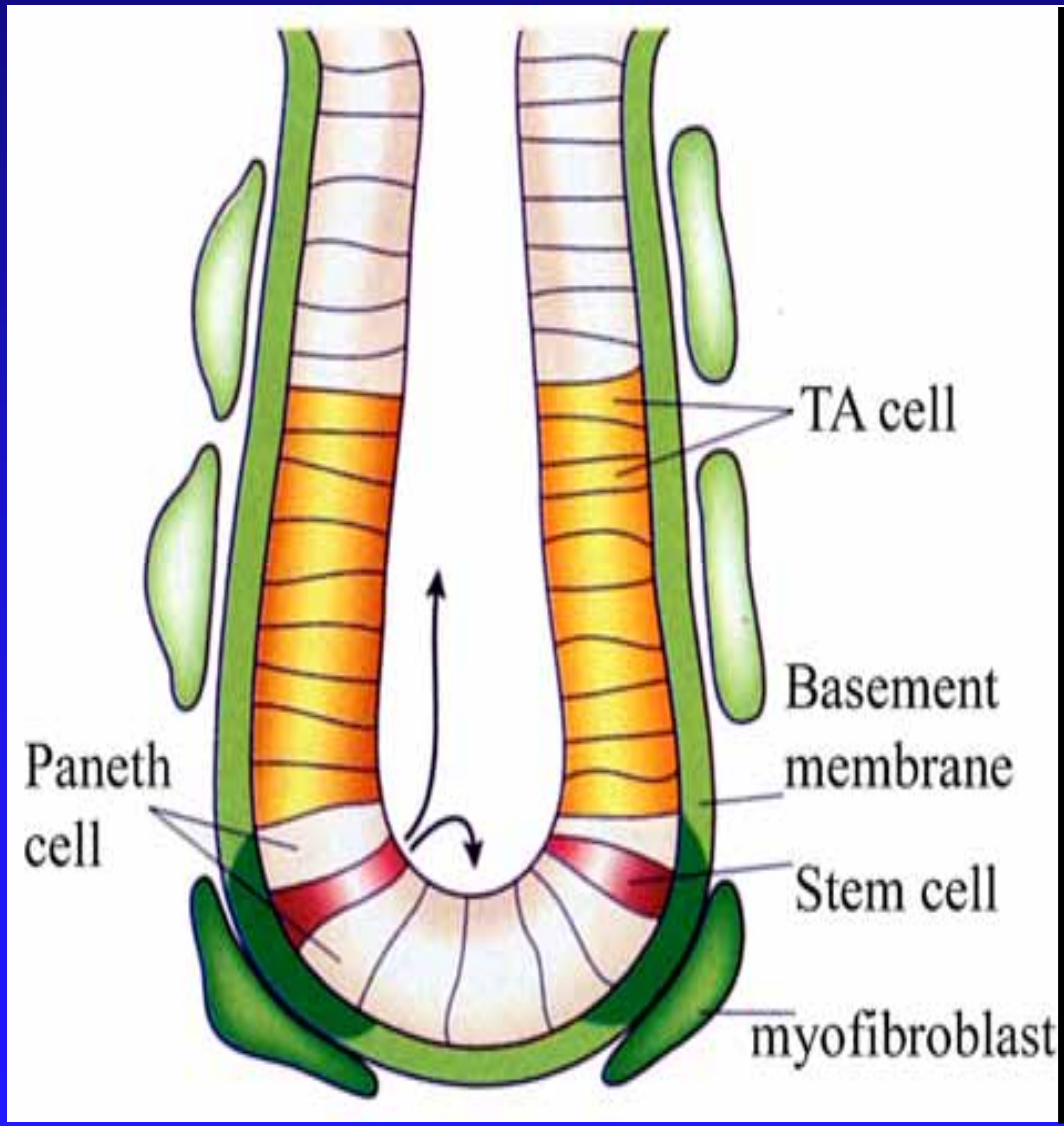
Low clonogenicity

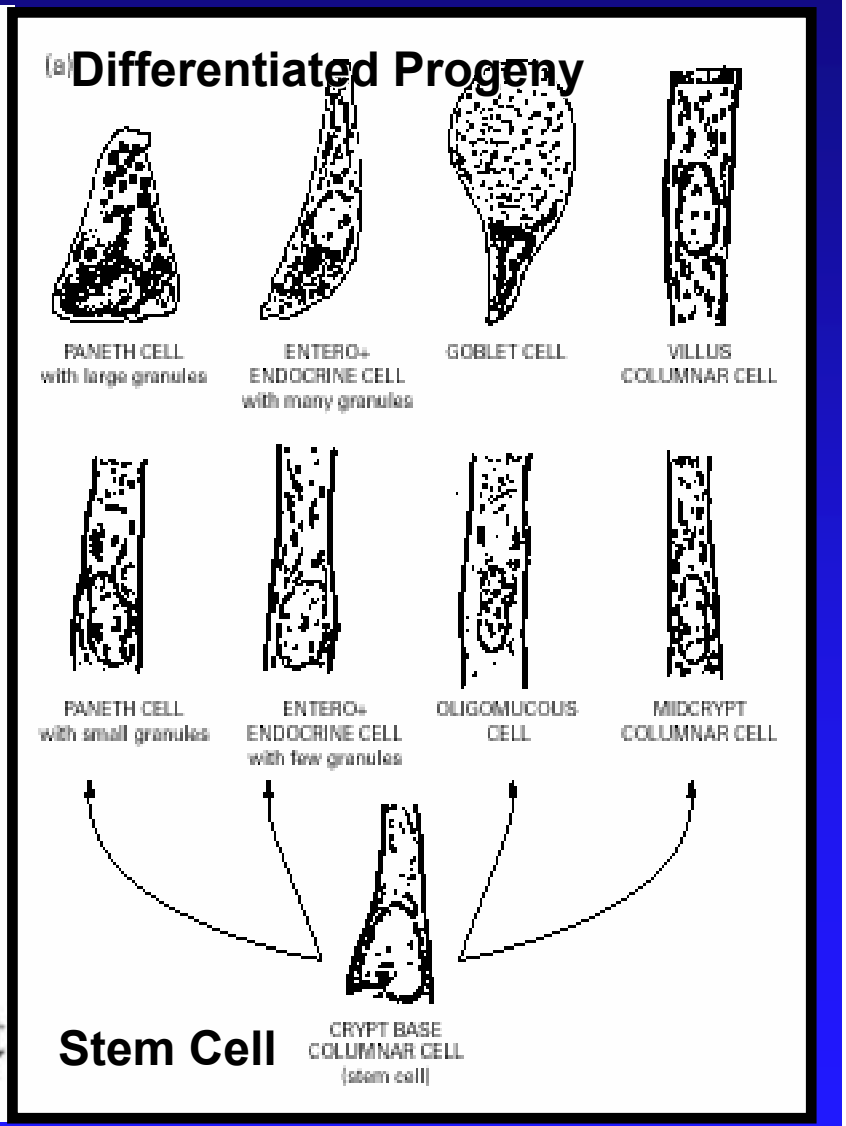
Reproductive sterility

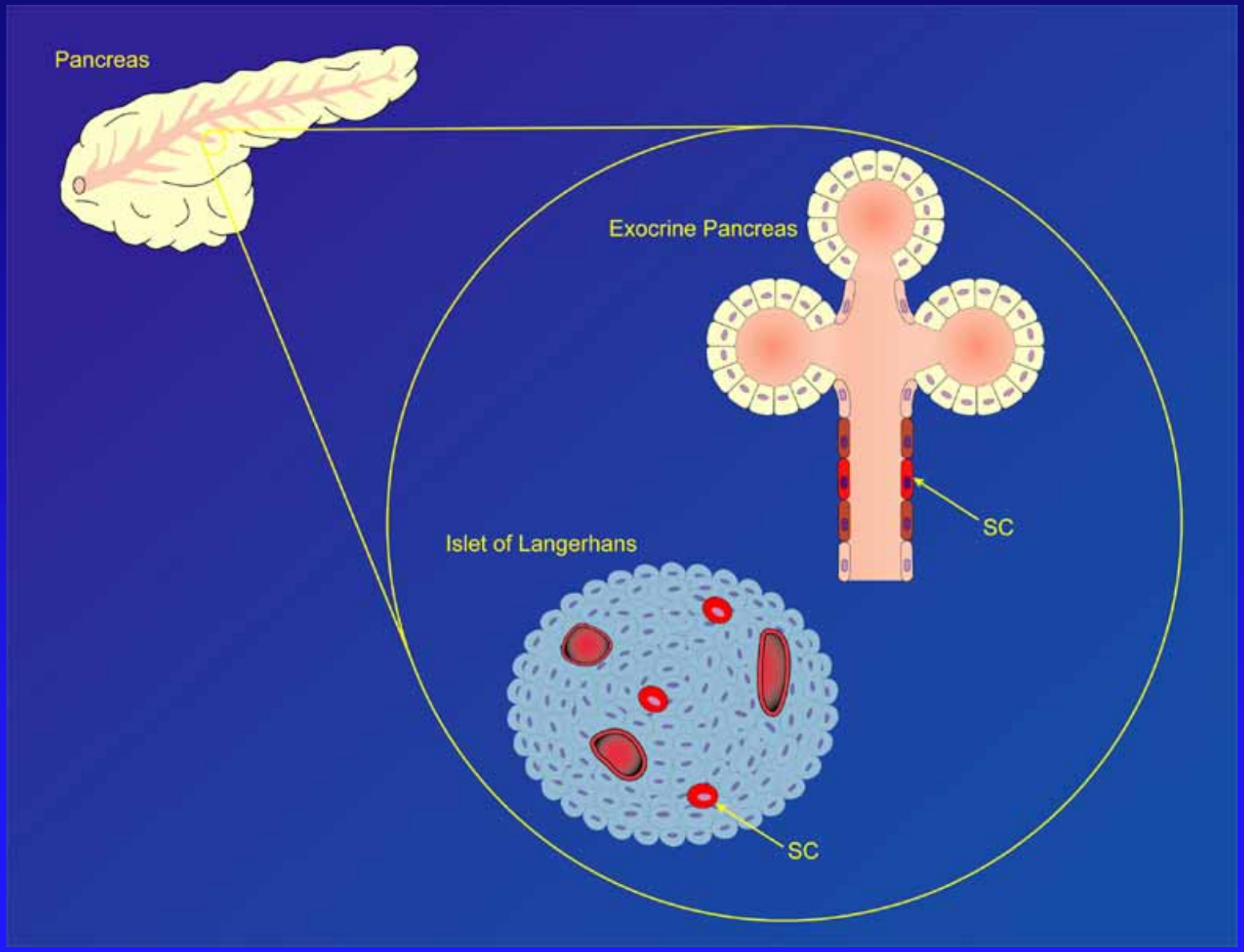
Stem Cells: a hierarchy of potential

- Totipotent - fertilized oocyte
- Pluripotent - capable of forming many cell types, contributing to all 3 germ layers
- Multipotent - gives rise to a limited number of cell types
- Unipotent - gives rise to a single cell type

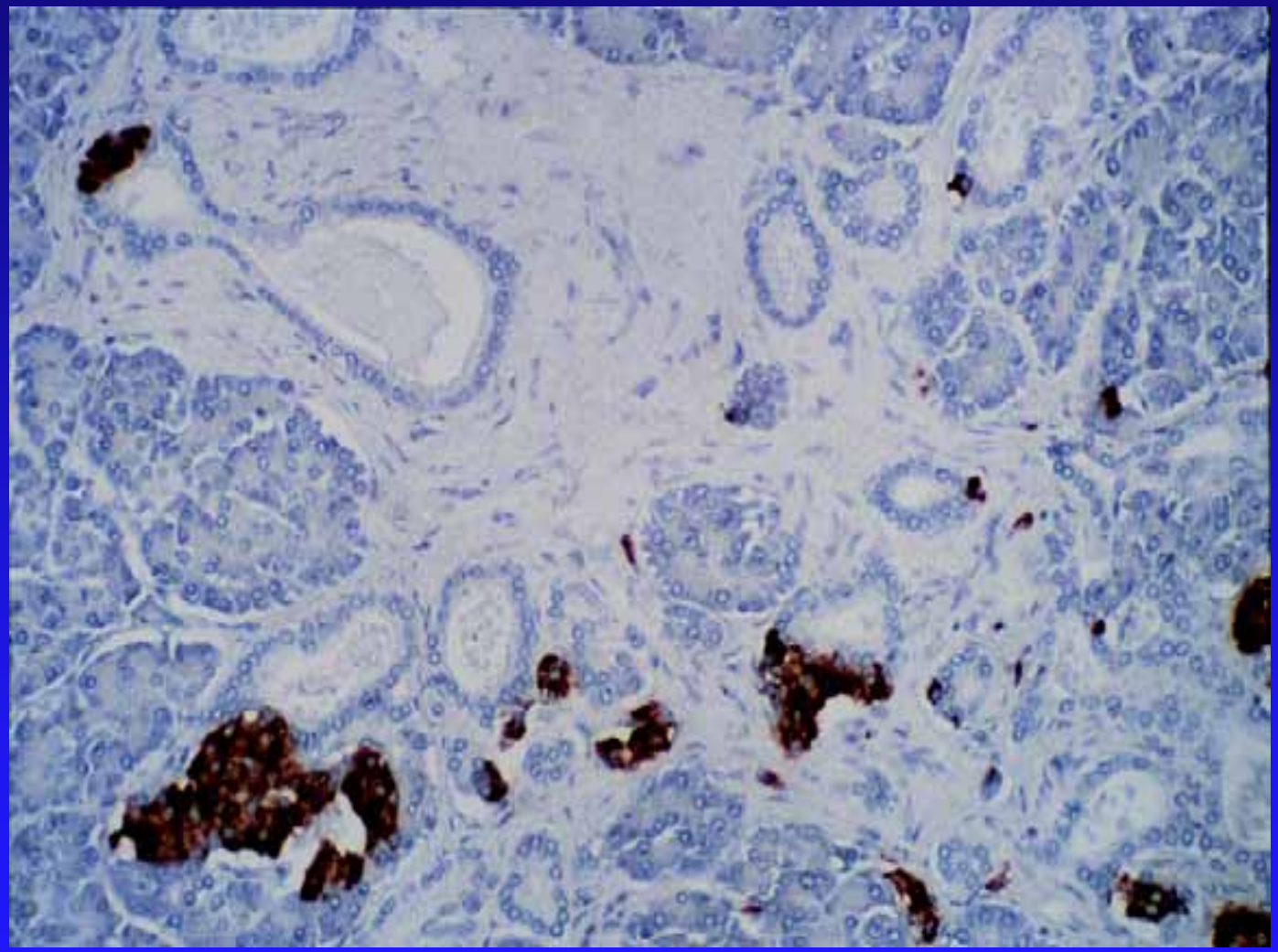
Adult tissue-specific stem cells: intestine






Pancreas
Exocrine Pancreas
SC
Islet of Langerhans
SC

Neogenesis more common than enlarged islets in obese human pancreas

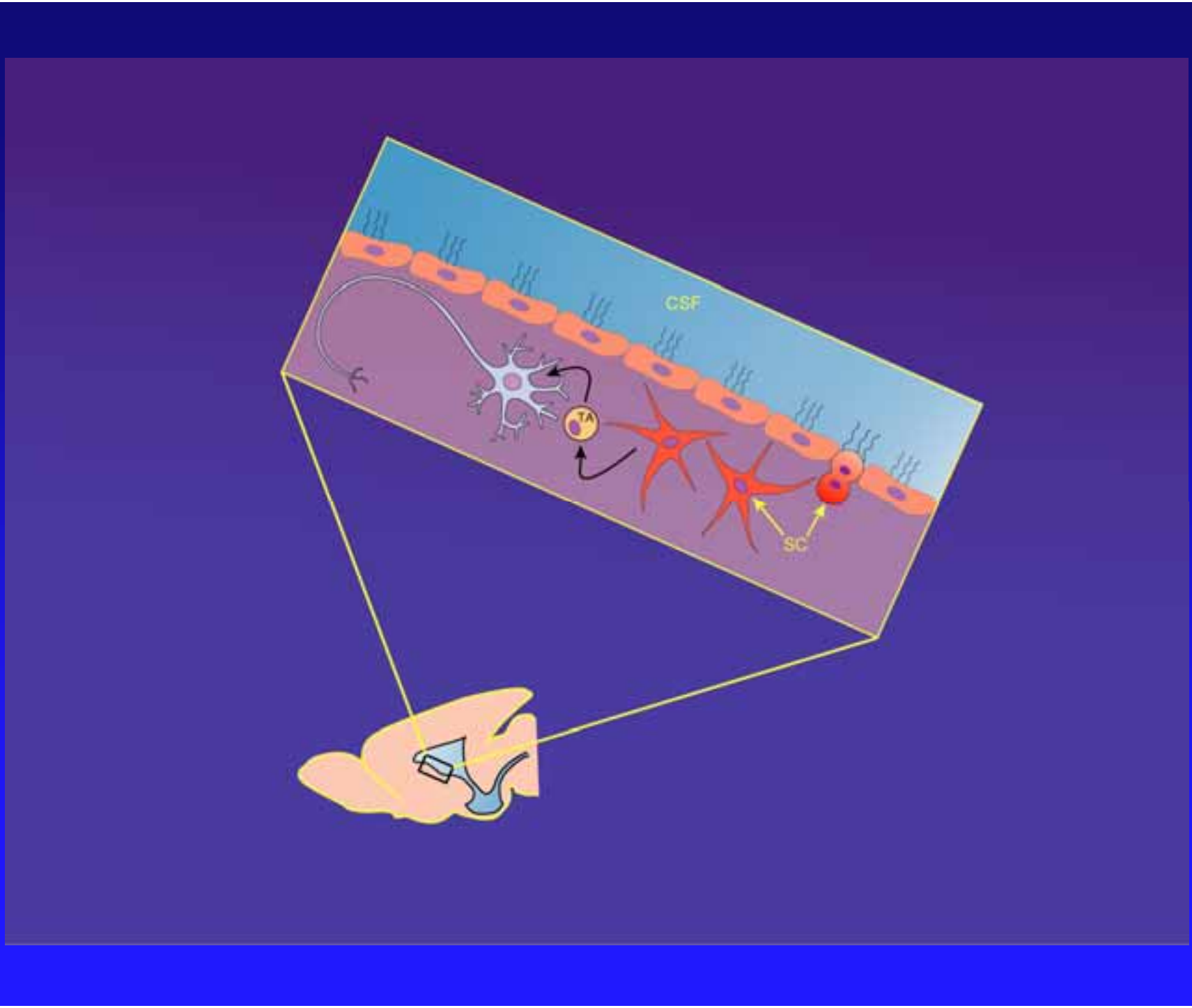


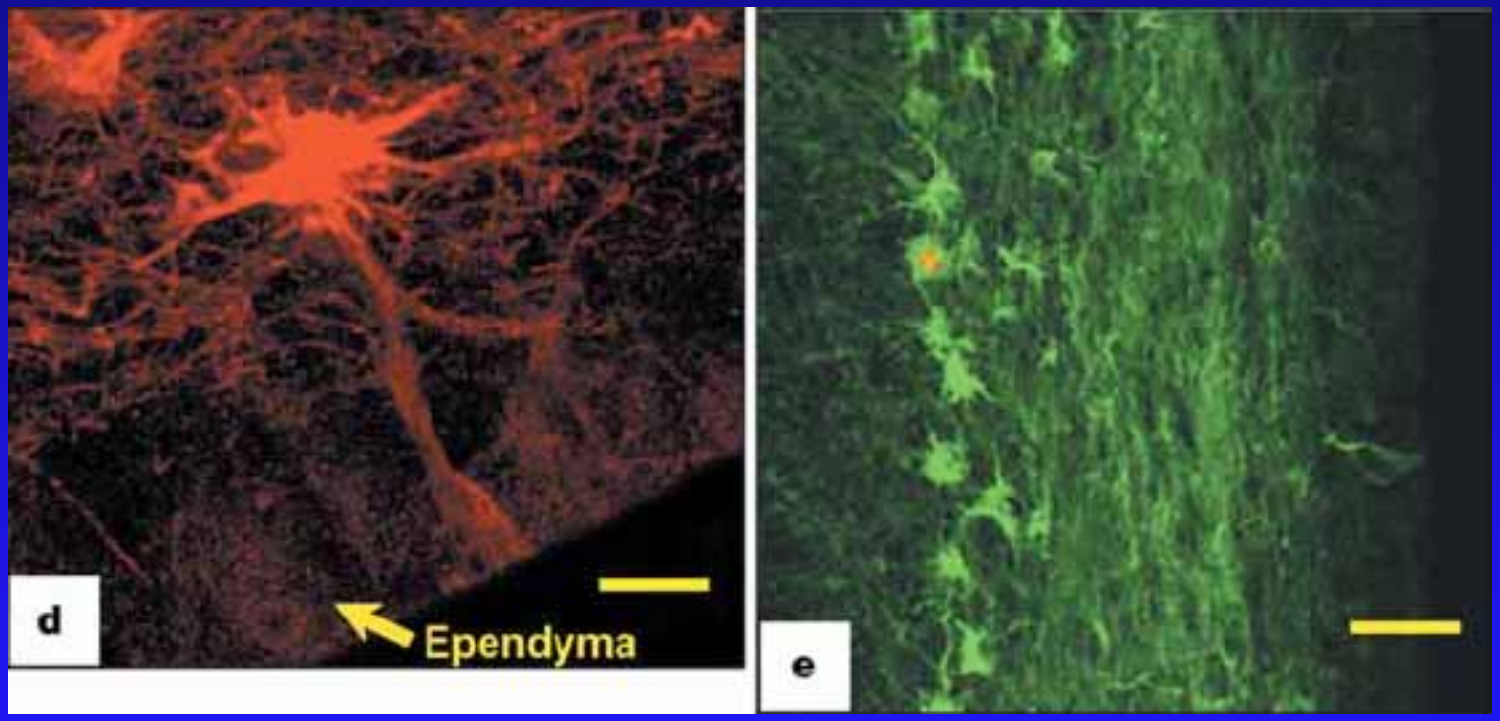
Mayo series, 48 yr male, obese, insulin stained

Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration

Nader Sanai[1,2], Anthony D. Tramontin[1,2], Alfredo Quiñones-Hinojosa[1], Nicholas M. Barbaro[1], Nalin Gupta[1], Sandeep Kunwar[1], Michael T. Lawton[1], Michael W. McDermott[1], Andrew T. Parsa[1], José Manuel-García Verdugo[3], Mitchel S. Berger[1] & Arturo Alvarez-Buylla[1,2]

NATURE | VOL 427 | 19 FEBRUARY 2004 | www.nature.com/nature

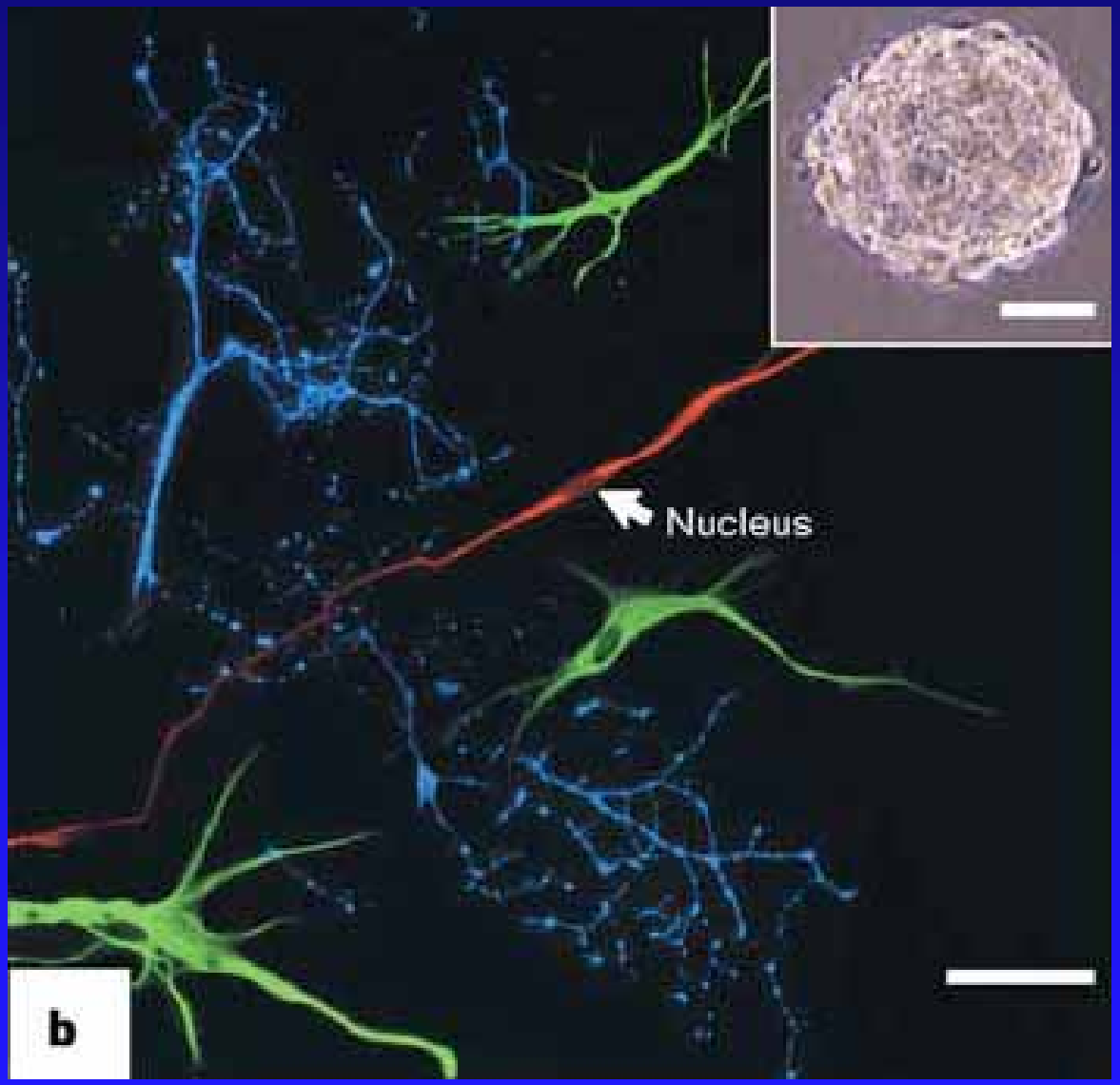

CSF
TA
SC



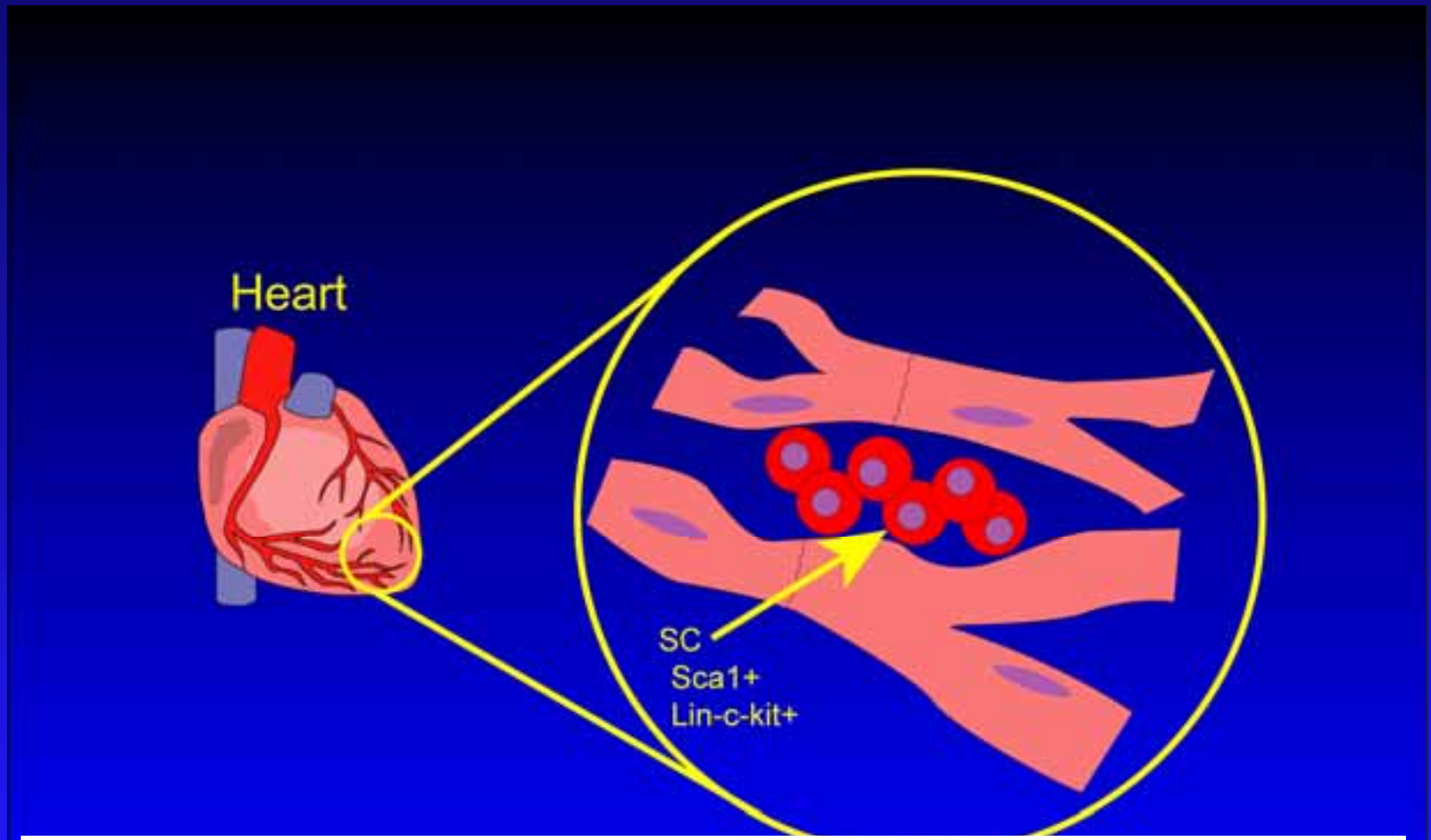
GFAP

Ki-67

Trilineage potential in vitro



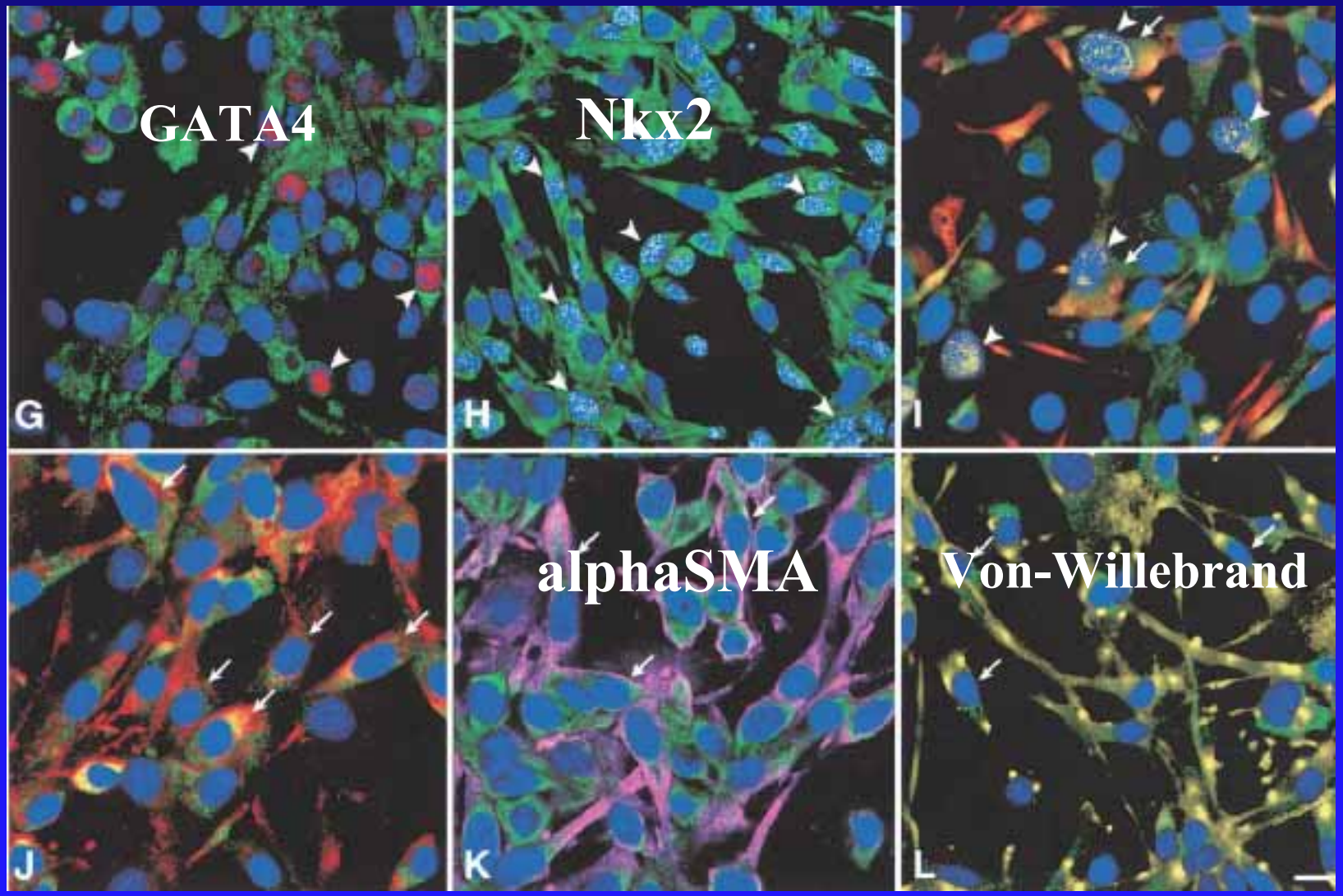
Are clonogenic



Cell, Vol. 114, 763–776, September 19, 2003, Copyright ©2003 by Cell Press

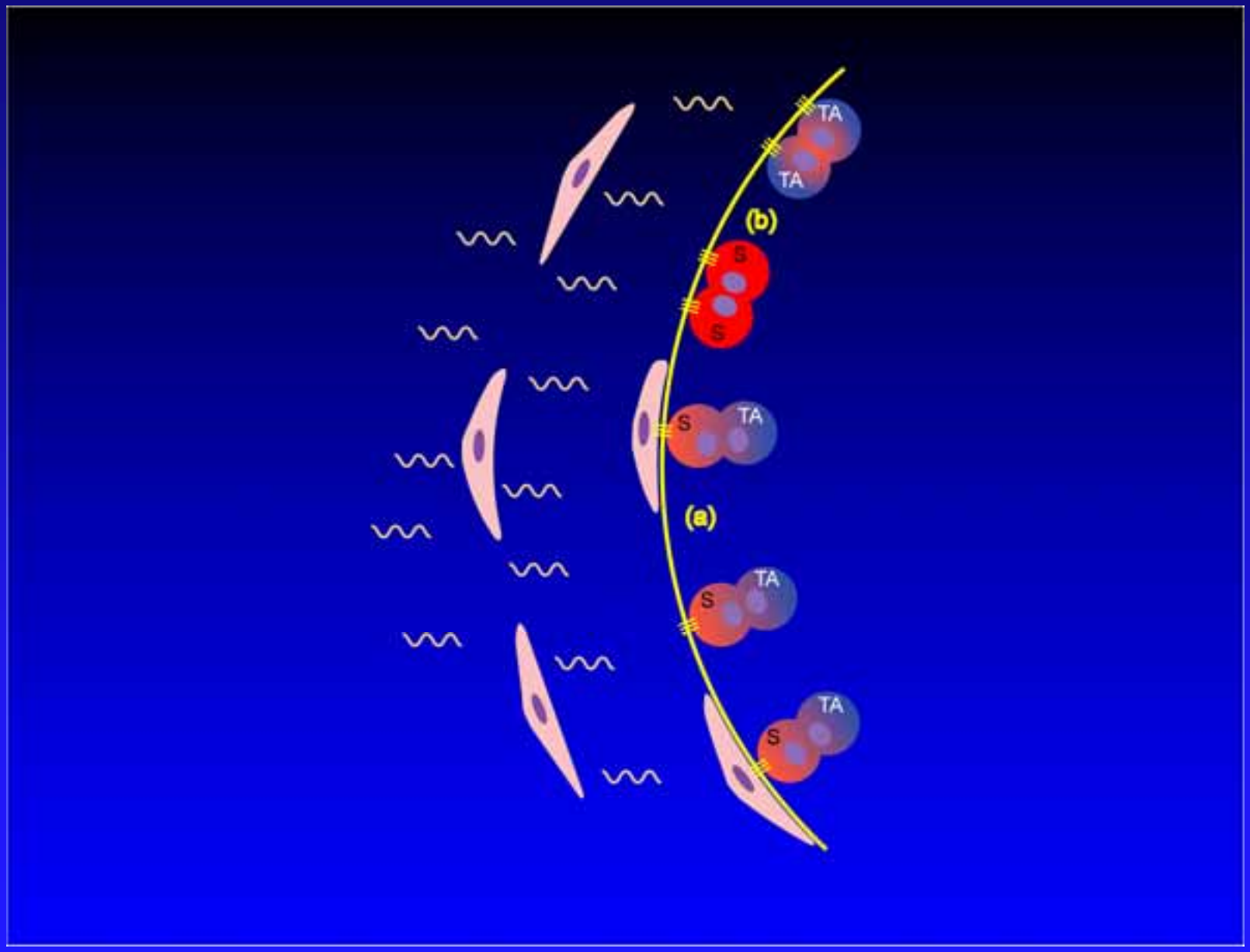
Adult Cardiac Stem Cells Are Multipotent and Support Myocardial Regeneration

Demonstrate clonal growth in vitro



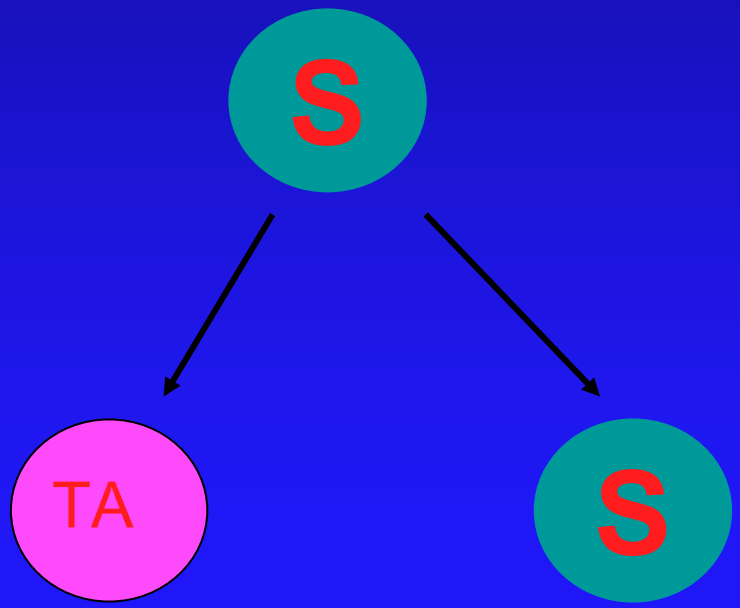
So are multipotential

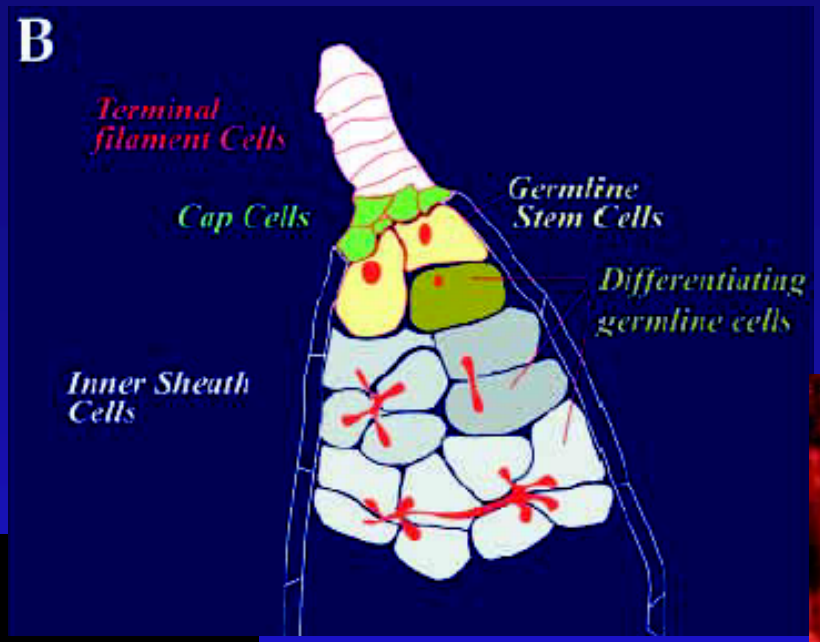
The stem cell niche (Fr. recess)



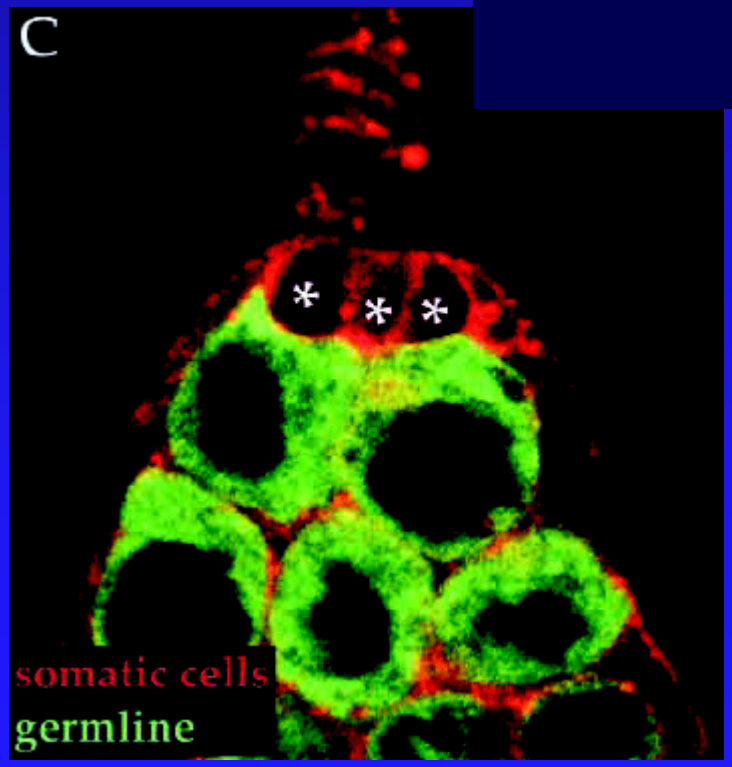
Stem cells are self-maintaining

Asymmetrical division

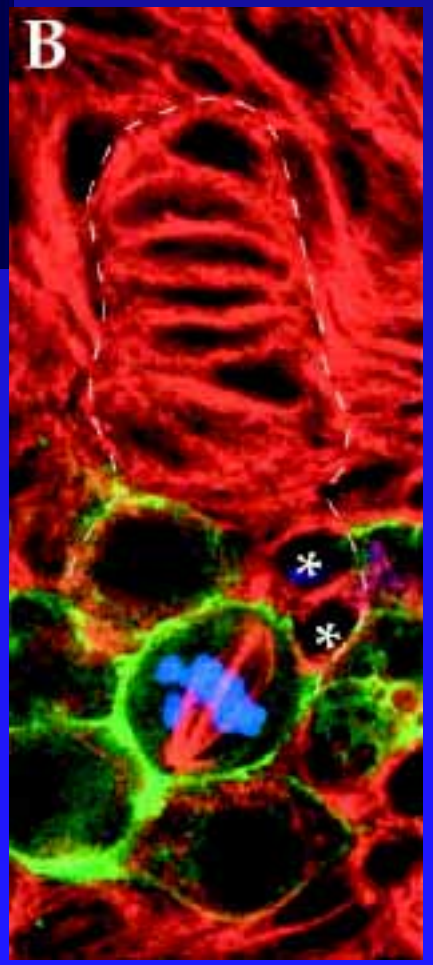




Cap cells secrete BMPs (dpp)

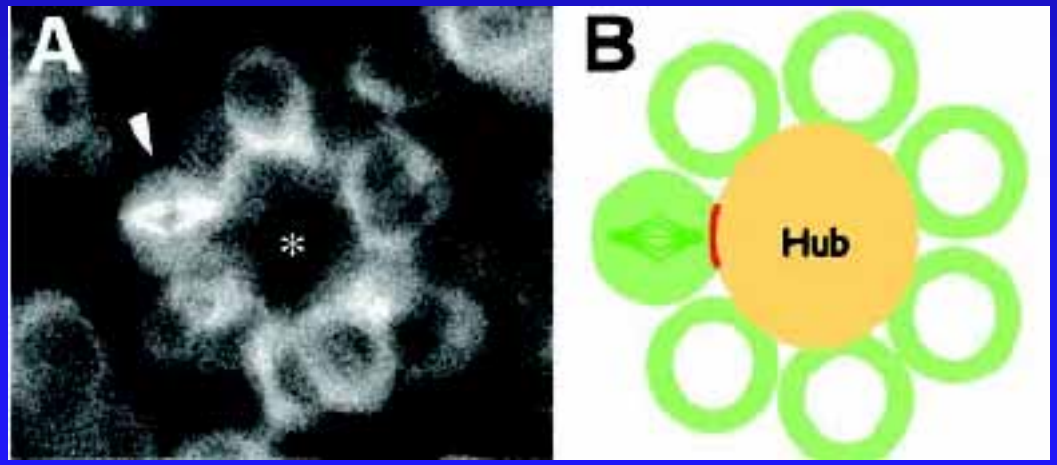


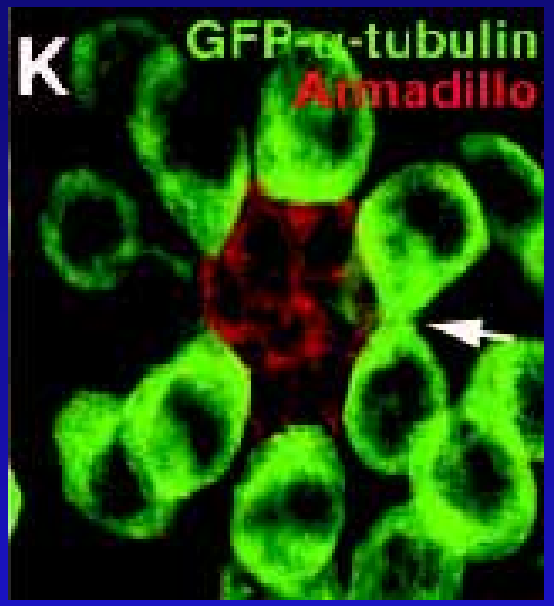
The Drosophila ovariole



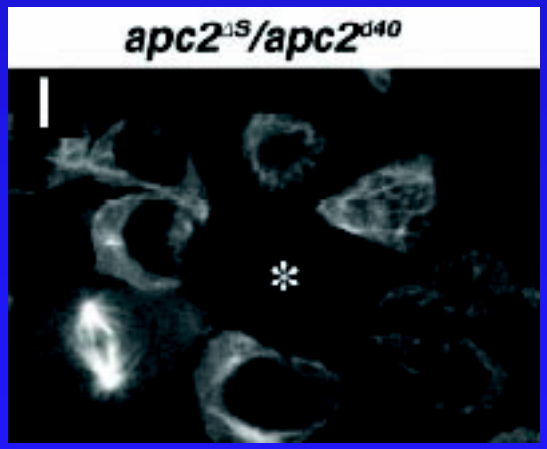
Orientation of Asymmetric Stem Cell Division by the APC Tumor Suppressor and Centrosome

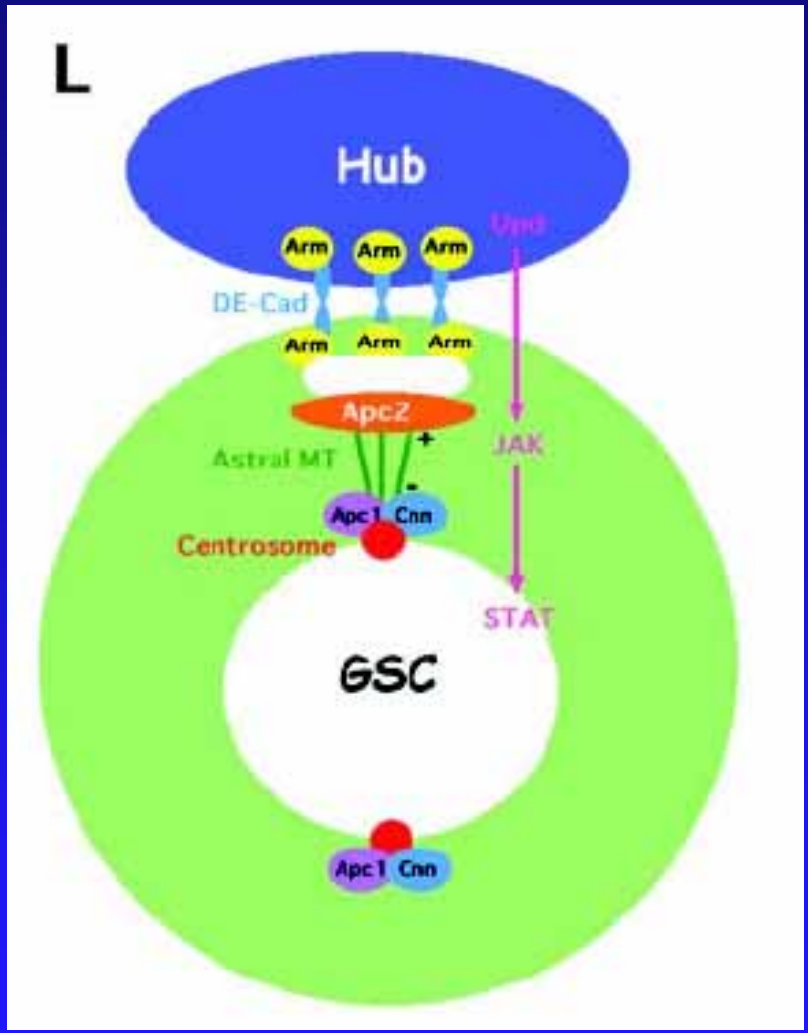
Yukiko M. Yamashita,[1] D. Leanne Jones,[1] Margaret T. Fuller[1,2*]

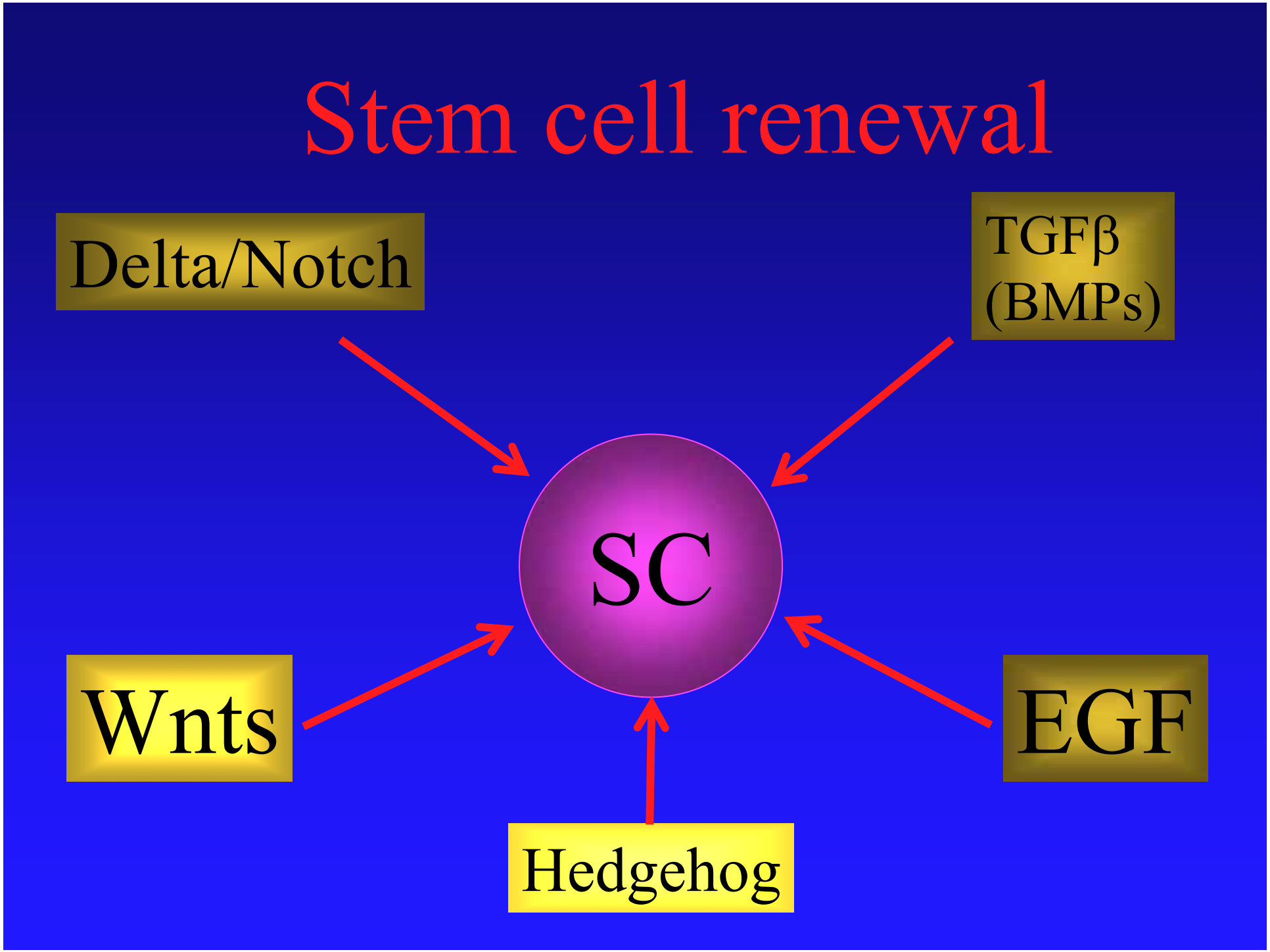


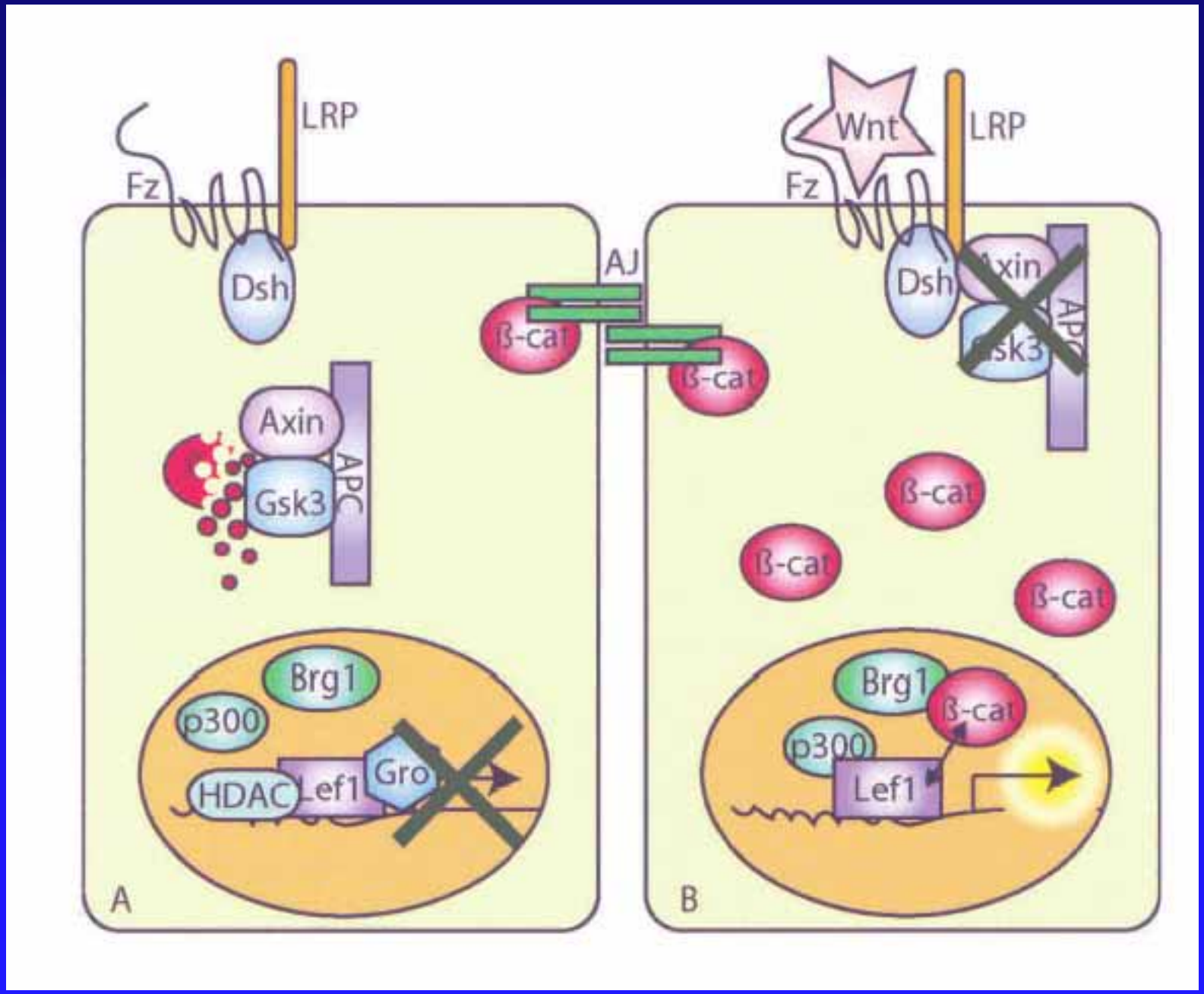


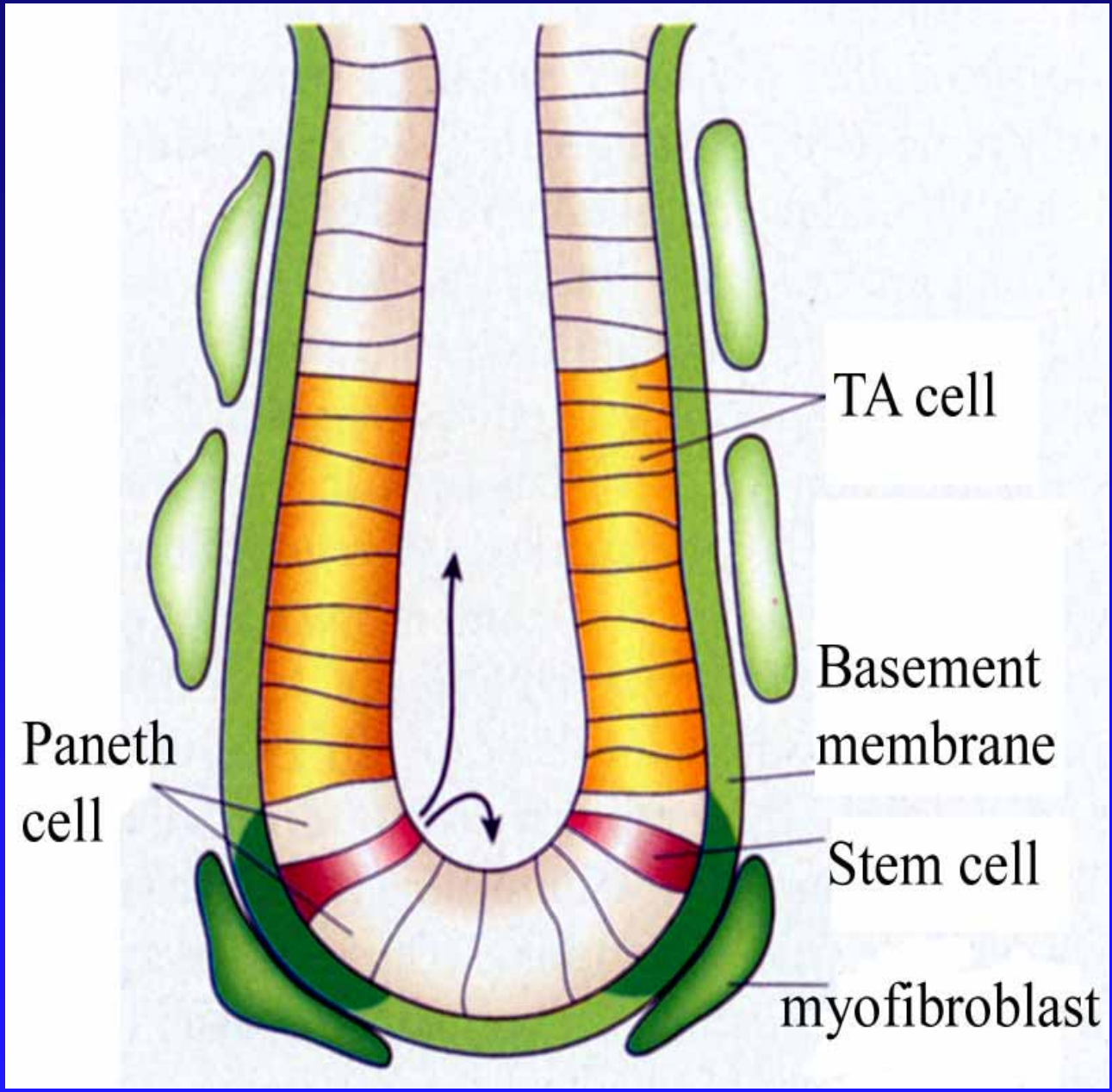
Centrosomin mutant



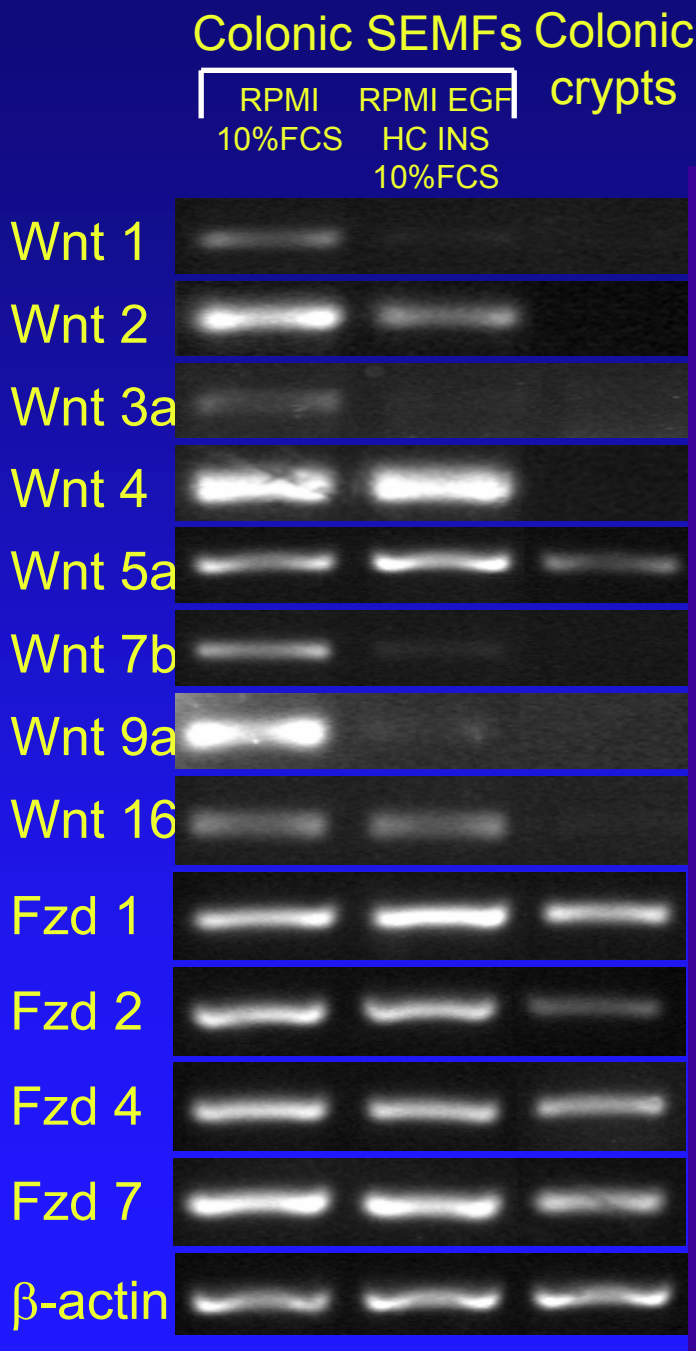



Stem cell renewal
Delta/Notch
TGFβ
(BMPs)
SC
Wnts
EGF
Hedgehog

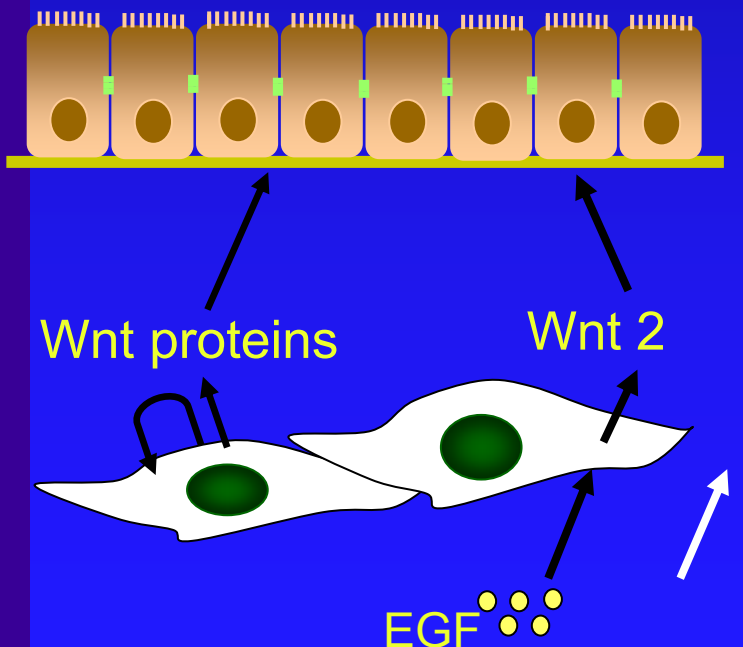

LRP
Fz
Dsh
AJ
ß-cat
Axin
Gsk3
APC
Brg1
p300
HDAC
Lef1
Gro
A
Wnt
LRP
Fz
Dsh
Axin
Gsk3
APC
ß-cat
ß-cat
ß-cat
ß-cat
Brg1
ß-cat
p300
Lef1
B


TA cell
Basement membrane
Paneth cell
Stem cell
myofibroblast

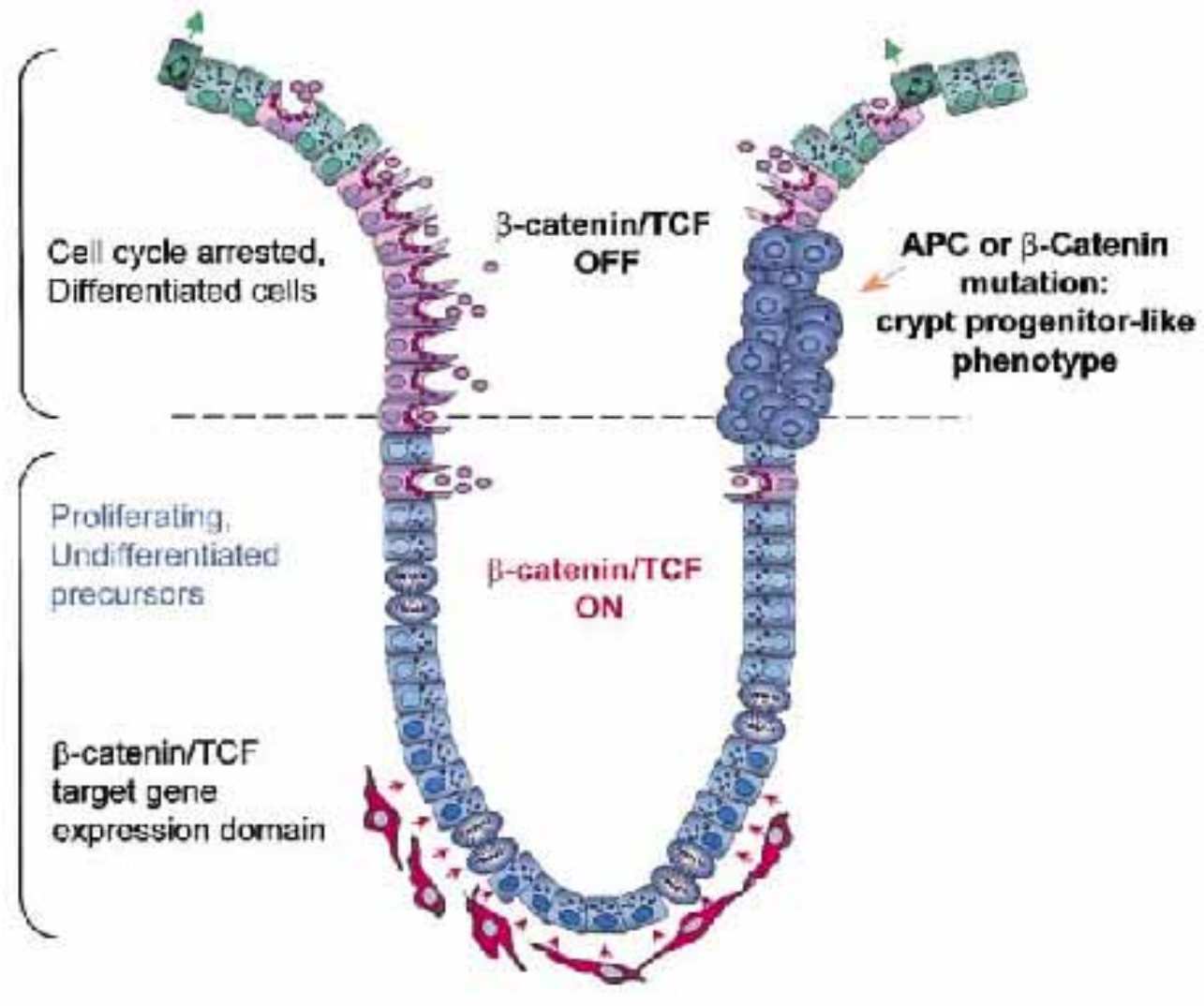
Wnt Expression in Colonic SEMFs



	Colonic SEMFs	Colonic crypts
Wnt	(+)	(-)
Fzd	(+)	(+)



Wnt signalling determines the stem cell phenotype



van de Wetering, Cell, Vol. 111, 241–250, October 18, 2002,

β-catenin is in the nuclei of crypt stem cells

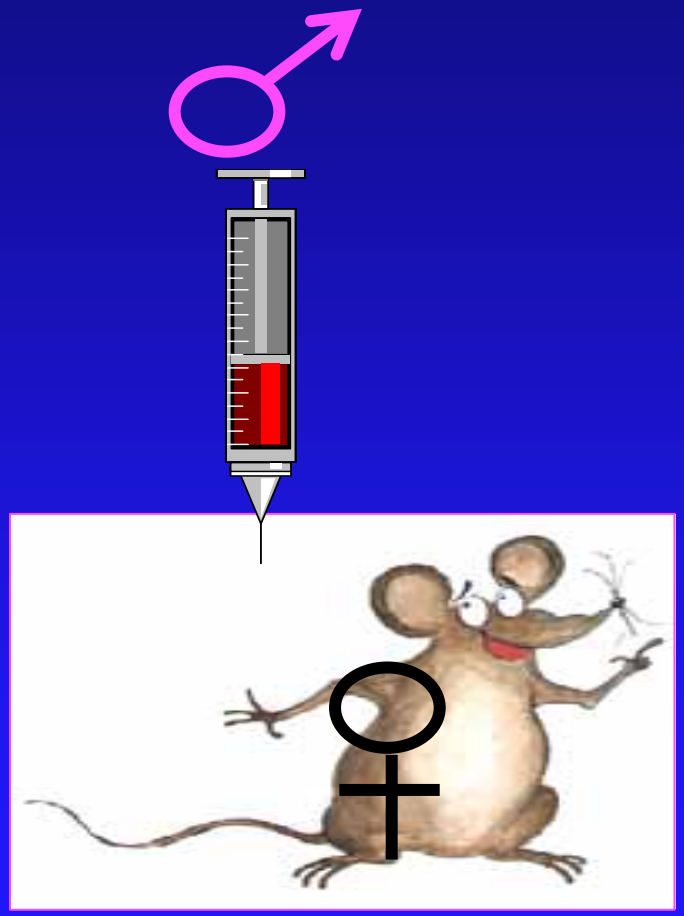
RAPID COMMUNICATION

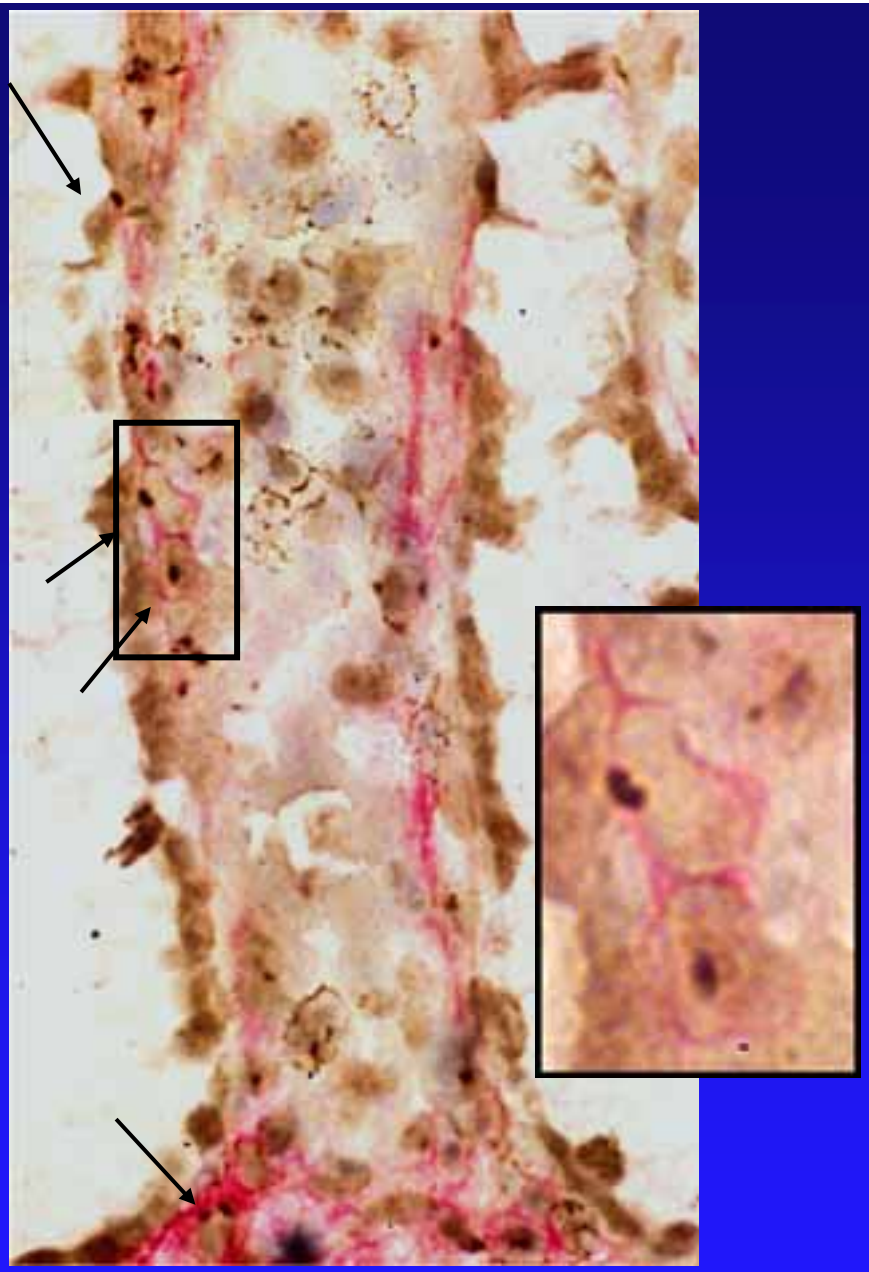
Bone marrow derivation of pericryptal myofibroblasts in the mouse and human small intestine and colon

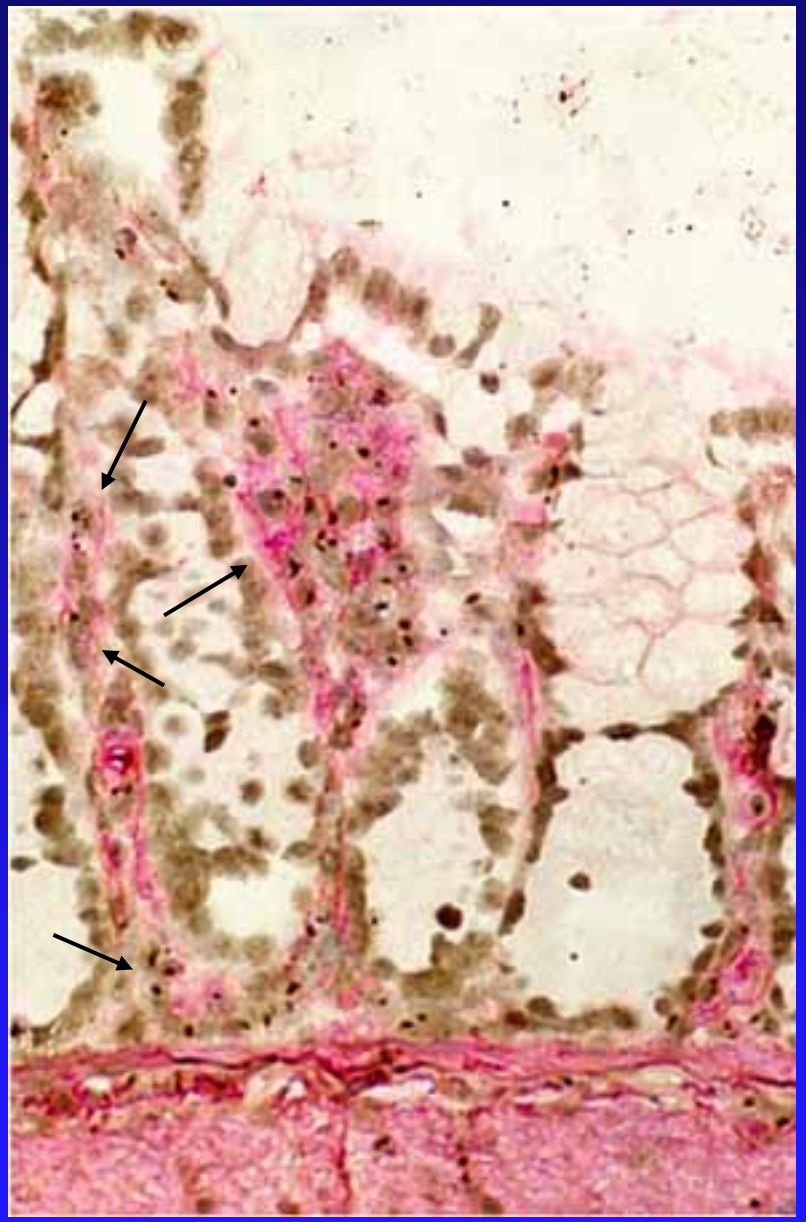
M Brittan, T Hunt, R Jeffery, R Poulsom, S J Forbes, K Hodivala-Dilke, J Goldman, M R Alison, N A Wright

Gut 2002;50:752–757

Bone marrow







Y chromosome, αSMA positive cells in lamina propria of female mouse colon 6wks after BMTx (arrows)

SELECTED PAPERS IN THIS ISSUE
Multiple Organ Engraftment by Bone-Marrow-Derived Myofibroblasts and Fibroblasts in Bone-Marrow-Transplanted Mice
Natalie C. Direkze, Stuart J. Forbes, Mairi Brittan, Toby Hunt, Rosemary Jeffery, Sean L. Preston, Richard Poulsom, Kairbaan Hodivala-Dilke, Malcolm R. Alison, Nicholas A. Wright

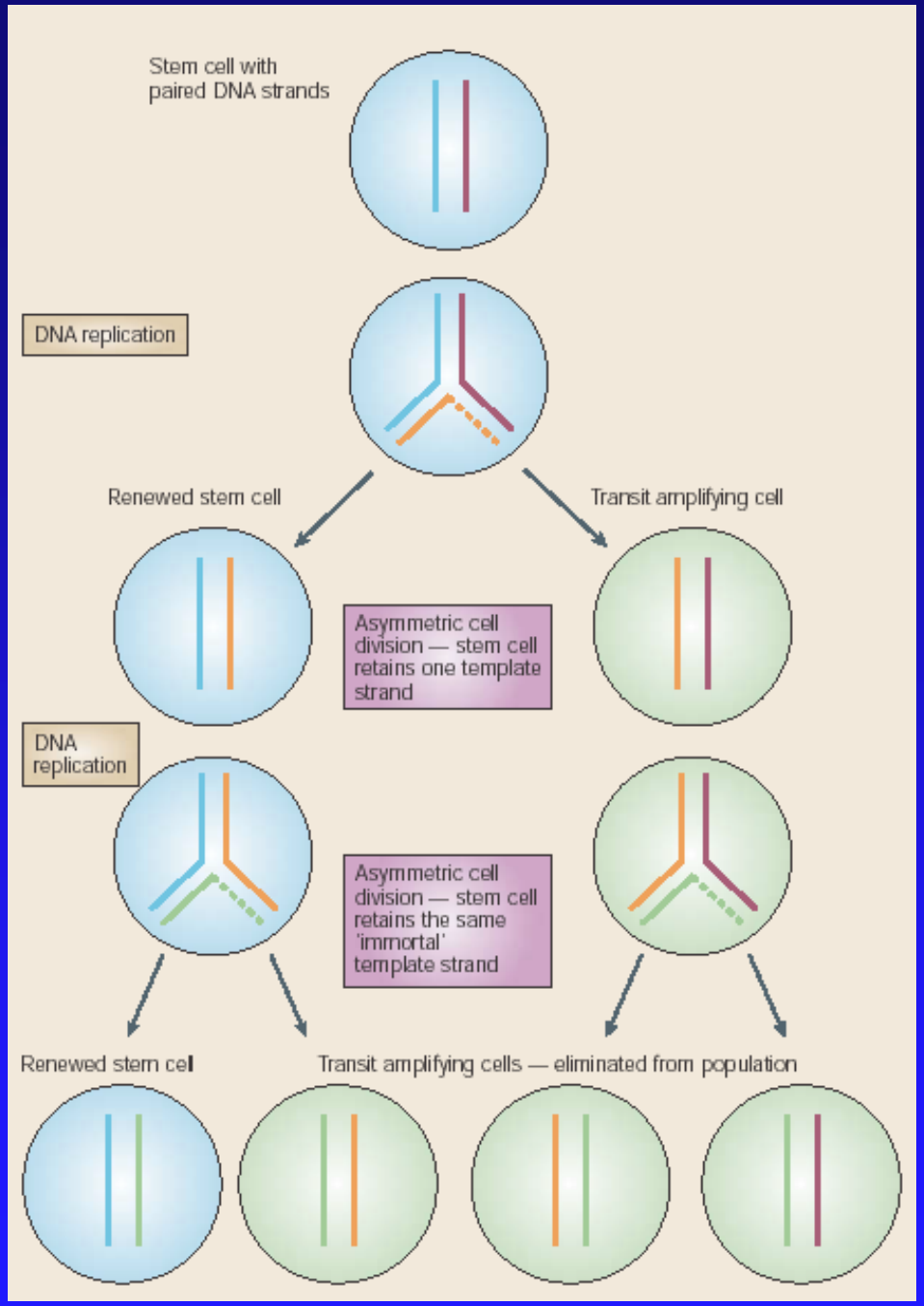
Lung
Kidney
Stomach
Skin
Adrenal capsule


How can you find stem cells?

Somatic stem cells and the kinetics of mutagenesis and carcinogenesis

John Cairns*

PNAS | August 6, 2002 | vol. 99 | no. 16 | 10567–10570

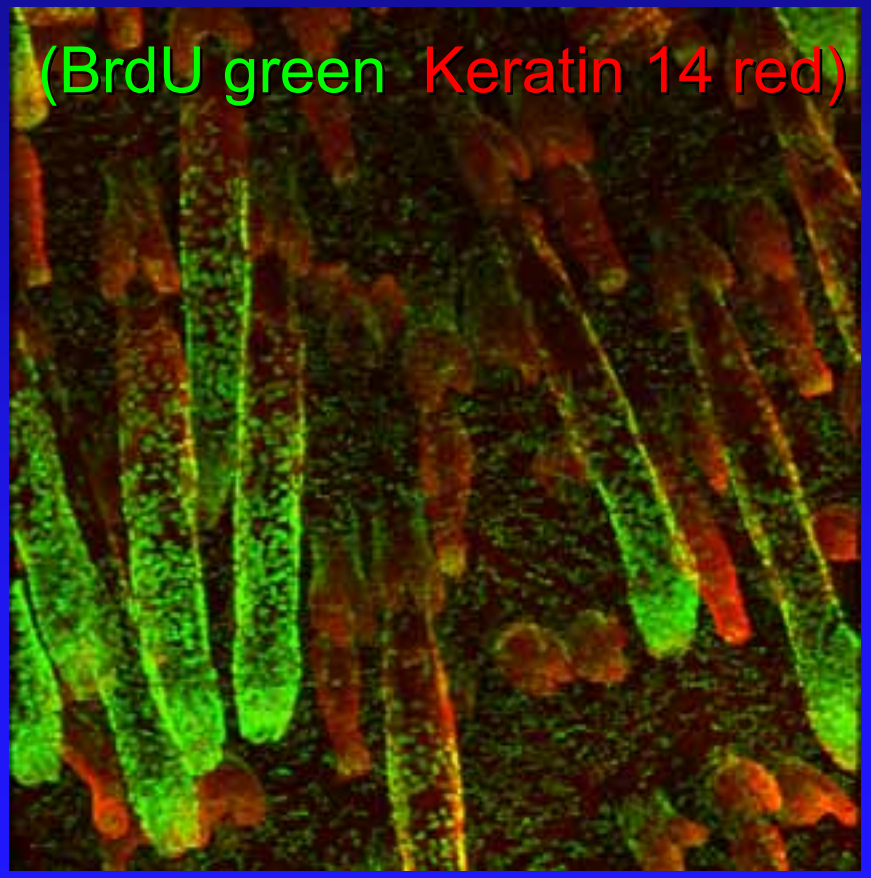


The immortal strand hypothesis

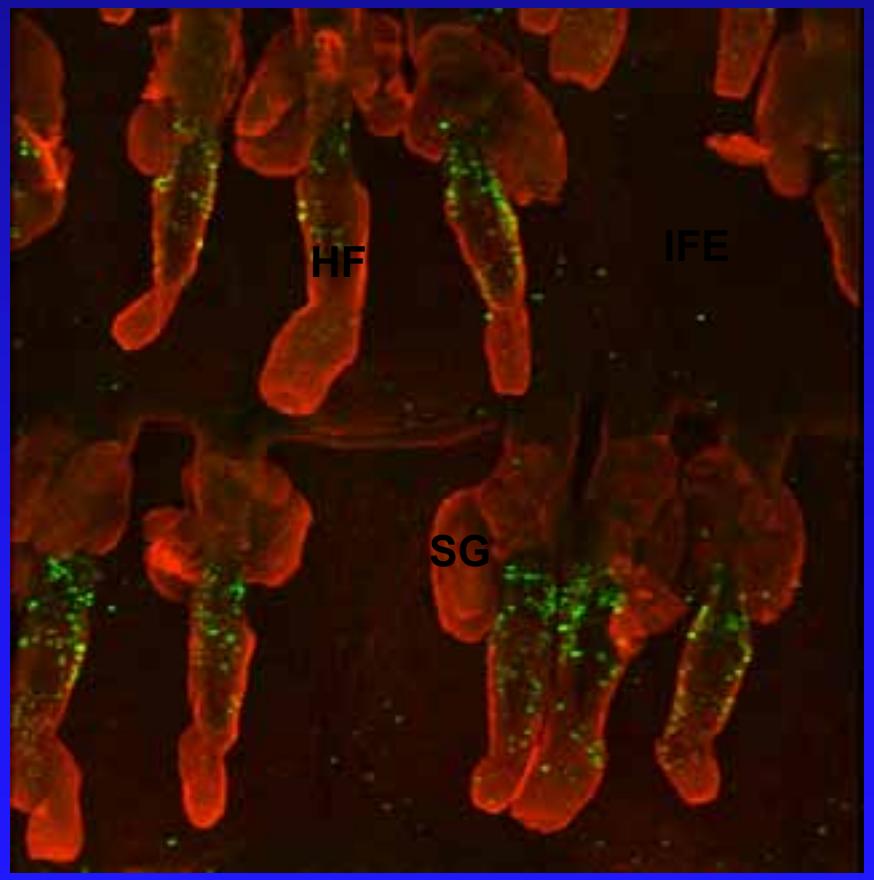
Stem cells can be identified as 'label-retaining' cells

Kristen Braun, *et al.* Development 2003; 130: 5241-55

Many injections of BrdU in neonatal mice - examine tail skin



2 days post-BrdU



140 days post-BrdU

Side population (SP) cells

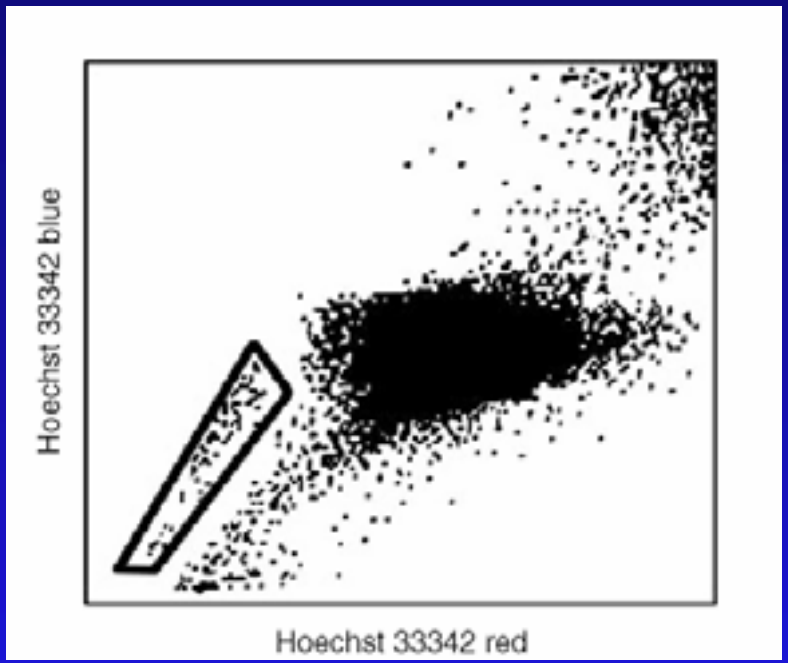


Table 1. ABC transporter families

Family	No of members	Symbols	ABC proteins found up-regulated in liver disease by Ros *et al* [8]
ABC1 (subfamily A)	12	ABCA1–ABCA12	
MDR/TAP (subfamily B)	11	ABCB1–ABCB11	ABCB1 (also known as MDR1, gp170, P-glycoprotein) 171 050*
CFTR/MRP (subfamily C)	12	ABCC1–ABCC12	ABCC1 (MRP1) 158 343* ABCC3 (MRP3) 604 323*
ALD (subfamily D)	4	ABCD1–ABCD4	
OABP (subfamily E)	1	ABCE1	
GCN20 (subfamily F)	3	ABCF1–ABCF3	
White (subfamily G)	5	ABCG1–ABCG5	

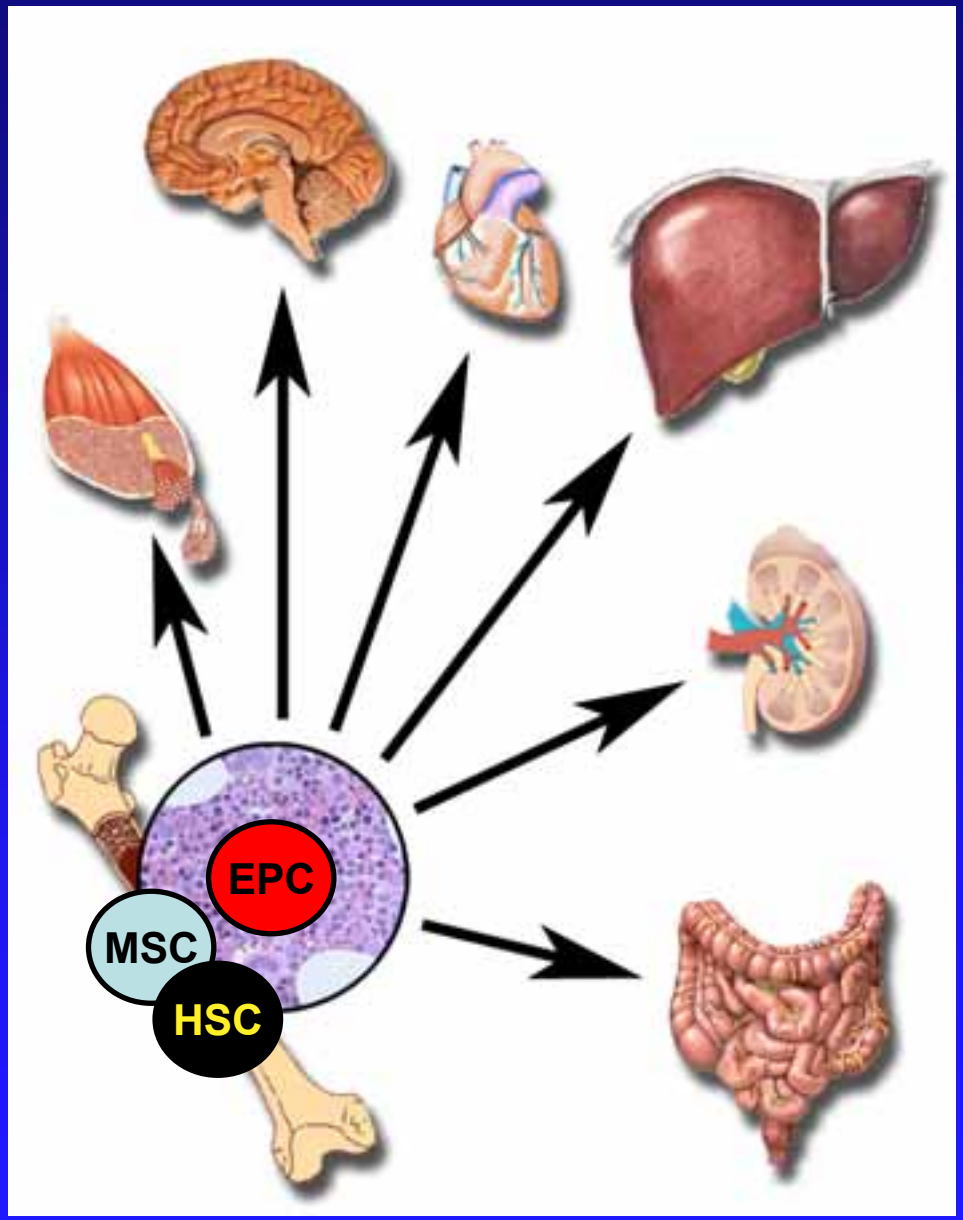
Journal of Pathology
J Pathol 2003; **200**: 547–550.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/path.1411

Commentary

Tissue-based stem cells: ABC transporter proteins take centre stage

Malcolm R Alison*
Department of Histopathology, Imperial College London at the Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

Bone Marrow hosts multipotent stem cells



Haematopoietic Stem Cells

Mesenchymal Stem Cells

Endothelial Precursor Cells

and what else?

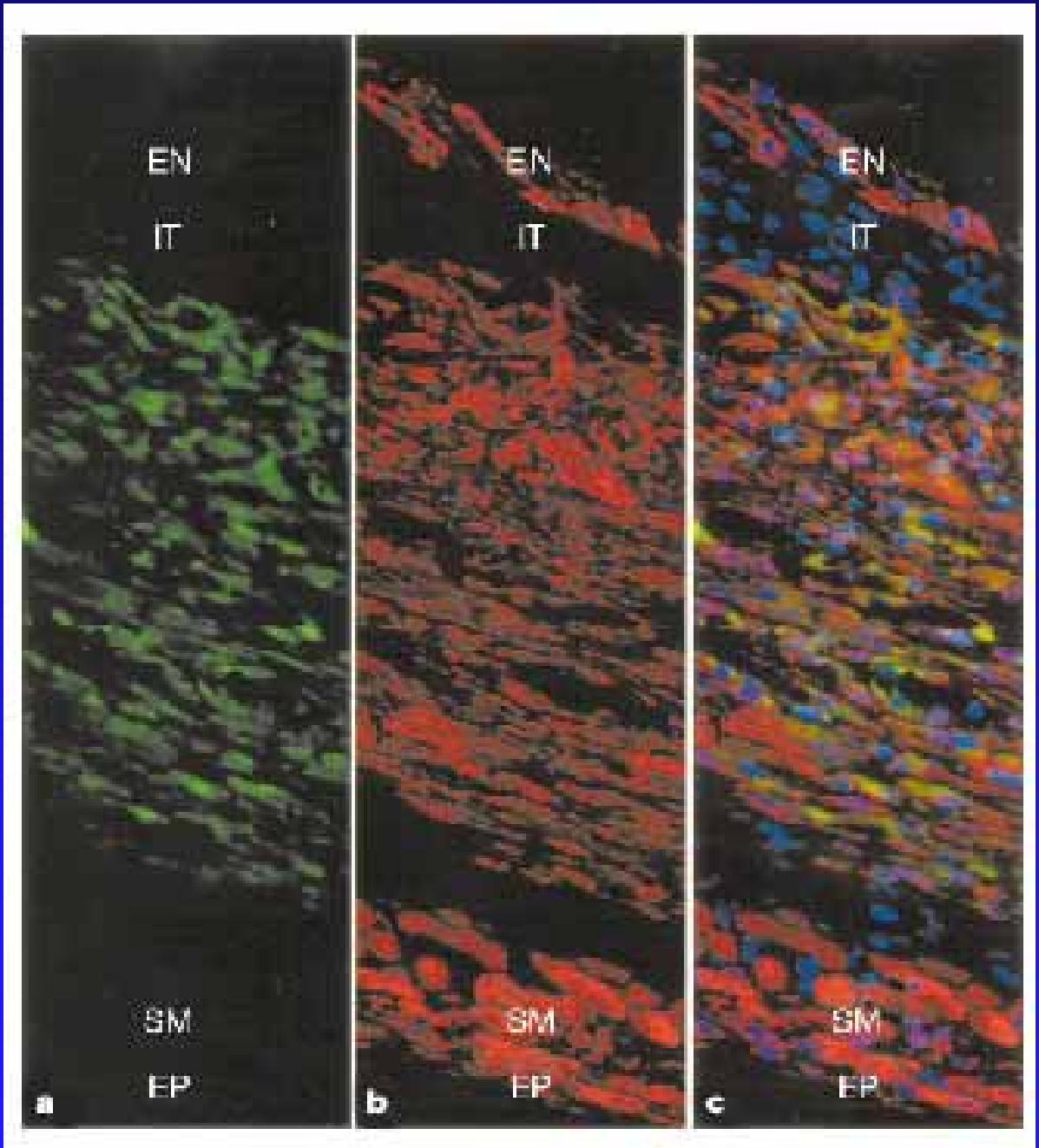
Stem Cell Plasticity - challenges traditional views of lineage commitment

- Against
- Cell fusion?
- For

Bone marrow cells regenerate infarcted myocardium

Donald Orlic†, Jan Kajstura*, Stefano Chimenti*, Igor Jakoniuk*, Stacie M. Anderson†, Baosheng Li*, James Pickel‡, Ronald McKay‡, Bernardo Nadal-Ginard*, David M. Bodine†, Annarosa Leri* & Piero Anversa*

- MI model
- BM lin-, c-kit +ve expressing eGFP
- Injected into heart
- New myocardium occupied 68% of infarcted ventricle
- LV developed pressure 41% higher in treated group



Orlic *et al*. 2001
Nature 410, 701

Lin- bone marrow from a GFP mouse co-expresses GFP and cardiac myosin in healing myocardium

Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts

Charles E. Murry[1], Mark H. Soonpaa[2], Hans Reinecke[1], Hidehiro Nakajima[2], Hisako O. Nakajima[2], Michael Rubart[2], Kishore B. S. Pasumarthi[2*], Jitka Ismail Virag[1], Stephen H. Bartelmez[3], Veronica Poppa[1], Gillian Bradford[2], Joshua D. Dowell[2], David A. Williams[2*] & Loren J. Field[2]

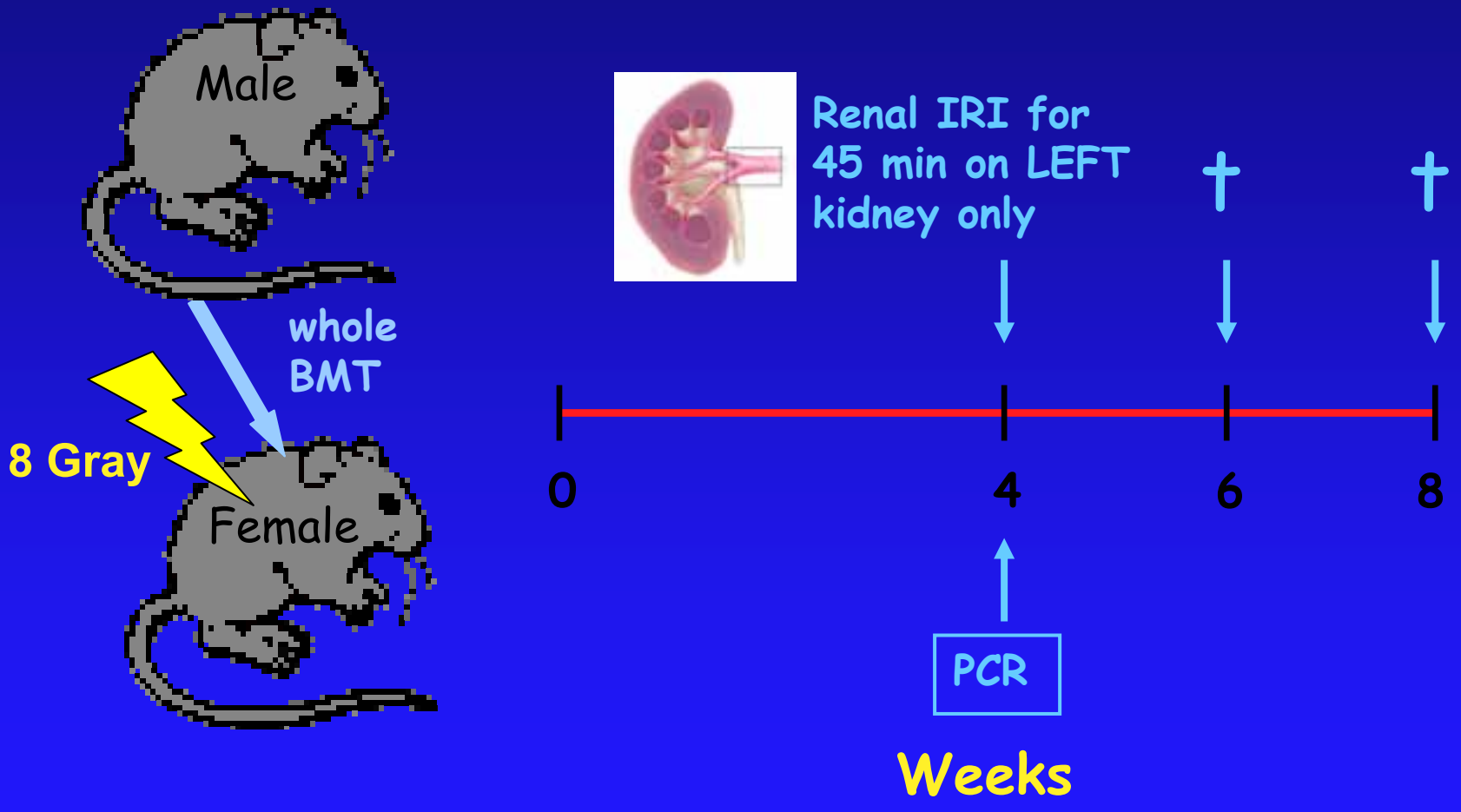
Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium

Leora B. Balsam[1], Amy J. Wagers[2,3], Julie L. Christensen[2,3], Theo Kofidis[1], Irving L. Weissman[2,3] & Robert C. Robbins[1]

Report from the American Association for Thoracic Surgery -Toronto April 25, 2004

- 1st randomized trial of adult stem cell (CD34+) injections in heart failure patients
- University of Pittsburgh, Baylor College, Benetti Foundation in Rosario, Argentina
- Significant improvements in ejection fraction
- Cellular therapy is an option for congestive heart failure patients

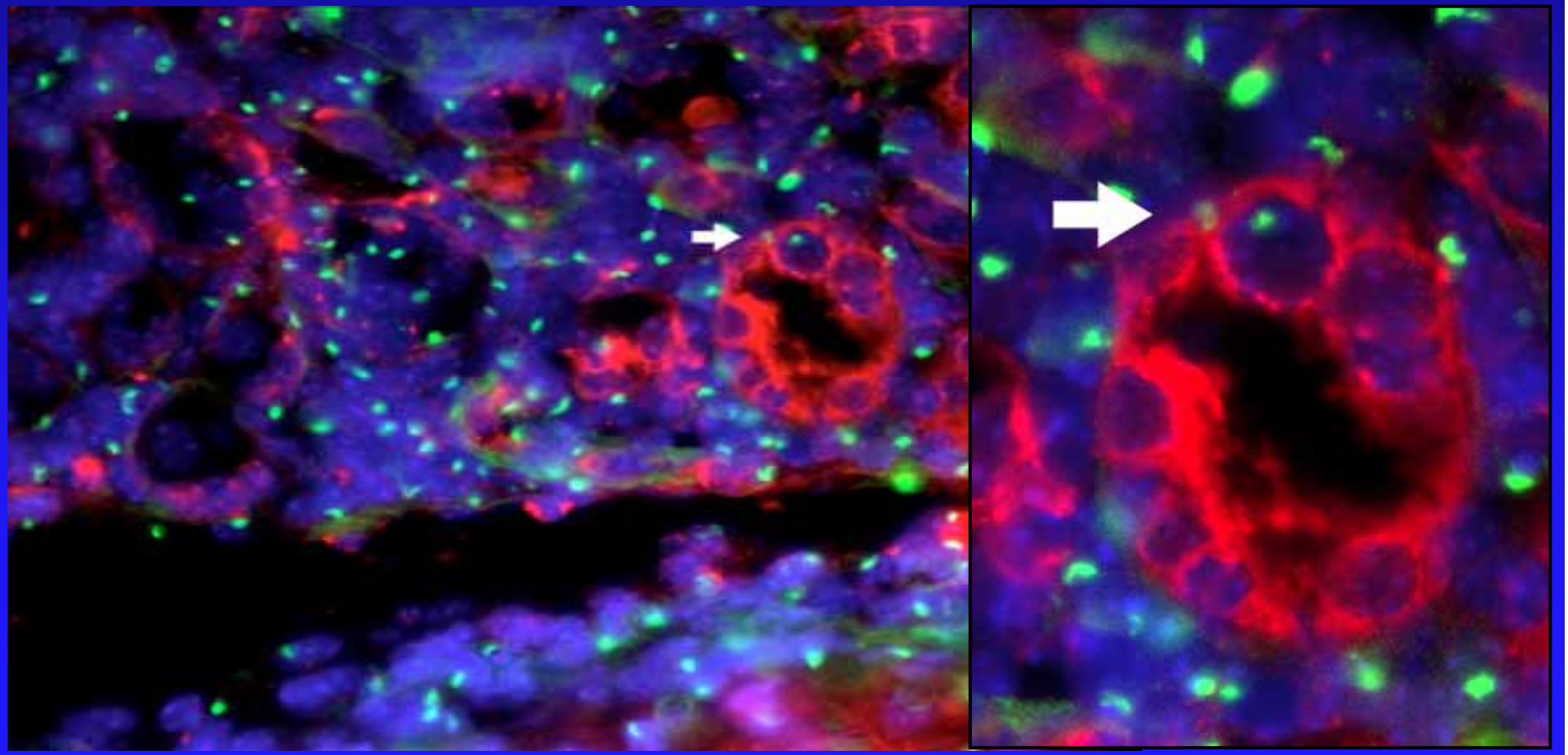
Renal Ischaemia-Reperfusion Injury (IRI) in C57BL/6 Mice: Experimental Design



Elina Prodromidi: NKRF

2 wks post-IRI: detection of donor-derived epithelium by Lectin histochemistry and Y-FISH

Y paint (dots) = donor-derived cells
***Lotus Tetragonolobus* Agglutinin,LTA** = proximal convoluted tubule epithelium
DAPI = nuclei



2 wks post-IRI: detection of donor-derived epithelium by Lectin histochemistry and Y-FISH

Y paint (dots) = donor-derived cells
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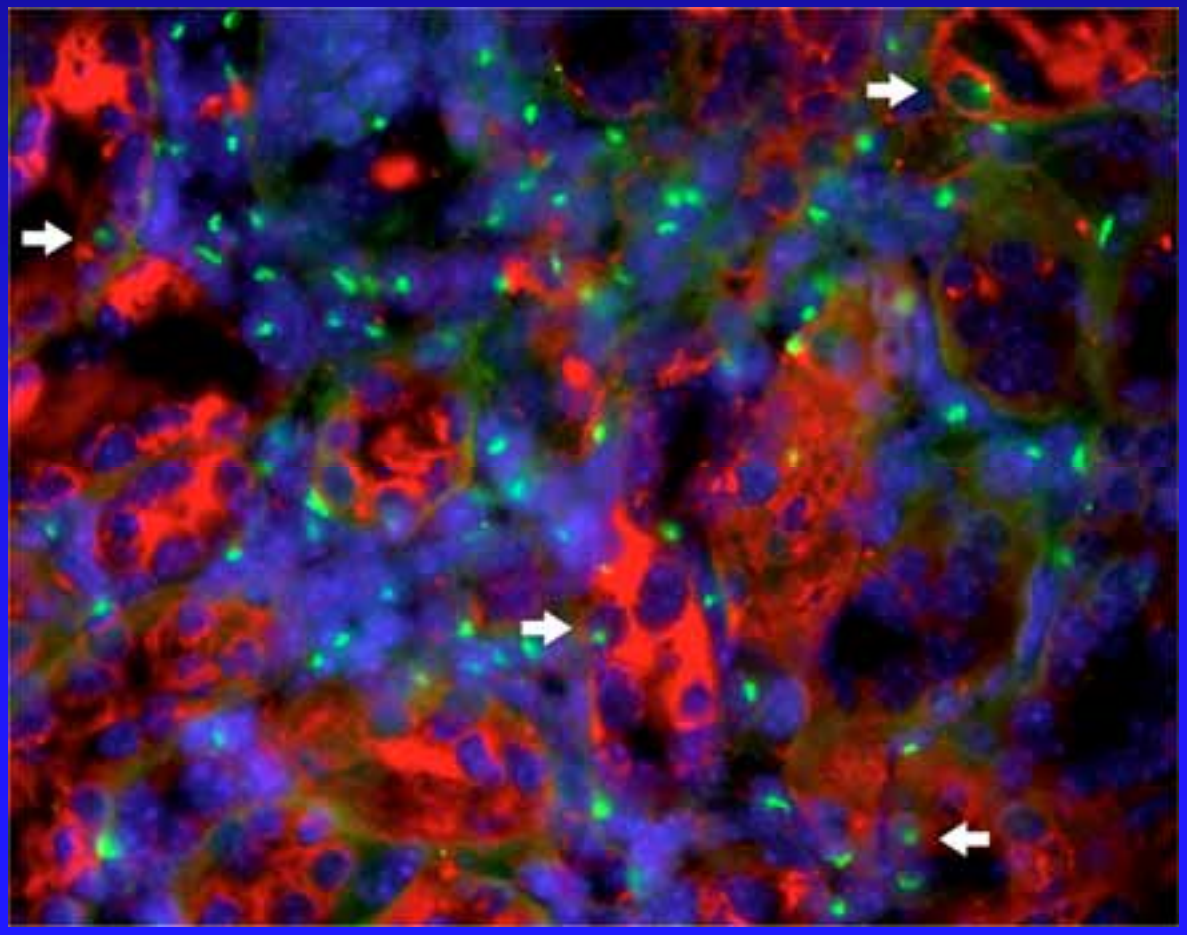
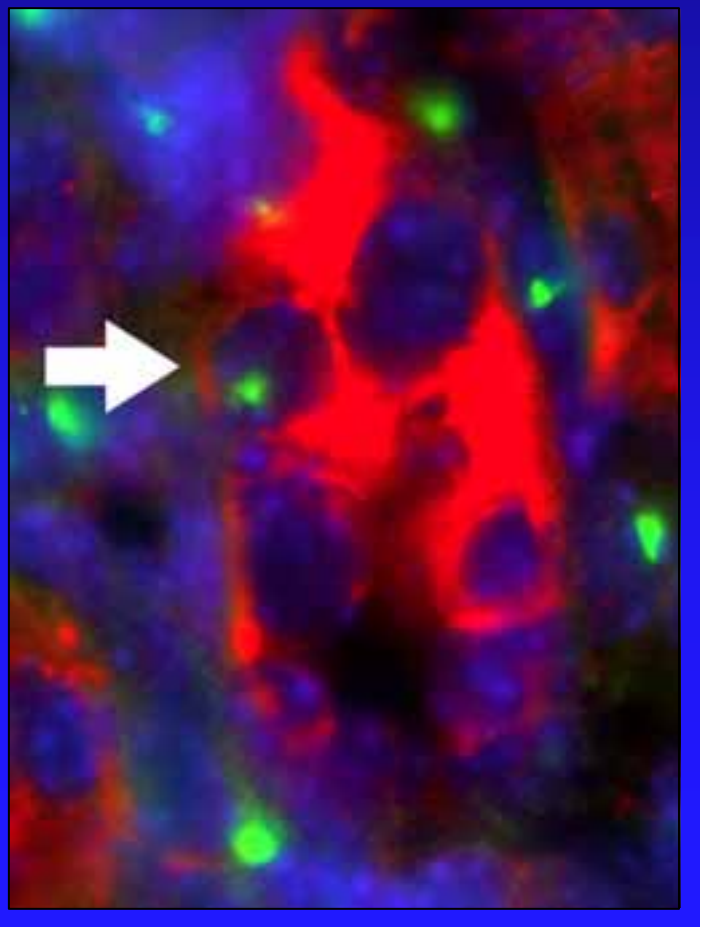
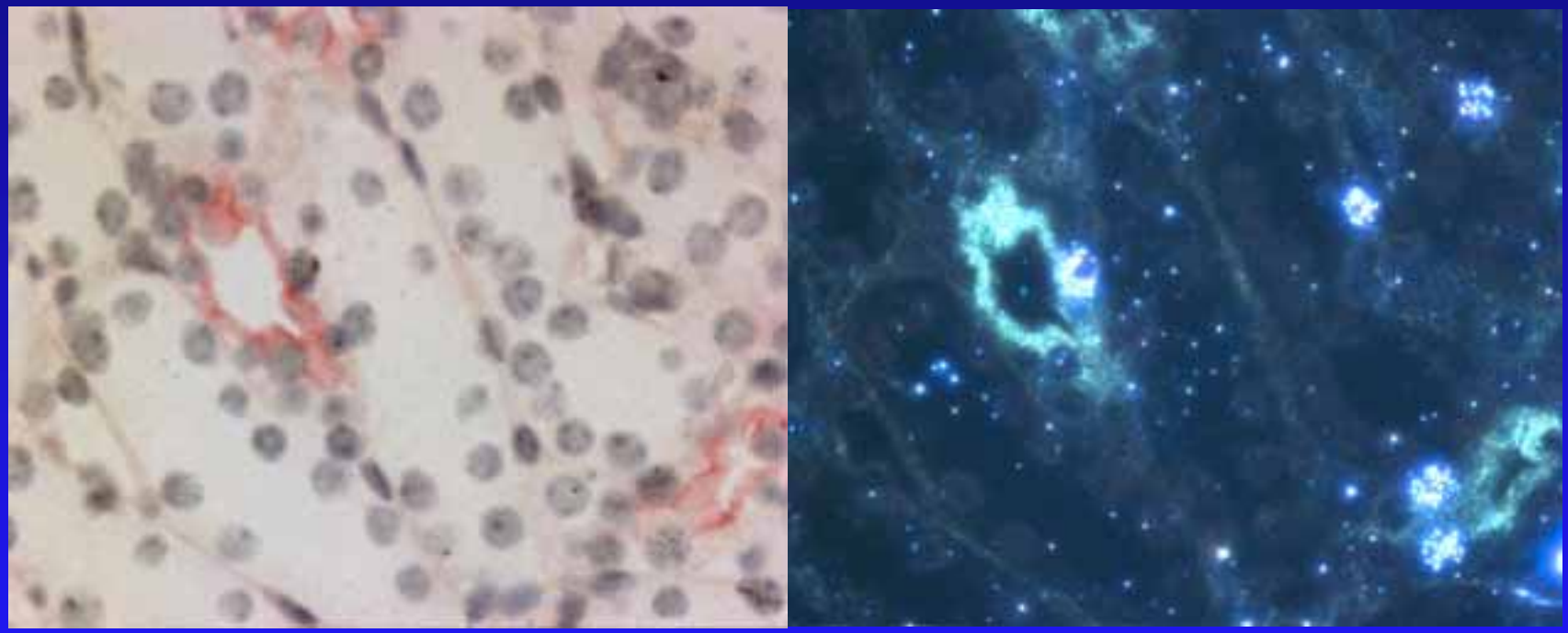




Distal tubule (PNA staining)

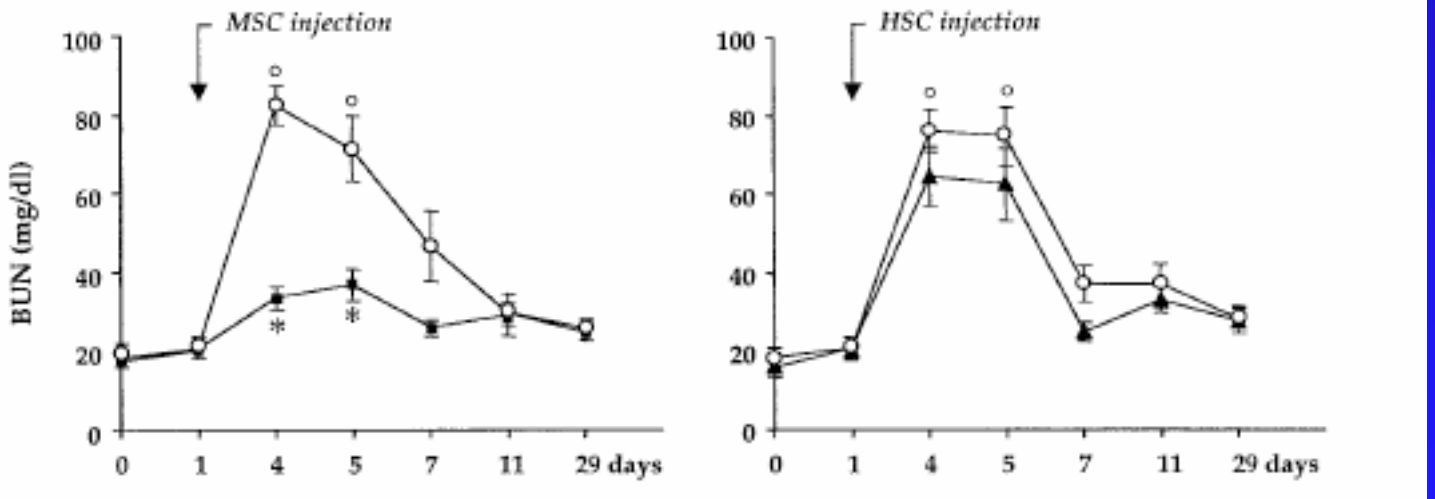


J Am Soc Nephrol 15: 1794–1804, 2004

Mesenchymal Stem Cells Are Renotropic, Helping to Repair the Kidney and Improve Function in Acute Renal Failure

MARINA MORIGI,* BARBARA IMBERTI,* CARLA ZOJA,* DANIELA CORNA,* SUSANNA TOMASONI,* MAURO ABBATE,* DANIELA ROTTOLI,* STEFANIA ANGIOLETTI,* ARIELA BENIGNI,* NORBERTO PERICO,* MALCOLM ALISON,† and GIUSEPPE REMUZZI*‡

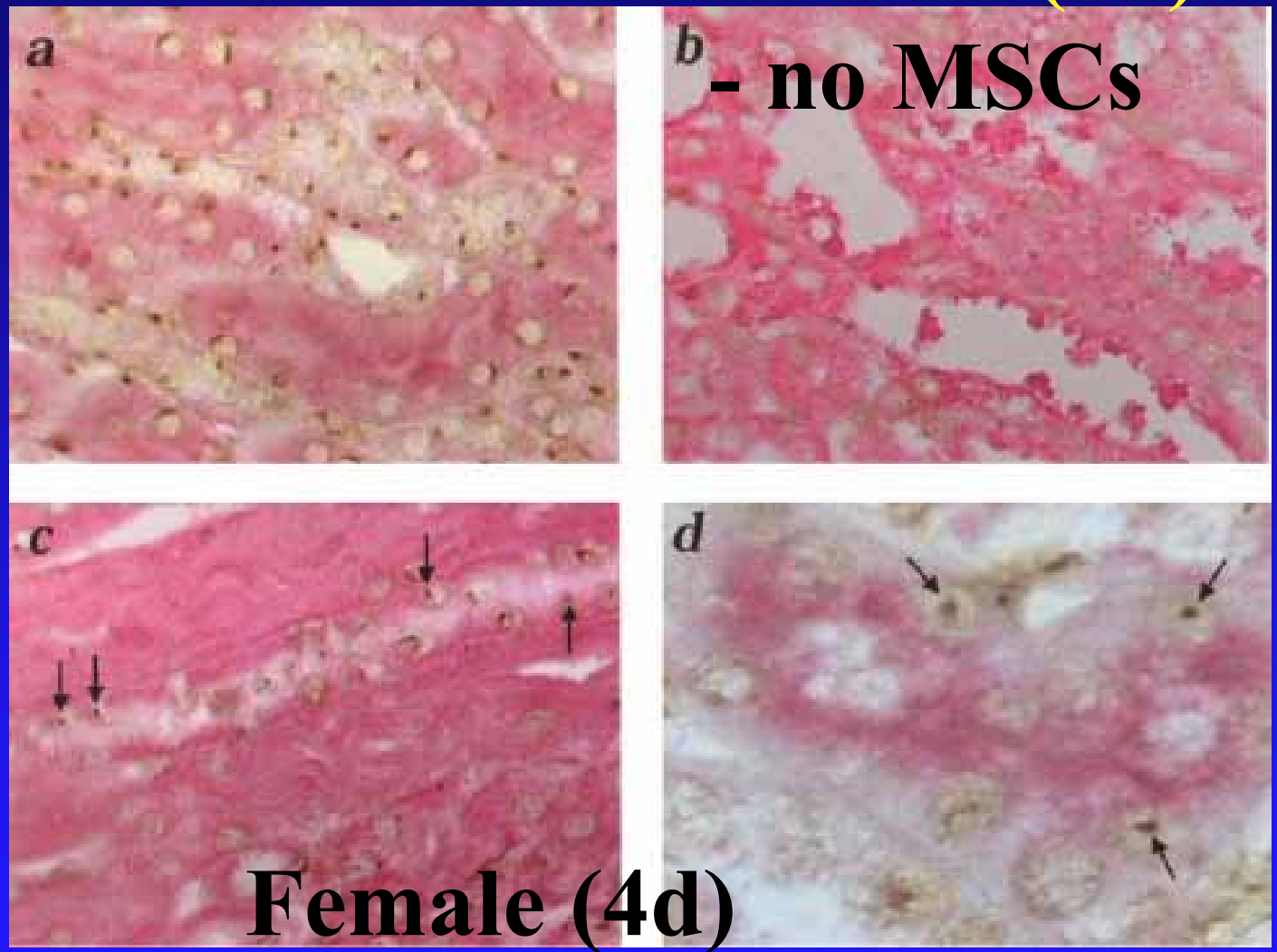
**Mario Negri Institute for Pharmacological Research, Bergamo, Italy; †Department of Histopathology, Imperial College London, Hammersmith Hospital, London, United Kingdom; and ‡Unit of Nephrology and Dialysis, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy*



Male

Female (4d)

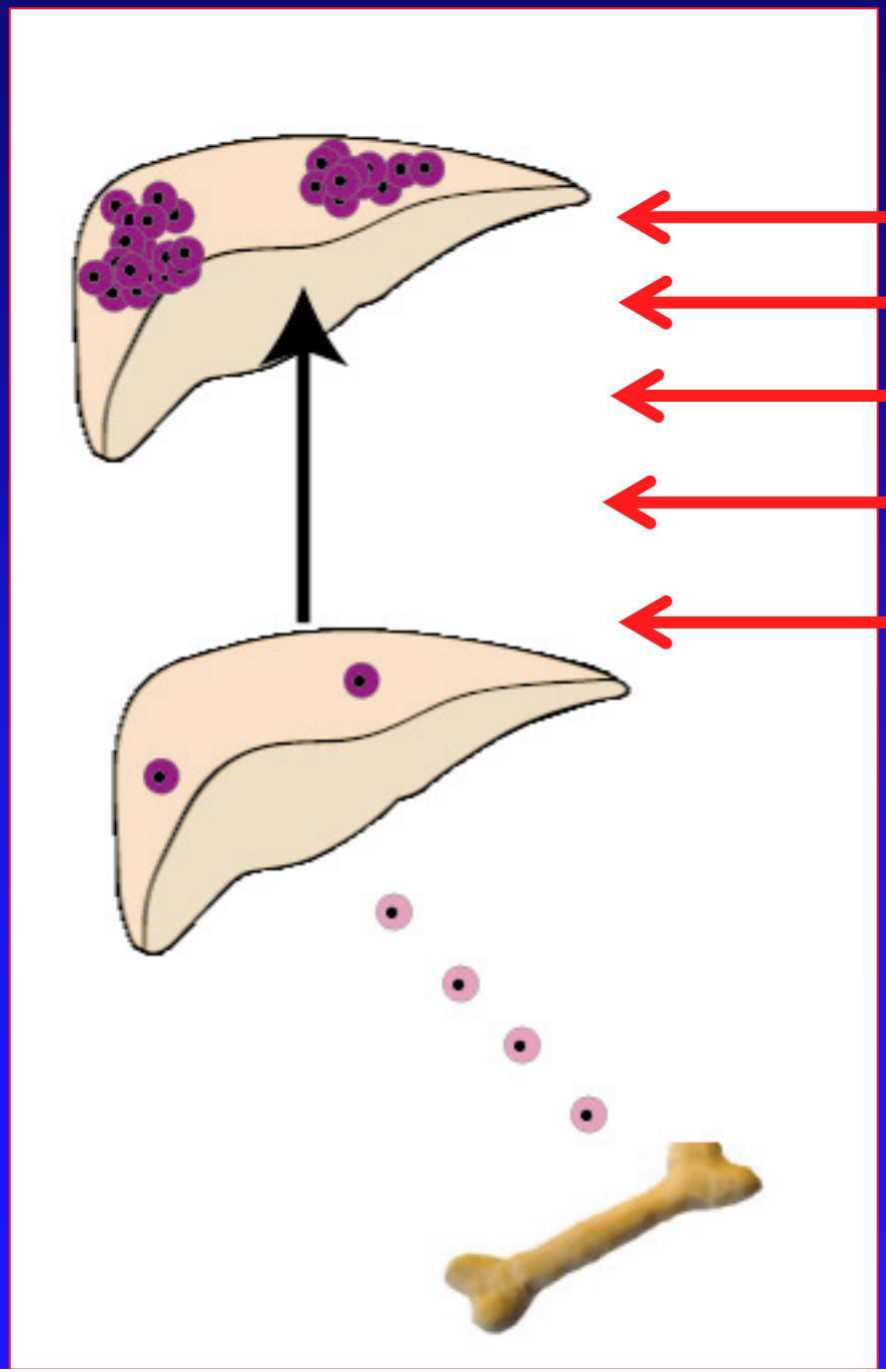
- no MSCs



Female (4d)

- with male MSCs

Can stem cells cross lineage boundaries?



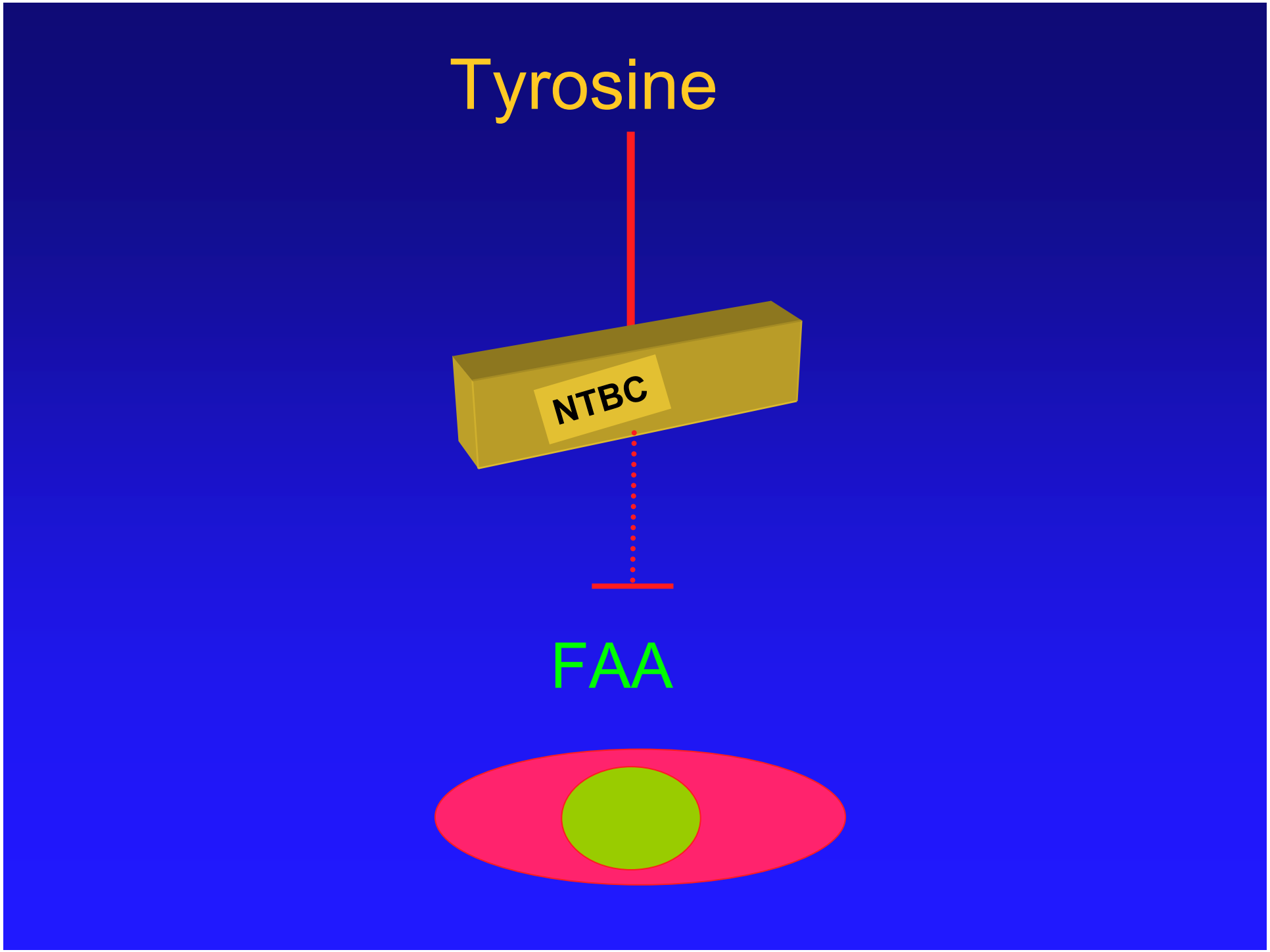
Positive selection pressure for transplanted cells

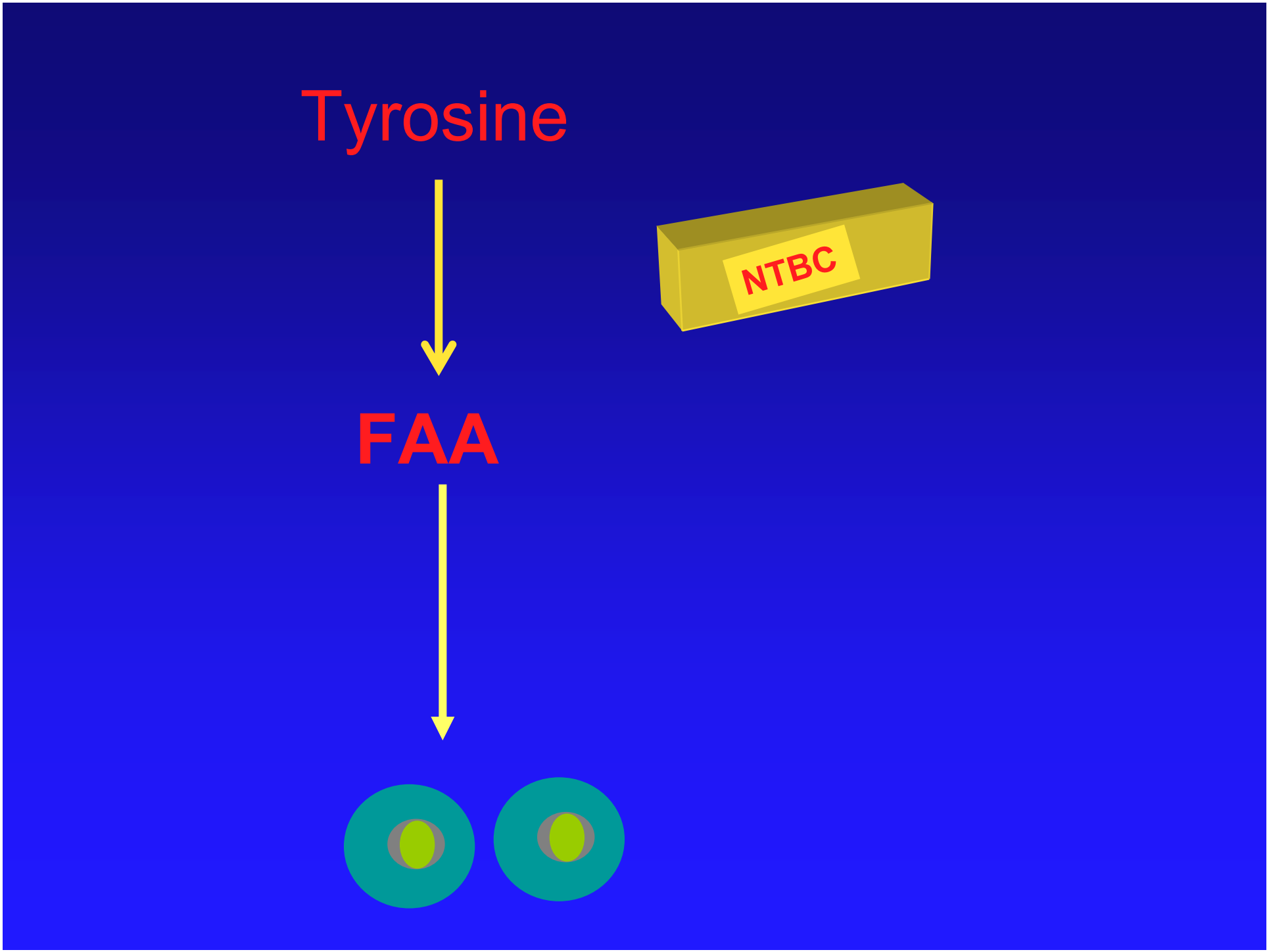
Hereditary type 1 tyrosinaemia

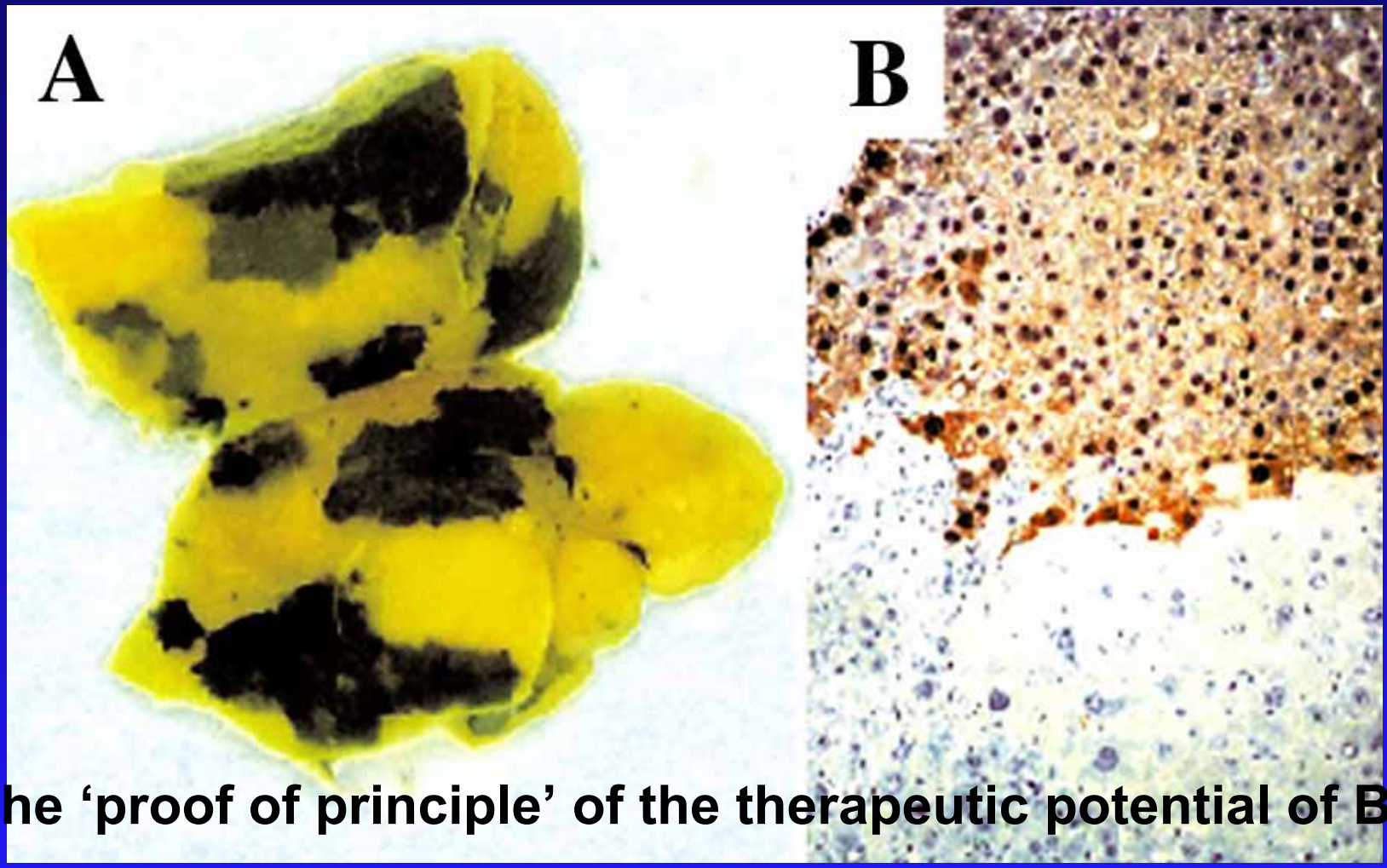
Lack fumarylacetoacetate hydrolase (FAH)

Accumulate fumarylacetoacetate (FAA)

Highly toxic to hepatocytes


Tyrosine
NTBC
FAA


Tyrosine
NTBC
FAA

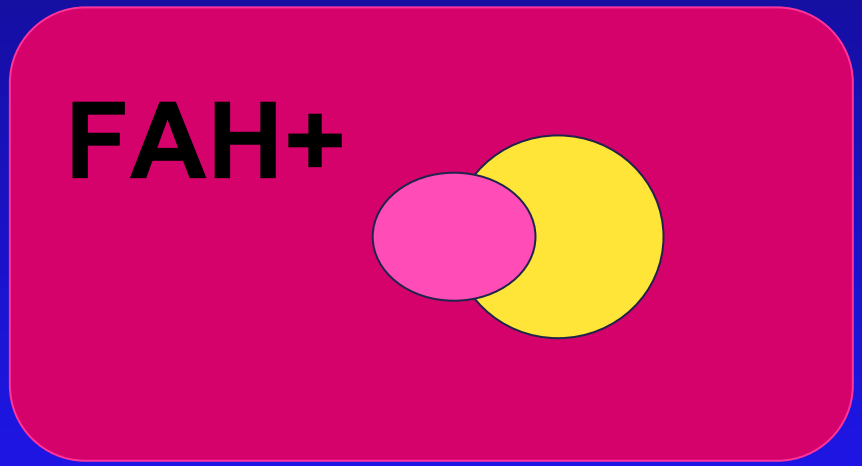


The 'proof of principle' of the therapeutic potential of BM?

1 million bone marrow cells from ROSA-26 mouse injected into lethally irradiated FAH- mouse - @ 7 months 50% liver replaced

Lagasse *et al.* (2000) Nature Medicine 6, 1229-1234

Reprogramming of deficient hepatocyte



Plastic adult stem cells: will they graduate from the school of hard knocks?

Malcolm R. Alison[1,2,*], Richard Poulsom[1], William R. Otto[1], Pamela Vig[1], Mairi Brittan[1], Natalie C. Direkze[1], Sean L. Preston[1] and Nicholas A. Wright[1,3]

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[2]Department of Histopathology, Imperial College London at the Hammersmith Hospital, London W12 0NN, UK
[3]Department of Histopathology, Bart's and the London, Queen Mary's School of Medicine and Dentistry, London E1 2AD, UK
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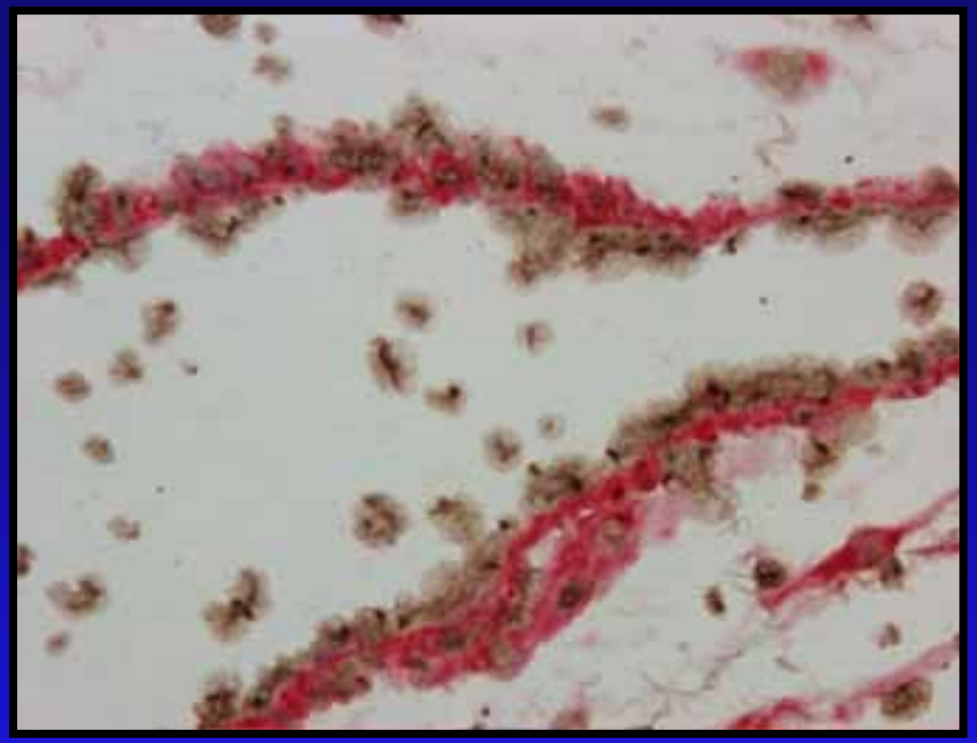
cells in the liver. Expressing a similar sentiment, Blau has suggested that if cell fusion is responsible for the apparent reprogramming of certain adult cells then there is something 'exciting' about rescuing damaged cells through fusion, with, for example, bone-marrow-derived cells providing a healthy and entire genetic complement, even one that has been manipulated for gene therapy (Blau, 2002).

Hematopoietic myelomonocytic cells are the major source of hepatocyte fusion partners

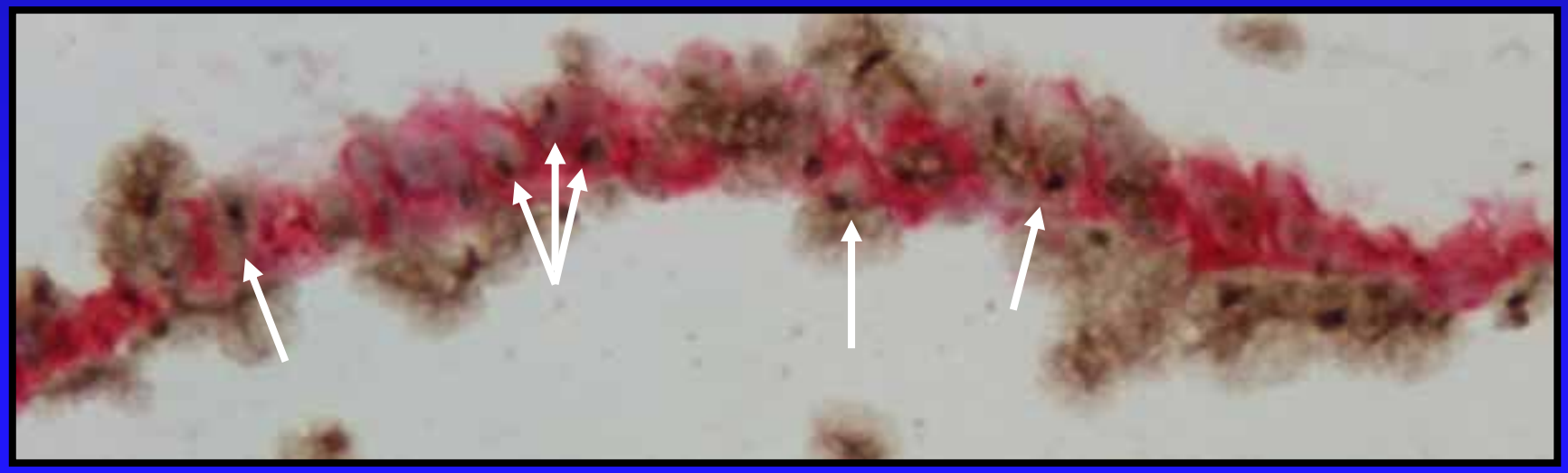
Fernando D. Camargo,[1,2] Milton Finegold,[3] and Margaret A. Goodell[1,2,4]

[1]Center for Cell and Gene Therapy, [2]Cell and Molecular Biology Program, [3]Department of Pathology, and [4]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 113 Number 9 May 2004



Venule formed *entirely* from transplanted bone marrow?



Courtesy of Mairi Brittan

Multipotent adult progenitor cells from bone marrow differentiate into functional hepatocyte-like cells

Robert E. Schwartz,[1] Morayma Reyes,[1] Lisa Koodie,[1] Yuehua Jiang,[1] Mark Blackstad,[1] Troy Lund,[1] Todd Lenvik,[1] Sandra Johnson,[1] Wei-Shou Hu,[2] and Catherine M. Verfaillie[1,3]

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Robert E. Schwartz and Morayma Reyes contributed equally to this work.

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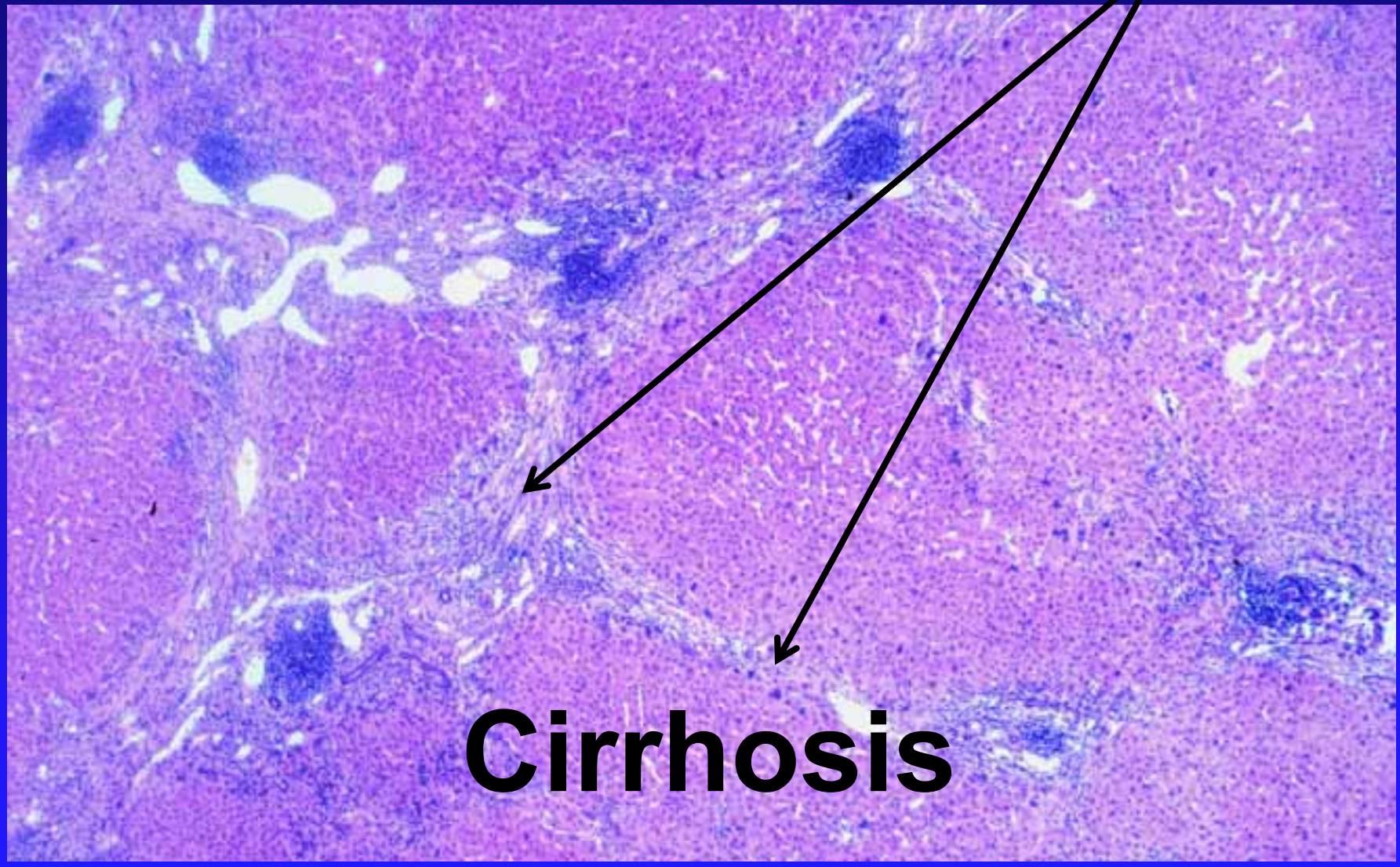
Stem Cell Diseases

Can bone marrow contribute to liver fibrogenesis?



GASTROENTEROLOGY 2004;126:955–963

RAPID COMMUNICATIONS

A Significant Proportion of Myofibroblasts Are of Bone Marrow Origin in Human Liver Fibrosis

STUART J. FORBES,* FRANCESCO P. RUSSO,* VIRGINIA REY,* PATRIZIA BURRA,† MASSIMO RUGGE,† NICHOLAS A. WRIGHT,§ and MALCOLM R. ALISON‖

*Hepatology Section and ‖Histopathology Department, Imperial College, London, England; †Histopathology Unit and Gastroenterology Section, University of Padova, Padova, Italy; and §Histopathology Unit, Cancer Research UK, London, England

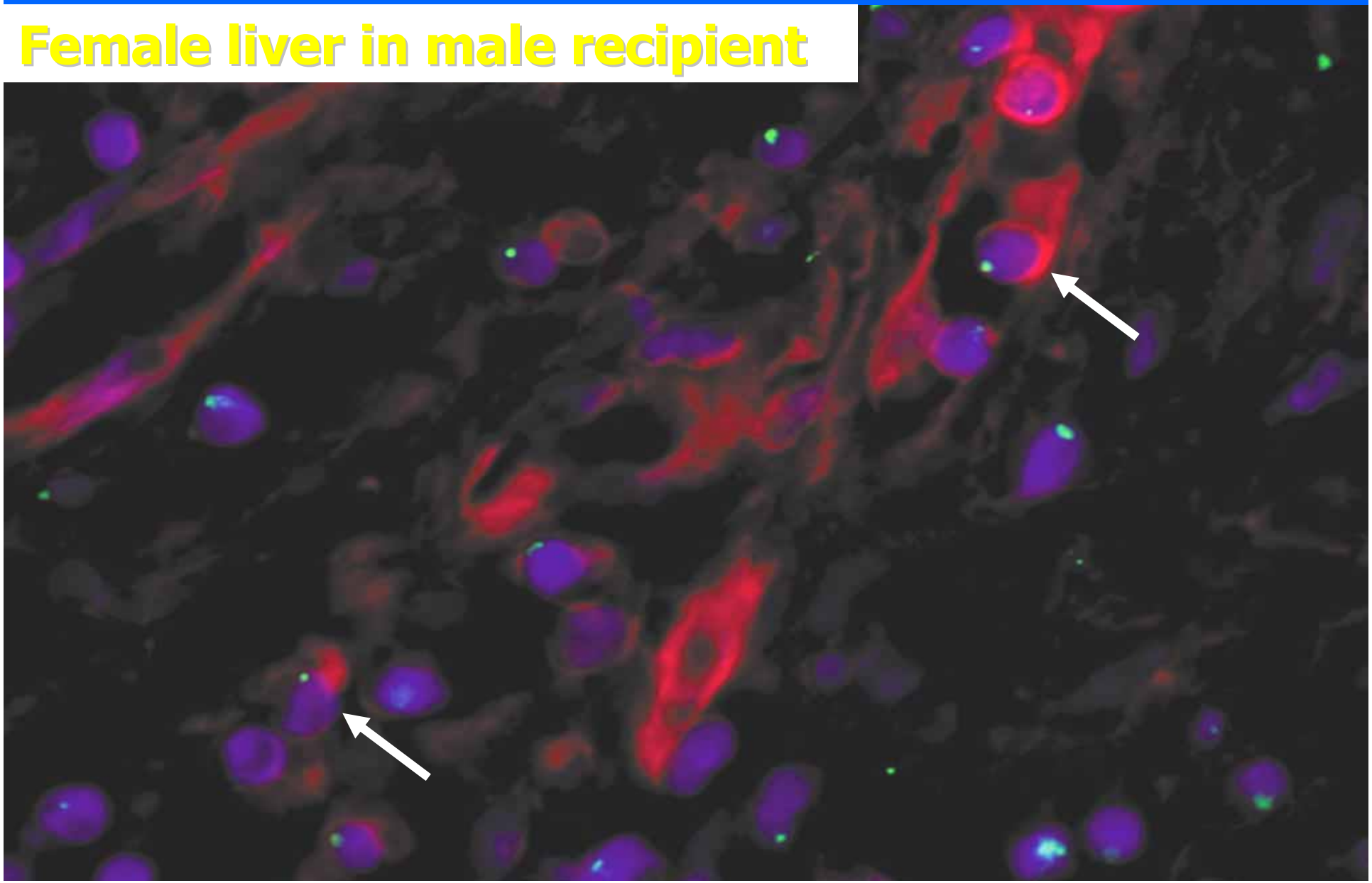
Section of Hepatology[1], Histopathology[2], Imperial College London

Section of Gastroenterology[3], Pathology[4], Universita' degli Studi di Padova

Histopathology Unit, Cancer Research UK London[5]

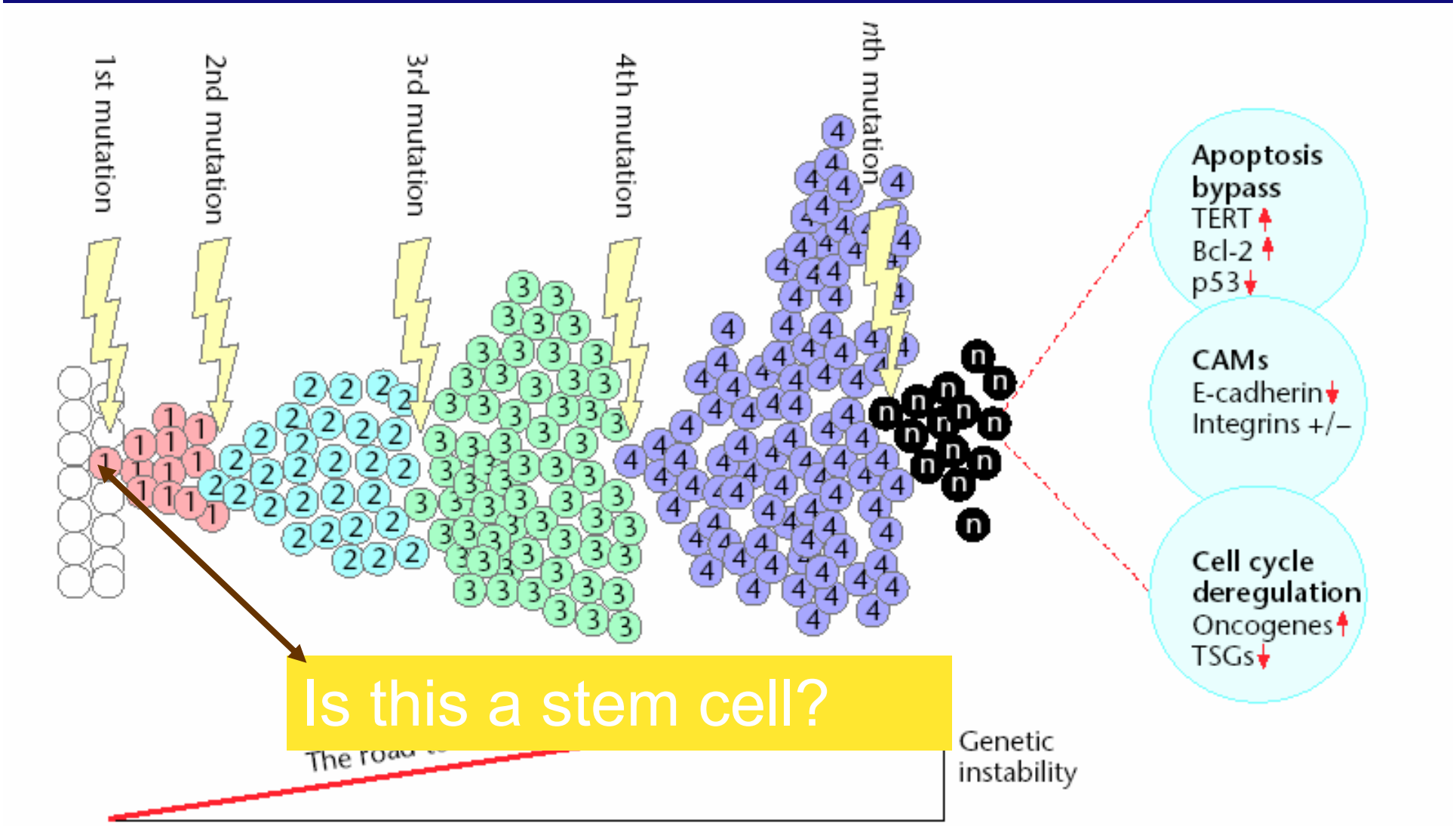
Y positive (green), Vimentin positive (red) cells within fibrotic band

Female liver in male recipient



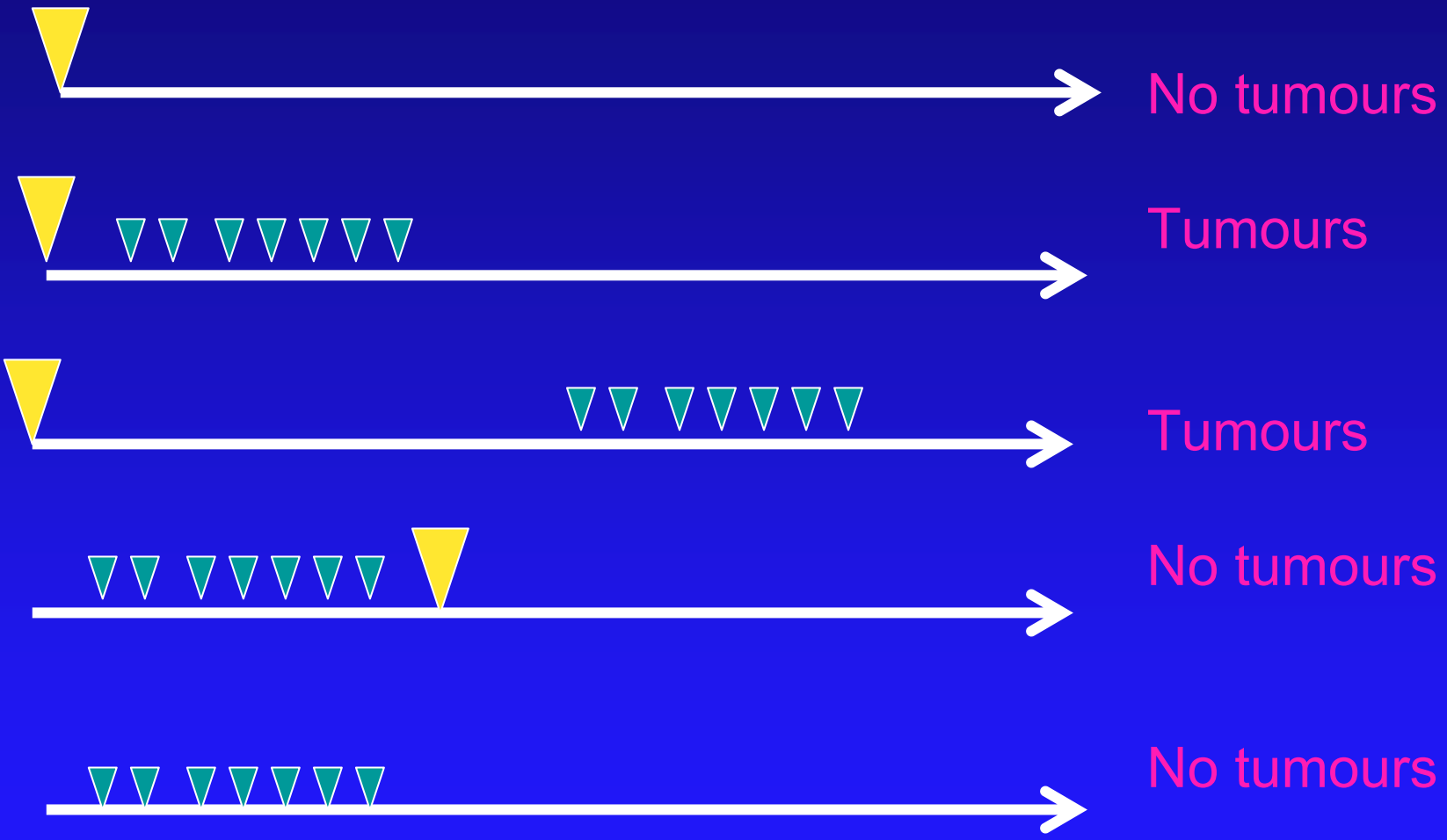

Mutant Stem Cells May Seed Cancer

- *Cancer is a stem cell disease*
- *Tumours have stem cells*



Alison MR 2001, Encyclopaedia of Life Sciences, Nature Publishing Group

Skin cancer in mice (initiators and promoters)



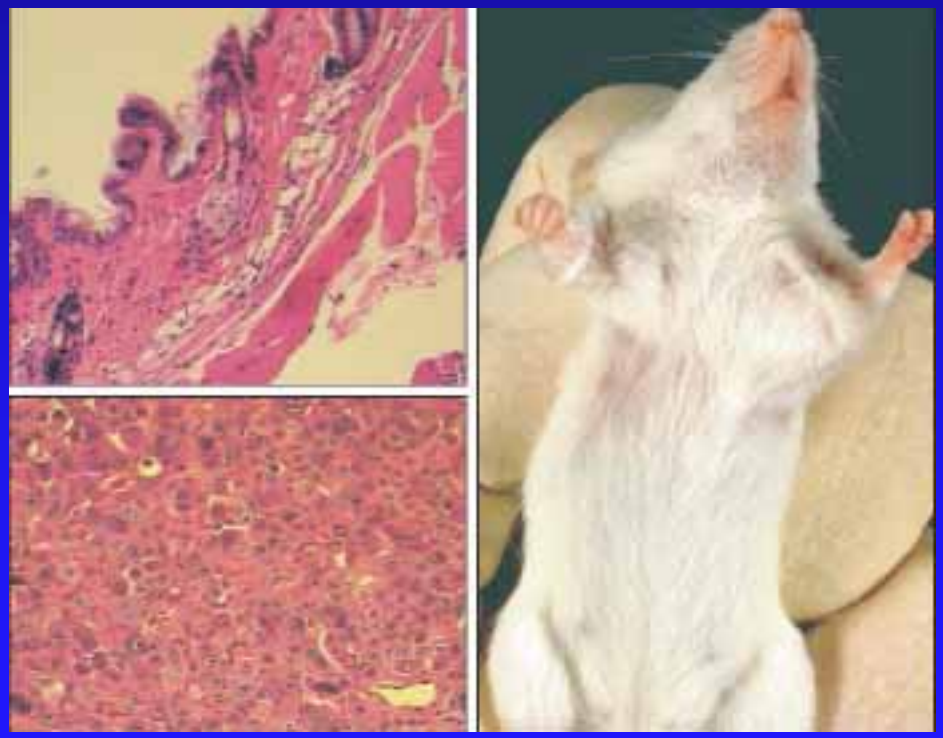
Evidence for cancer stem cells

CD34+, CD38- are only 0.2% of AML cells
but they are the only cells to form
tumours in NOD/SCID mice

Some cancers are sustained by a small minority of cells; their resemblance to normal stem cells might explain why many cancers are so hard to eradicate, and it has researchers rethinking cancer treatments

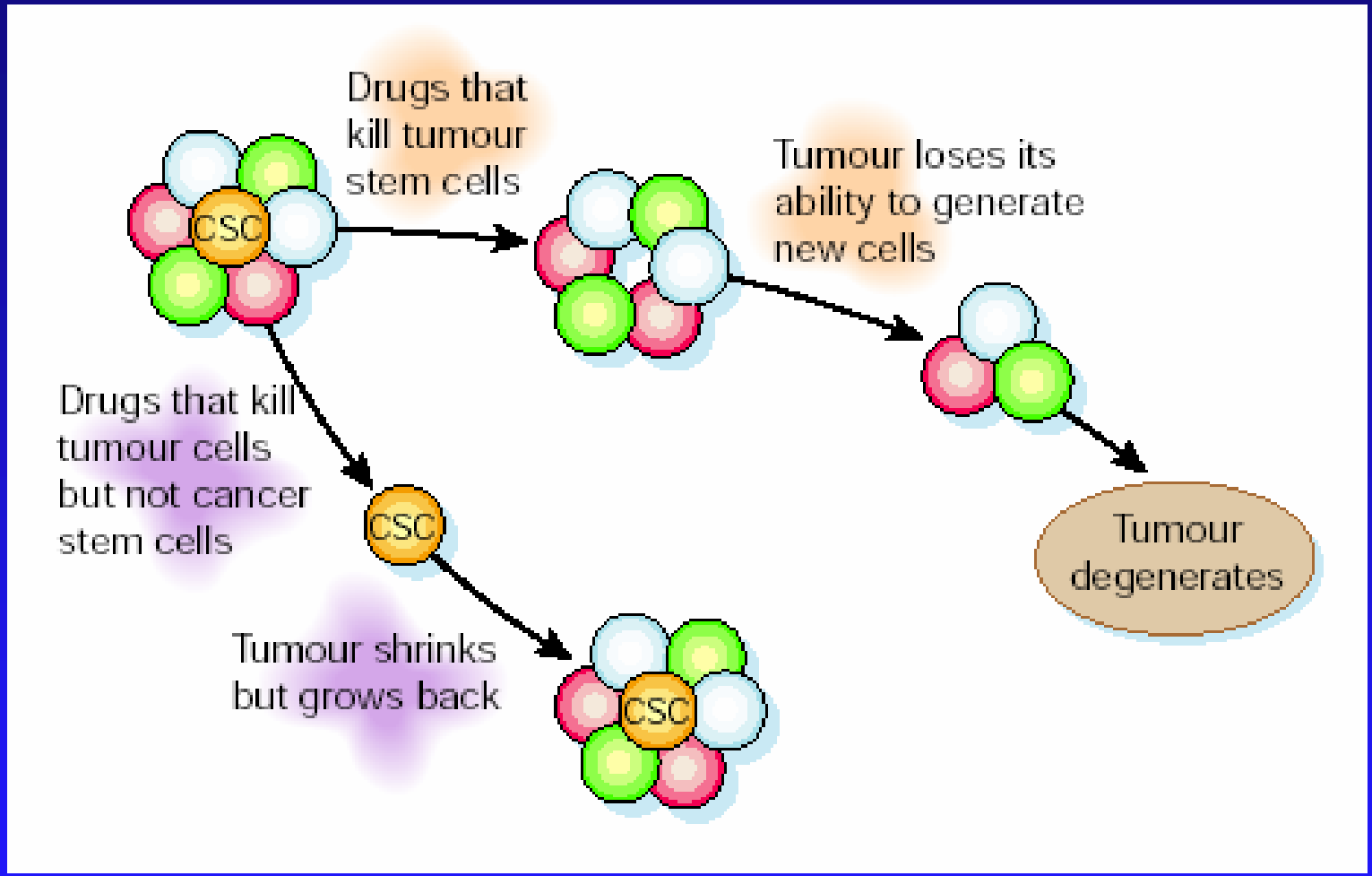
Mutant Stem Cells May Seed Cancer

5 SEPTEMBER 2003 VOL 301 SCIENCE www.sciencemag.org

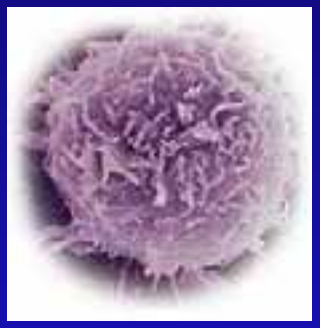


CD44+ CD24- Lin- can make tumours in NOD/ SCID mice

Successful chemotherapy: kill the stem cells!



are stem cells



or

Enemies


...and to win it, I just kicked the ball over the bar...
ball...
bar...
over...
win...


14
14
7
6


23