Stem Cells, Cancer Cells and Cancer Stem Cells

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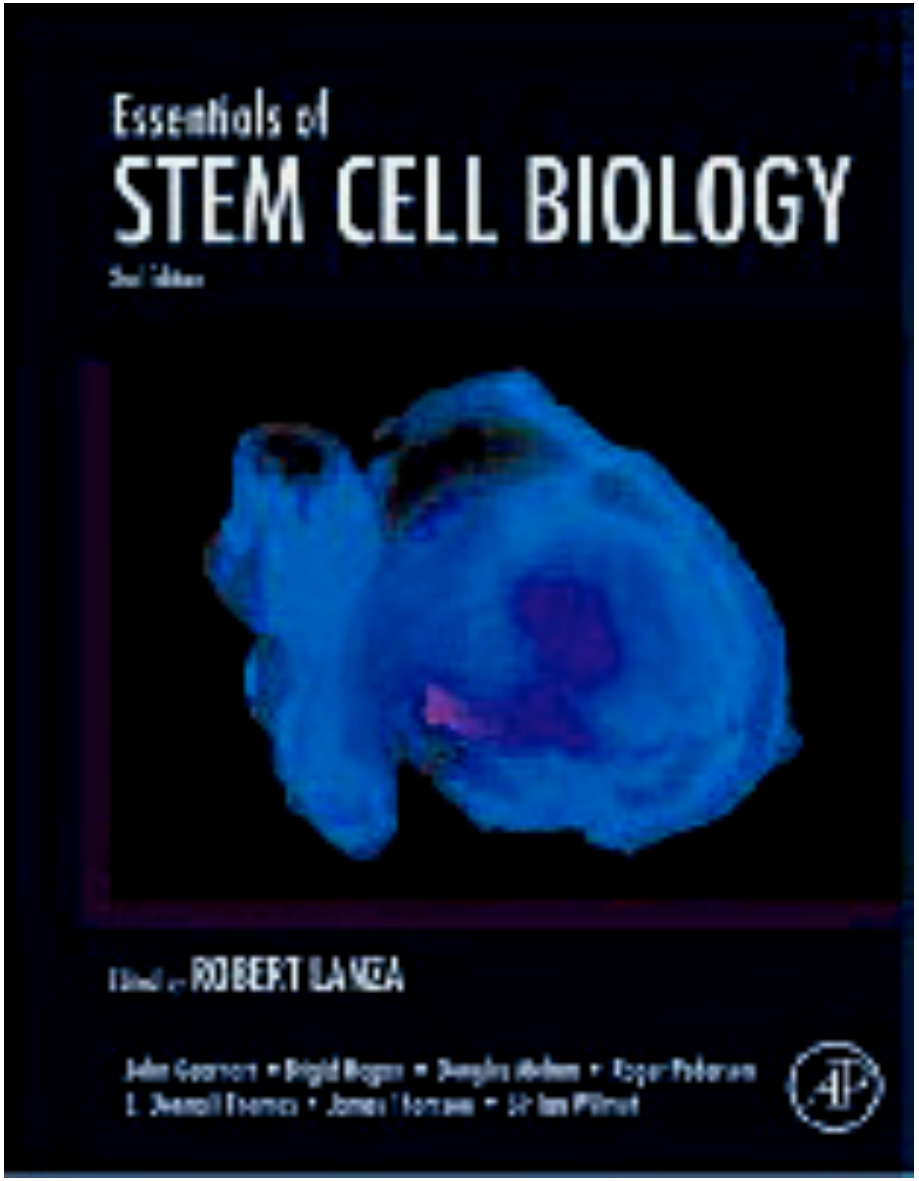
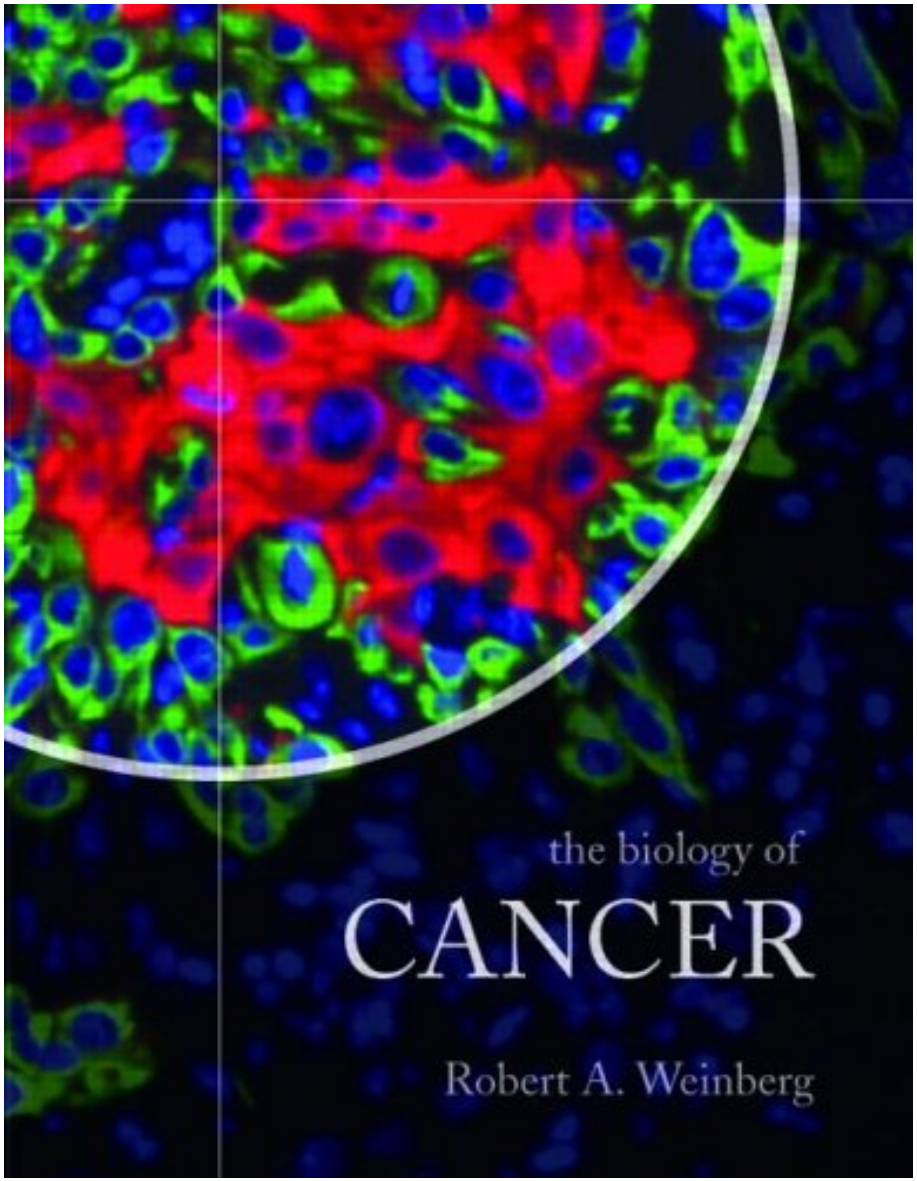
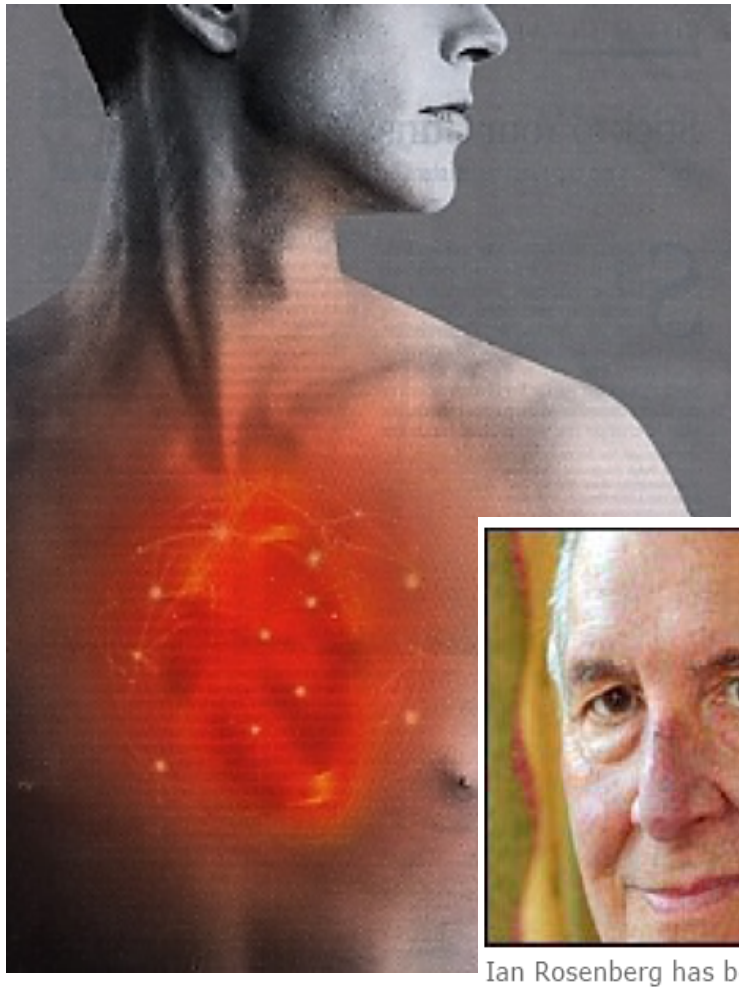
基因體研究中心
Genomics Research Center
ACADEMIA SINICA

Reference textbook





Hype and hope of stem cells and regenerative medicine



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Stem cell heart cure to be tested

Doctors have launched a trial to test whether heart disease can be treated using a patient's own stem cells.

Different therapies will be tested

The study, at Barts and the London NHS Trust, is funded by a charity set up by a man who underwent stem cell treatment for his heart condition in Germany.

The aim will be to determine whether adult stem cells taken from bone marrow can repair damaged heart muscle.

In total, 700 patients will take part in the study, which will test three different forms of stem cell therapy.

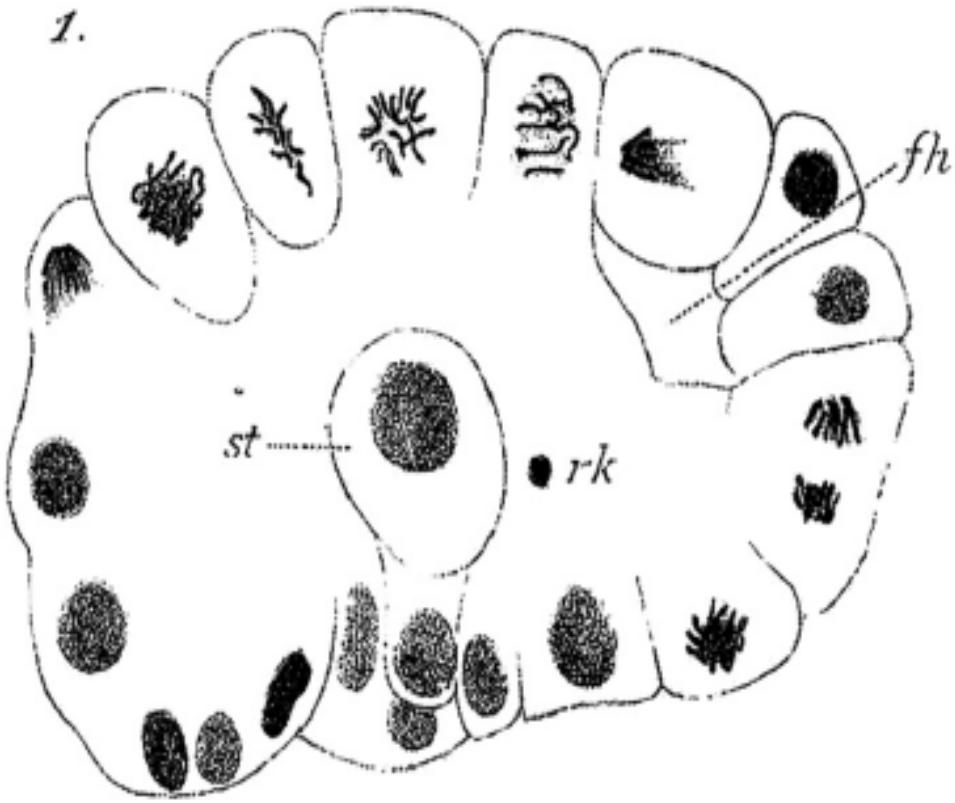
What are stem cells ?

◆**'Stem cell' is a scientific concept**

◆Historically, the word *stammzelle* (German for stem cell) had a dual meaning:

(1)the evolutionary **unicellular ancestor** of multicellular organisms, and

(2) the second being the **ancestral (ontological) stem cell of a tissue** in an organism, initially in the germ line. Subsequently, the term became more widely applied to other tissues.

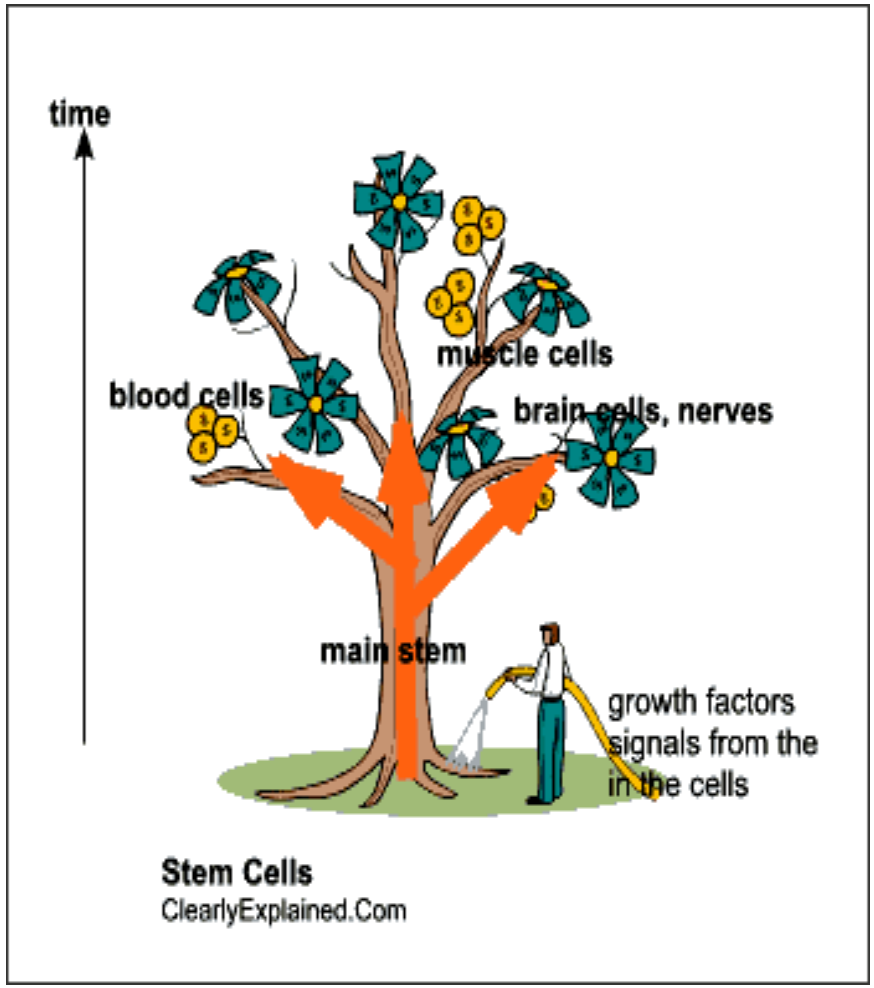


Nature Reports Stem Cells | doi:10.1038/stemcells.2009.90;
Ramalho-Santos and Willenbring Cell Stem Cells 2007

What are stem cells ?

Definition of stem cells:

- **Undifferentiated/unspecialized cells**
- **Capacity for self-renewal (generally slowly cycling in vivo) which enabled to generate at least one daughter cell (self-renewal capacity)**
- **Able to undergo multi-lineage differentiation (capable of producing progeny in at least 2 lineages)**
- **Functional, capable for tissue reconstitution**



Shafritz et al., 2006 Hepatology; NIH Stem Cells; Verfaillie C.M. 2002 Trends Cell Biol.

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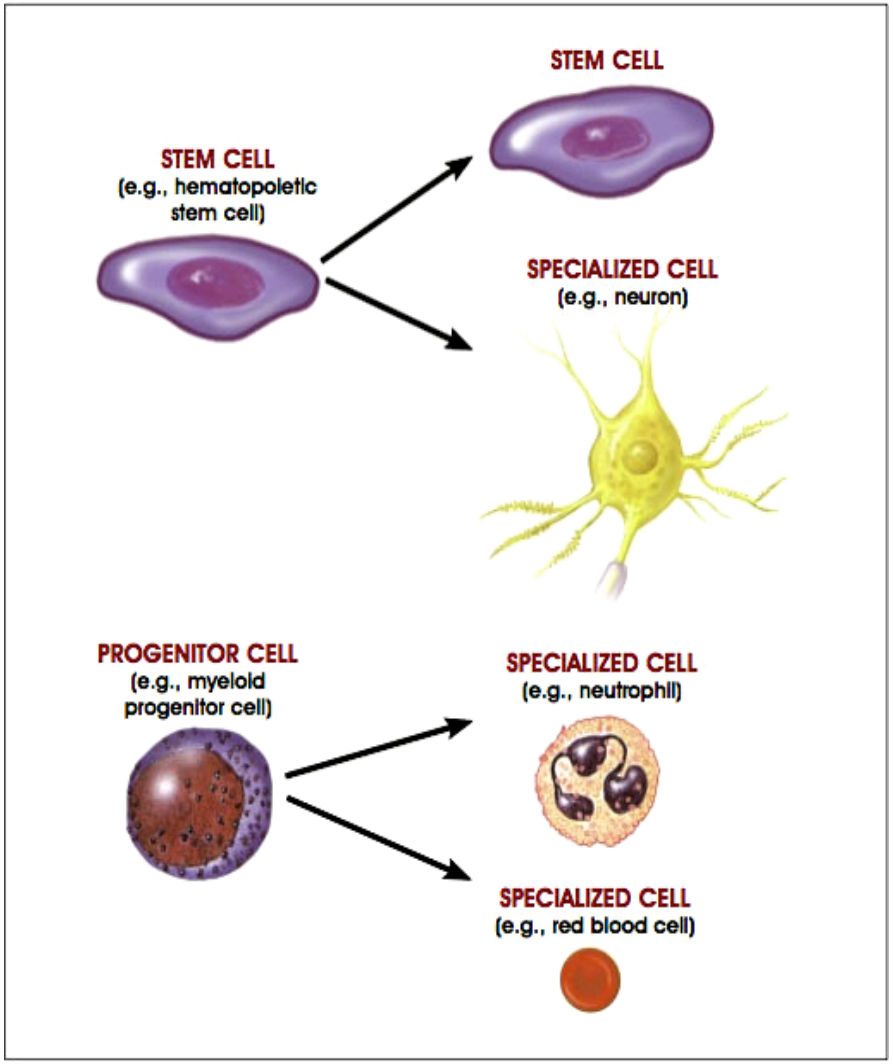
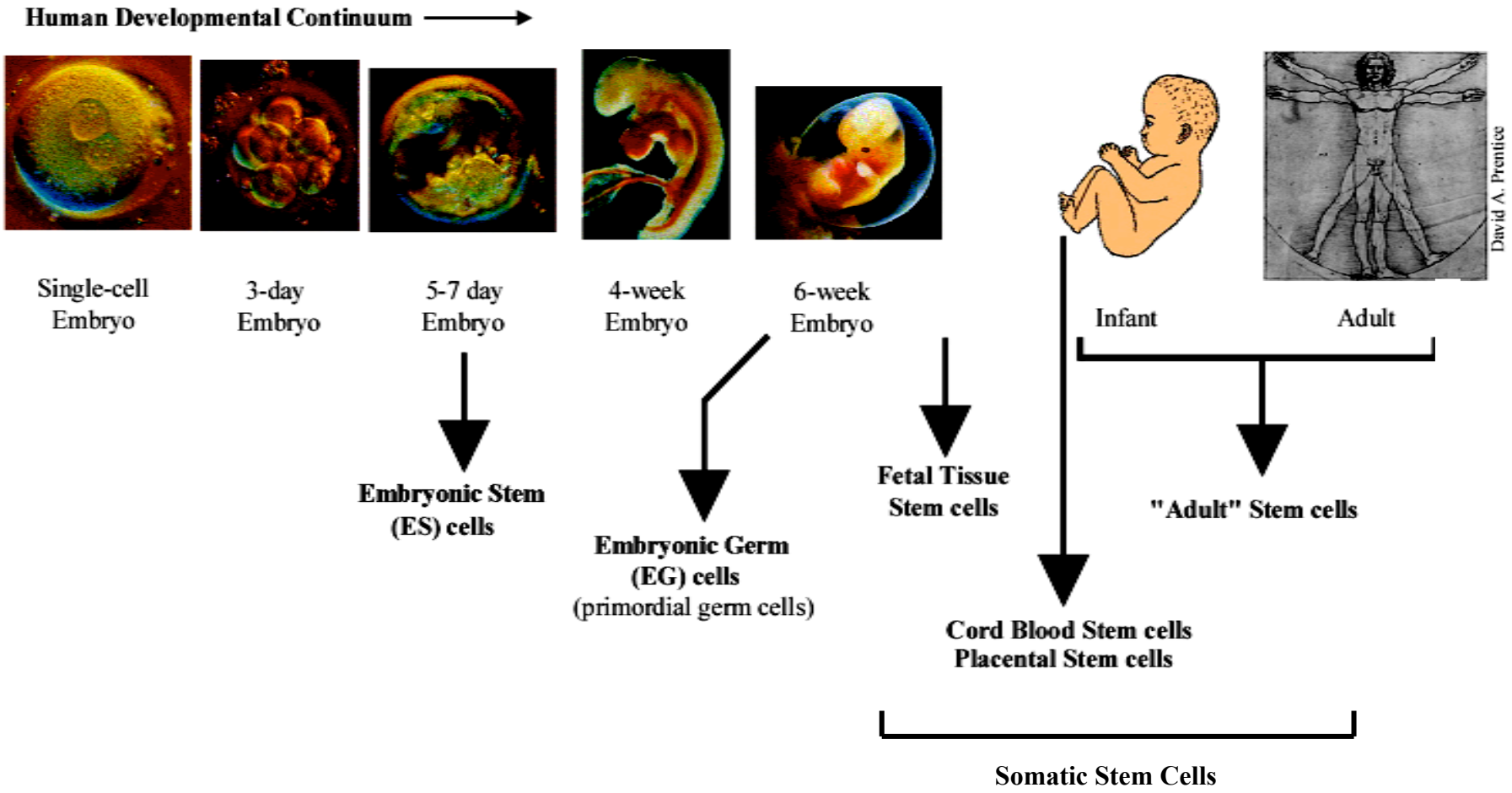


Shafritz et al., 2006 Hepatology; NIH Stem Cells; Verfaillie C.M. 2002 Trends Cell Biol.

Types of stem cells



Differentiation potential of stem cells

Totipotent:

the fertilized egg (zygote) and probably its immediate progeny

Pluripotent:

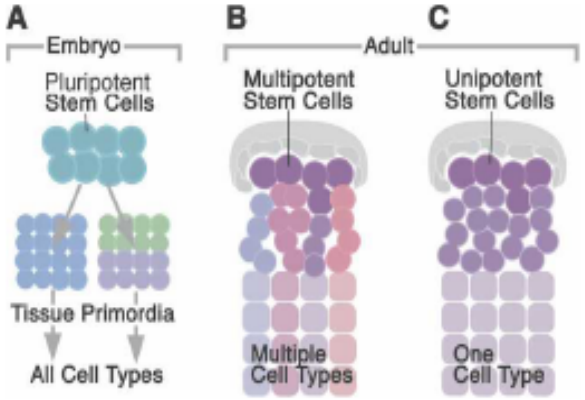
the embryonic stem cell is capable to differentiate into most cell type in the body

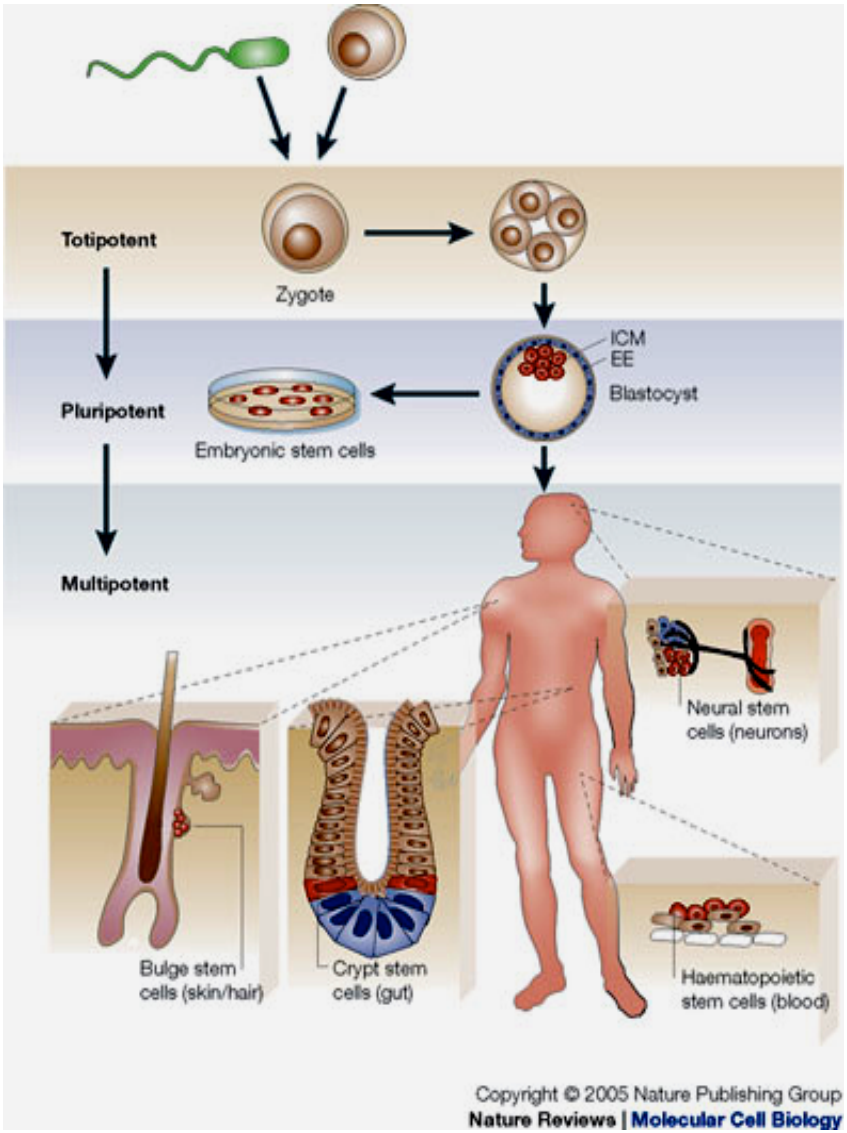
Multipotent (or pluripotent):

Adult (somatic) stem cells have more limited differentiation ability

Unipotent:

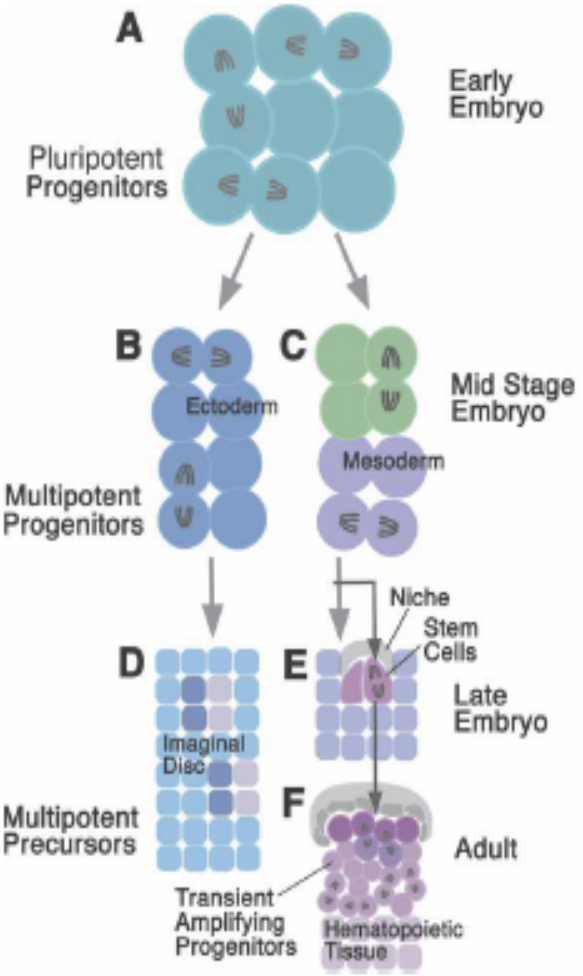
Adult tissue progenitor is able to differentiate into one specific lineage





Nat. Rev 2005; Genes & Dev. 2007 21: 3044-3060

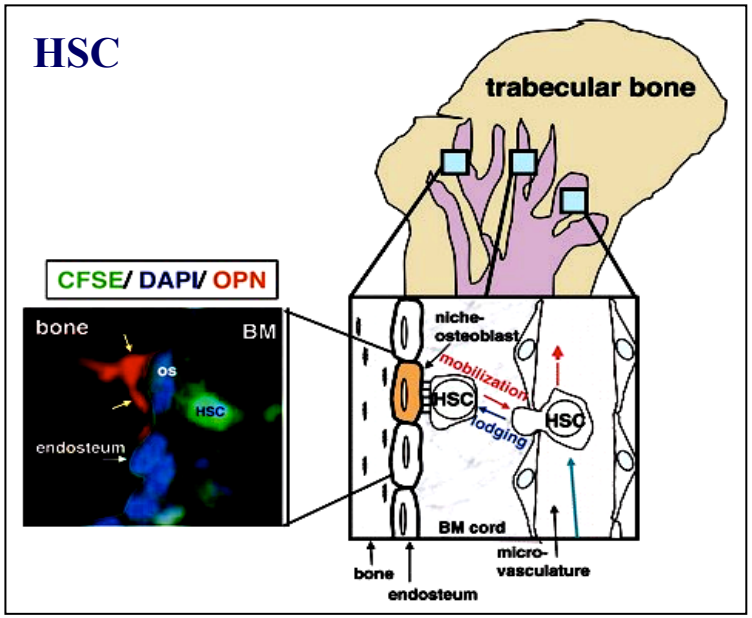
Stem cells in the context of development

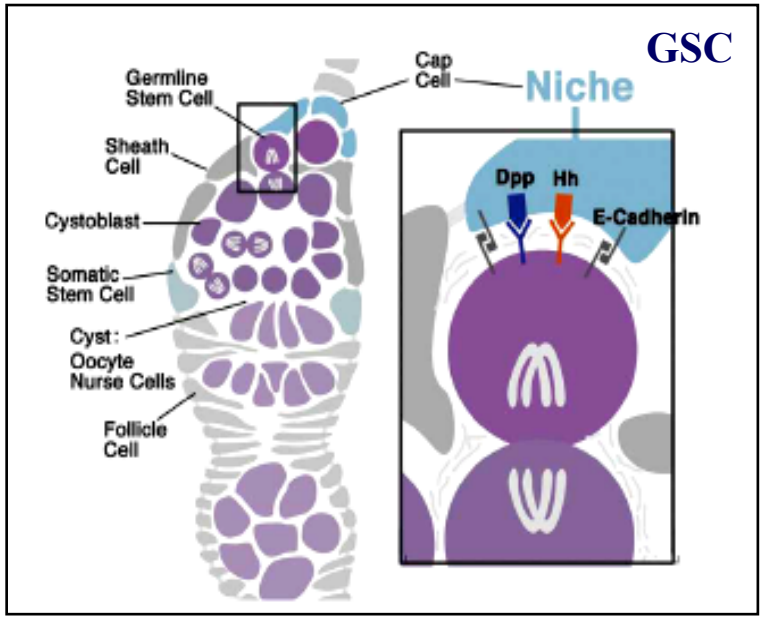


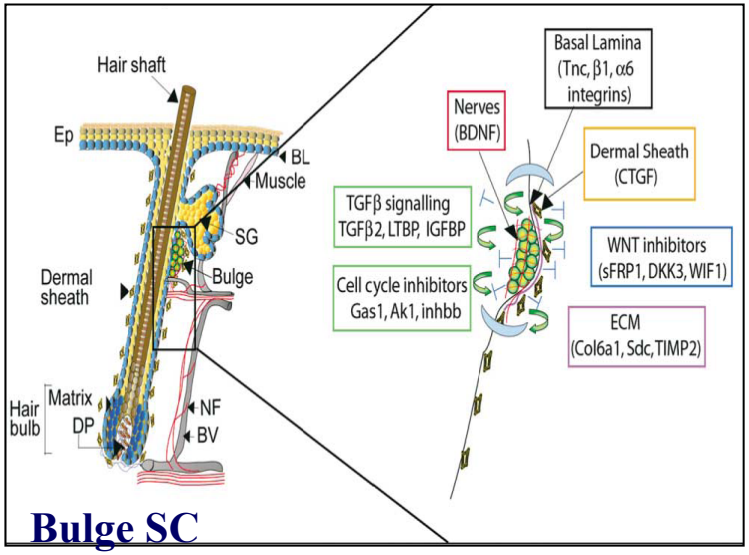
- Embryos consist of mitotically dividing cells called **progenitors**. Progenitors can be pluripotent or multipotent.
- *At* later developmental stages, cells exit the mitotic cycle. Generally called **precursors**, these cells can still be multipotent
- *At* some point, precursors become committed to a particular fate and differentiate.
- **Stem cells (e.g., HSCs) develop from embryonic progenitors that are prevented from exiting the mitotic cycle by specific microenvironments, called niches.**
- *In the adult organism,* stem cells undergo asymmetric cell divisions and produce mitotically active daughter cells also called progenitors ("transient amplifying cells")

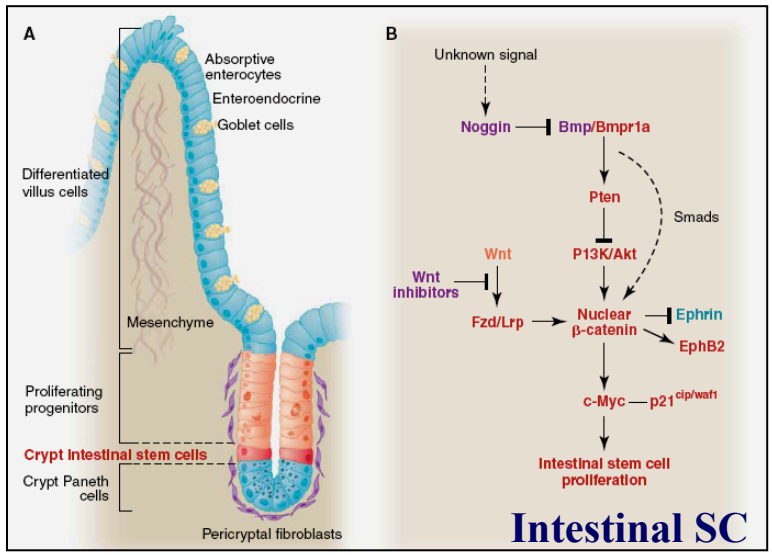
Genes & Dev. 2007 21: 3044-3060

Somatic stem cells reside in a niche that expressed specific features

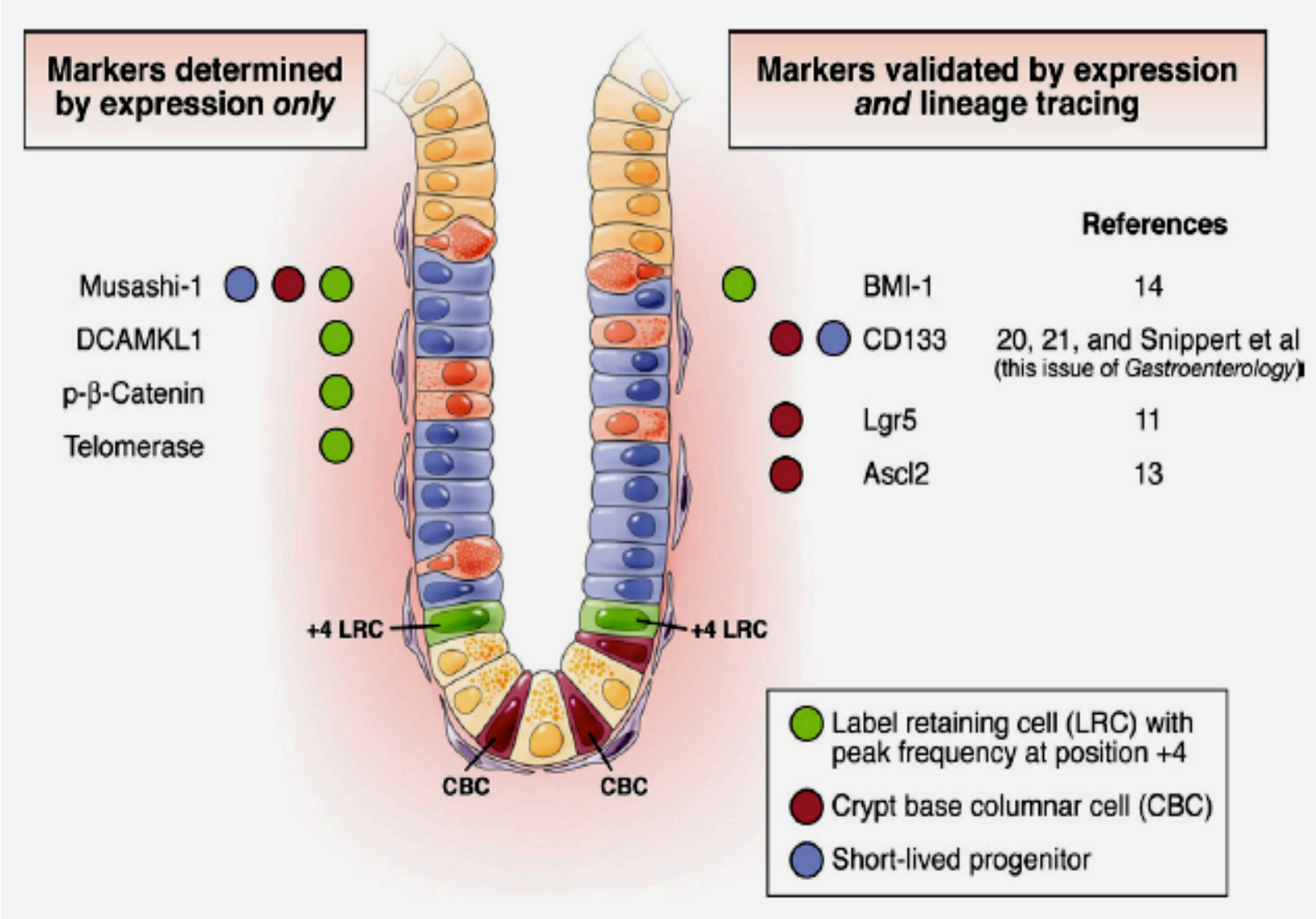






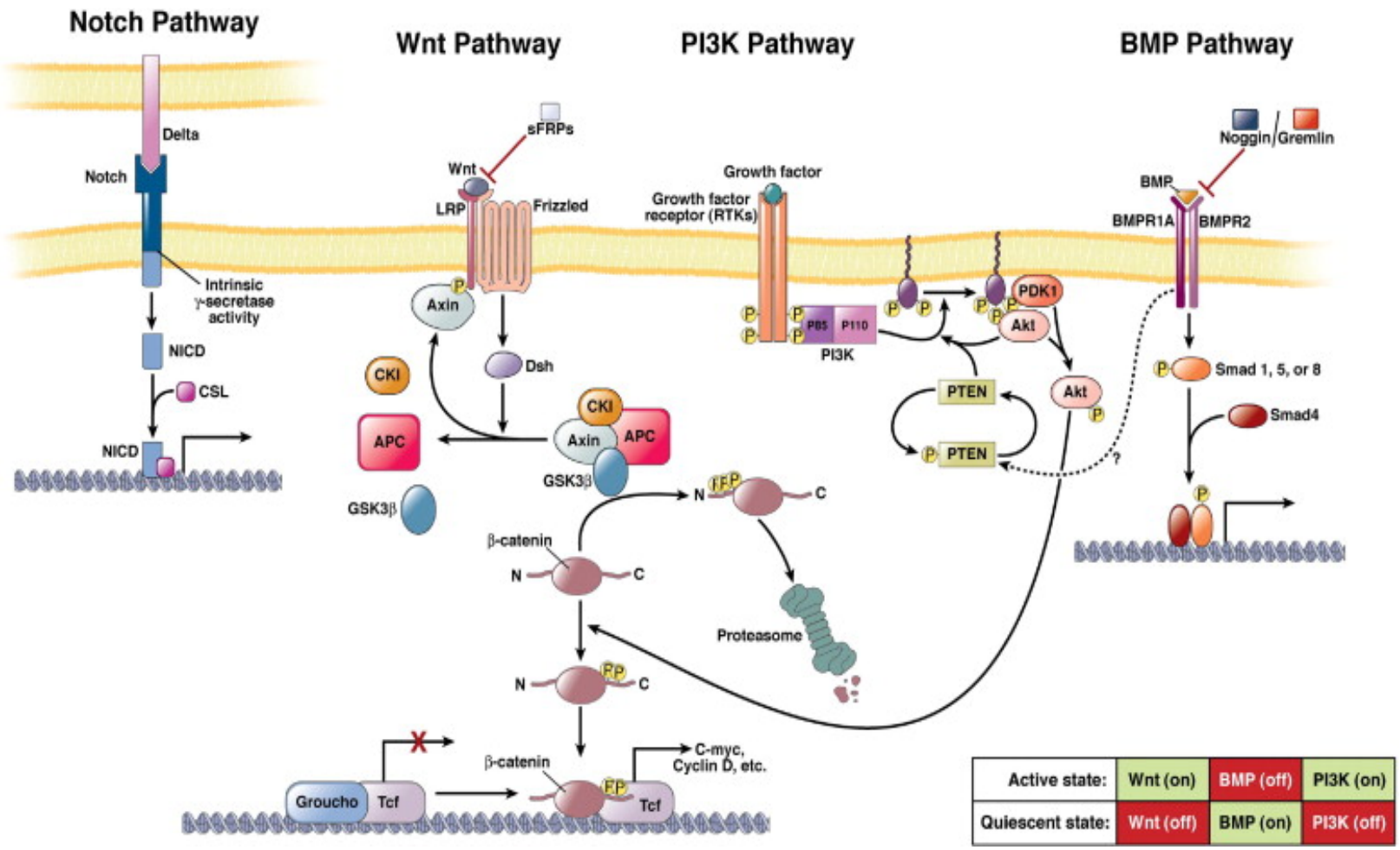


Intestinal stem cells



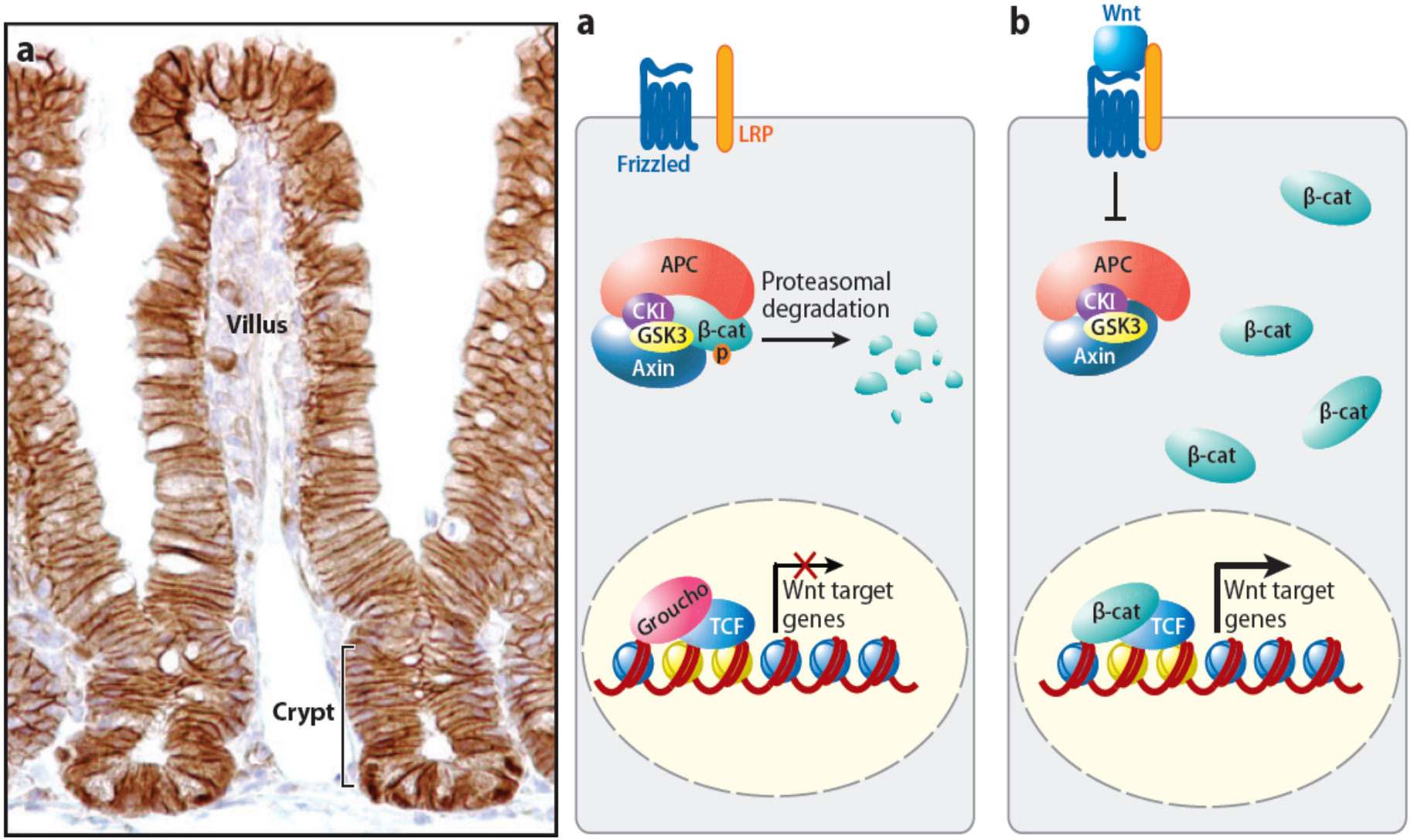
Snippert et al., 2009 Gastroenterology

Intestinal stem cells and their niches



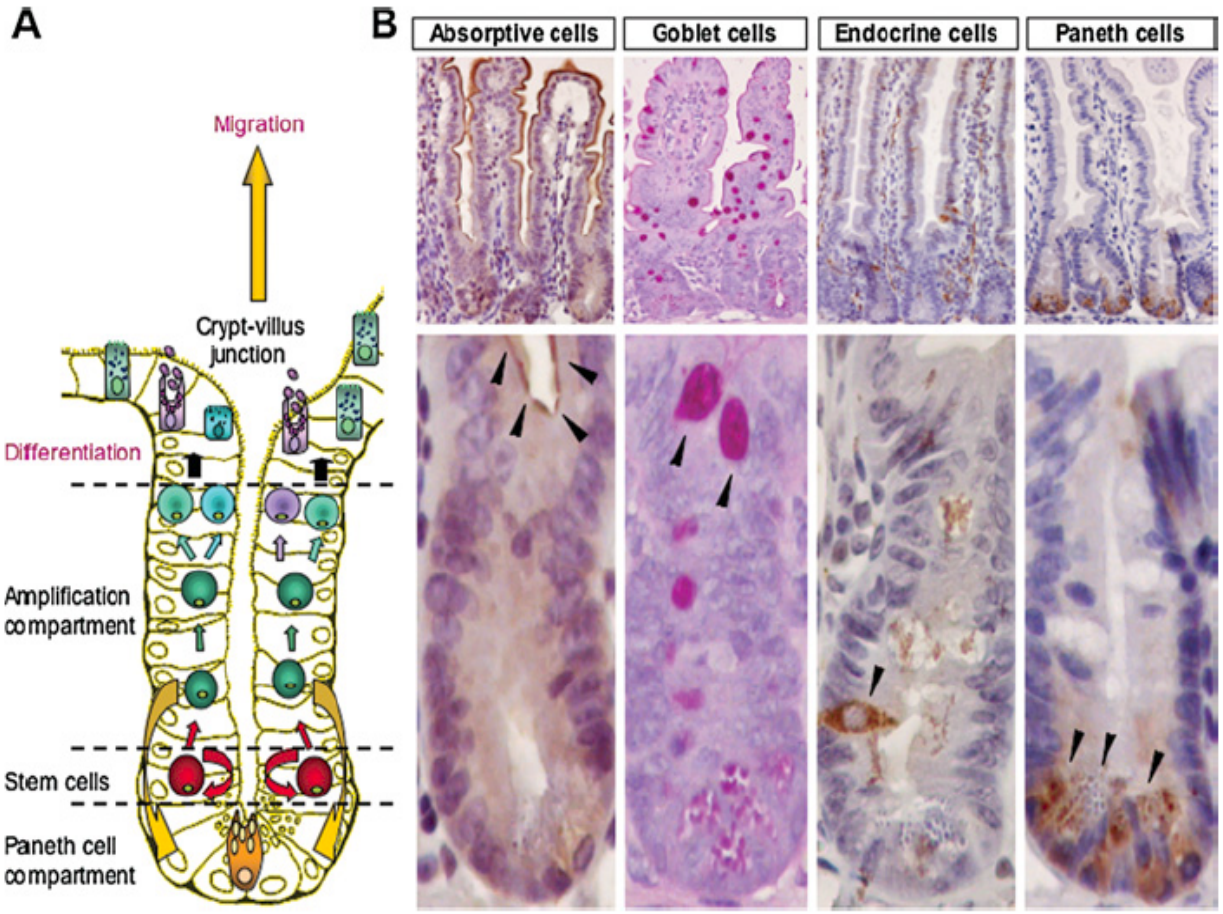
Moore & Lemischka 2006. Science

Intestinal stem cells and their niches



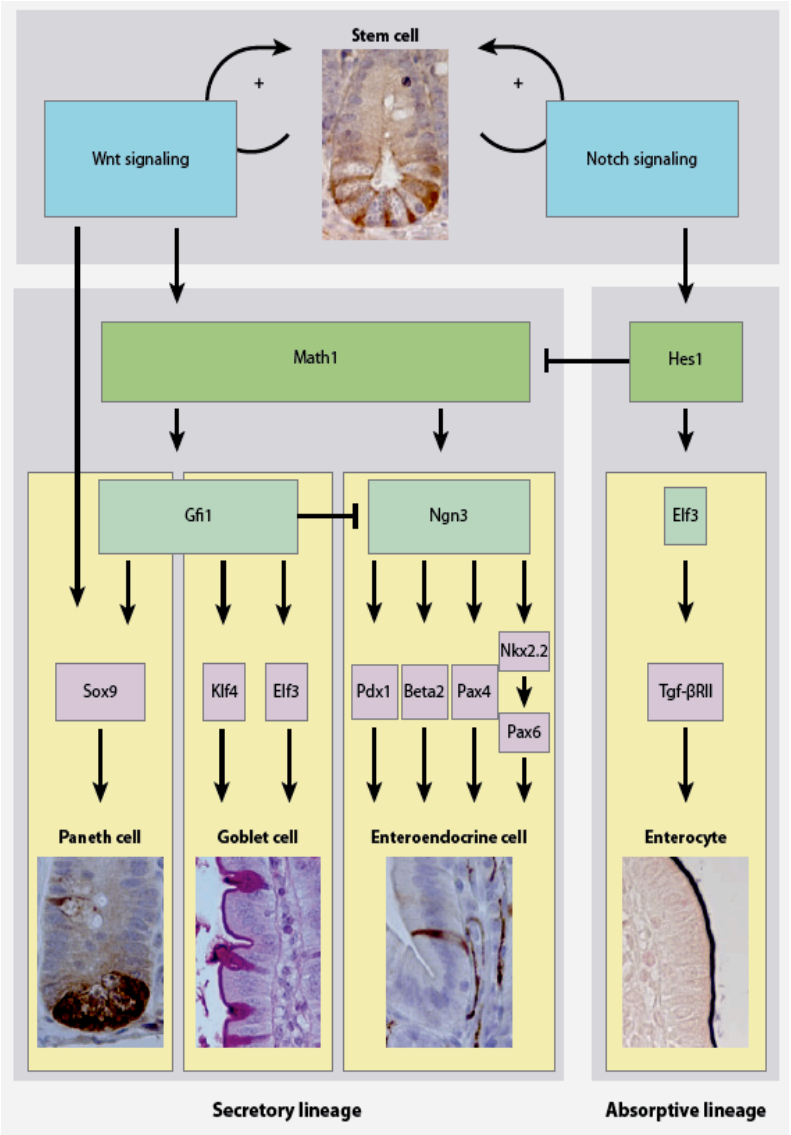
Annu. Rev. Physiol. 2009. 71:5.1–5.20

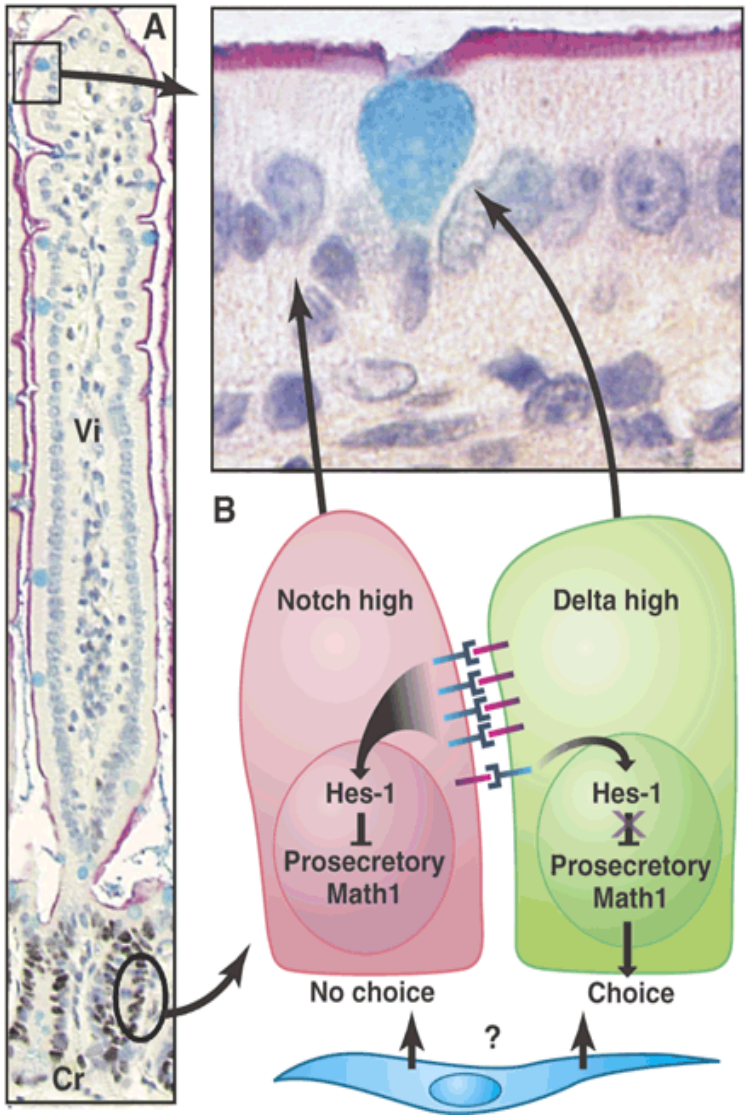
Differentiation of intestinal stem cells



Pinto & Clevers 2005 Biol. Cell 97, 185–196

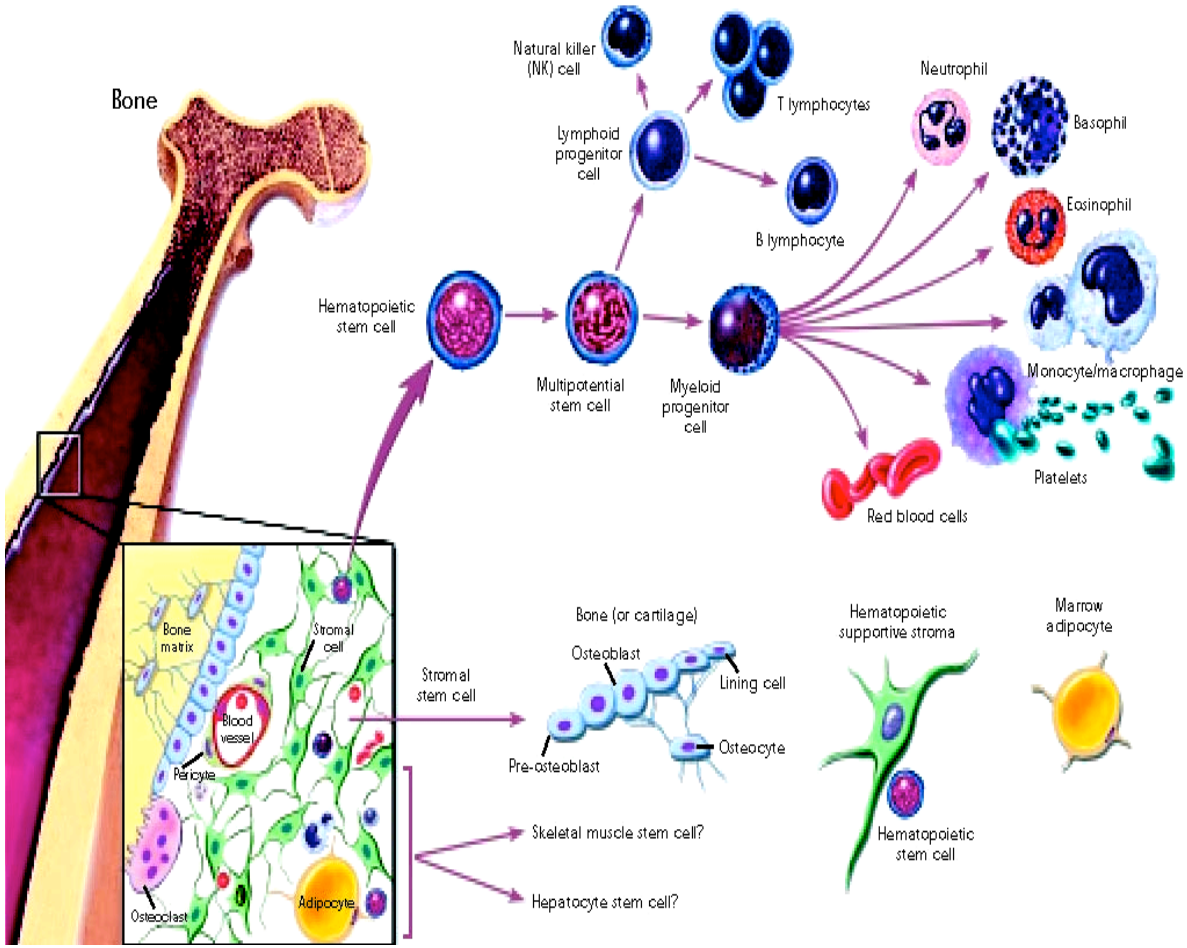
Wnt and Notch pathways in intestinal epithelial proliferation and differentiation





Somatic stem cells in bone marrow

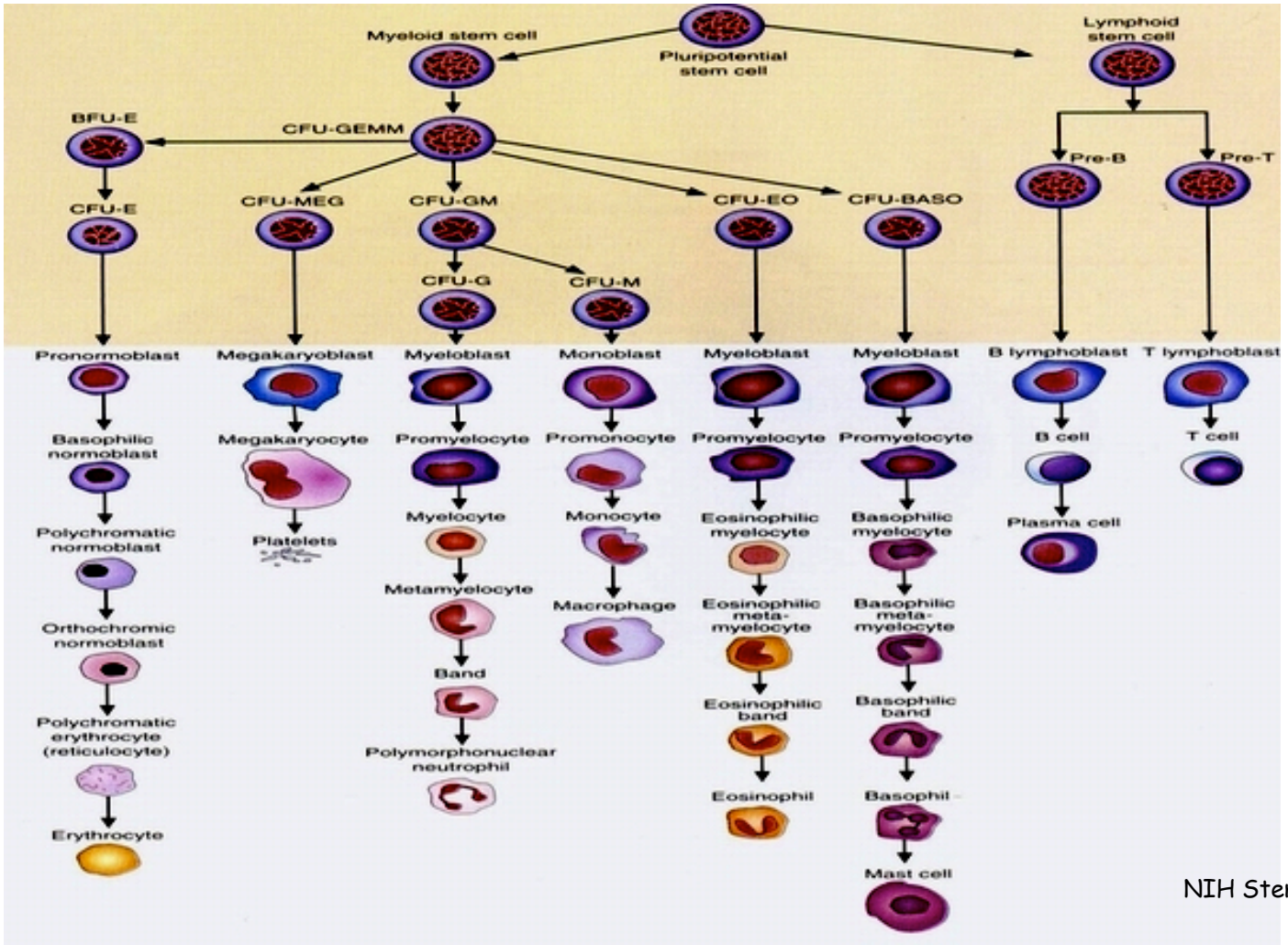
- In the 1960s, researchers discovered that the bone marrow contains **hematopoietic stem cells**, which forms all the types of blood cells in the body.
- A second population, called **bone marrow stromal cells or mesencymal stem cells**, was discovered a few years later which can give rise to bone, cartilage, fat, and fibrous connective tissue lineages.



NIH Stem Cells: Scientific Progress and Future Research Directions

Hematopoietic stem cells

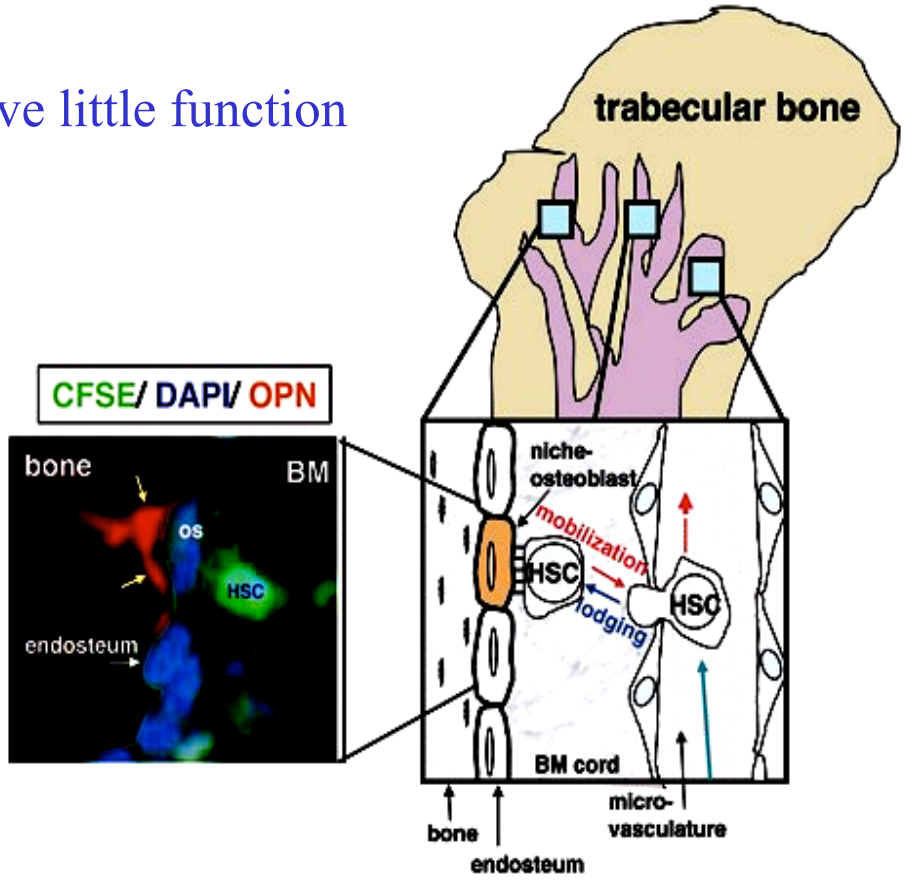
Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, macrophages, and platelets.



NIH Stem Cells

HSCs with their niches in bone marrow

- Haematopoietic stem cells regenerates the entire blood and immune system, and also makes copies of itself after limit-dilution transplantation.
- HSCs circulate freely, but seem to have little function outside specific anatomic locations.
- Hematopoietic stem cells (HSCs) are mainly located in the trabecular part of the long bones. The endosteum lines the inner bone surfaces and is comprised of stromal cells and osteoclasts (white) as well as spindle shaped osteoblasts (brown).
- The osteoblasts are thought to serve as niche cells to maintain quiescence and prevent differentiation of attached HSCs.



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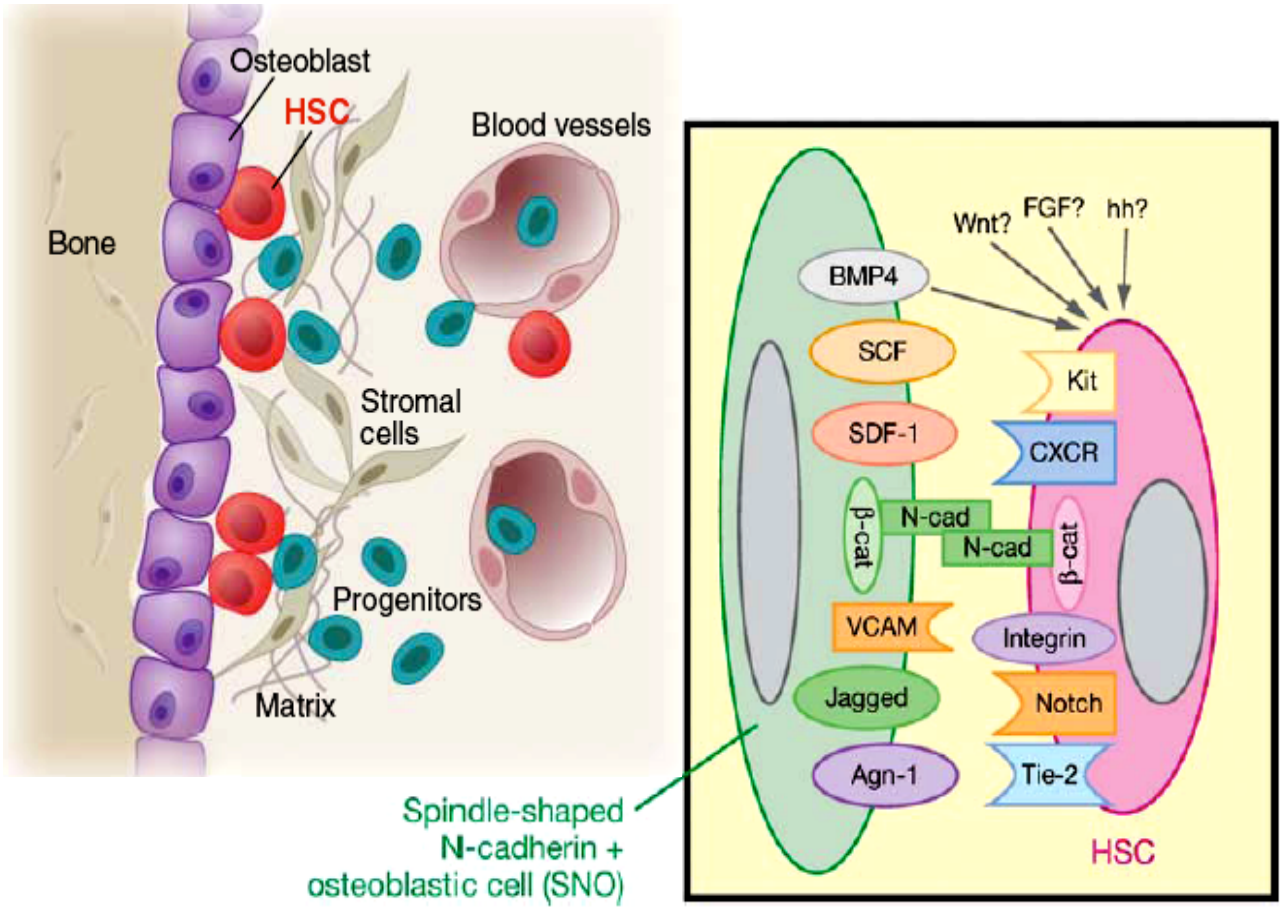
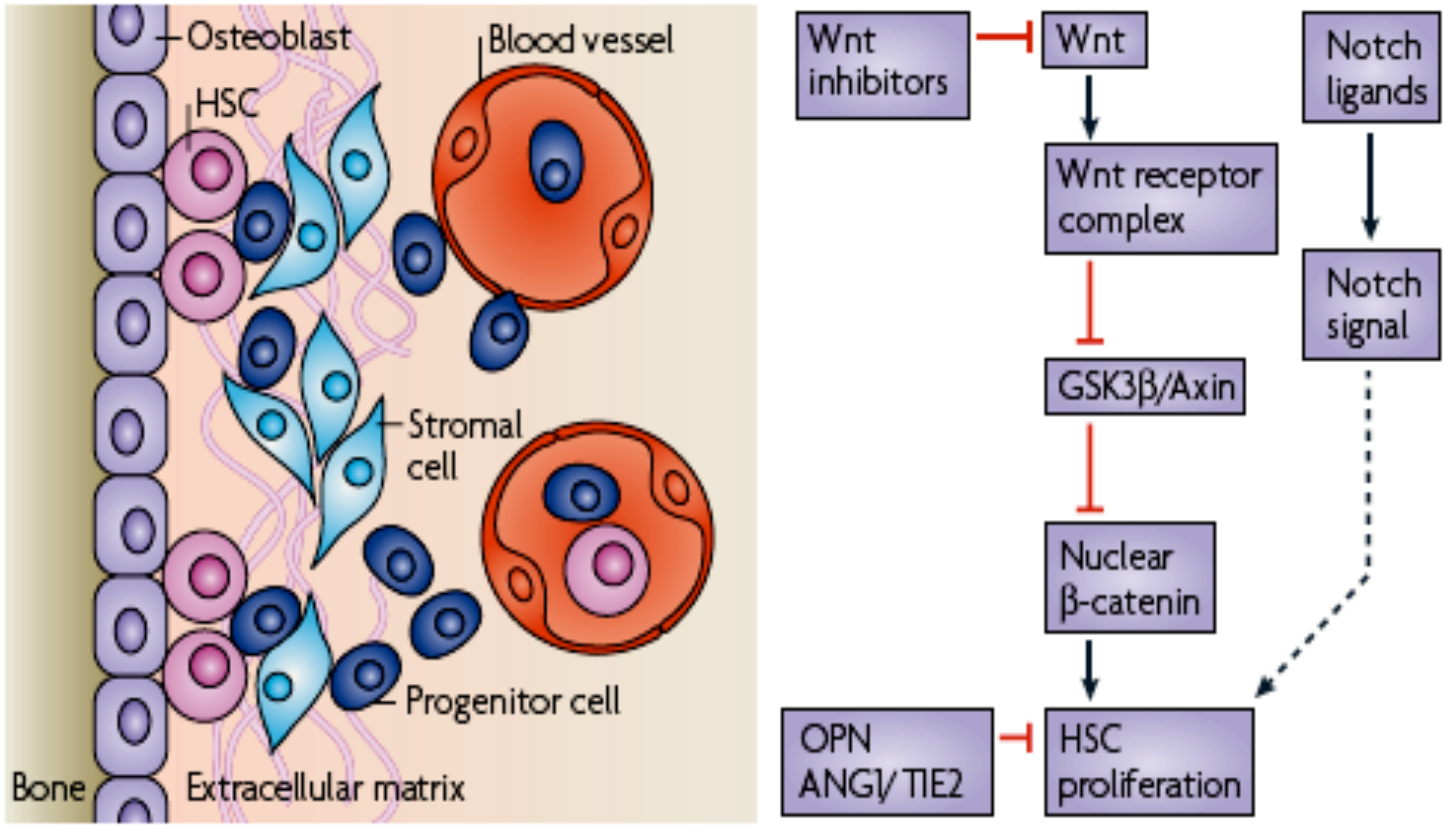


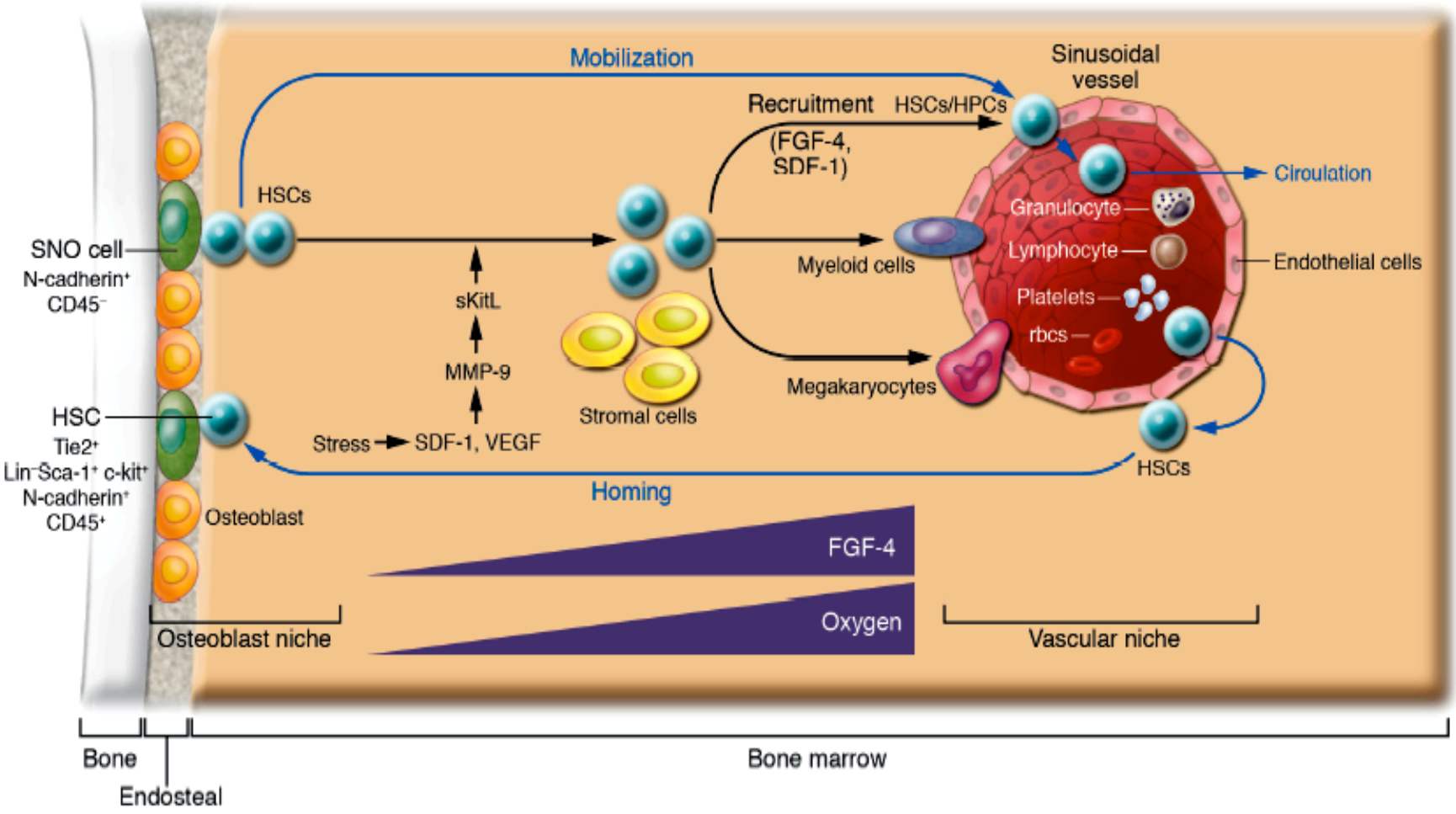
Moore & Lemischka 2006. Science; Li & Xie 2005. Ann. Rev. Cell. Biol.

HSCs with their niches in bone marrow



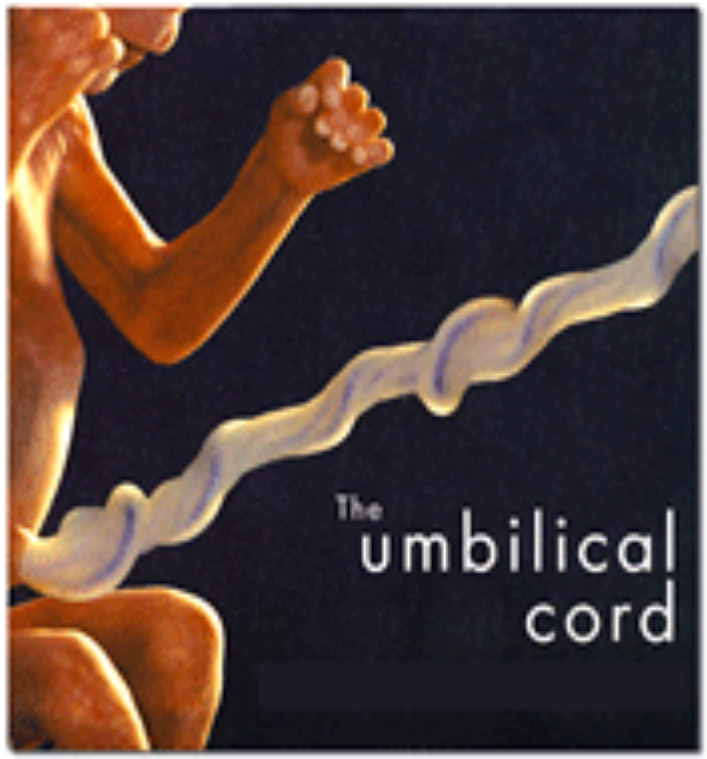
Nat Rev Mol Cell Biol 2008 9: 11-21

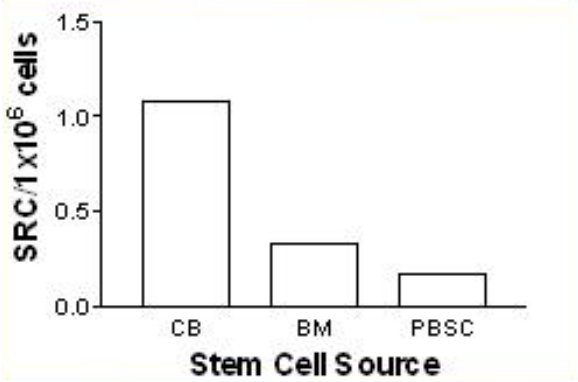
HSCs with their niches in bone marrow



Yin & Li 2006. J. Clin. Invest.

Stem cells in umbilical cord blood





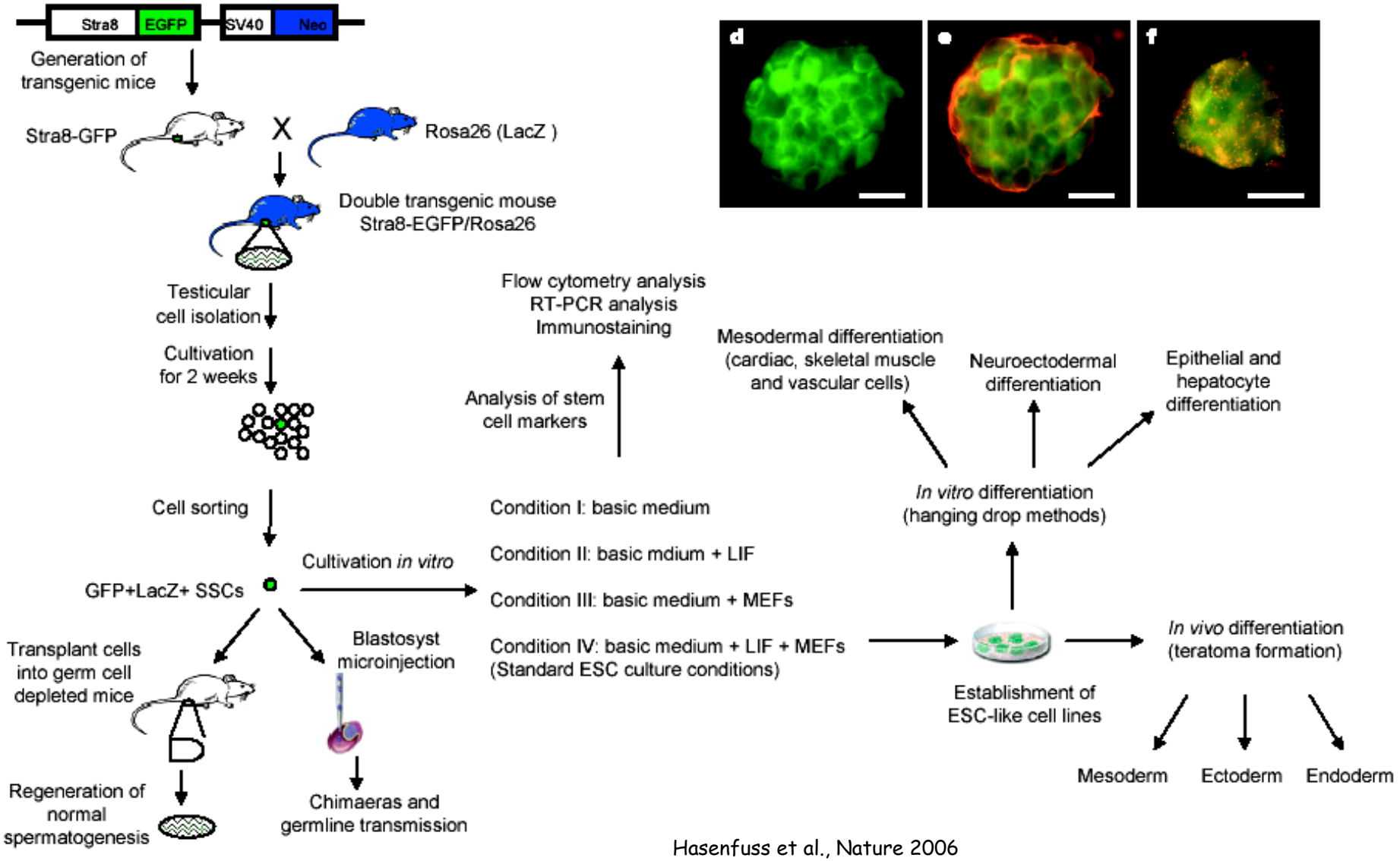
- "Cord blood" is the blood that remains in the umbilical cord and the placenta after the delivery of a baby. This "afterbirth treasure" was traditionally discarded.

- It was discovered that the blood remaining in the umbilical cord and the placenta is extremely rich in stem cells including

- It also contains **hematopoietic stem cells, mesencymal stem cells and endothelial progenitors**

Wang et al., Blood 1997

Dervation of pluripotent germ stem cells



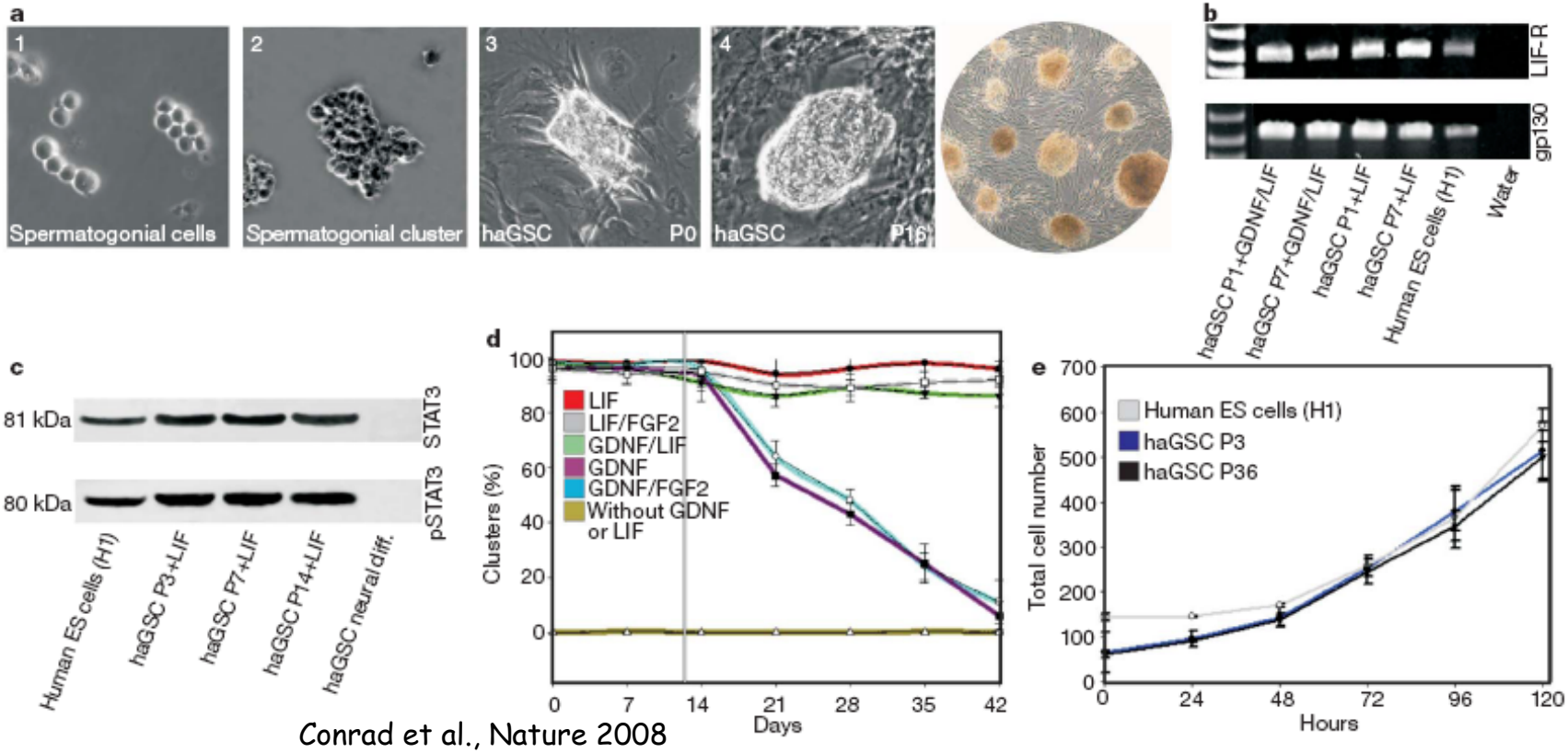
Hasenfuss et al., Nature 2006

Dervation of pluripotent germ stem cells

doi:10.1038/nature07404 nature

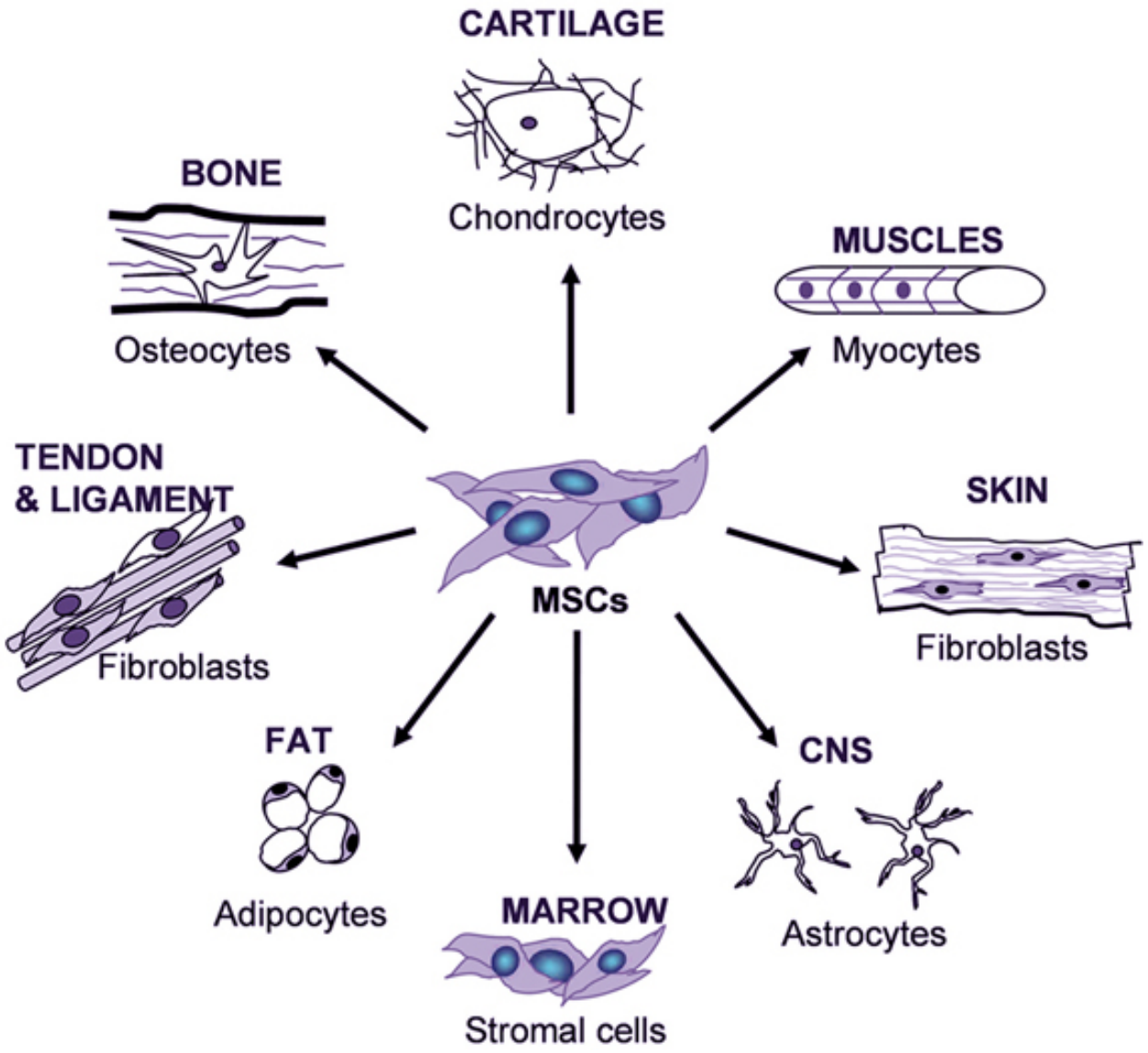
ARTICLES

Generation of pluripotent stem cells from adult human testis



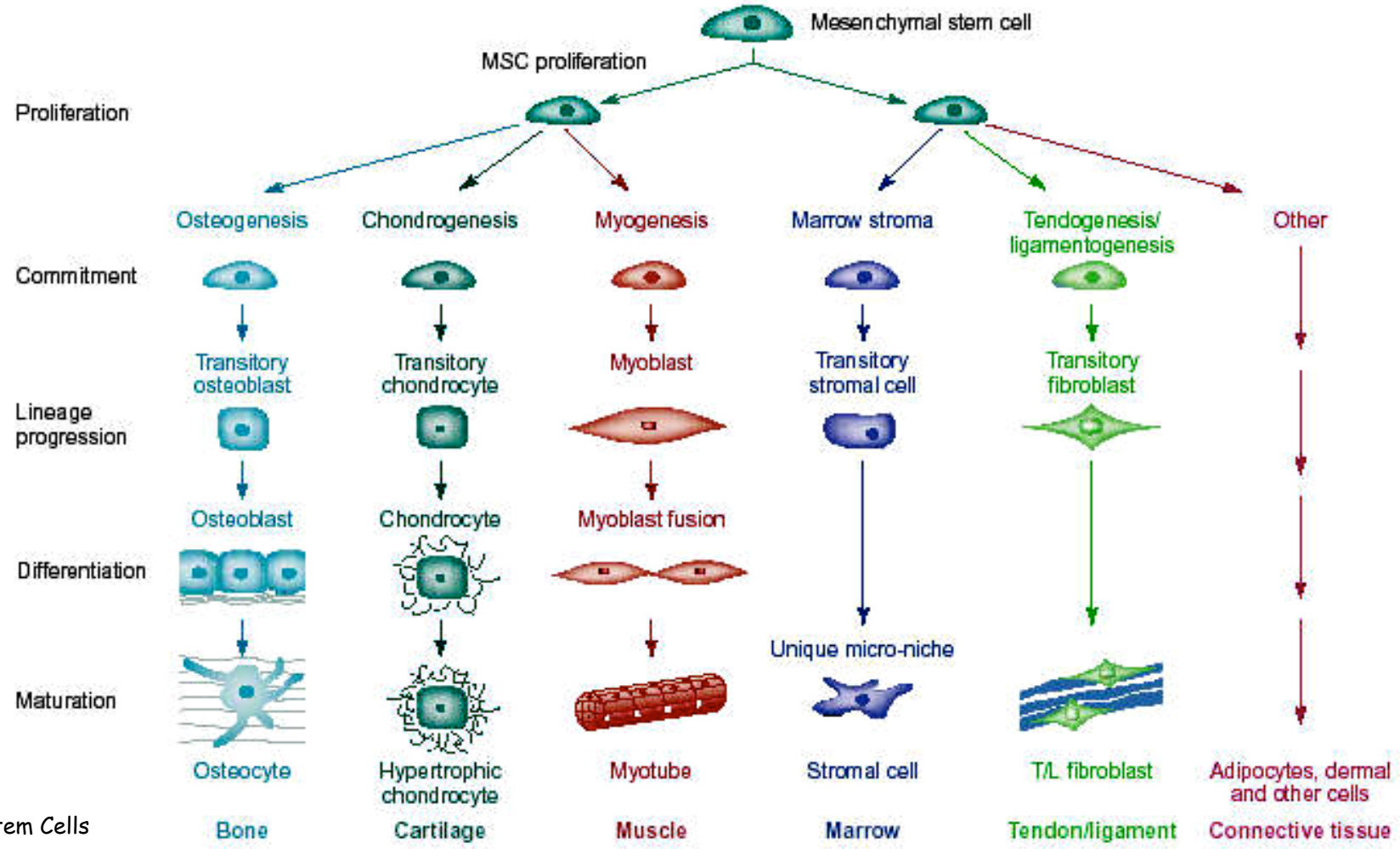
Conrad et al., Nature 2008

Stem cells isolated from undefined tissue position that expressed specific features



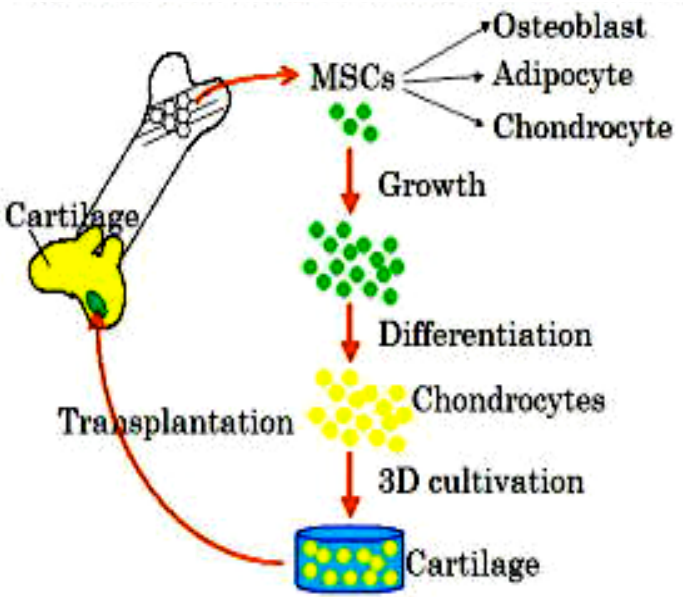
Mesenchymal stem cells

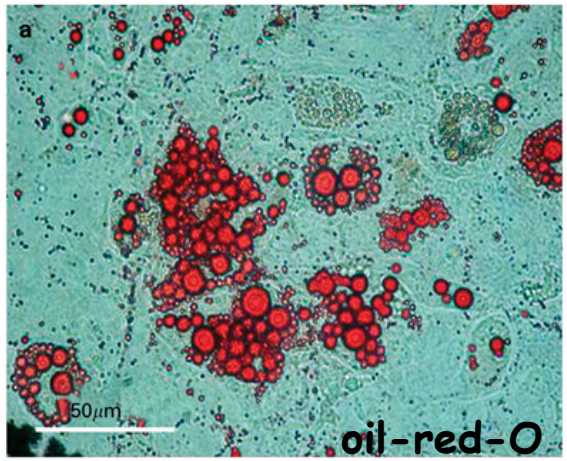
Mesenchymal stem cells give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

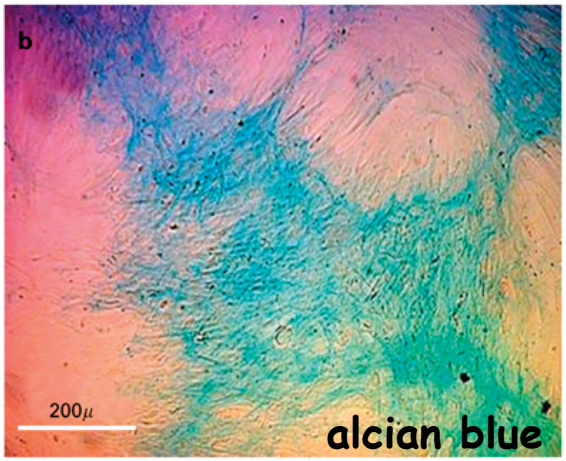


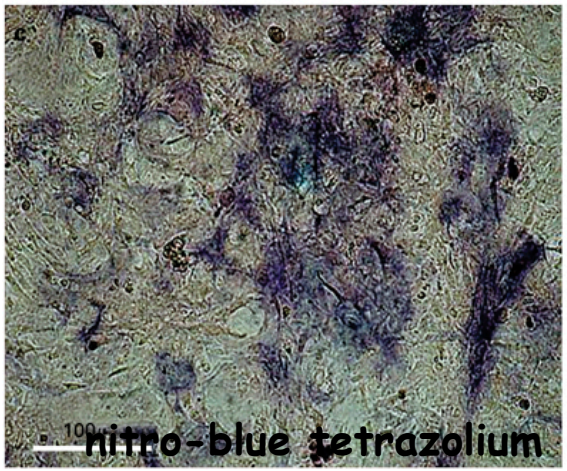
NIH Stem Cells

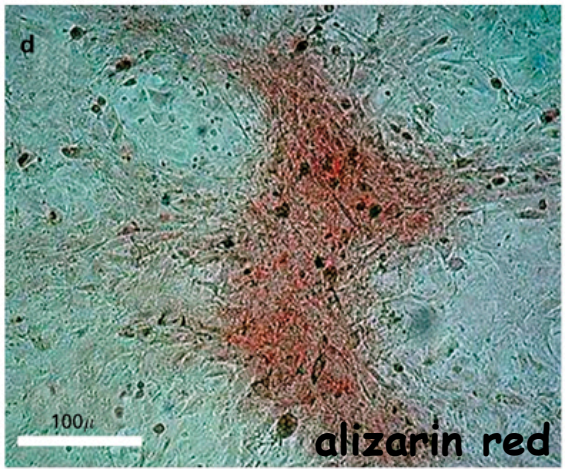
Bone and cartilage repairing with MSC





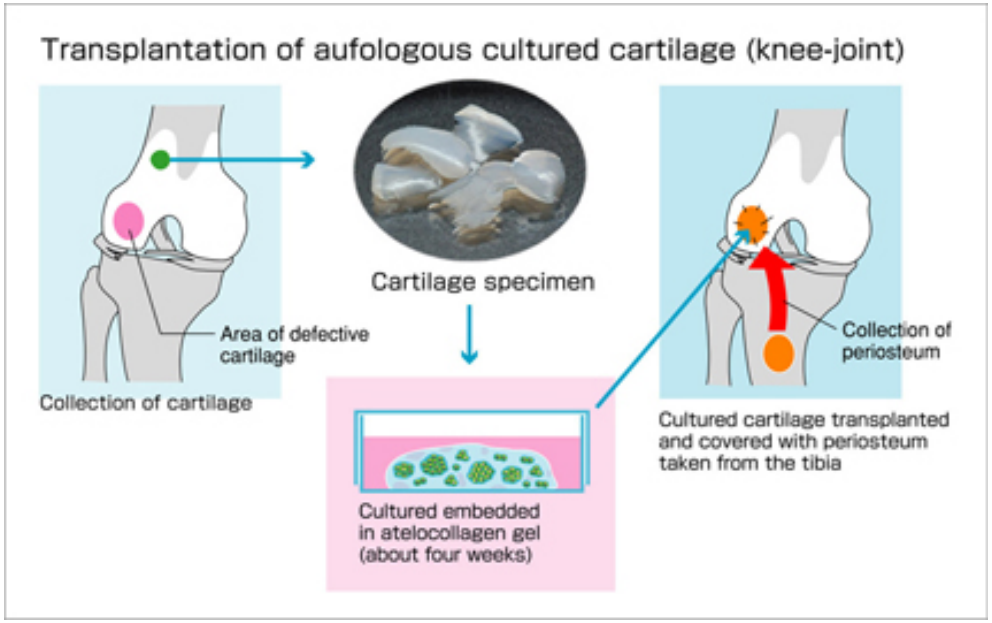


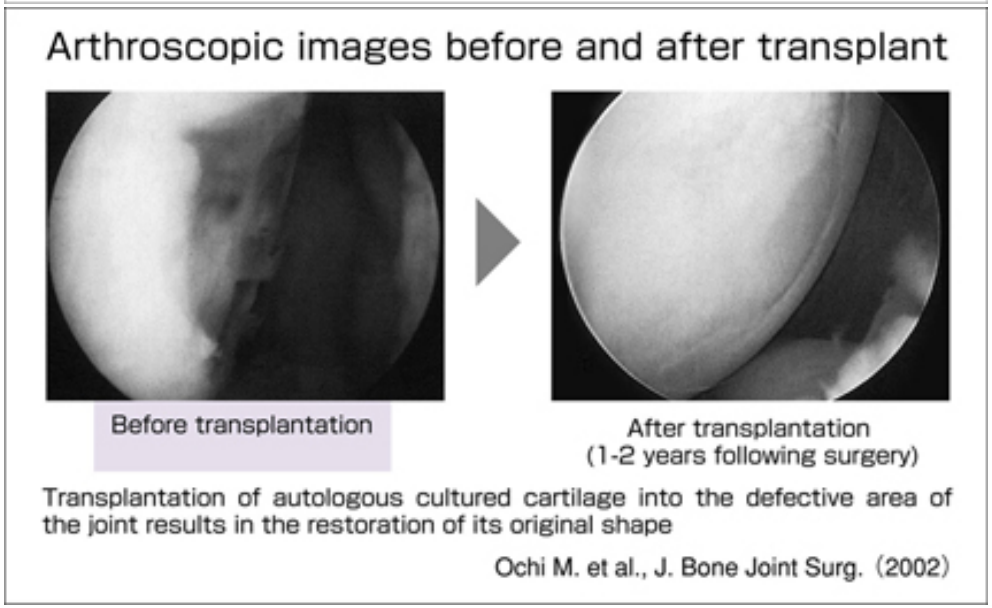


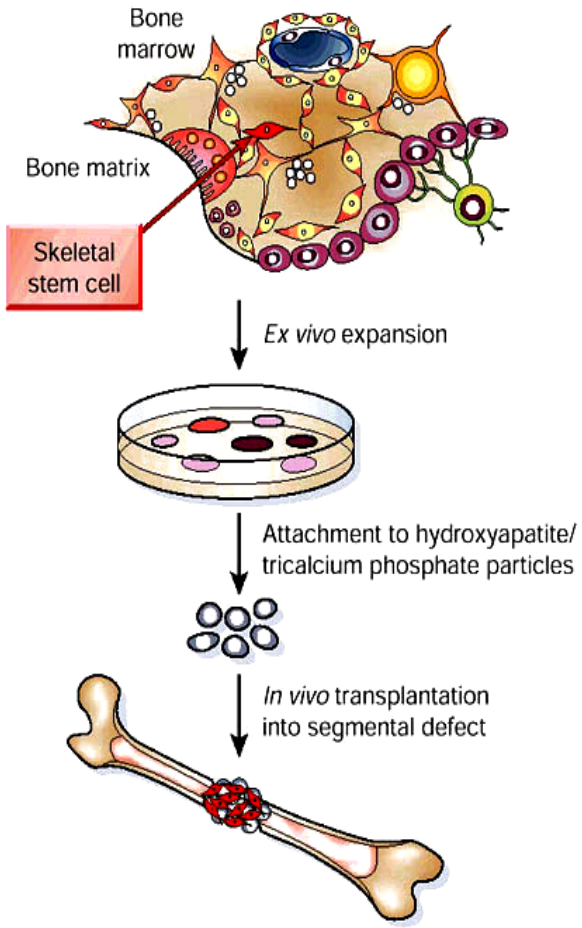


Kassis et al., BMT 2006

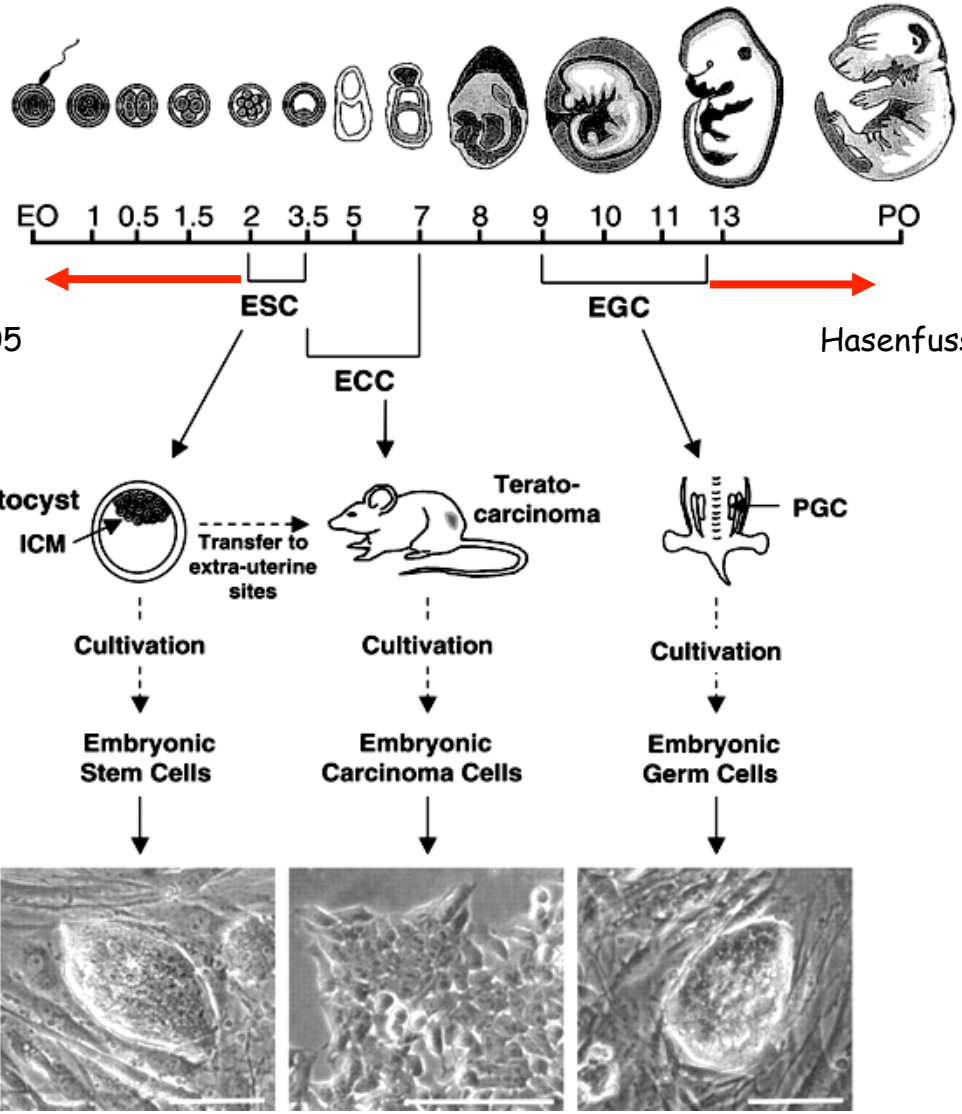
Bone and cartilage repairing with MSC







Derivation of pluripotent stem cells from *in-vitro* culture of embryonic cells

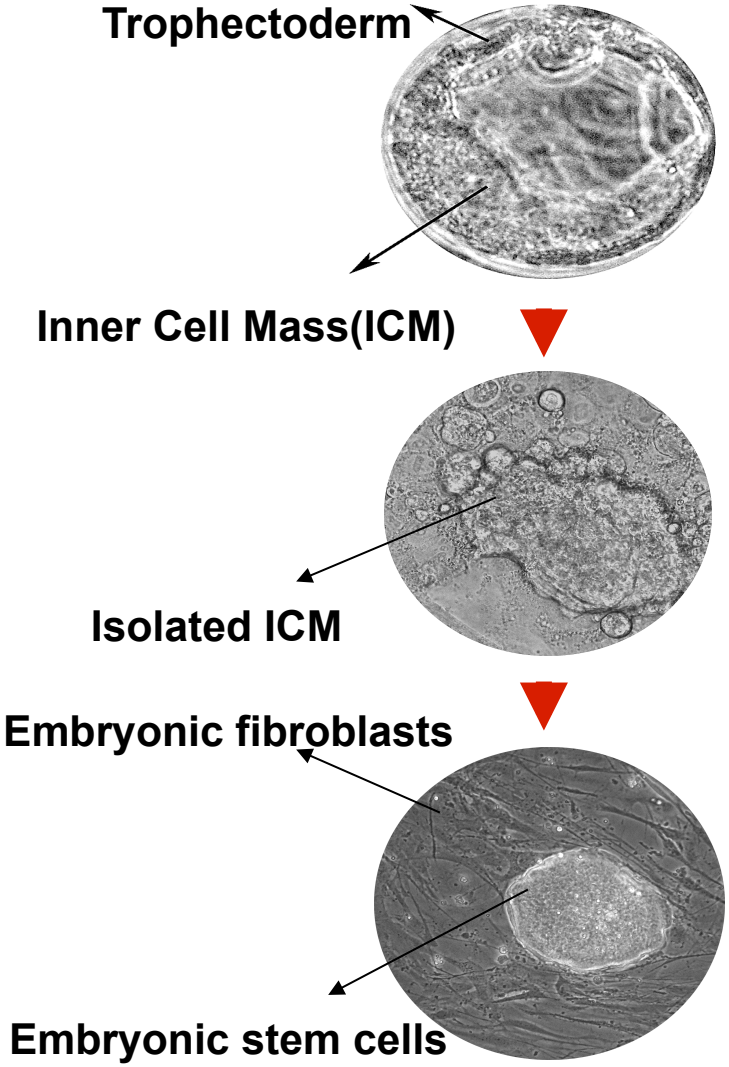


Lanza et al., Nature 2005

Hasenfuss et al., Nature 2006

Wobus and Boheler 2005. Physiol. Rev. 85: 635-678,

Establishment of embryonic stem cells from blastocysts embryo



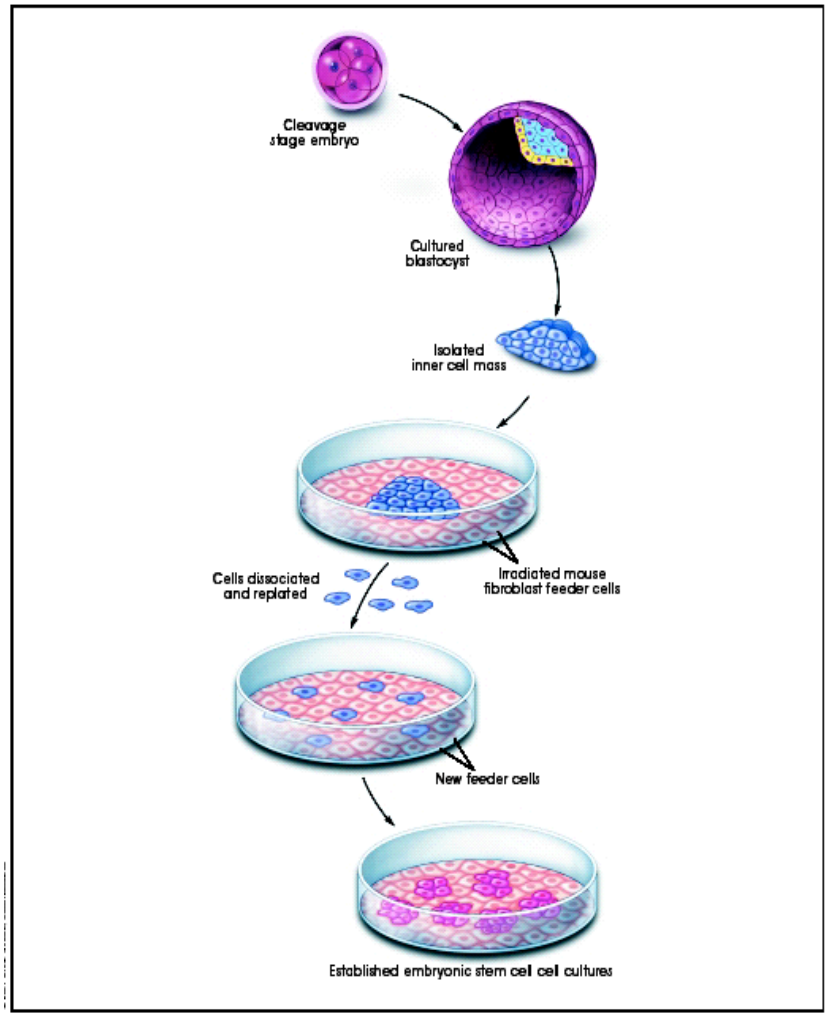
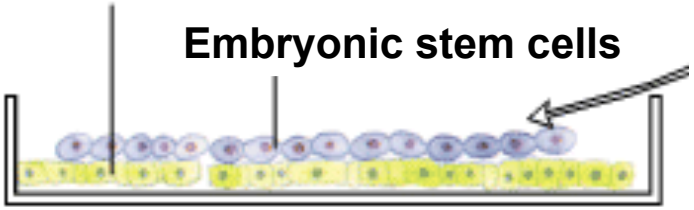


Figure C.1. Techniques for Generating Embryonic Stem Cell Cultures.

Maintaining embryonic stem cells in cultures with MEF feeder or certain factors

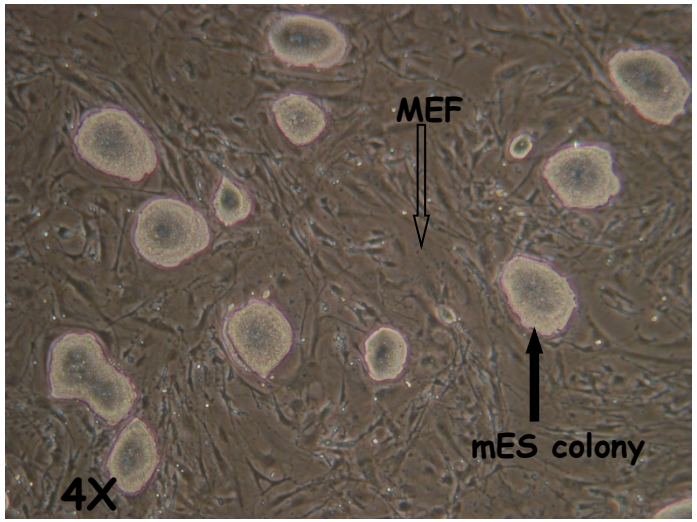
Mitomycin C treated MEFs

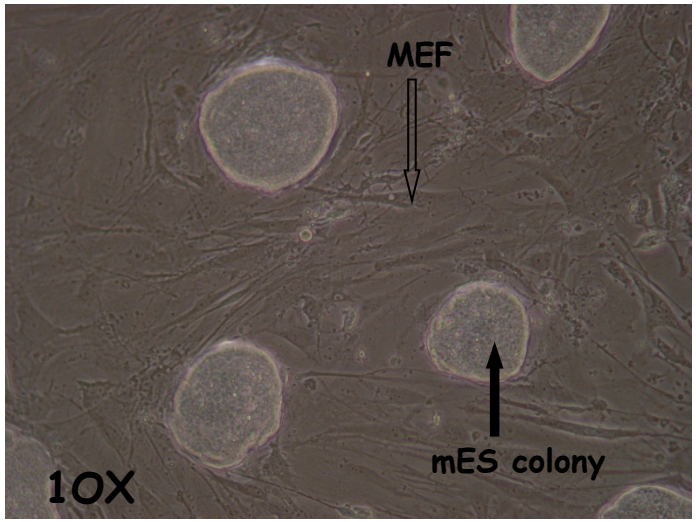


Feeder cells: Mitomycin C treated E13.5 MEF (mouse embryonic fibroblast)

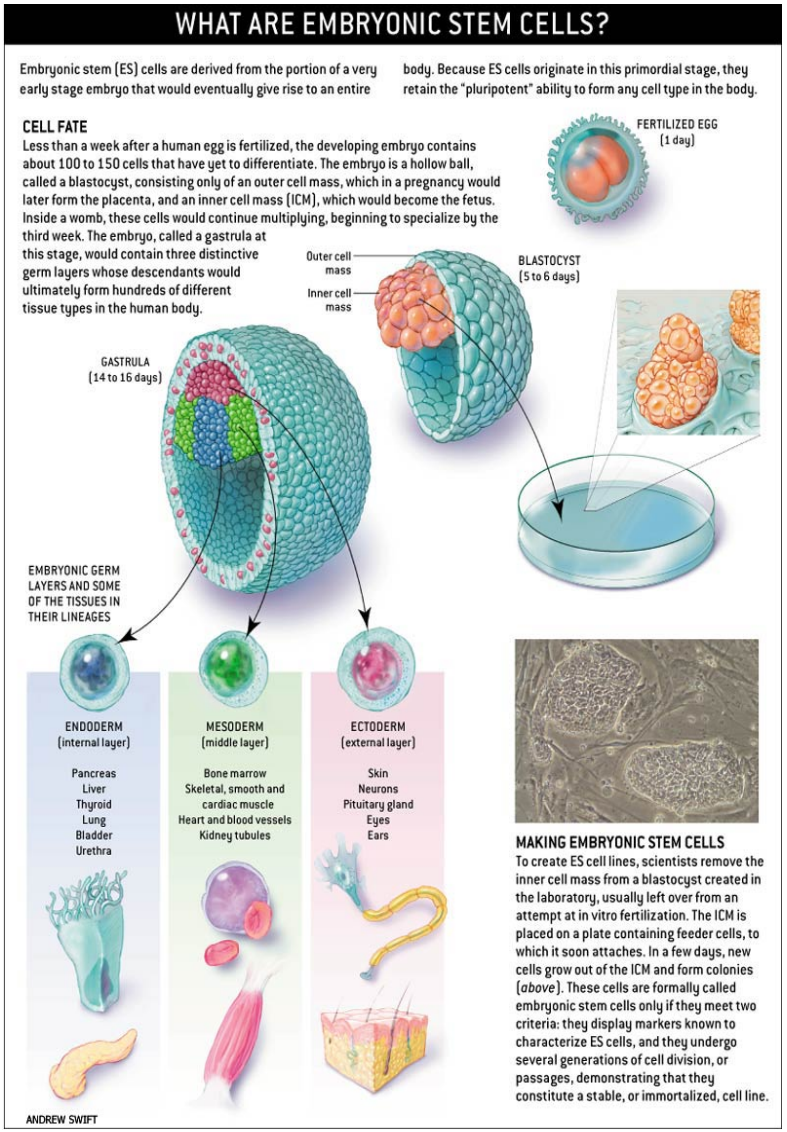
0.1% gelatin coating

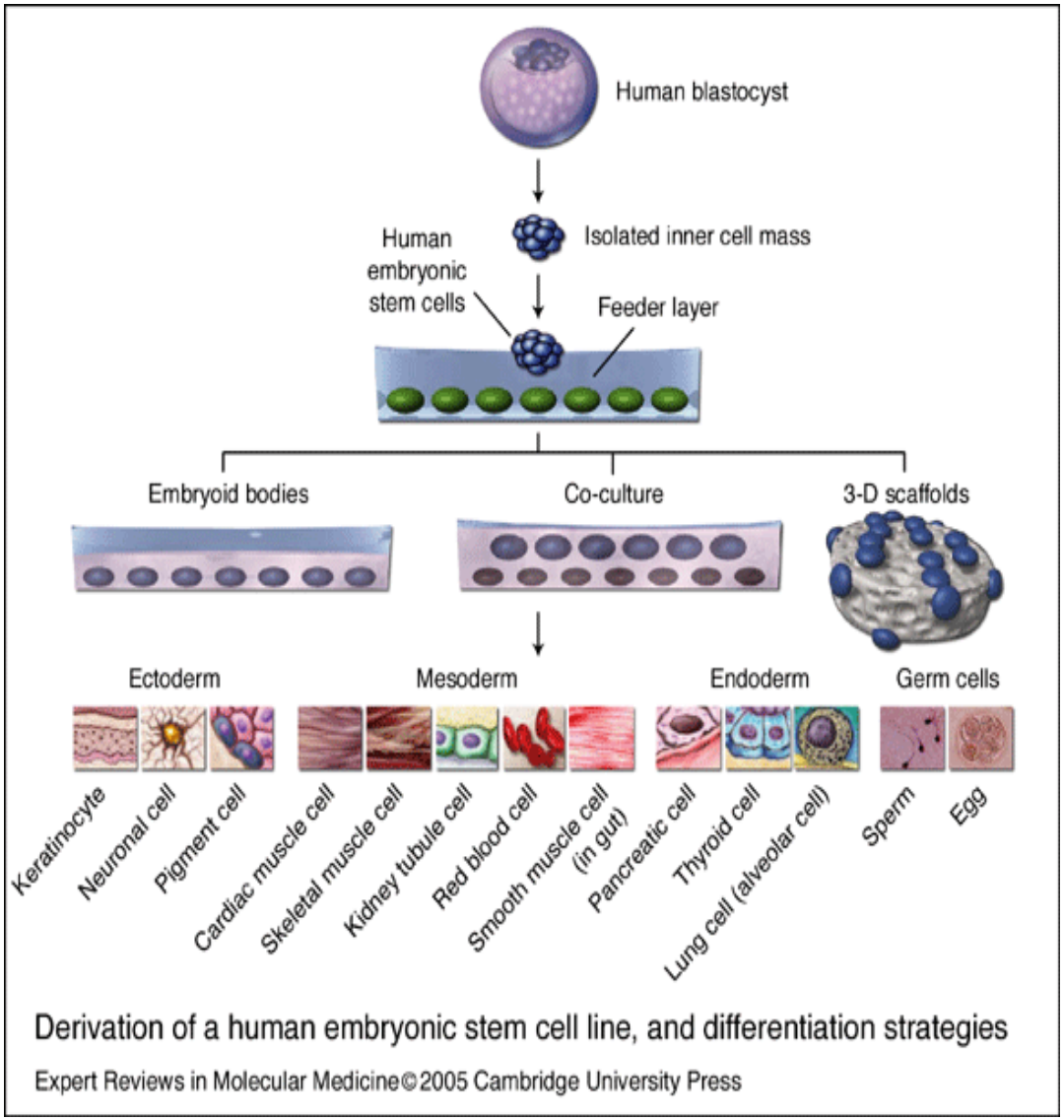
Medium:1000U/ml LIF



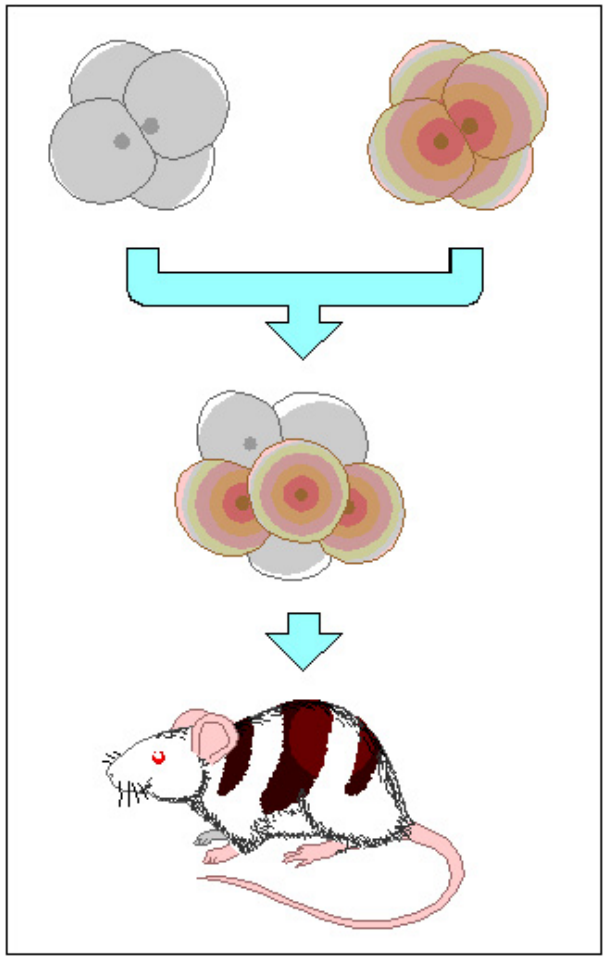


Pluripotency of embryonic stem cells

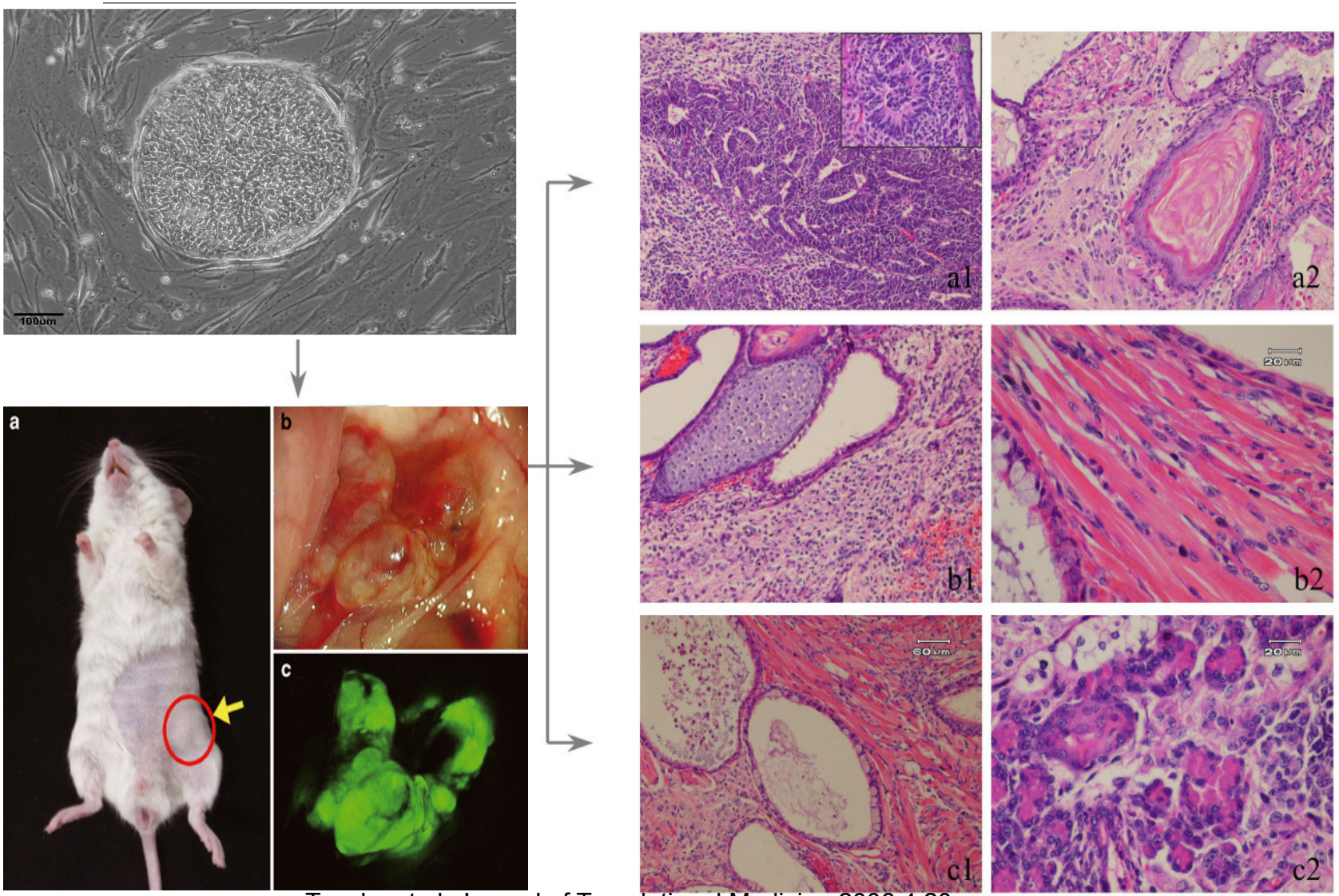




Differentiation capability of embryonic stem cells (Derivation of chimera mice)

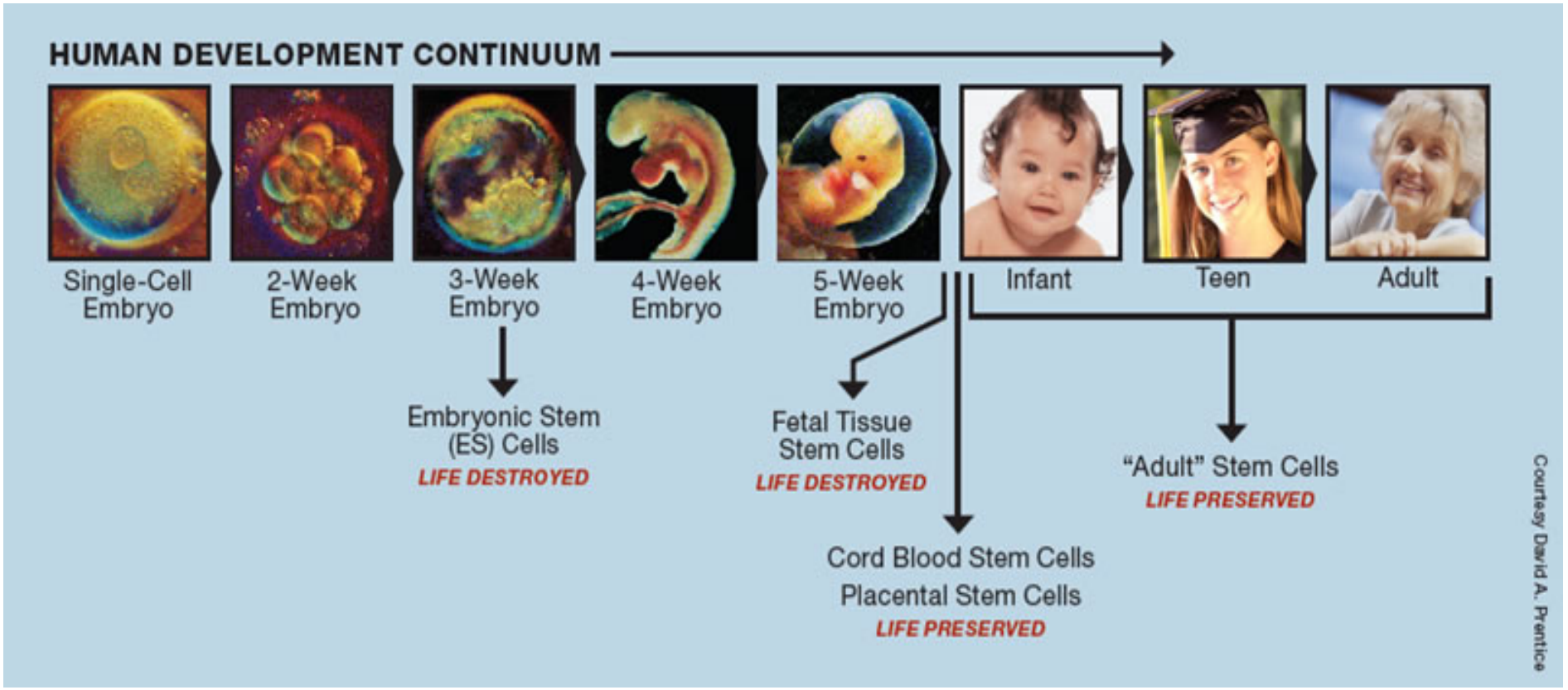


Differentiation capability of embryonic stem cells (Teratoma)



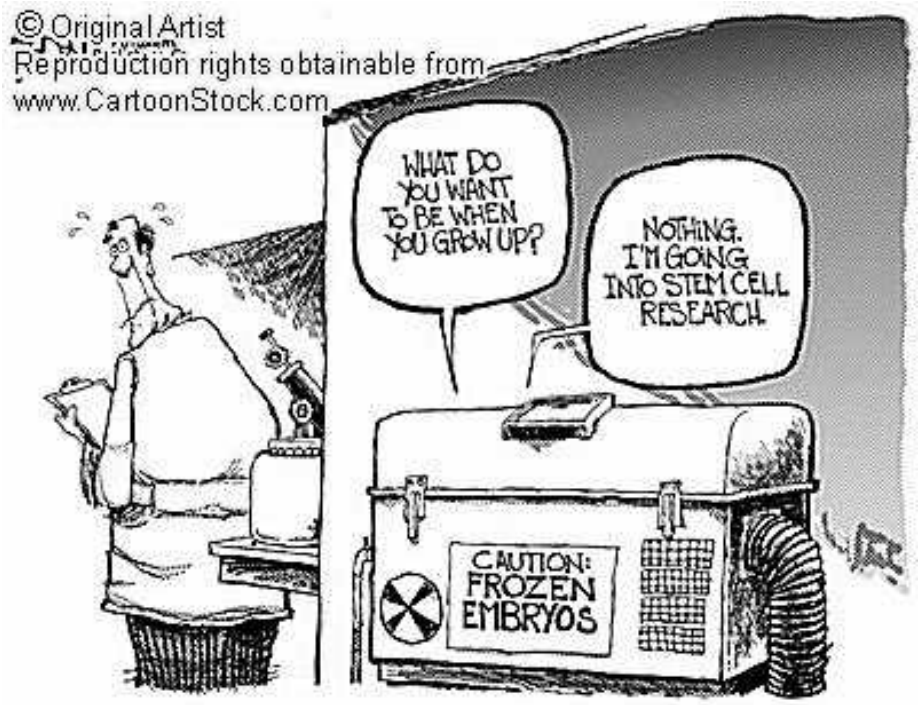
Tanaka et al. Journal of Translational Medicine 2006 4:20

Challenges for embryonic stem cells: ethical issue



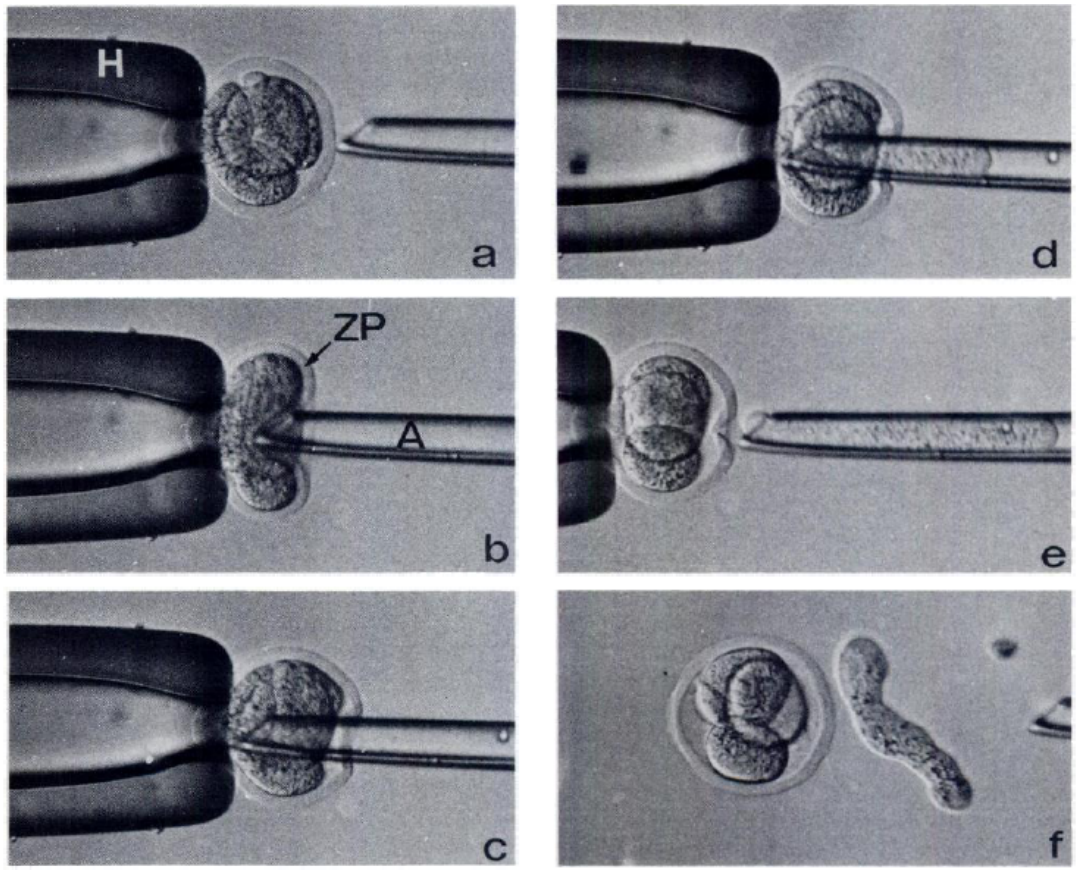
Challenges for embryonic stem cells

- At present most human embryonic stem cells can only be obtained by destroying live human embryos at the blastocyst stage
- They proliferate rapidly and are extremely versatile, but there is scant scientific evidence that embryonic stem cells will form normal tissues in a culture dish
- Embryonic stem cells are difficult to develop into a stable cell line. It spontaneously accumulate genetic abnormalities in embryonic-stem cell cultures
- Embryonic stem cells are prone to uncontrollable growth and tumor formation when placed in animals



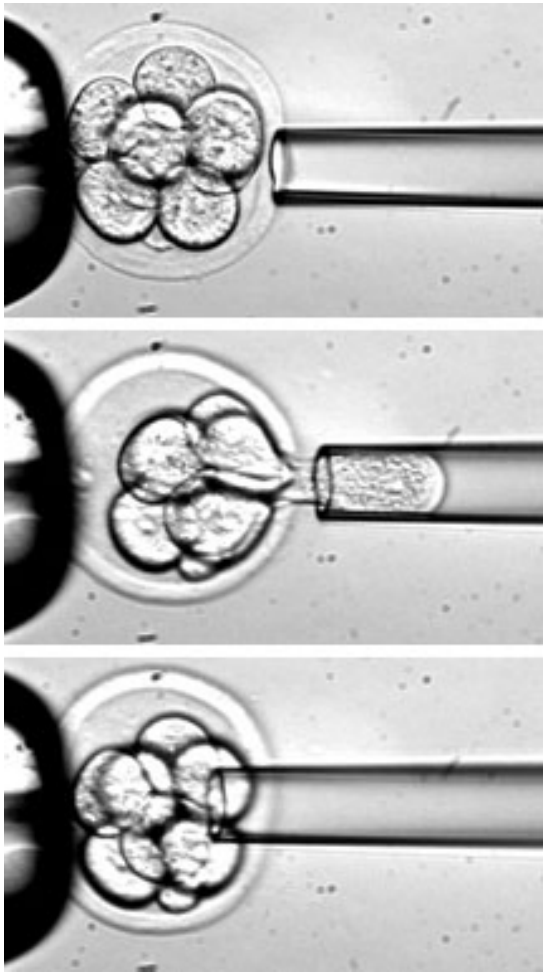
Establishment of embryonic stem cells without destroying embryo

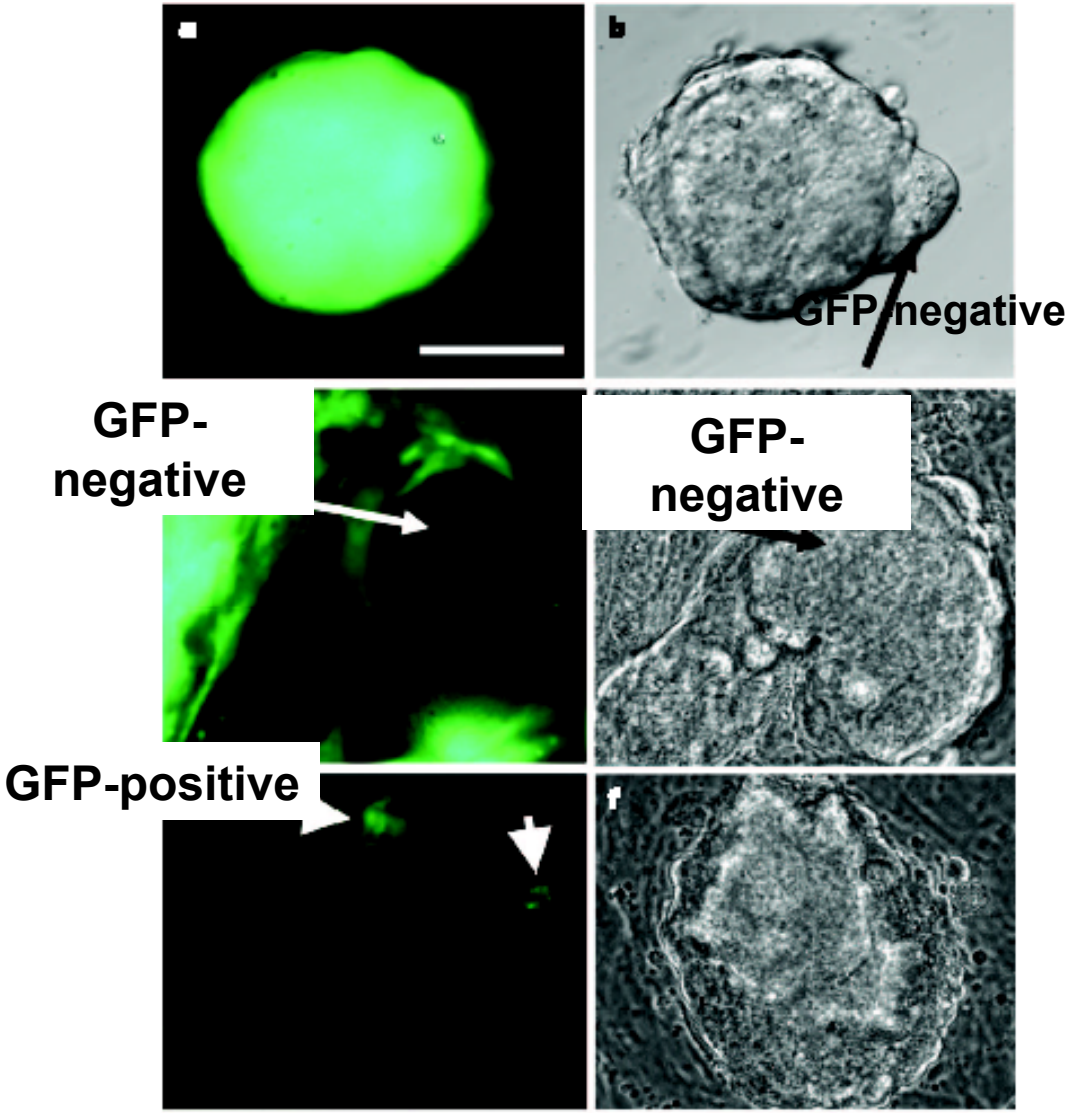
- PGD **(Pre-Implantation Genetic Diagnosis)**



LEEANDA J. WILTON,et al. BIOLOGY OF REPRODUCTION 40, 145-1 *52* (1989)

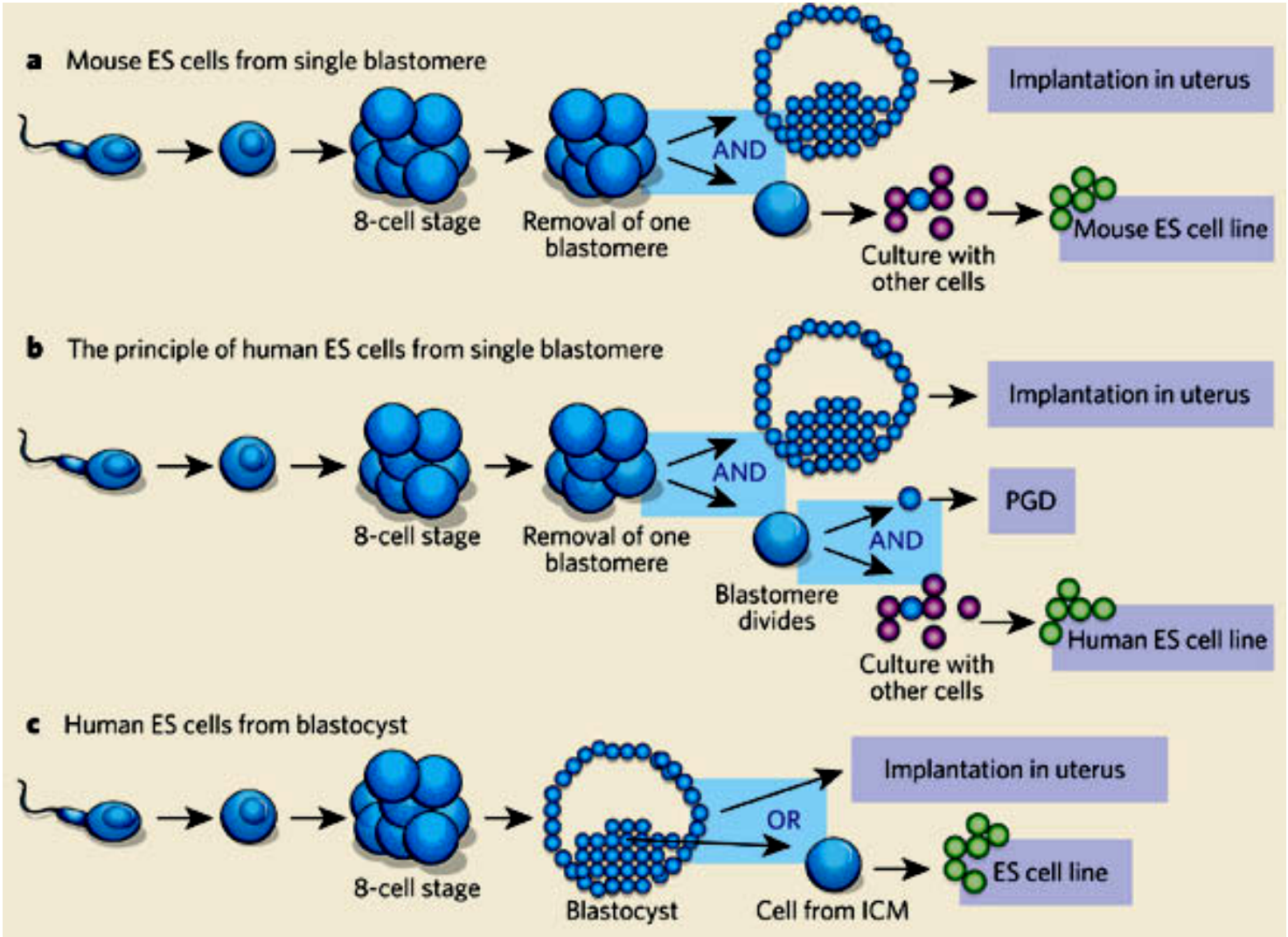
Embryonic stem cell lines derived from single mouse blastomere





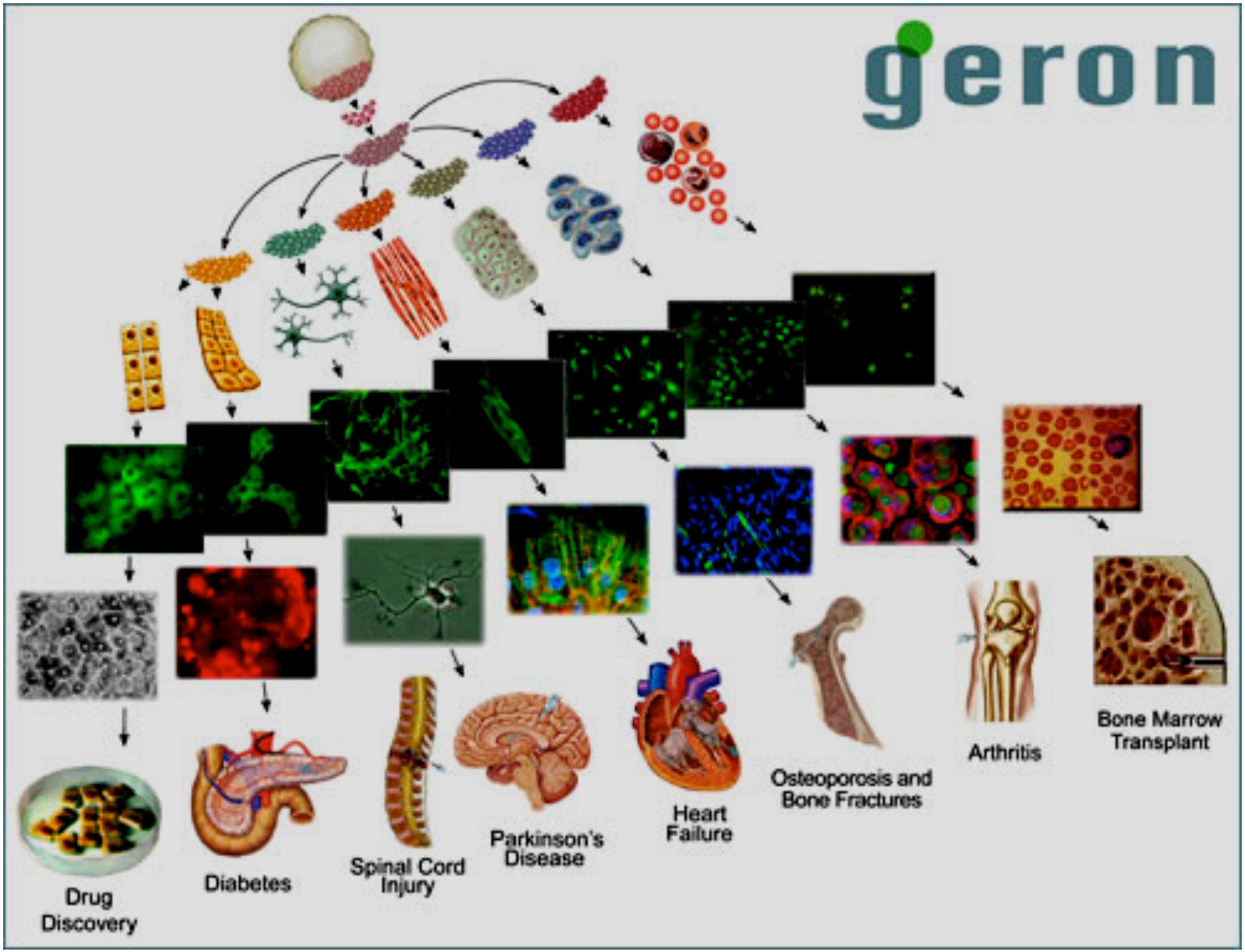
Lanza et al., Nature 2006 Jan

Embryonic stem cells derived from single blastomere without destroy embryos

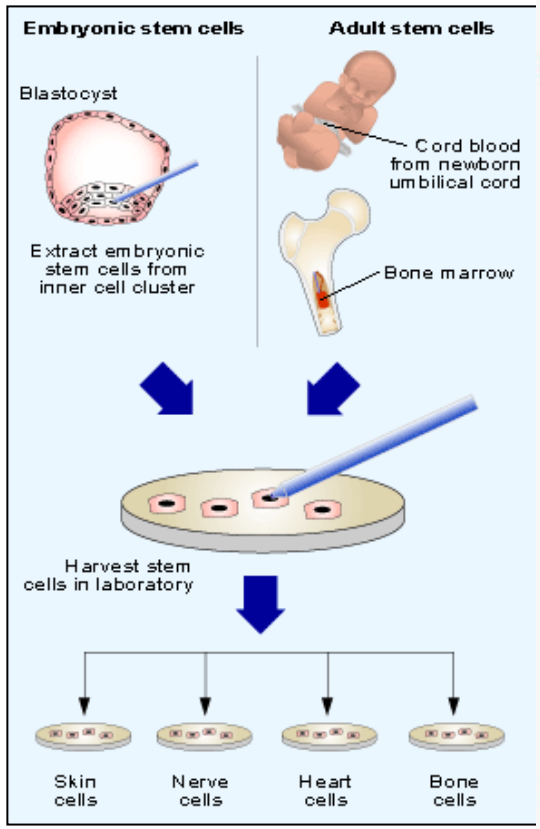


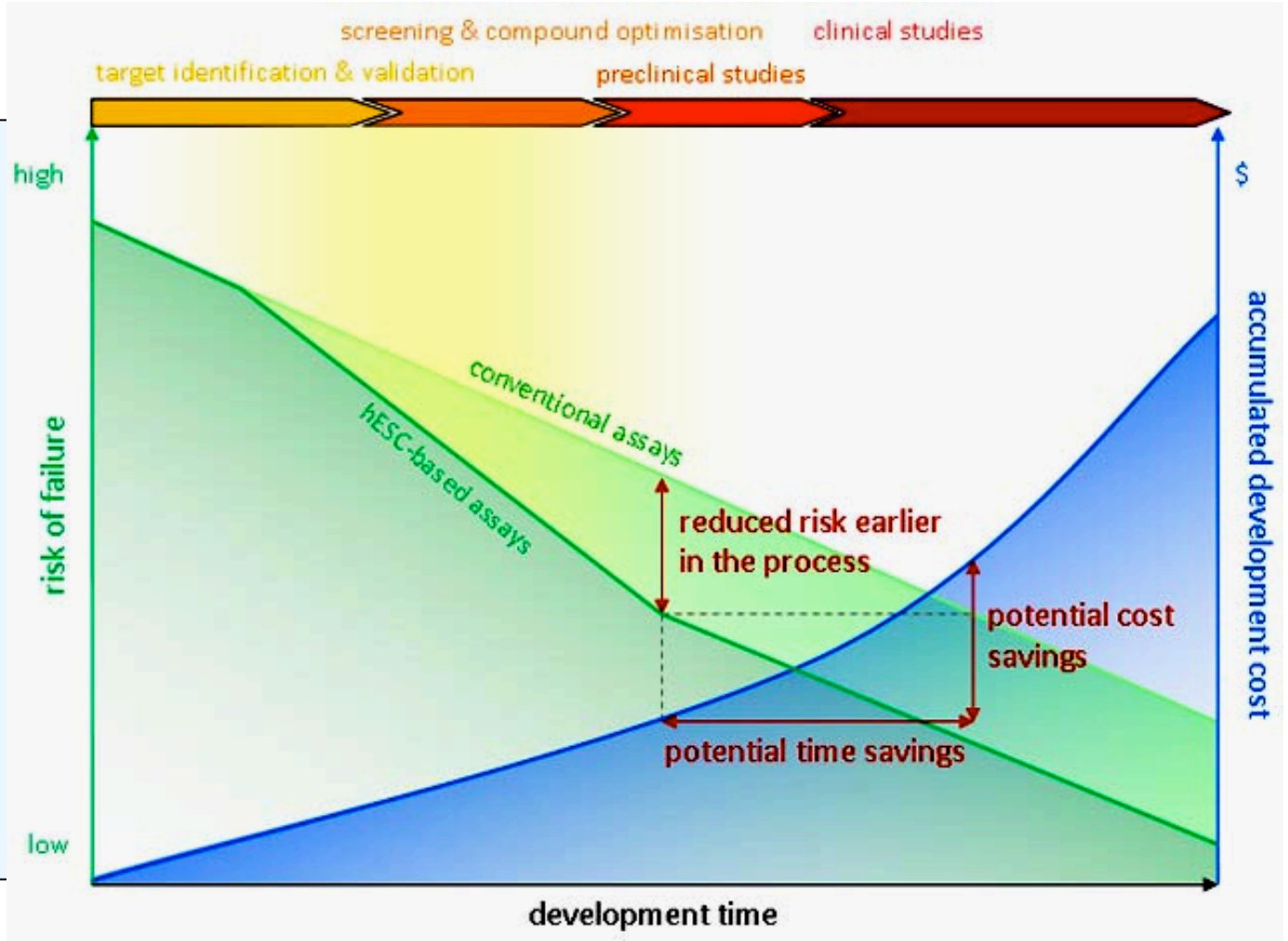
Simpson Nature 2006 Nov

Potential uses of stem cells



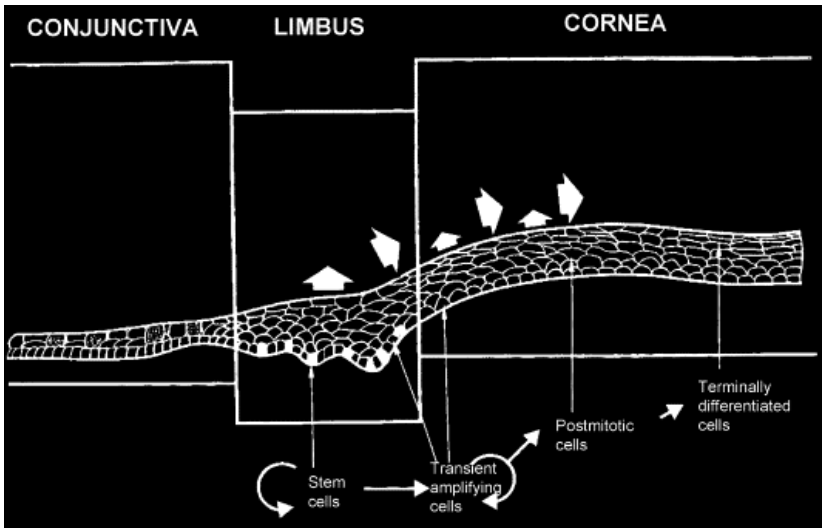
Potential uses of stem cells in drug testing

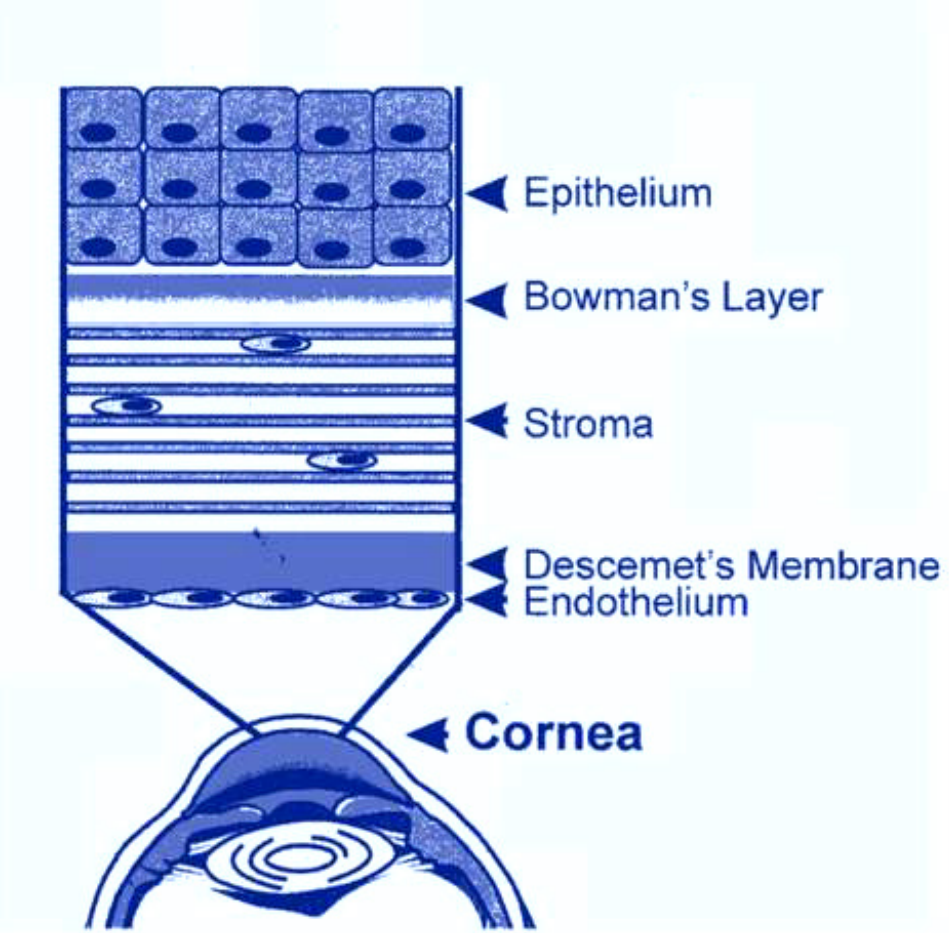




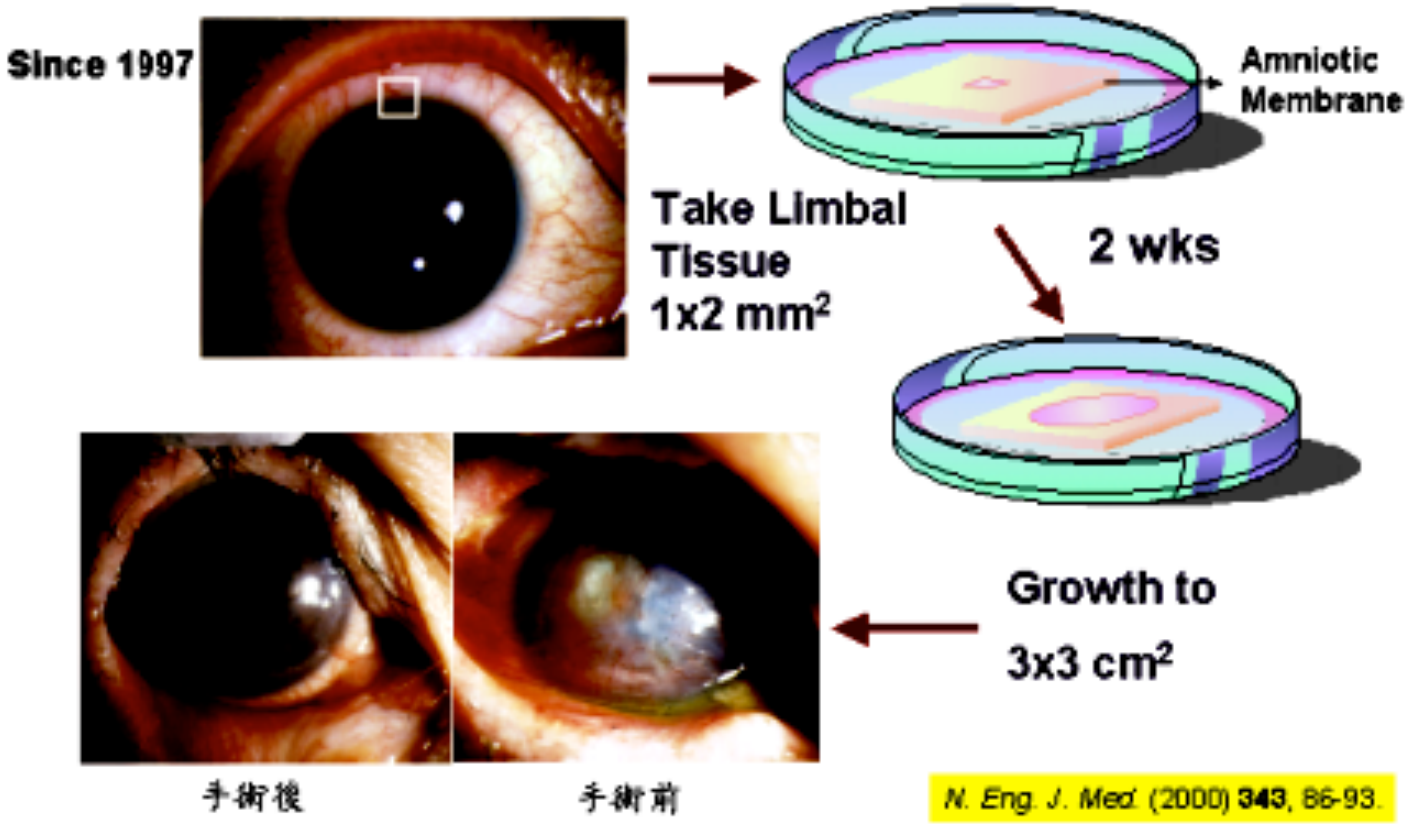
Limbus stem cells for corneal repairing

Limbus





Limbus stem cells for corneal repairing



N. Eng. J. Med. (2000) **343**, 86-93.

Growing airway utilizing patient-specific mesenchymal stem cells

Clinical transplantation of a tissue-engineered airway

Paolo Macchiarini, Philipp Jungebluth, Tetsuhiko Go, M Adelaide Asnaghi, Louisa E Rees, Tristan A Cogan, Amanda Dodson, Jaume Martorell, Silvia Bellini, Pier Paolo Parnigotto, Sally C Dickinson, Anthony P Hollander, Sara Mantero, Maria Teresa Conconi, Martin A Birchall

Summary

Background The loss of a normal airway is devastating. Attempts to replace large airways have met with serious problems. Prerequisites for a tissue-engineered replacement are a suitable matrix, cells, ideal mechanical properties, and the absence of antigenicity. We aimed to bioengineer tubular tracheal matrices, using a tissue-engineering protocol, and to assess the application of this technology in a patient with end-stage airway disease.

Methods We removed cells and MHC antigens from a human donor trachea, which was then readily colonised by epithelial cells and mesenchymal stem-cell-derived chondrocytes that had been cultured from cells taken from the recipient (a 30-year old woman with end-stage bronchomalacia). This graft was then used to replace the recipient's left main bronchus.

Findings The graft immediately provided the recipient with a functional airway, improved her quality of life, and had a normal appearance and mechanical properties at 4 months. The patient had no anti-donor antibodies and was not on immunosuppressive drugs.

Interpretation The results show that we can produce a cellular, tissue-engineered airway with mechanical properties that allow normal functioning, and which is free from the risks of rejection. The findings suggest that autologous cells combined with appropriate biomaterials might provide successful treatment for patients with serious clinical disorders.

Funding Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III, Fondo de Investigación Sanitaria, Spain; Charles Courtenay-Cowlin Fund, University of Bristol; UK Arthritis Research Campaign; and the James Tudor Foundation.

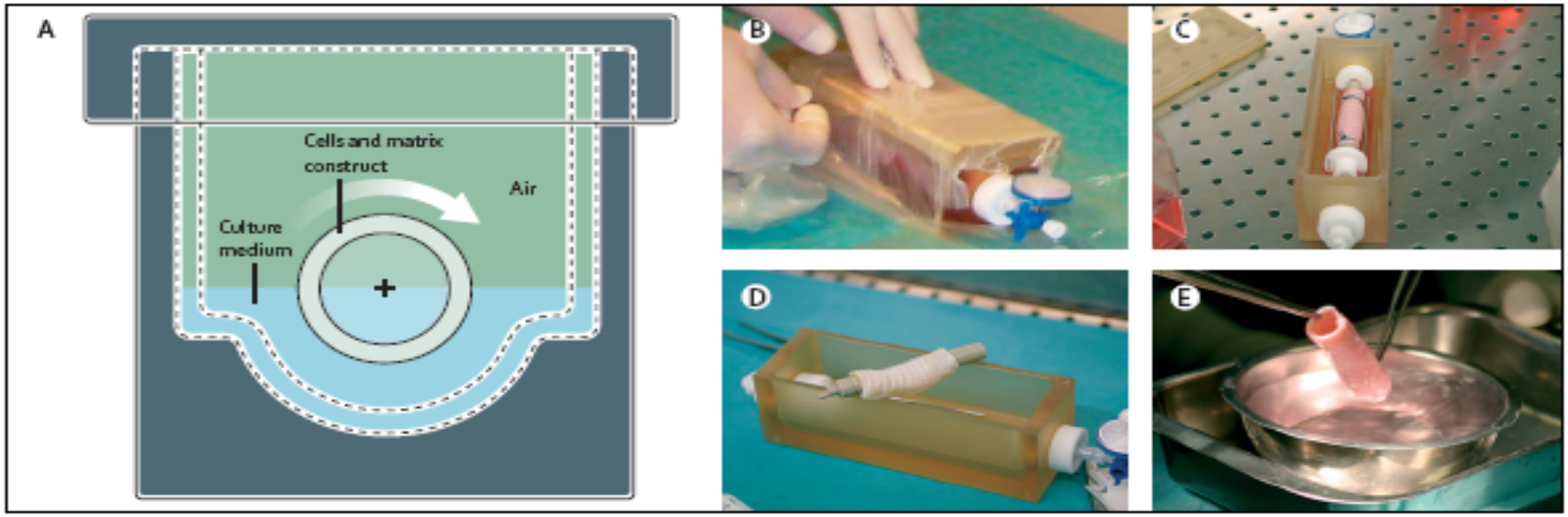
Lancet 2008; 372: 2023–30

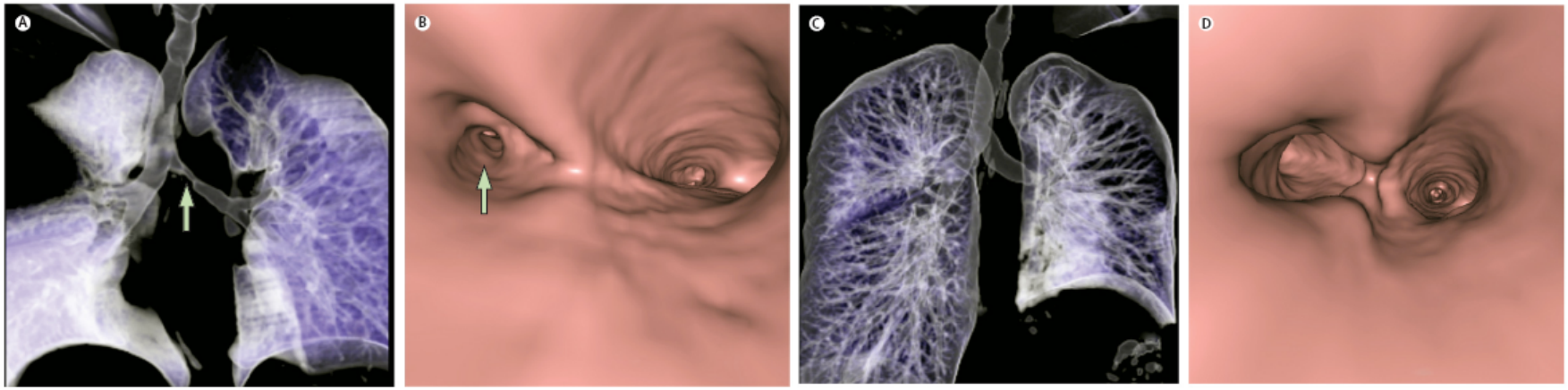
Published Online November 19, 2008 DOI:10.1016/S0140-6736(08)61598-6

See Comment page 2003

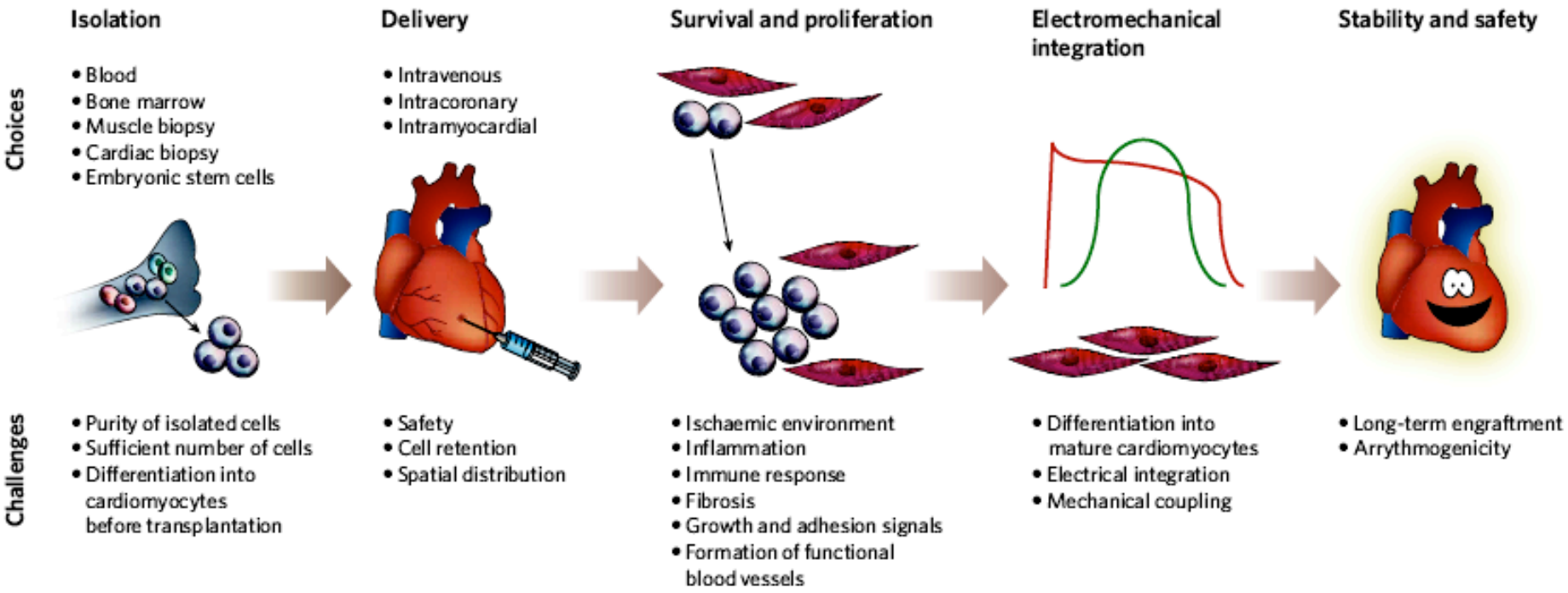
Department of General Thoracic Surgery, Hospital Clinic, Barcelona, Spain (Prof P Macchiarini MD, P Jungebluth MD, T Go MD); Fundació Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain (P Macchiarini); CIBER Enfermedades Respiratorias, Universitat de Barcelona, Barcelona, Spain (P Macchiarini); Bioengineering, Politecnico di Milano, Milan, Italy (M A Asnaghi MSc, S Mantero PhD); Pharmaceutical Sciences, University of Padua, Padua, Italy (S Bellini PhD, Prof P P Parnigotto PhD, M T Conconi PhD);

Growing airway utilizing patient-specific mesenchymal stem cells

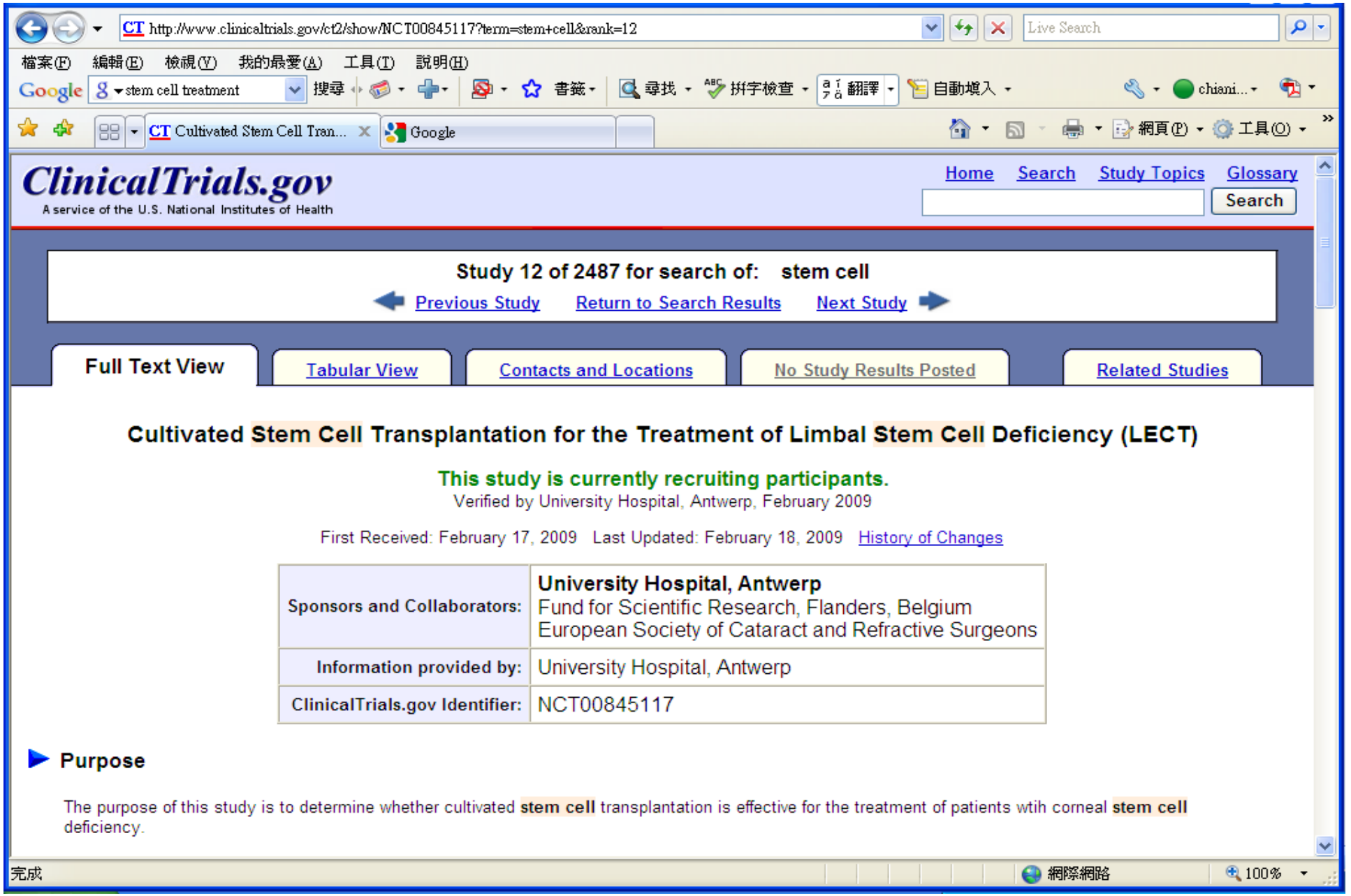




Challenges of stem cell-based therapeutics



Clinical Trials

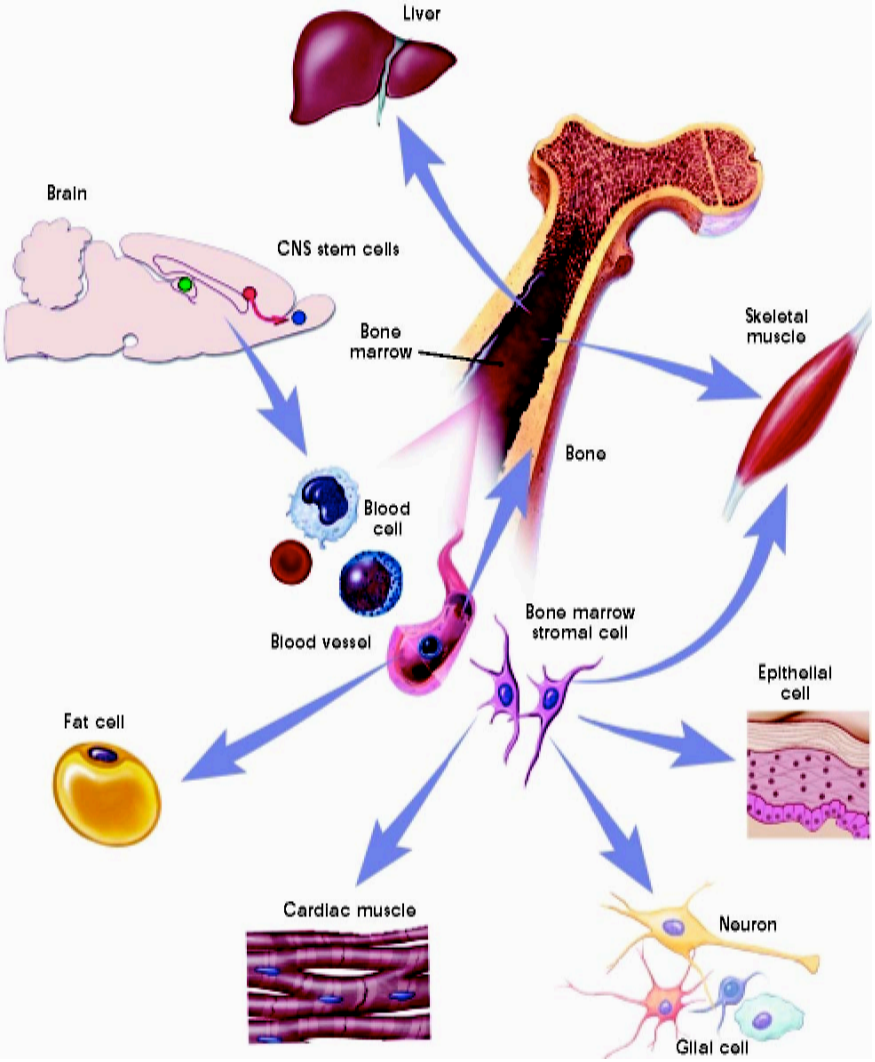


Somatic (adult tissue-derived) stem cells

- Stem cells can be derived from various tissues in adults. To date, stem cells have been found in bone marrow, blood, skin, muscle, brain, the cornea and retina of the eye, the lining of the gastrointestinal tract, lung, liver and probably pancreas.
- The primary role of tissue stem cells is to maintain and to repair the tissue in which they are found.
- Tissue stem cells usually only produce cells specific to the tissue in which they are found (i.e. original, somatic stem cells were thought to have the potential to make a limited range of cell types in the body only).
- **The possibility that a somatic stem cell from one tissue may give rise to cell types of another tissue. This is a phenomenon called "stem cell plasticity".**

Plasticity of somatic stem cells

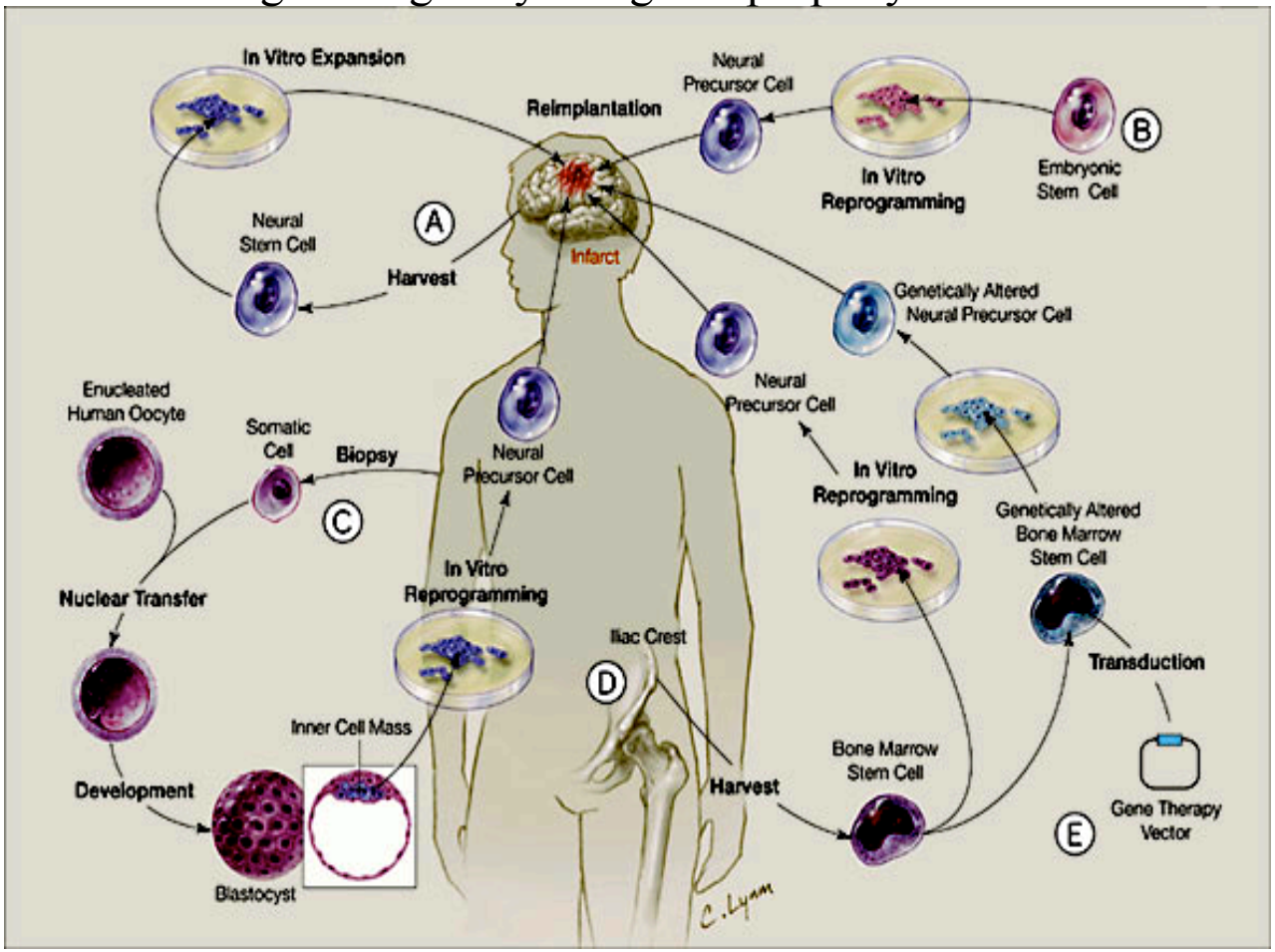
- **Hematopoietic stem cells(HSC)** may differentiate into: three major types of brain cells (neurons, oligodendrocytes, and astrocytes); skeletal muscle cells; cardiac muscle cells; and liver cells.
- **Bone marrow stromal cells (MSC)** may differentiate into neuronal, cardiac muscle, skeletal muscle, endothelial and liver cells.
- **Brain neural stem cells (NSC)** may differentiate into: blood cells and skeletal muscle cells.



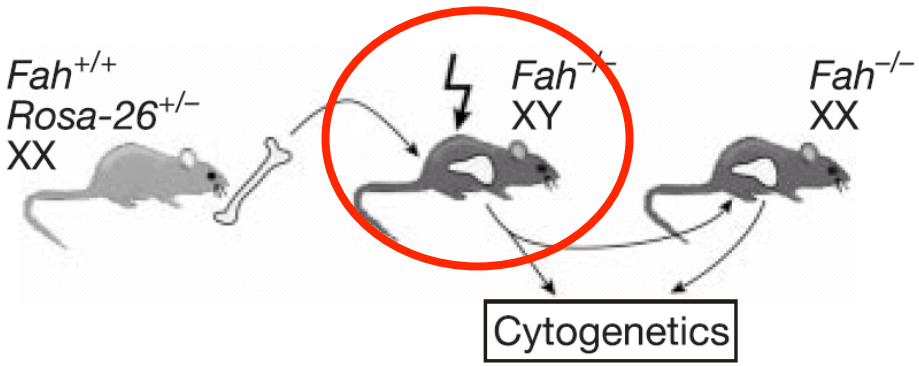
Verfaillie C.M. 2002 Trends Cell Biol. ;Wagers and Weissman 2004 Cell 116:639-648;
Shen et al., 2004 Organogenesis 1: 31-44

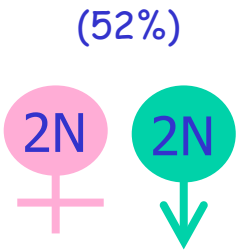
Understanding the stem cell potential can increase the therapeutic potentials

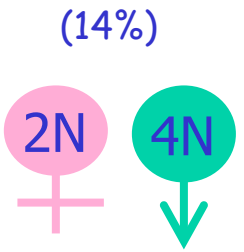
- A stem cell that can easily be expanded or grown *in vitro* and then implanted into a microenvironment which may alter the cell fate that the host requires. Therefore, it could be very important for regenerative medicine as it may be possible to for us to overcome the shortage of organ by using this property



Bone marrow derived hepatocytes were resulted from cell fusion







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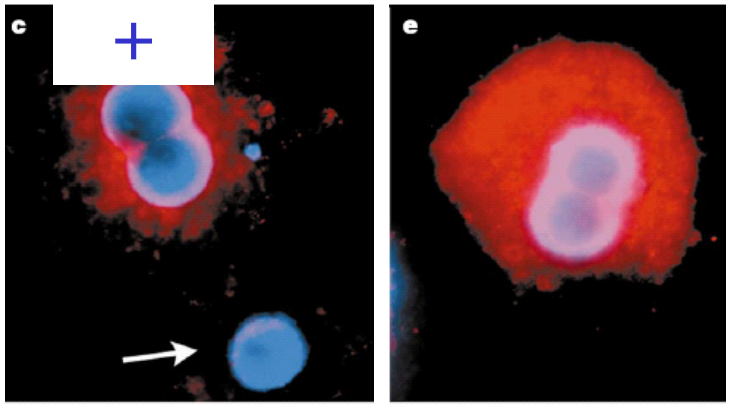
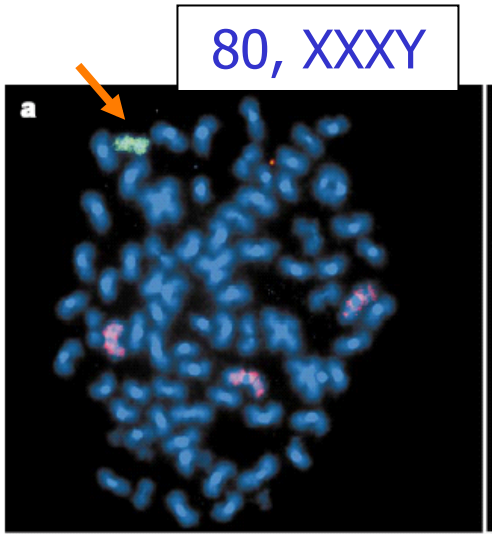
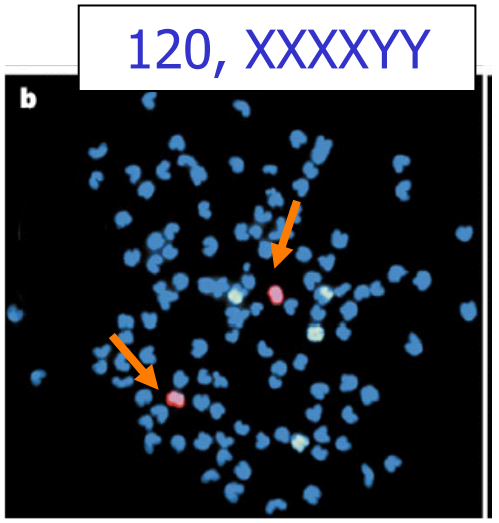
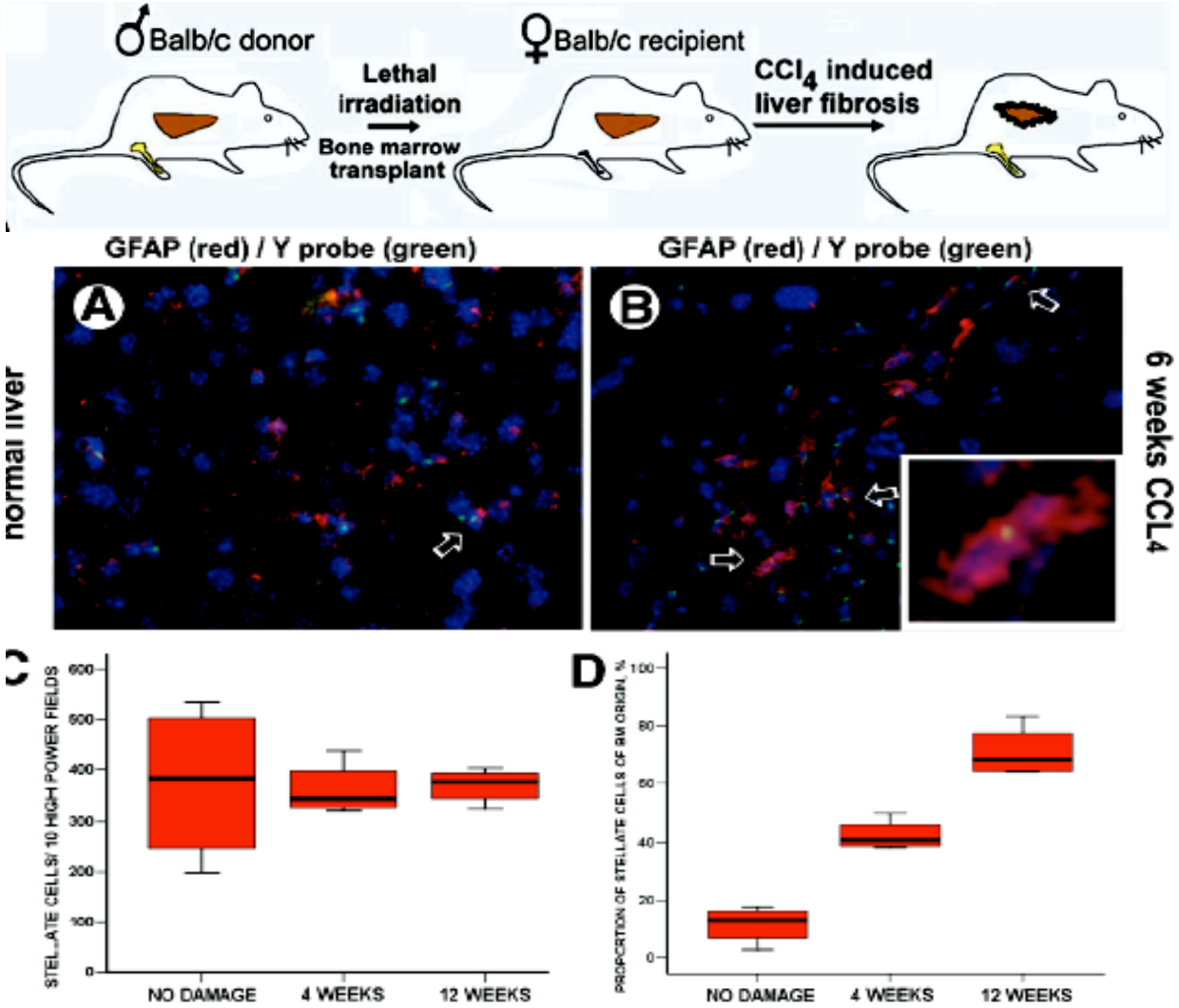






Wang et al., Nature 422, 897-901, 2003

Bone marrow stem cells functionally contribute to liver fibrosis



Russo et al., 2006 Gastroenterology

News

Nature Reports Stem Cells
Published online: 26 February 2009 | doi:10.1038/stemcells.2009.32

Unregulated stem cell transplant causes tumours

Monya Baker[1]

Researchers say cells were poorly characterized prior to transplantation

Foetal stem cells transplanted to a boy with a hereditary neurodegenerative disease have grown into noncancerous tumours in his brain and spinal cord. Though the poorly documented procedure did not occur as part of a clinical trial, it marks the first reported case of a brain tumour resulting from stem cell transplantation and highlights potential risks of cell-based therapies.

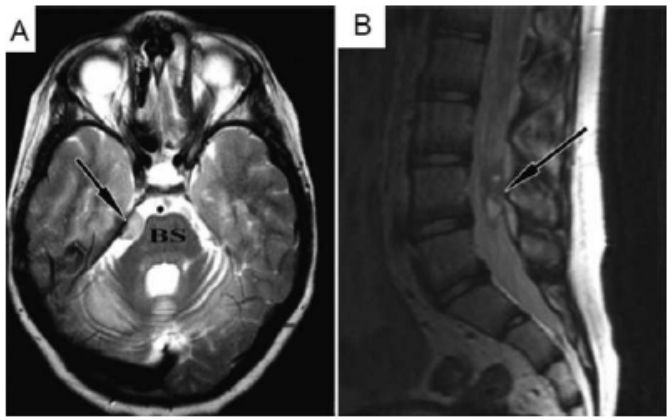
Transplants of neural stem cells led to tumors in brain & spinal cord

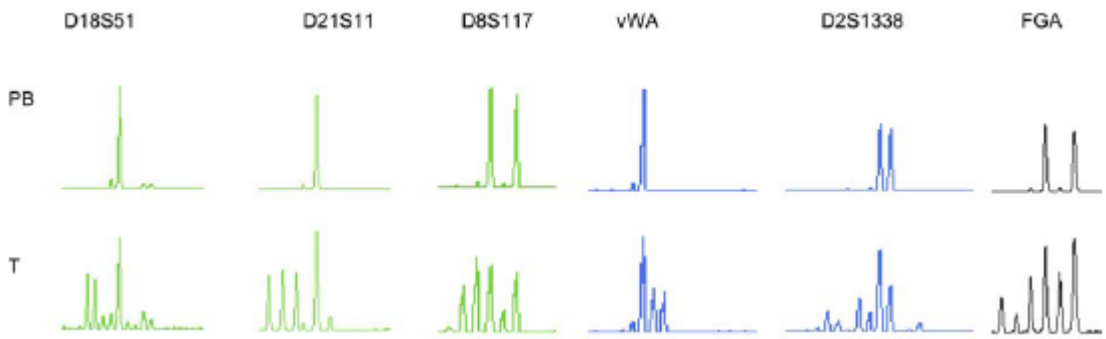
OPEN ACCESS Freely available online

PLoS MEDICINE

Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio[1,2], Abraham Hirshberg[3], Bernd W. Scheithauer[4], Yoram Cohen[1], Ron Loewenthal[5], Luba Trakhtenbrot[2], Nurit Paz[1], Maya Koren-Michowitz[2], Dalia Waldman[6], Leonor Leider-Trejo[7], Amos Toren[6], Shlomi Constantini[8], Gideon Rechavi[1,6*]

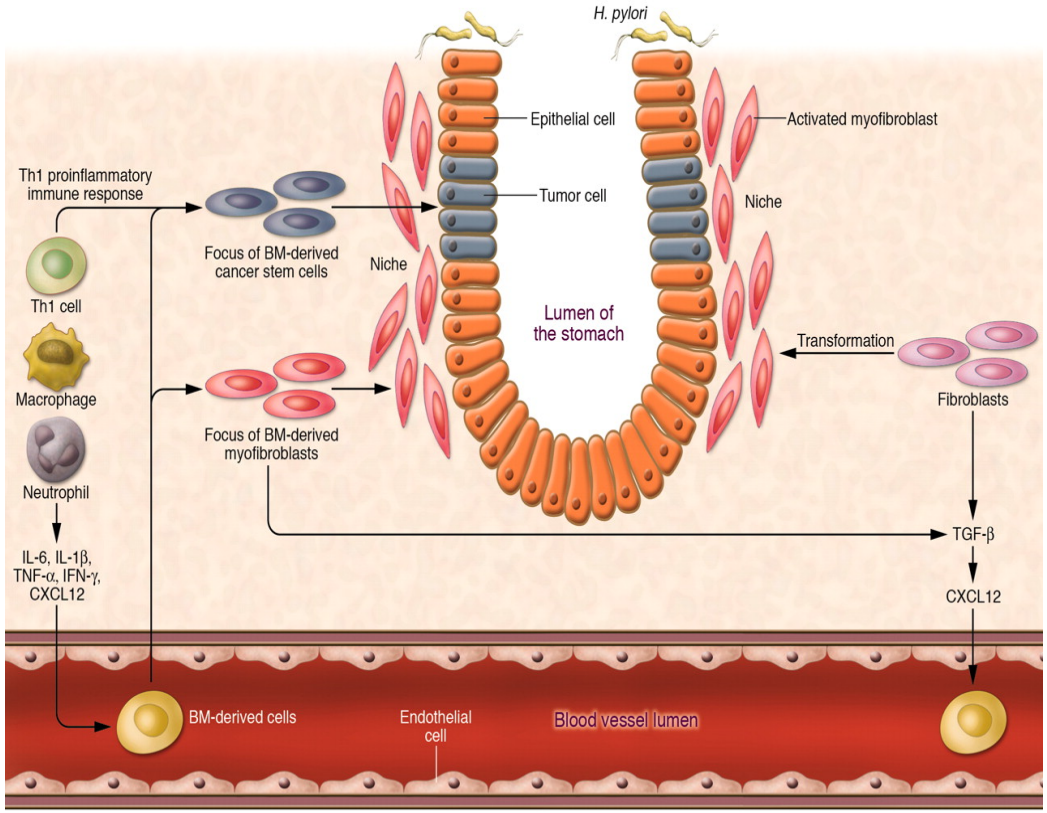


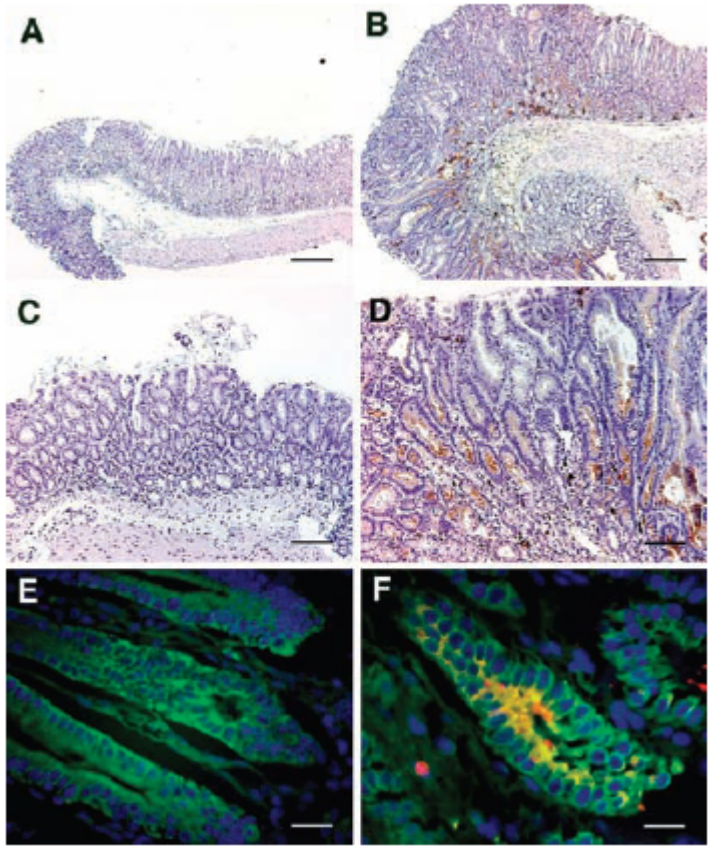


Bone Marrow Cells: The Source of Gastric Cancer?

Science
AAAS

Gastric Cancer Originating from Bone Marrow-Derived Cells
JeanMarie Houghton, *et al.*
Science **306**, 1568 (2004);
DOI: 10.1126/science.1099513





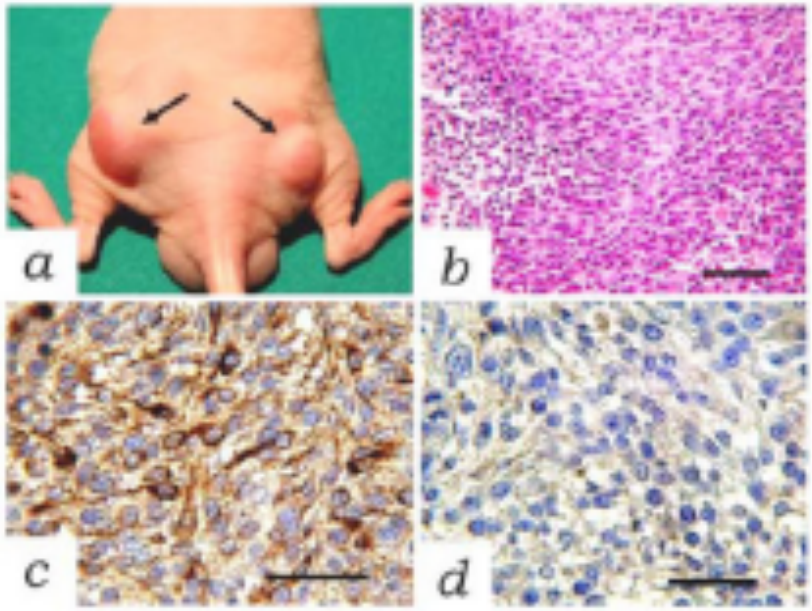
Transplants of neural stem cells of OB led to tumors in mice

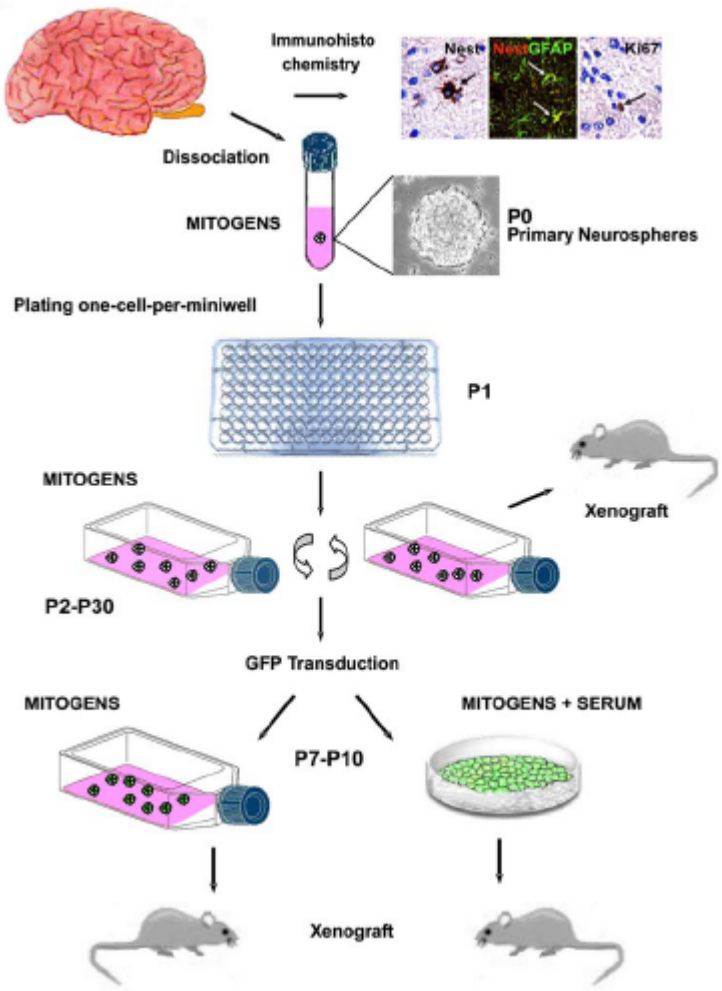
OPEN ACCESS Freely available online

PLoS one

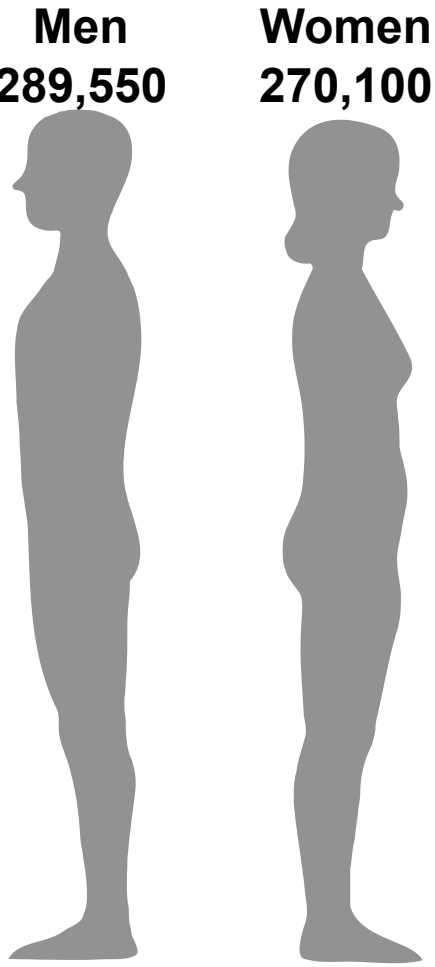
Tumorigenic Potential of Olfactory Bulb-Derived Human Adult Neural Stem Cells Associates with Activation of TERT and NOTCH1

Patrizia Casalbore[1☯], Manuela Budoni[1,4☯], Lucia Ricci-Vitiani[2], Carlo Cenciarelli[1,4], Giovanna Petrucci[3], Luisa Milazzo[2], Nicola Montano[4], Elisabetta Tabolacci[5], Giulio Maira[4], Luigi M. Larocca[3], Roberto Pallini[4]*





Top 10 leading causes of cancer deaths in USA



Men		Women	
Lung & bronchus	31%	26%	Lung & bronchus
Prostate	9%	15%	Breast
Colon & rectum	9%	10%	Colon & rectum
Pancreas	6%	6%	Pancreas
Leukemia	4%	6%	Ovary
Liver & intrahepatic bile duct	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Brain/ONS
Kidney	3%	2%	Liver & intrahepatic bile duct
All other sites	24%	23%	All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2007.

Cancer

◆**Cancer:**

➢A large group of diseases characterized by uncontrolled growth and spread of abnormal cells

➢Cancer cells usually do not achieve same level of differentiation as normal cells

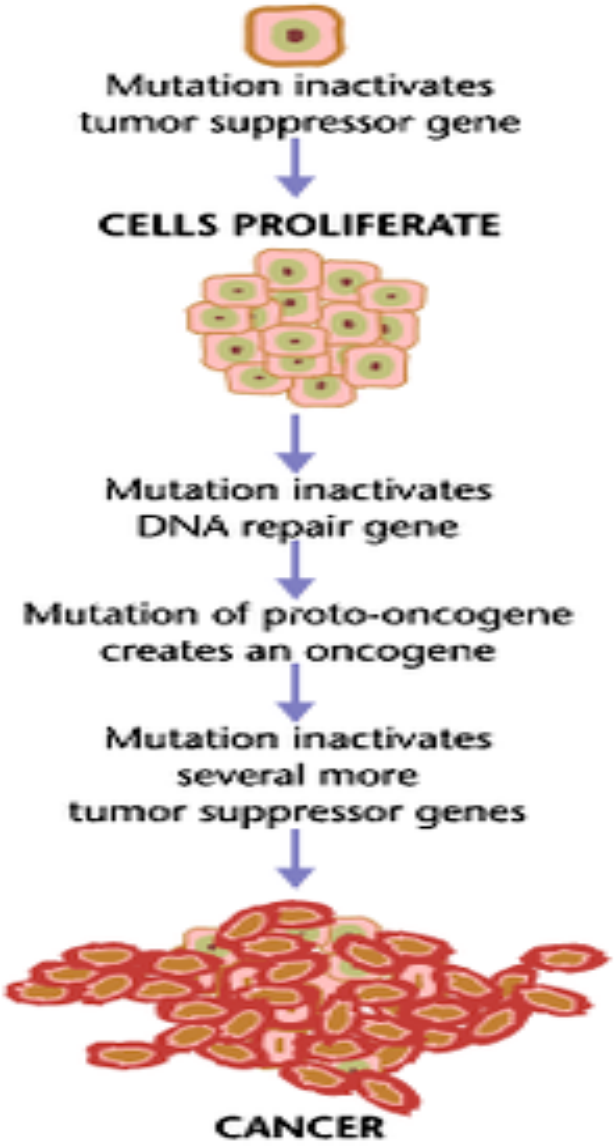
➢They are autonomous, excessive and disorganized

◆**Neoplasm or Tumor:** A mass of new tissue growth independent of its surrounding structures

Changes occur at a cellular level

- **Cells out of control**
  - Proliferating abnormally
    - Abnormal daughter cell division
    - Mature cells begin to divide
    - Differentiation is abnormal

- **Abnormal cell differentiation**
  - The degree to which a cell resembles its cell of origin in morphology and function.
  - Cancer cells usually do not achieve same level of differentiation as normal cells
  - They are autonomous, excessive and disorganized



Changes occur at a genetic level

- **Protooncogenes**
  - growth and differentiation (precursors of oncogenes).

- **Oncogenes**
  - Cancer genes, associated with abnormal cell proliferation.
  - May cause from DNA mutation
    -point mutations
    -translocations
    -gene amplification

- **Tumor suppressor genes**
  - Inactivation of tumor suppressor genes allows the malignant process to flourish.

Tumor Classification

- **Anatomical Site**
- **Cell of Origin**
- **Biological behavior**

✓ There are a large variety of tumors because tumors can originate from any cell type

- **Degree of differentiation:**

➢ **Well differentiated**

- closely resemble the cell of origin
- easily classified by histology

➢ **Undifferentiated**

- do not resemble normal cells
- more difficult to classify
- also called “anaplastic”

Tumor Classification

➢**There are at least two Tumor Categories**

- **Benign-**
  - Usually well differentiated
  - Does not metastasize
  - Encapsulated
  - Slow growing
  - Benign tumors usually cause little harm
- **Malignant-**
  - Well differentiated to undifferentiated
  - Can metastasize or spread to a site in the body distant from the primary site
  - Often invade/destroy normal tissue
  - If left untreated can cause death

How to name cancer

- **Sarcomas**- tumors arise from mesenchymal cells cartilage, bone, muscle. From cells other than epithelial. ‘
  - Example: Chondrosarcoma or sarcoma of cartilage

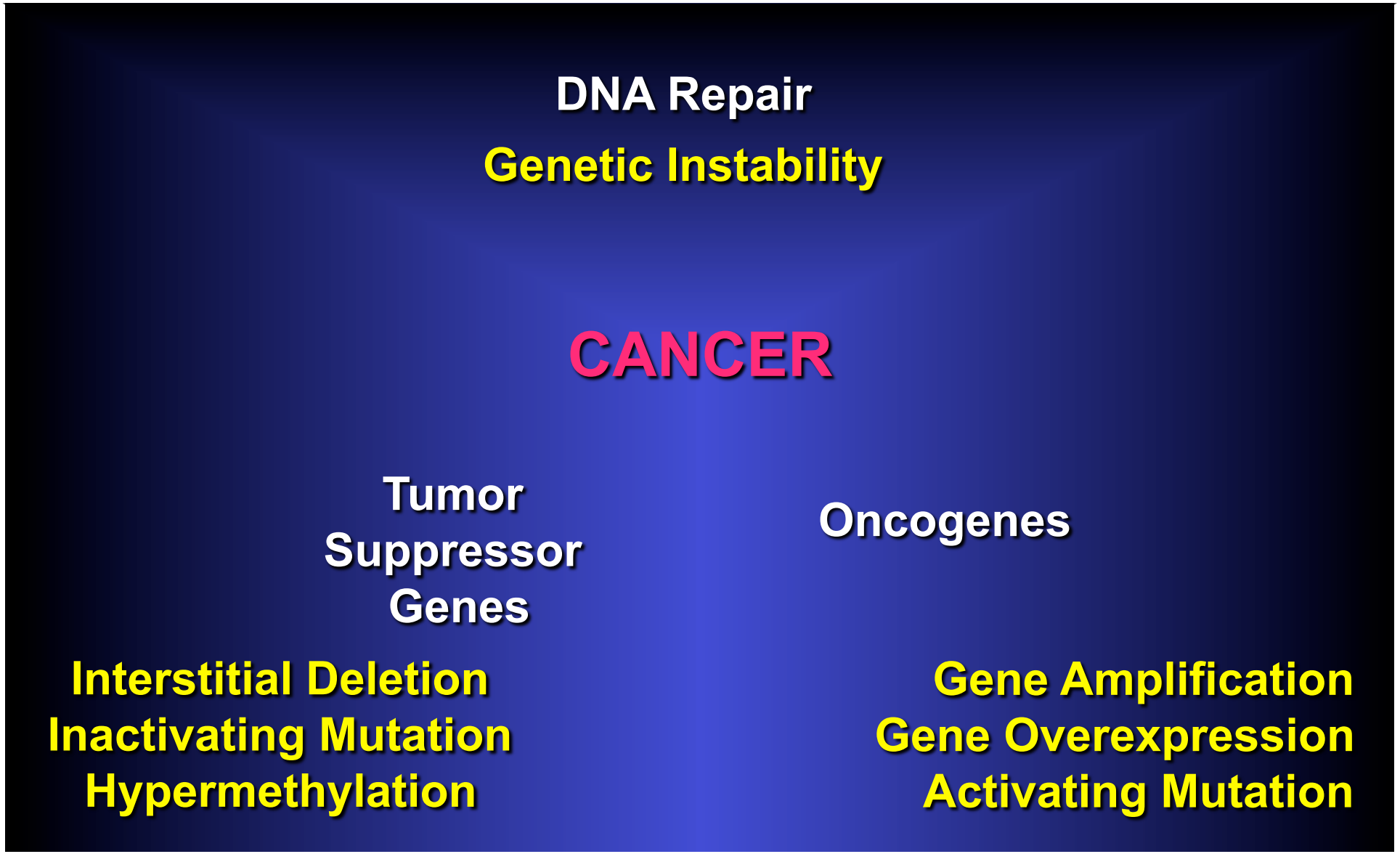
- **Carcinomas-** from epithelium cells. All tissues that cover a surface or line a cavity.
  - Example: Squamous cell carcinoma of the lung is a tumor originating from the lining of the lung.

- **Adenocarcinoma**- tumors arising from epithelial cells that are glandular.
  - Example: Lining of stomach is adenocarcinoma of the stomach.

Causes of Cancer

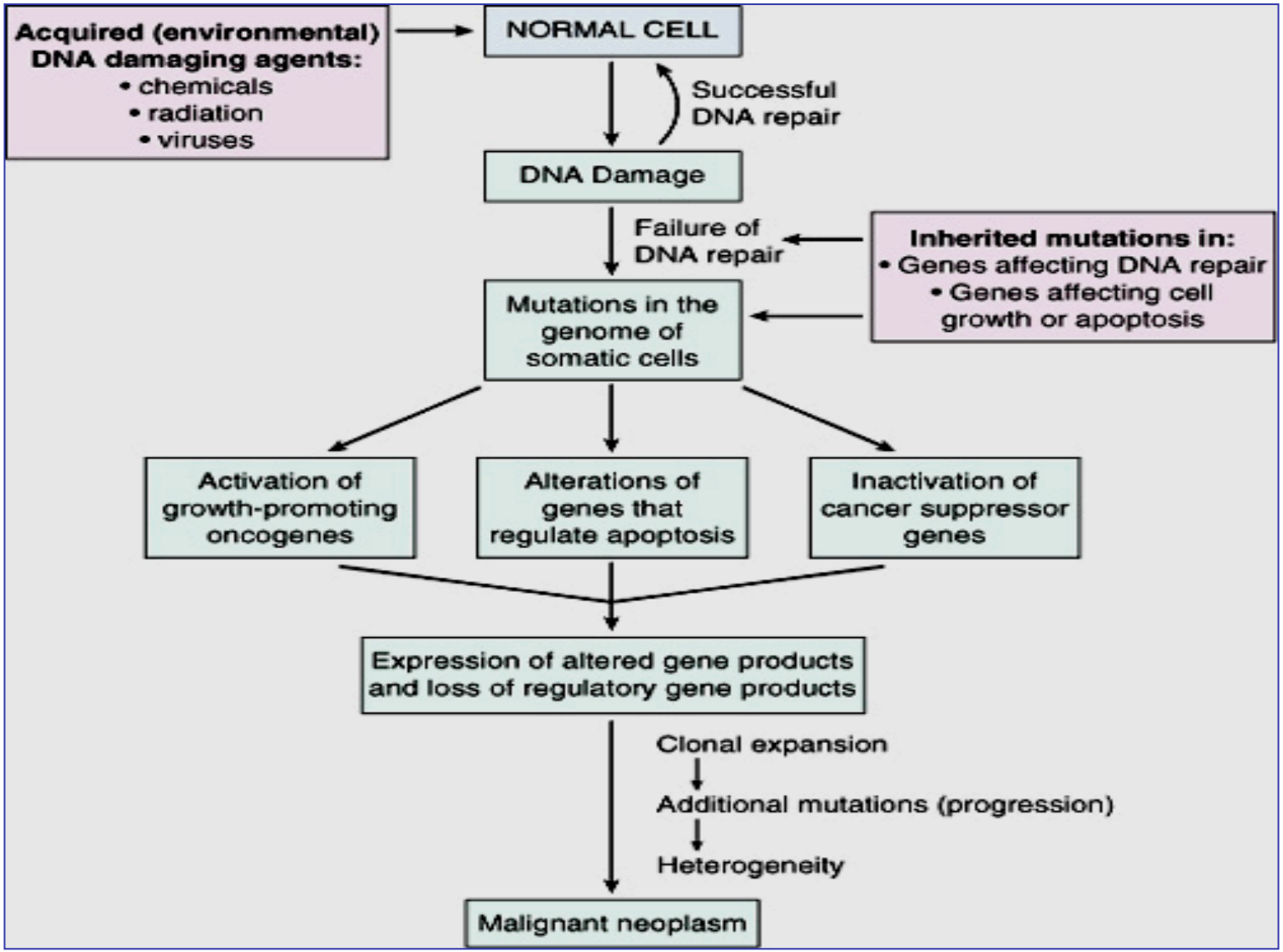
- Chemicals in the environment
  - Tobacco smoking is associated with lung cancer and bladder cancer.
  - Hundreds of chemicals have been identified as carcinogens.
- Ionizing Radiation
  - Sources of ionizing radiation, such as radon gas, can cause cancer.
  - Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies.
- Infectious Diseases
  - Virus - The main viruses associated with human cancers are human papillomavirus, hepatitis B and C virus, Epstein-Barr virus, and human T-lymphotropic virus.
- A number of recognized syndromes of cancer with a hereditary component, often a defective tumor suppressor allele.

Basic aspects of tumorigenesis



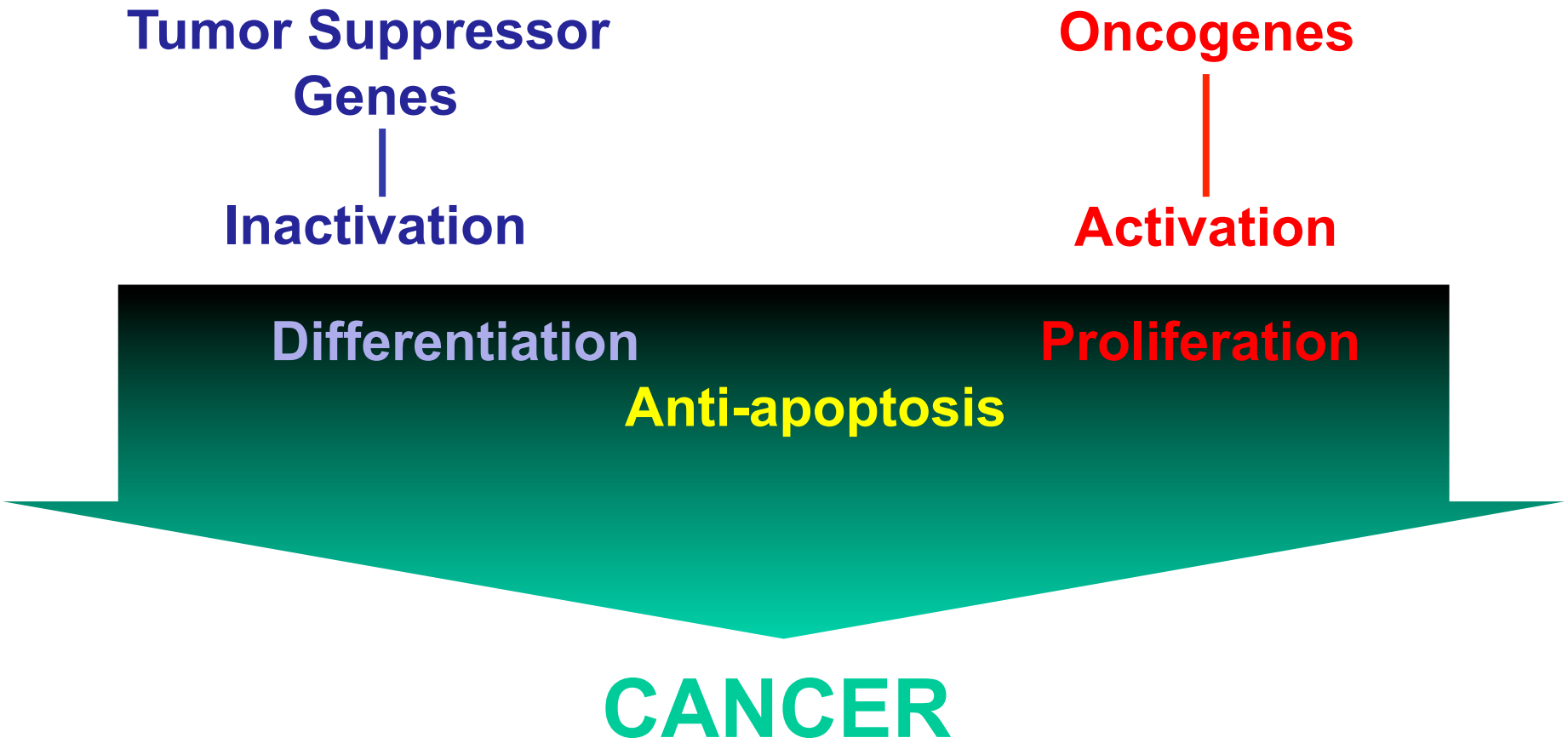
Basic aspects of tumorigenesis

➢General Etiology and Pathogenesis of Cancer



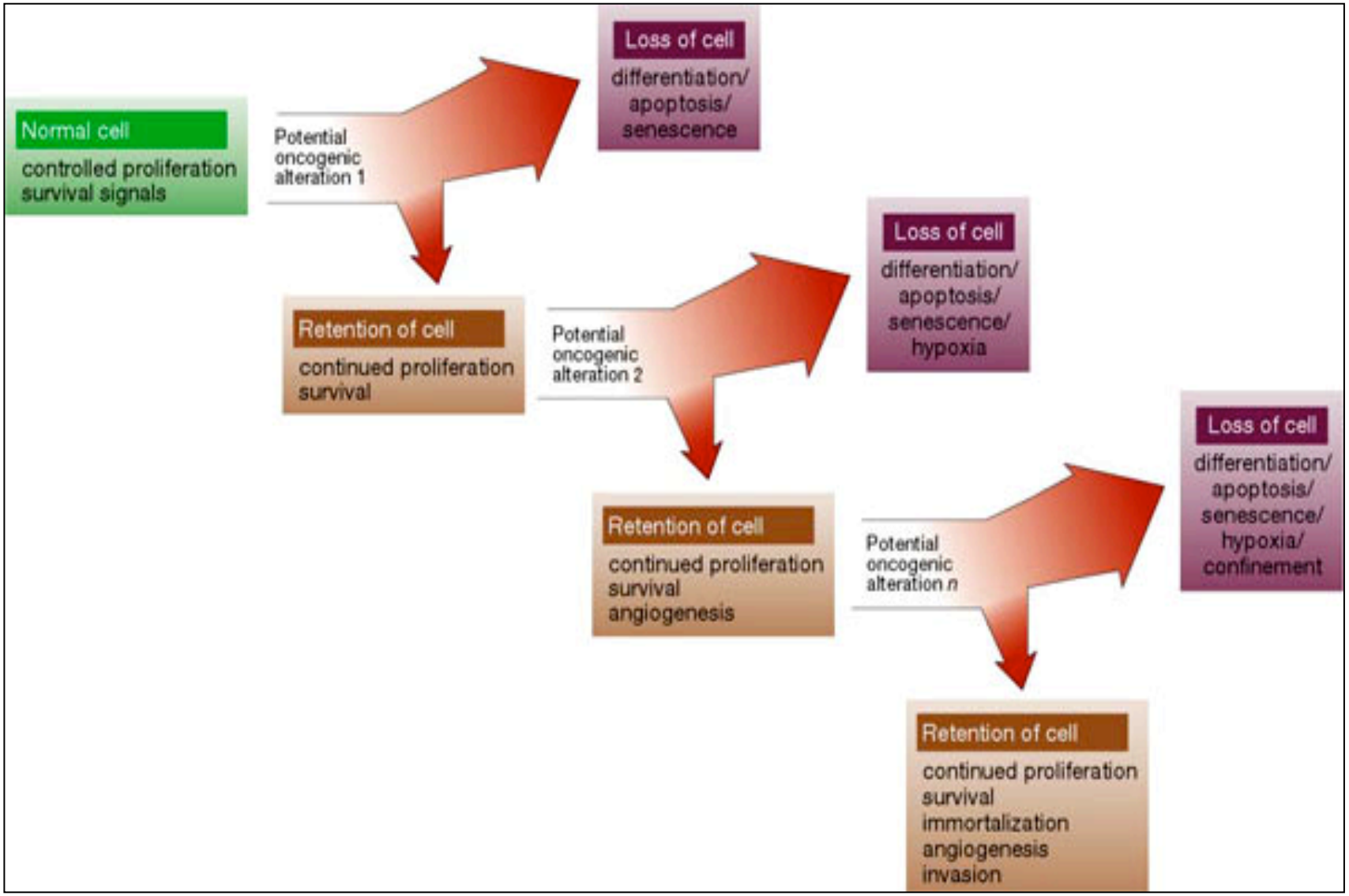
Basic aspects of tumorigenesis

➢ **Alterations of Specific Cellular Functions in Cancer**



Basic aspects of tumorigenesis

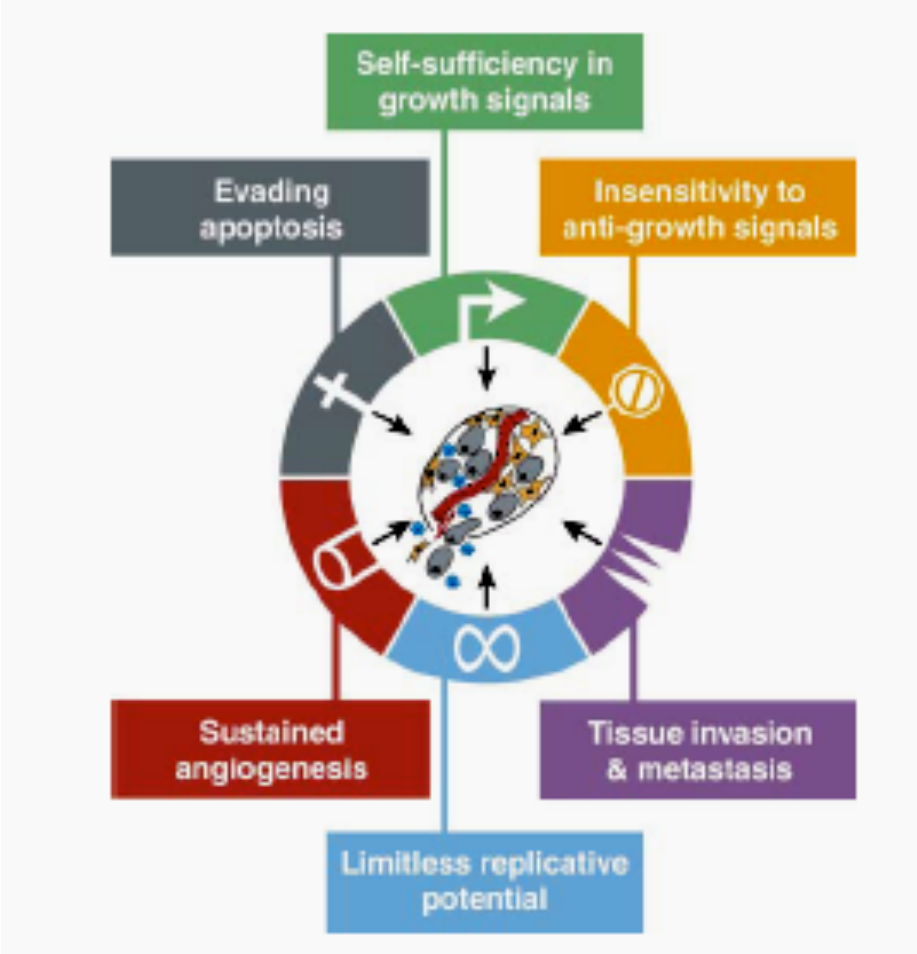
➢**Progressive Acquisition of Neoplastic Features**



Hallmarks of Cancer Cells

- Summarized by Hanahan and Weinberg (2000): Cell Six changes for cancer – found in most, if not all, cancers

- Self-maintained replication
- Longer survival
- Genetic instability
- Capable of inducing neoangiogenesis
- Capable of invasion and metastasis



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- Self-maintained replication
- Longer survival
- Genetic instability
- Capable of inducing neoangiogenesis
- Capable of invasion and metastasis

  - **Apoptosis down-regulation**
  - **Lack of response to inhibitory factors**
  - **Self-sustained proliferation**

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- Longer survival
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- Capable of inducing neoangiogenesis
- Capable of invasion and metastasis

  - **Apoptosis down-regulation**
  - **Telomerase reactivation**

Hallmarks of Cancer Cells

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- Self-maintained replication
- Longer survival
- Genetic instability
- Capable of inducing neoangiogenesis
- Capable of invasion and metastasis

  - **Cooperative genetic damage**
  - **Mutagenic agents**
  - **Defective repair systems**

Hallmarks of Cancer Cells

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◆Longer survival

◆Genetic instability

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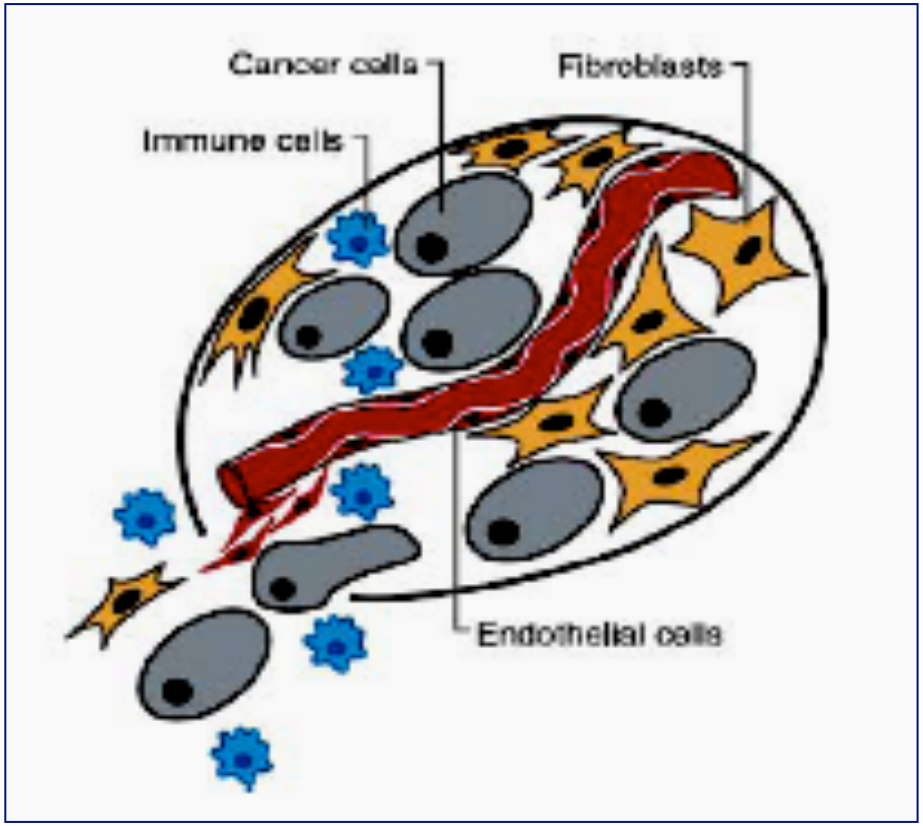

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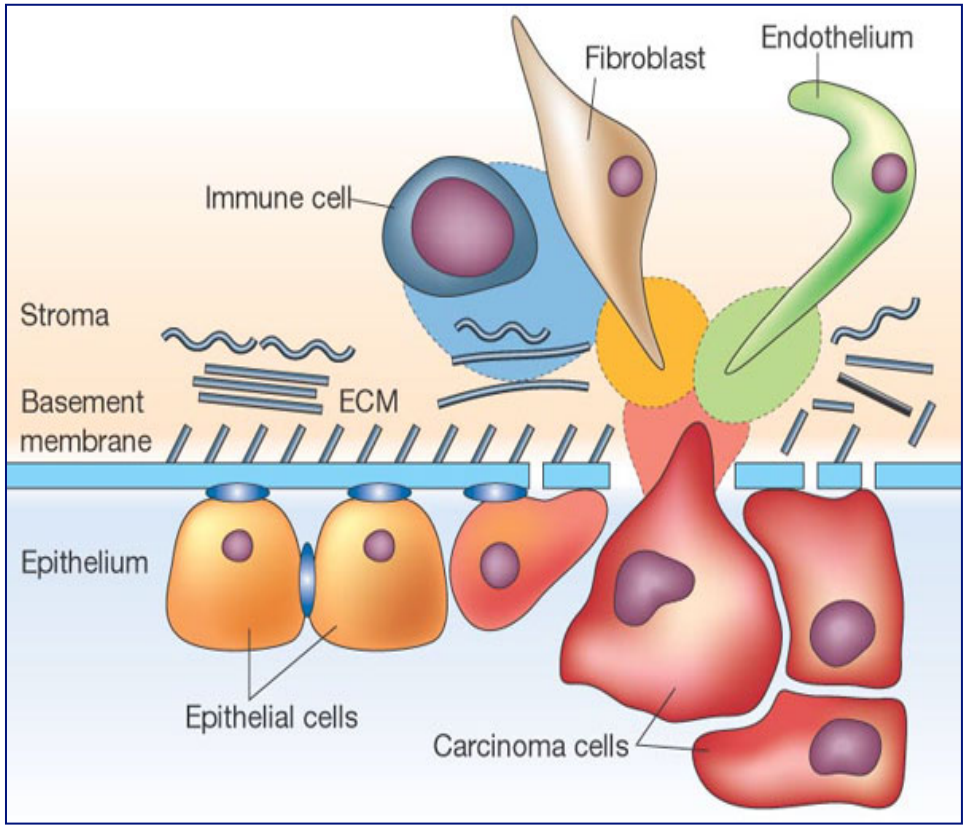
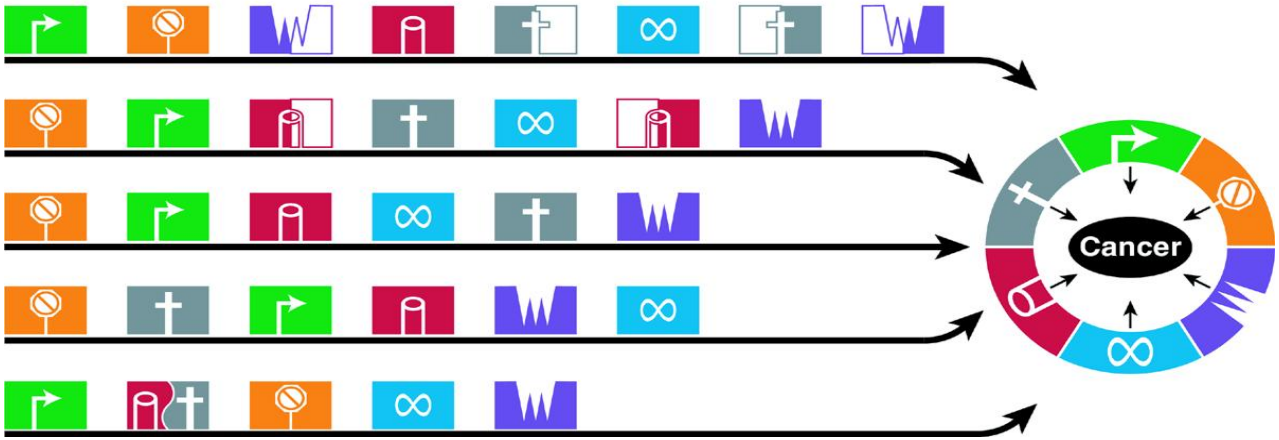


Parallel Pathways of Tumorigenesis

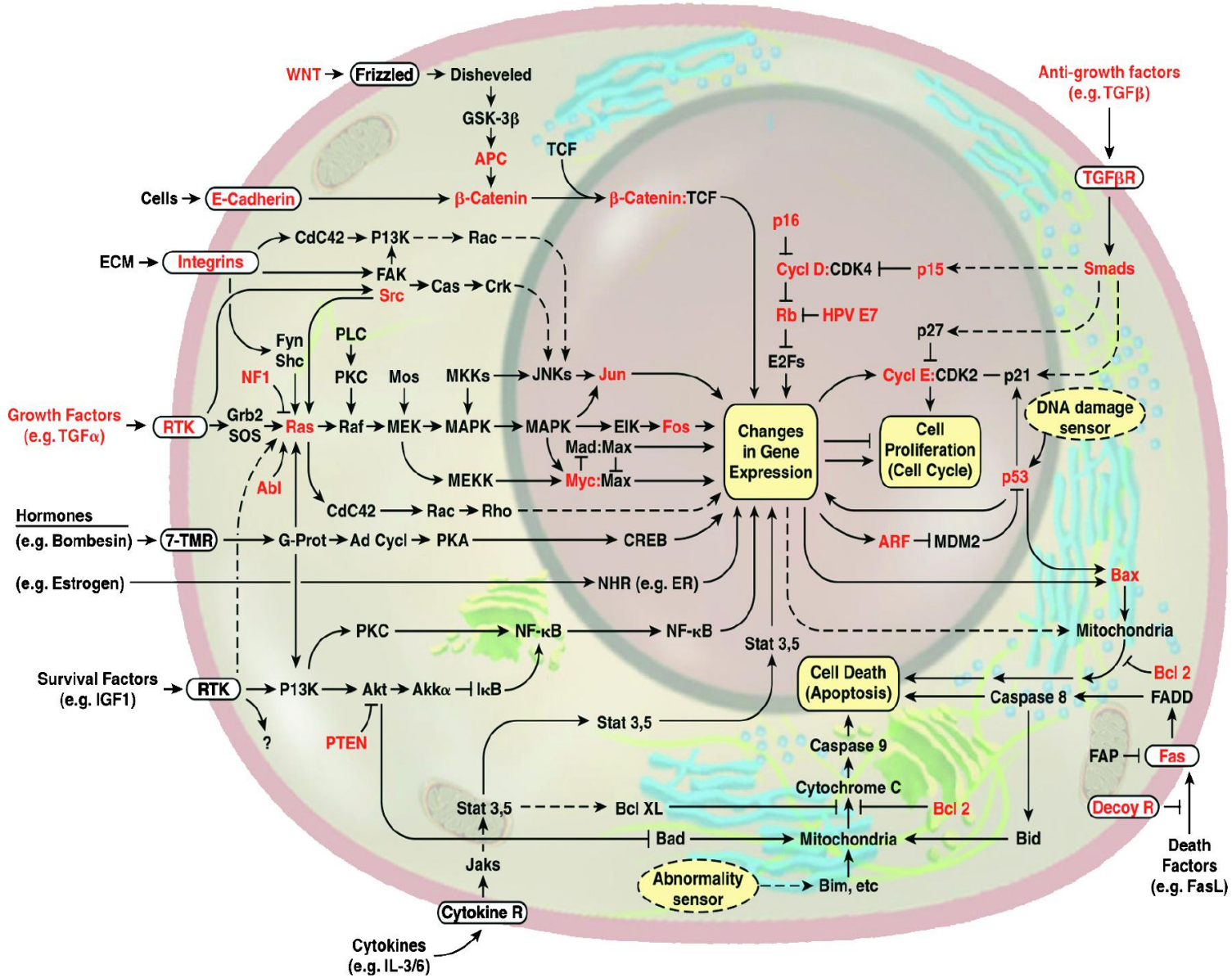
A

Component	Acquired Capability	Example of Mechanism
	Self-sufficiency in growth signals	Activate H-Ras oncogene
	Insensitivity to anti-growth signals	Lose retinoblastoma suppressor
	Evading apoptosis	Produce IGF survival factors
	Limitless replicative potential	Turn on telomerase
	Sustained angiogenesis	Produce VEGF inducer
	Tissue invasion & metastasis	Inactivate E-cadherin

B



Parallel Pathways of Tumorigenesis



Cancer Treatment

- **Surgery**
- **Radiation Therapy**
- **Chemotherapy**
- **Immunotherapy**

Cancer Treatment

- **Surgery**
- **Radiation Therapy**
- **Chemotherapy**
- **Immunotherapy**

- **Alone- It is limited by tumor accessibility, patient's medical condition, tumor's extent**
- **In combination with other modalities-RT and/or chemo**

Cancer Treatment

- **Surgery**
- **Radiation Therapy**
- **Chemotherapy**
- **Immunotherapy**

- **Can be used alone or in combination with other modalities – 50% of all cancer patients receive RT**
- **Can preserve organ function**
- **Limited by critical structures**
- **Patient must be able to endure treatment**

Cancer Treatment

- Surgery
- Radiation Therapy
- Chemotherapy
- Immunotherapy

- Can be used alone or in combination with surgery and RT
- Combination of drugs kill cells in different phases
- Limited by amount of normal cell death

Cancer Treatment

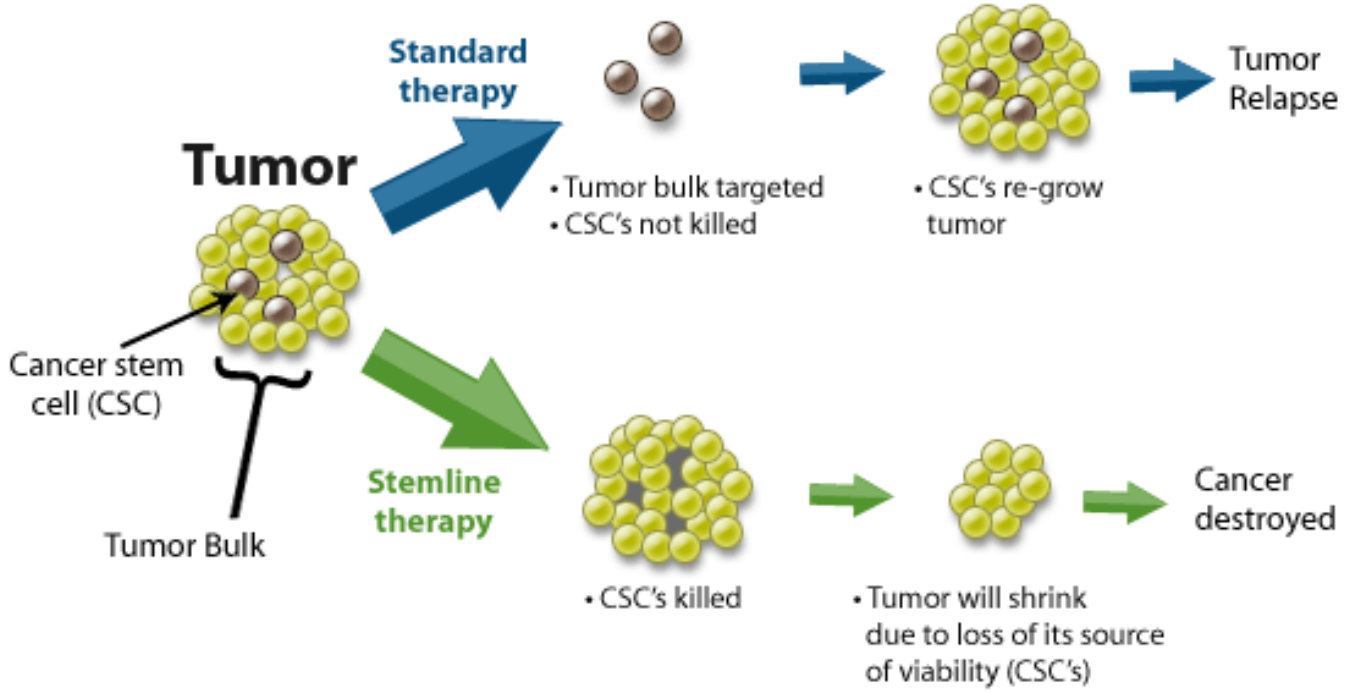
- Surgery
- Radiation Therapy
- Chemotherapy
- Immunotherapy

- Uses the body's own immune system
- B and T cells
- Natural killer cells
- Monoclonal antibodies which can be produced to react to a specific tumor antigen
- Interferons
- Interleuken-2 (IL-2) which stimulates more T cell production

Cancer Relapse and Cancer Stem Cells

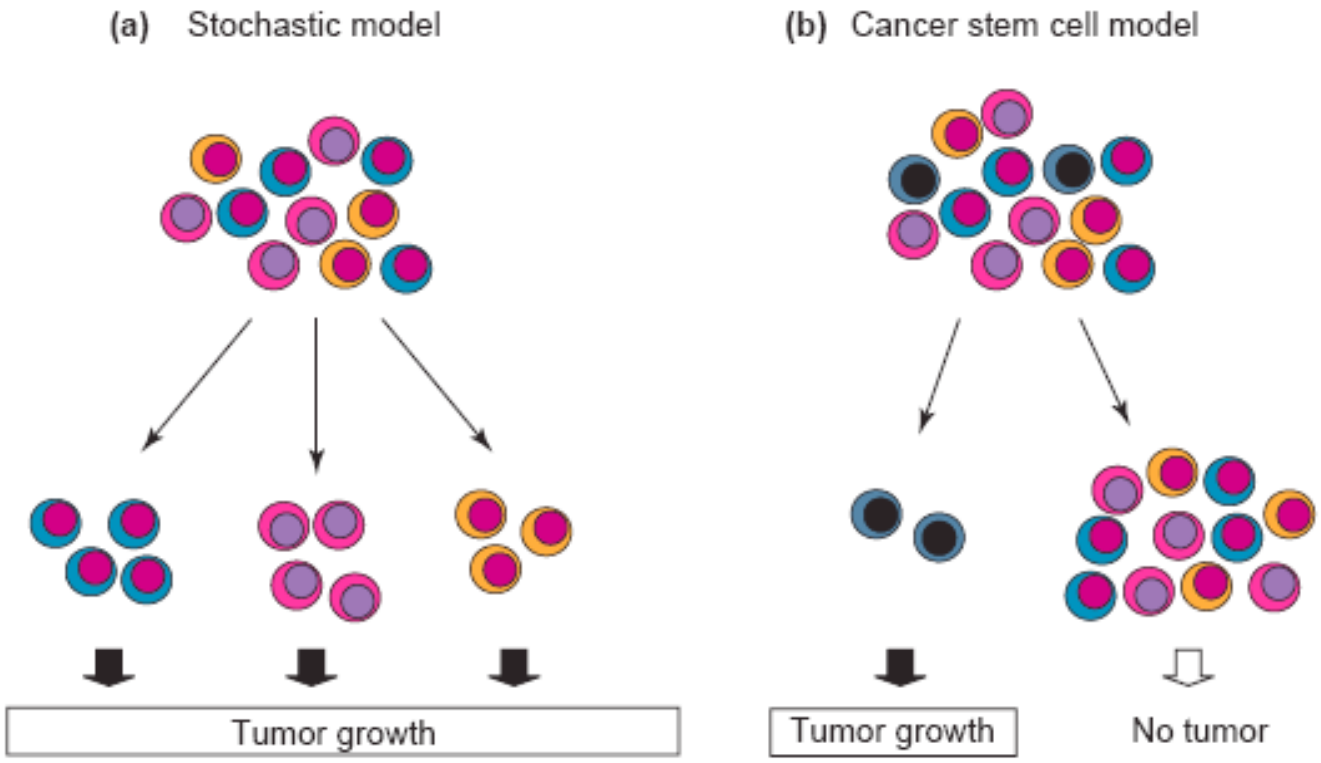
◆Cancer Stem Cells (CSCs) comprise a unique subpopulation of neoplastic cells within tumors that is highly tumorigenic and relatively resistant to standard therapy.

◆Importantly, while conventional anti-cancer treatments (e.g. chemotherapy and radiation) can often transiently shrink tumors by targeting tumor bulk, these therapies fail to target and kill CSCs leading to treatment failure, relapse, and ultimately death.



Cancer Stem Cell Hypothesis

- **There is a small subset of cancer cells, the cancer stem cells, which constitute a reservoir of self-sustaining cells with the exclusive ability to self-renew and maintain the tumor.**



Experimental evidences lead to cancer stem cell hypothesis

Only a small subset of cancer cells is capable of extensive proliferation!

Liquid Tumors

In vitro colony forming assays:

- 1 in 10,000 to 1 in 100 mouse myeloma cells obtained from ascites could form colonies

In vivo transplantation assays:

- Only 1-4% of transplanted leukaemic cells could form spleen colonies

Solid Tumors

- A large number of cells are required to grow tumors in xenograft models
- 1 in 1,000 to 1 in 5,000 lung cancer, neuroblastoma cells, ovarian cancer cells, or breast cancer cell from cell lines can form colonies in soft agar or *in vivo*

Cancer Stem Cells: Historical Perspective

- **Mid-1800s** Tumors arise from misplaced embryonic cells ***Recamier JCA. (1829). R. Virchow. (1855), J. Cohnheim (1867), F. Durante (1874)***

- **1907** Microscopic analysis of ovarian teratomas: differentiated teratoma cells develop from a single multipotent cell ***Askanazy***

- **1937** Transmission of leukemia in mice with a single cell ***Jacob Furth et. al.***

- 1**960s** Only a small subset of primary cancer tissue was able to proliferate *in vivo* **Robert Bruce and Hugo Van der Gaag:**

- **1973** Rare subpopulation of acute myeloid leukemia (AML) can self-renew and to give rise to new tumors ***M. More et. al.***

- ***1997 Dick et. al.*** Stem cell potential of leukemia cells in mouse

- **2003** ***Clarke et. al*** Isolation of **human breast** cancer stem cells
- **2003** ***Dirks et. al.*** Isolation of **human brain** tumor stem cells
- **2003** ***Weissman et.al.*** Isolation of **human leukemia** stem cells
- **2005-2009** Isolation of **lung, pancreatic, colon, prostate, ovary** CSC

What are Cancer Stem Cells?

Special Workshop Report

Cancer Stem Cells—Perspectives on Current Status and Future Directions: AACR Workshop on Cancer Stem Cells

Michael F. Clarke,[1] John E. Dick,[2] Peter B. Dirks,[3] Connie J. Eaves,[4] Catriona H.M. Jamieson,[5] D. Leanne Jones,[6] Jane Visvader,[7] Irving L. Weissman,[8] and Geoffrey M. Wahl[6]

[1]Stanford University School of Medicine, Stanford, California; [2]University Health Network; [3]University of Toronto Hospital for Sick Children, Toronto, Ontario, Canada; [4]Terry Fox Laboratory BC Cancer Research Center, Vancouver, British Columbia, Canada; [5]Moores University of California San Diego Cancer Center; [6]The Salk Institute for Biological Studies, La Jolla, California; [7]Walter and Eliza Hall Institute, Parkville, Victoria, Australia; and [8]Stanford University Medical Center, Palo Alto, California

- **An accurate definition is critical to enable researchers working in the same or different systems to compare cells exhibiting a common set of properties.**
- **a cell within a tumor that possess the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor.**
- **Cancer stem cells can thus only be defined experimentally by their ability to recapitulate the generation of a continuously growing tumor.**

Cancer Res 2006; 66: (19). October 1, 2006

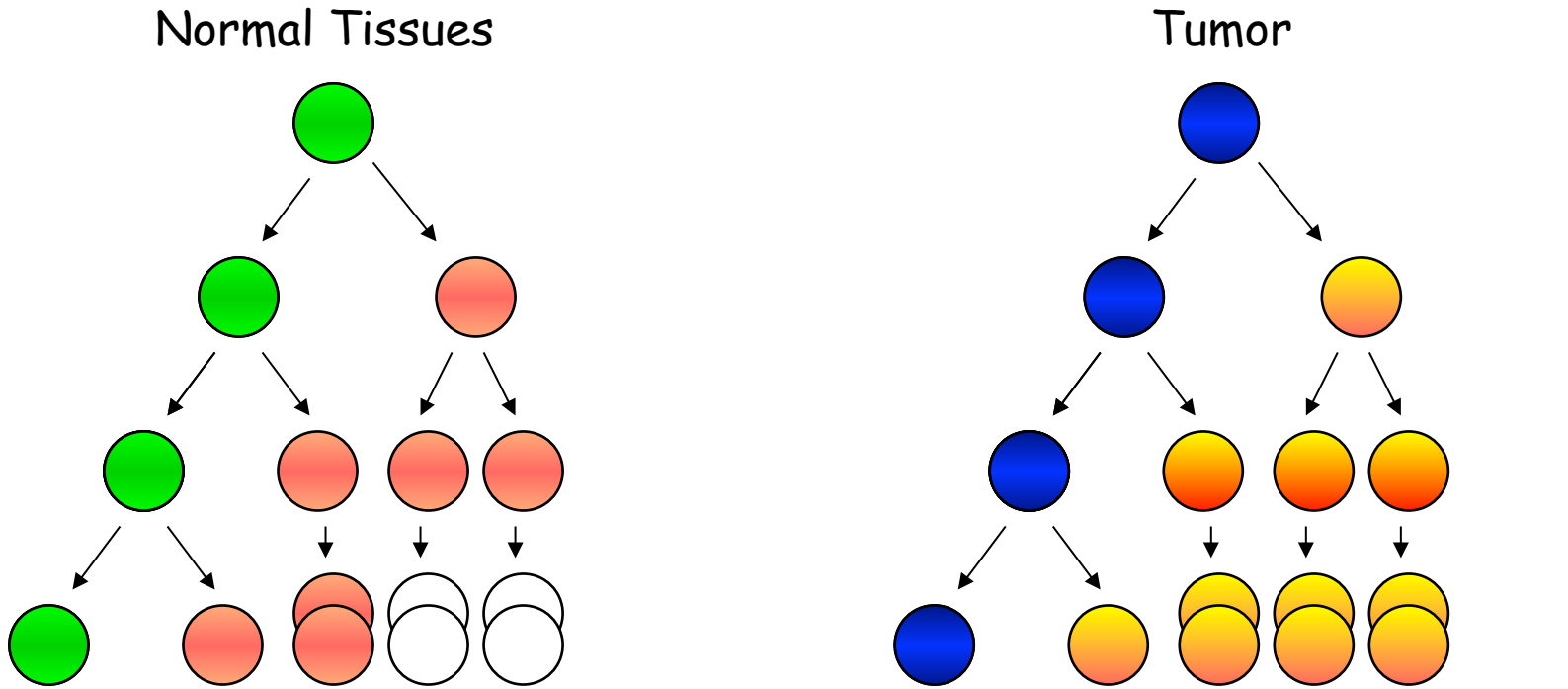
Normal stem cells

Rare cells within organs that can self-renew and give rise to diverse cell types within the organ to drive organogenesis

Cancer stem cells

Rare tumor cells that can self-renew and give rise to phenotypically diverse tumor cell population to drive tumorigenesis

Tumor growth v.s. normal tissue growth



Adult stem cell = undifferentiated

Transit amplifying cell

Normal differentiated cell

Cancer stem cell = tumorigenic

Non-tumorigenic cell

Why we named “cancer stem cells”?

Cell Stem Cell
Forum

Cancer Stem Cells: Controversial or Just Misunderstood?

Craig T. Jordan[1,*]
[1]James P. Wilmot Cancer Center, University of Rochester, 601 Elmwood Avenue, Box 704, Rochester, NY 14642, USA
*Correspondence: craig_jordan@urmc.rochester.edu
DOI 10.1016/j.stem.2009.02.003

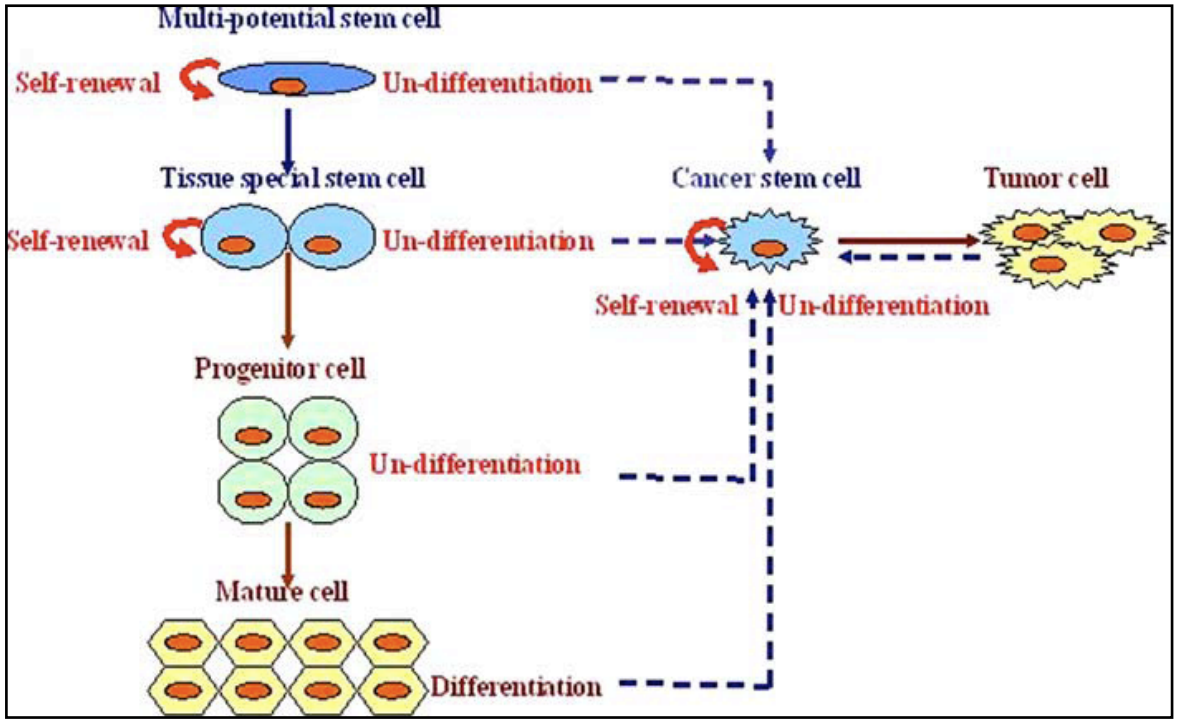
- Stem cells, in the true sense of the word, are defined solely by their functional properties, and thus, the application of that label does not reflect the derivation of the cell or imply a normal cell of origin.
- Although normal stem cells may give rise to CSC in some cases, this ancestry cannot be inferred purely from the nomenclature.
- A“true” cancer stem cell in that it must have undergone self-renewal and is capable of recapitulating the entire tumor population.
- The origin of such a cell need not necessarily be a normal stem cell!

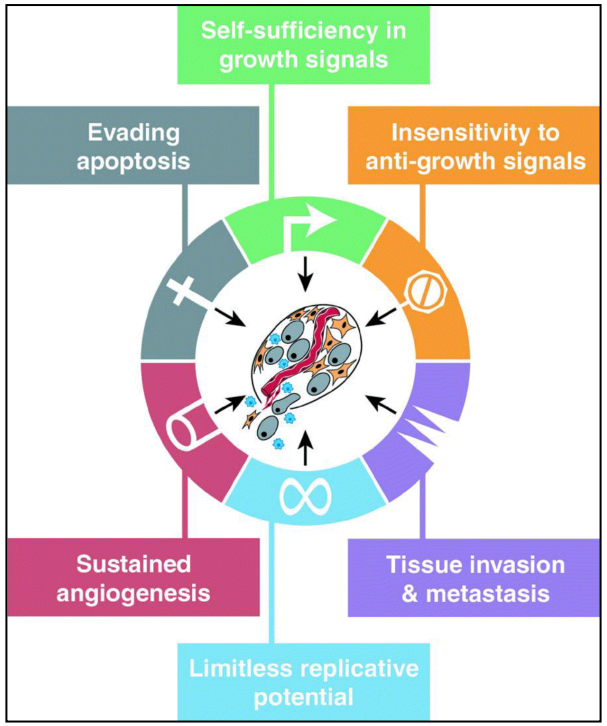
Why we named “cancer stem cells”?

- **Cancer stem cells** (CSCs) are cancer cells that possess characteristics associated with normal stem cells.
- These cells are therefore “tumorigenic” in contrast to other non-tumorigenic cancer cells
- CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types.
- **CSCs are proposed to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors**

Wikipedia

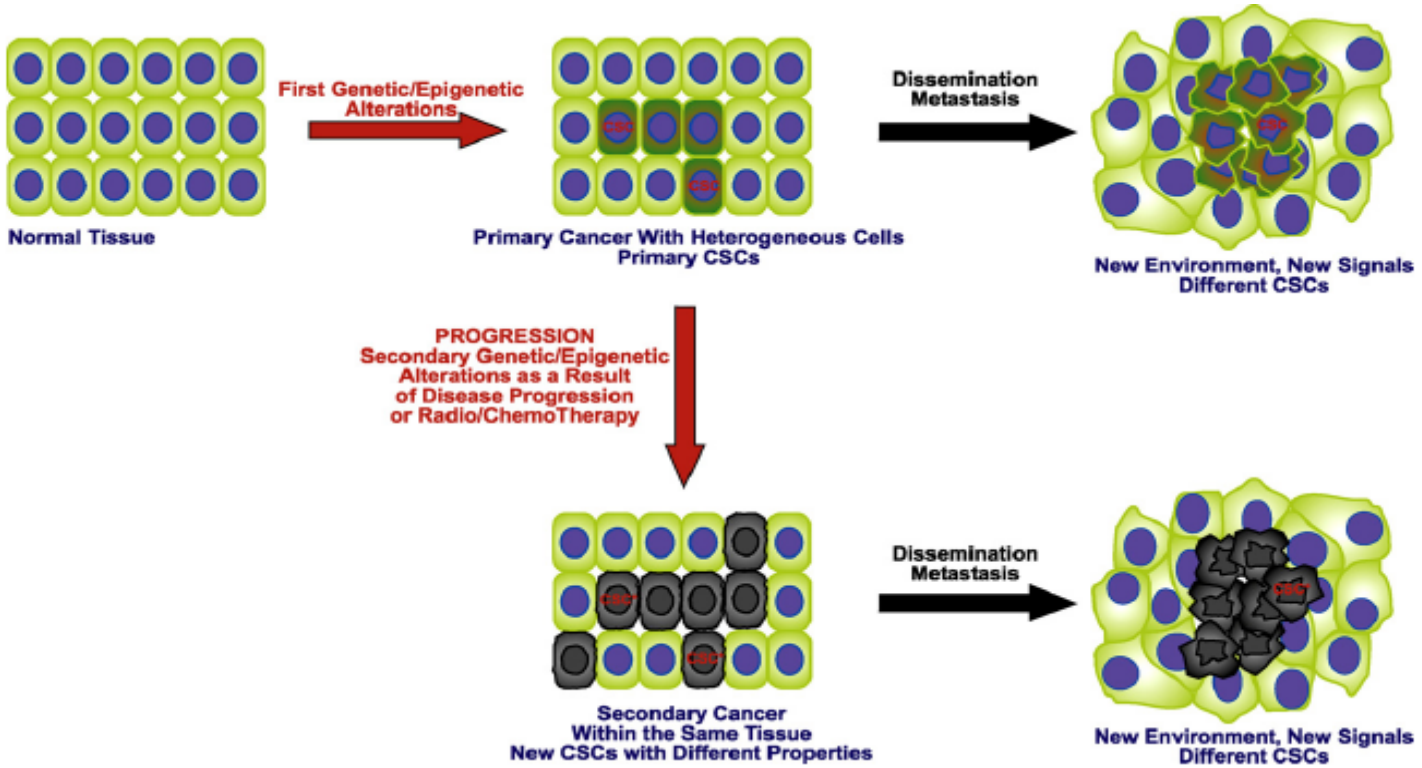
Origin of cancer stem/initiating cells





- **Stem cells are long-lived cells which can acquire the necessary number of sequential mutations to convert a normal cell into a malignant one?**
- **Not only stem cells have the ability to self-renew and neoplasia is essentially dysregulated self renewal?**

Cancer progression involves a multistage evolution process for CSC



➢The evolution of a particular CSC clone can lead to phenotype changes in the repopulating cells. and can take place through the acquisition of secondary genetic/ epigenetic alterations as a result of pressure selection along the disease progression or after chemotherapy and/or radiotherapy regimens leading to treatment resistance.

A. Castellanos et al. / Seminars in Cancer Biology *20 (2010) 93–97*

Therapeutic implications of Cancer Stem Cells

- As CSCs would form a very small proportion of the tumor, this may not necessarily select for drugs that act specifically on the stem cells
- Most therapies (chemotherapy and radiation) target rapidly proliferating, non-tumorigenic cells and spare the relatively quiescent cancer stem cells
- Cancer stem cells have greater invasive and migratory properties and can home to specific tissue niches
- Drug resistance (e.g. pump out the anti-cancer drug by ABC transporters which are widely expressed in CSCs)

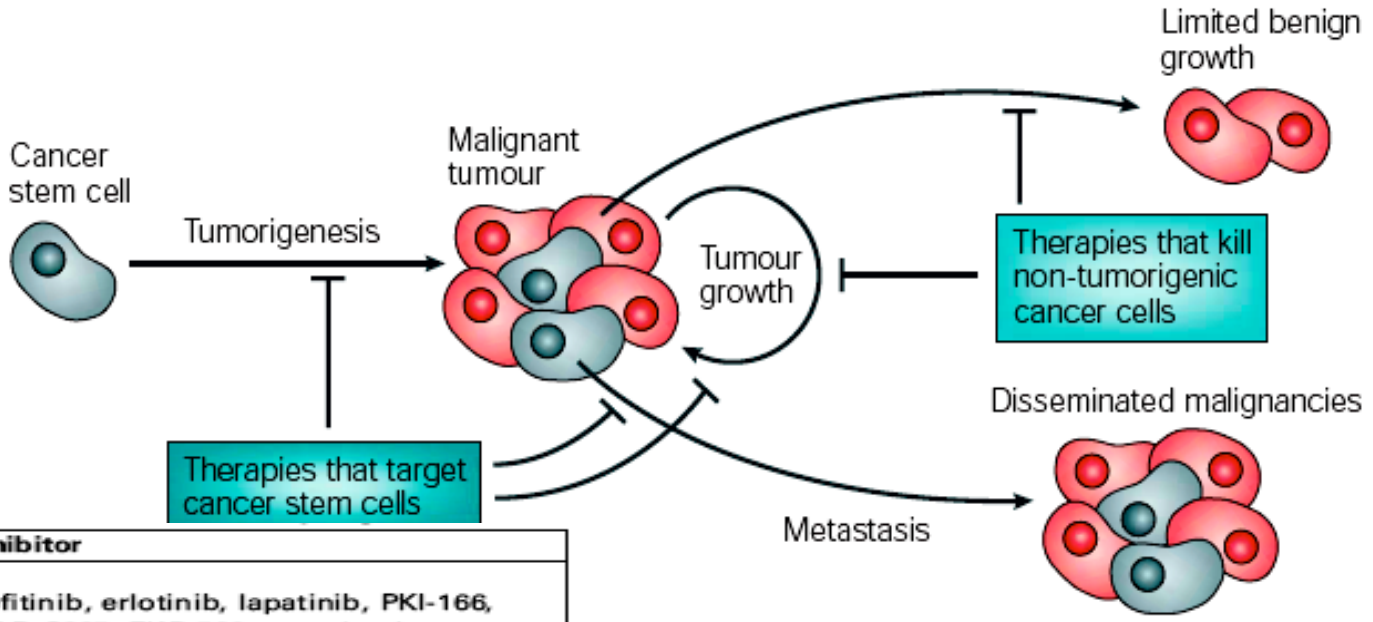
Is the CSC signature prognostic?

- 2007 Clarke et al NEJM :CSCs signature correlates with poor outcome (6 tumors)

-2007 Polyak et al Cancer Cell: CD44+ CD24+ Breast Cancer signature is poor prognostic indicator

-2009 Diehn et al Nature: Association of reactive oxygen species levels and radioresistance in breasrt cancer stem cells

Are we targeting the right cells?



Target	Inhibitor
Tyrosine kinase receptors	
ErbB1	Gefitinib, erlotinib, lapatinib, PKI-166, mAB-C225, EKB-569, cetuximab
ErbB2/Neu	Trastuzumab, PKI-166, lapatinib, TAK165
ErbB1–4	CI1033
PDGFRβ/KIT/ABL	Imatinib mesylate, sunitinib malate (SU11248)
PDGFRβ/FLT3	Sorafenib, SU11248
VEGFR1–3/PDGFRβ/KIT	CEP-7055, AZD2171, AMG-706, Vatalanib, SU11248
Hedgehog	Cyclopamine, anti-SHH antibody
Wnt/β-catenin	Anti-Wnt antibody, WIF-1
Notch	DAPT, GSI-18
ABC multidrug efflux transporters	
MDR1/ABCB1	Gefitinib, CI1033, tamoxifen, MS-209, Cyclopamine
ABCG2	Gefitinib, CI1033, tamoxifen, MS-209, Cyclopamine
MRP1/ABCC1	MS-209

Trends in Molecular Medicine 2008 Vol.14 No.10

Identification of human Cancer Stem Cells

Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors

Antonio Cozzio,[1,2] Emmanuelle Passegué,[1] Paul M. Ayton,[1] Holger Karsunky, Michael L. Cleary, and Irving L. Weissman[3]

GENES & DEVELOPMENT 17:3029–3035 © 2003

Stem cells, cancer, and cancer stem cells

Tannishtha Reya*§||, Sean J. Morrison†||, Michael F. Clarke‡ & Irving L. Weissman*

*Departments of Pathology and Developmental Biology, Stanford University School of Medicine, Palo Alto, California 94305, USA (e-mail: irv@stanford.edu)
†Howard Hughes Medical Institute, and Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109-0934, USA
‡Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan 48109-0936, USA
§Present address: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina 27710, USA
||These authors contributed equally to this work

Stem cell biology has come of age. Unequivocal proof that stem cells exist in the haematopoietic system has given way to the prospective isolation of several tissue-specific stem and progenitor cells, the initial delineation of their properties and expressed genetic programmes, and the beginnings of their utility in regenerative medicine. Perhaps the most important and useful property of stem cells is that of self-renewal. Through this property, striking parallels can be found between stem cells and cancer cells: tumours may often originate from the transformation of normal stem cells, similar signalling pathways may regulate self-renewal in stem cells and cancer cells, and cancer cells may include 'cancer stem cells' — rare cells with indefinite potential for self-renewal that drive tumorigenesis.

Prospective identification of tumorigenic breast cancer cells

Muhammad Al-Hajj*, Max S. Wicha*, Adalberto Benito-Hernandez†, Sean J. Morrison*‡§, and Michael F. Clarke*‡¶

PNAS | April 1, 2003 | vol. 100 | no. 7 | 3983–3988

Identification of a Cancer Stem Cell in Human Brain Tumors

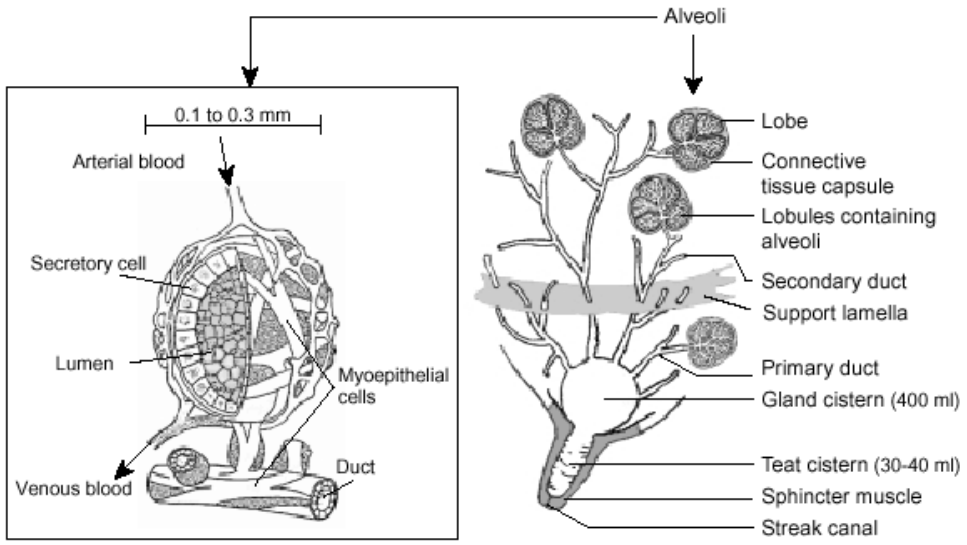
Sheila K. Singh, Ian D. Clarke, Mizuhiko Terasaki, Victoria E. Bonn, Cynthia Hawkins, Peter B. Dirks

[CANCER RESEARCH 63, 5821–5828, September 15, 2003]

Table 1. Stem cells and their respective markers and pathways

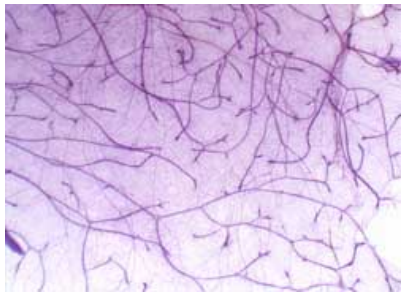
Sites	Frequency in cancer	Surface markers	Target pathways
Colon[10-12]	0.7–24.5%	CD133, CD44, GRP49	Wnt, Sonic Hedgehog
Liver[27,119,120]	<2%	CD133, G	Akt/PKB, BCL-2
Pancreas[23]	0.2–0.8%	CD44/CD24/ESA/CD133	Wnt?
Kidney[26]	0.9±0.17%	CD133	
Prostate[14,15,121]	1%	CD133/CD44/α2β1,Sca-1,CXCR2	PTEN/AKT, SDF1/CXCR4
Melanoma[24,25]	<1%	CD133/ABCG2	Notch4
Lung & Head/neck[19,21]	10%	CD133	?
Brain[17,18,74,122]	1–27.5%	CD133	Notch
Myeloid (AML)[4-6]	0.2%	CD34+/CD38-	Fas, Wnt
Breast[13]	2–4%	CD44+/CD24-/ESA+	Wnt, Oct4

Structure and Renewal Cycle of Mammary Gland

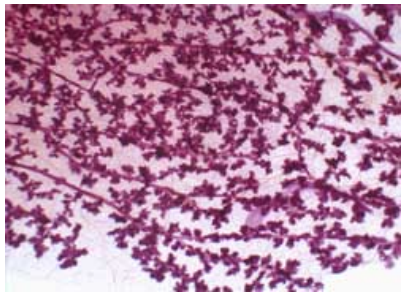


Three types of mammary epithelial cells

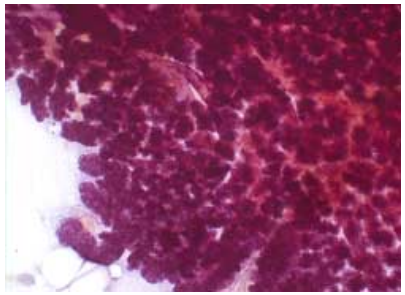
- Myoepithelial
- Luminal
  - -Ductual
  - -Alveolar



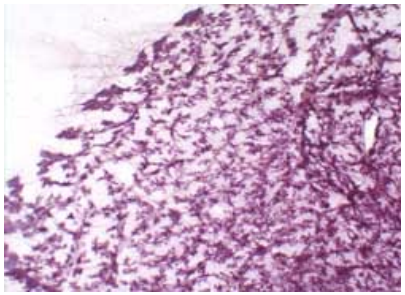
Virgin



Pre-lactating

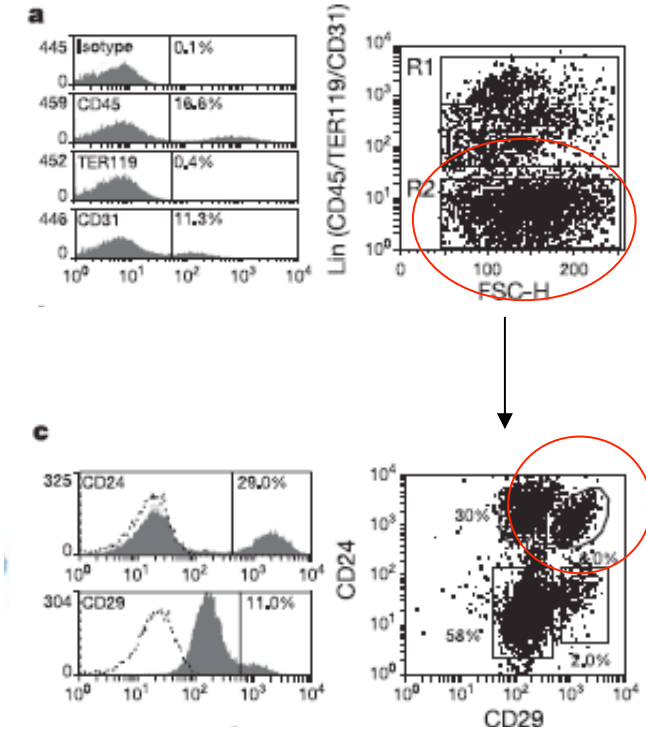


lactating

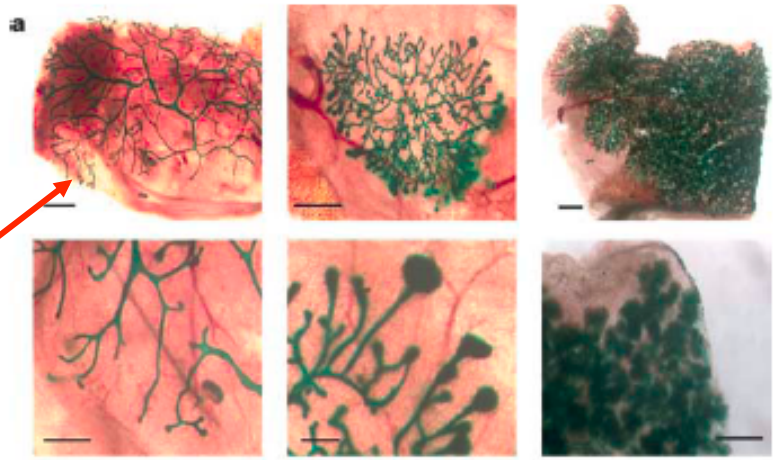


Post-weaning

Generation of a functional mammary gland from a single mammary stem cell

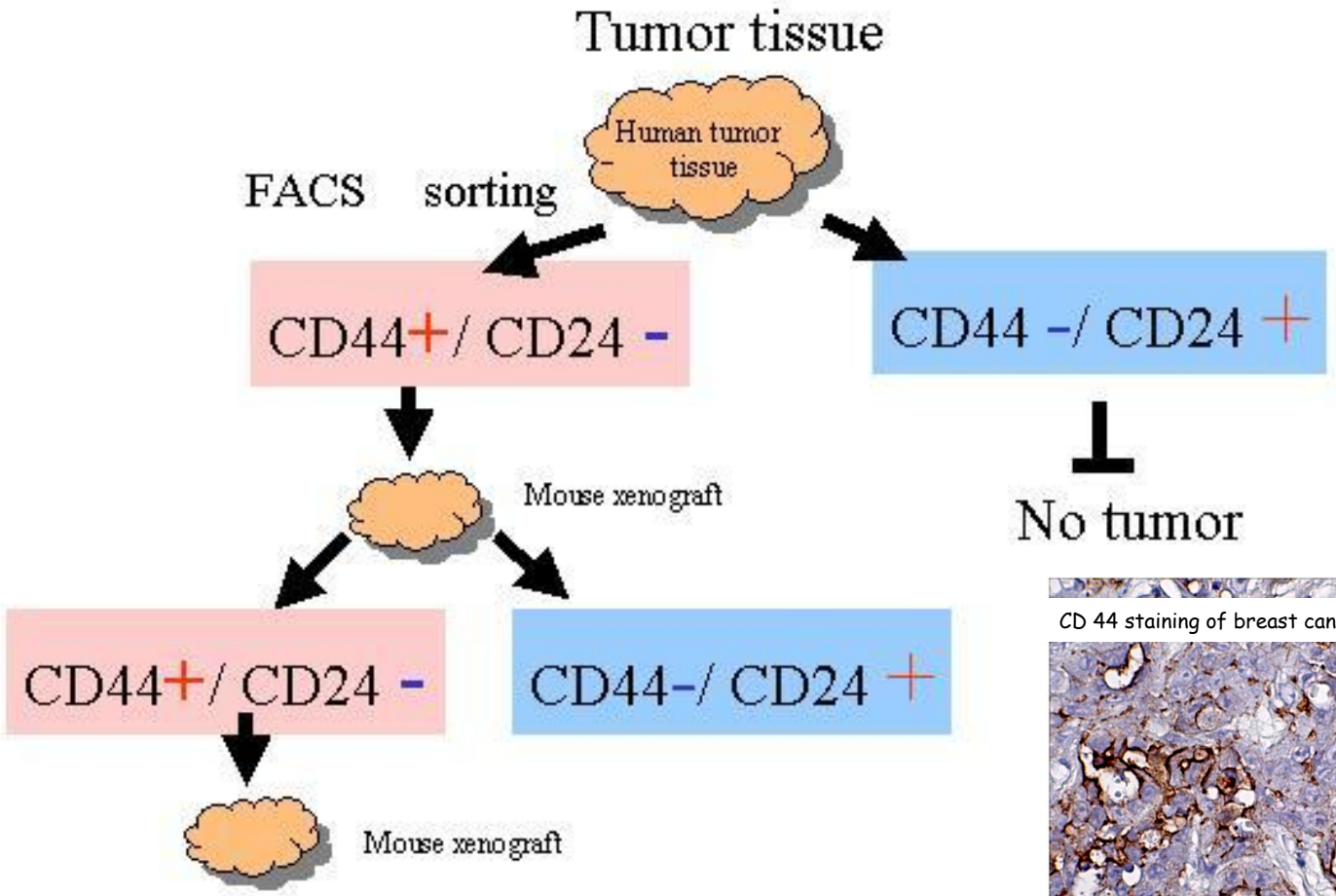


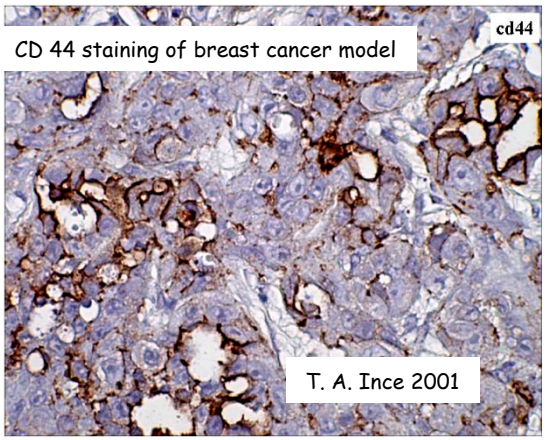
Single Cell



Shackleton M,….Visvader JE, Nature 2006

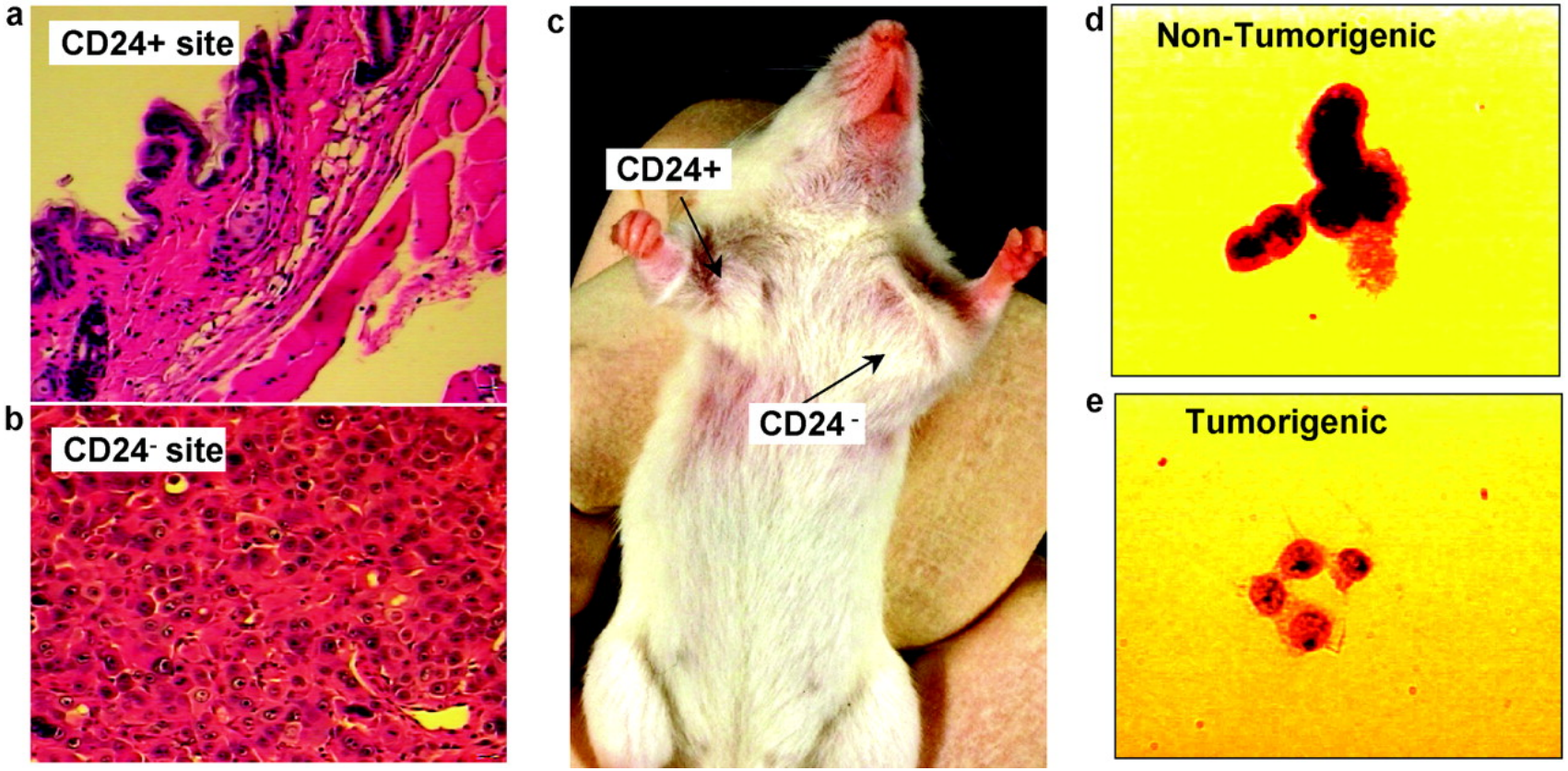
Isolation of Breast Cancer Initiating Cells





Breast Cancer Stem Cells: $CD44^{+}$ $CD24^{low}$ Lin^{-} $B38.1^{+}$ ESA^{+}

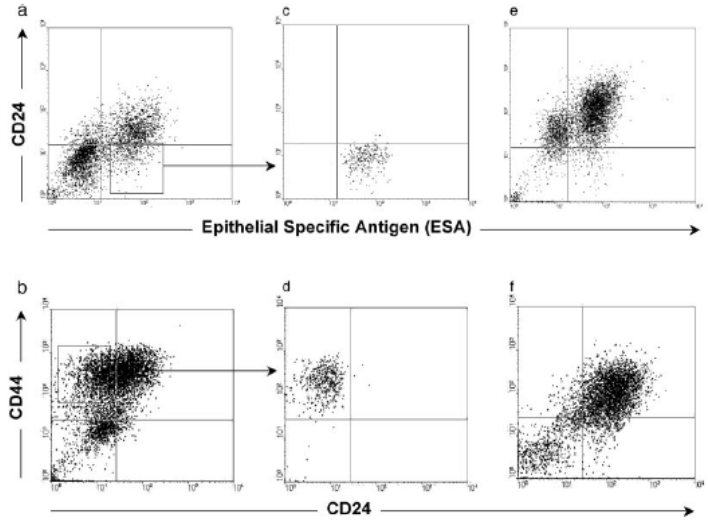
CD44 and CD24 – adhesion molecules
B38.1 – breast/ovarian cancer-specific marker
ESA – epithelial specific antigen

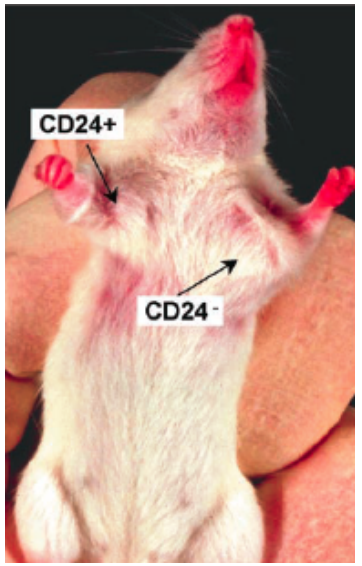


Al-Hajj (2003) PNAS 100, 3983

Self-renewaltumorigenic cells highly enriched in $CD44^{+}CD24^{-/low}ESA^{+}$ Cells

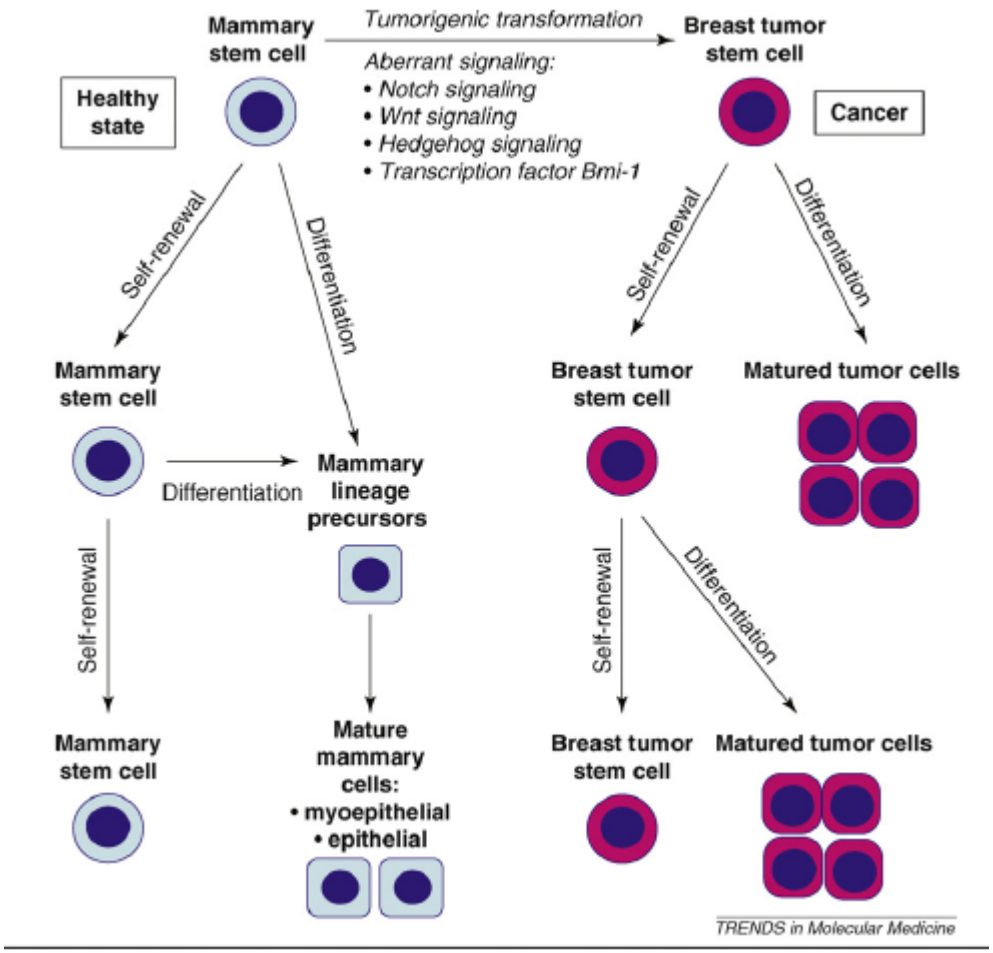
	Tumors/Injections									
	5×10^5	10^5	5×10^4	2×10^4	10^4	5×10^3	10^3	500	200	100
Mouse passage 1										
Unsorted	8/8	8/8	10/10		3/12		0/12	—	—	—
$CD44^{+}CD24^{+}$	—	—	—	0/10	0/10	0/14	0/10	—	—	—
$CD44^{+}CD24^{-/low}$	—	—	—	10/10	10/10	14/14	10/10	—	—	—
$CD44^{+}CD24^{-/low}ESA^{+}$	—	—	—	—	—	—	10/10*	4/4	4/4	1/6
$CD44^{+}CD24^{-/low}ESA^{-}$	—	—	—	—	—	—	0/10*	0/4	0/4	0/6
Mouse passage 2										
$CD44^{+}CD24^{+}$	—	—	—	—	0/9	—	—	—	—	—
$CD44^{+}CD24^{-/low}$	—	—	—	—	9/9	—	—	—	—	—
Patients' tumor cells										
$CD44^{+}CD24^{+}$	—	0/3	0/4	0/8	1/13	0/2	—	—	—	—
$CD44^{+}CD24^{-/low}$	—	3/3	4/4	—	11/13	1/1	—	—	—	—
$CD44^{+}CD24^{-/low}ESA^{+}$	—	—	—	—	—	2/2	2/2	—	—	—
$CD44^{+}CD24^{-/low}ESA^{-}$	—	—	—	—	—	2/2†	0/2	—	—	—





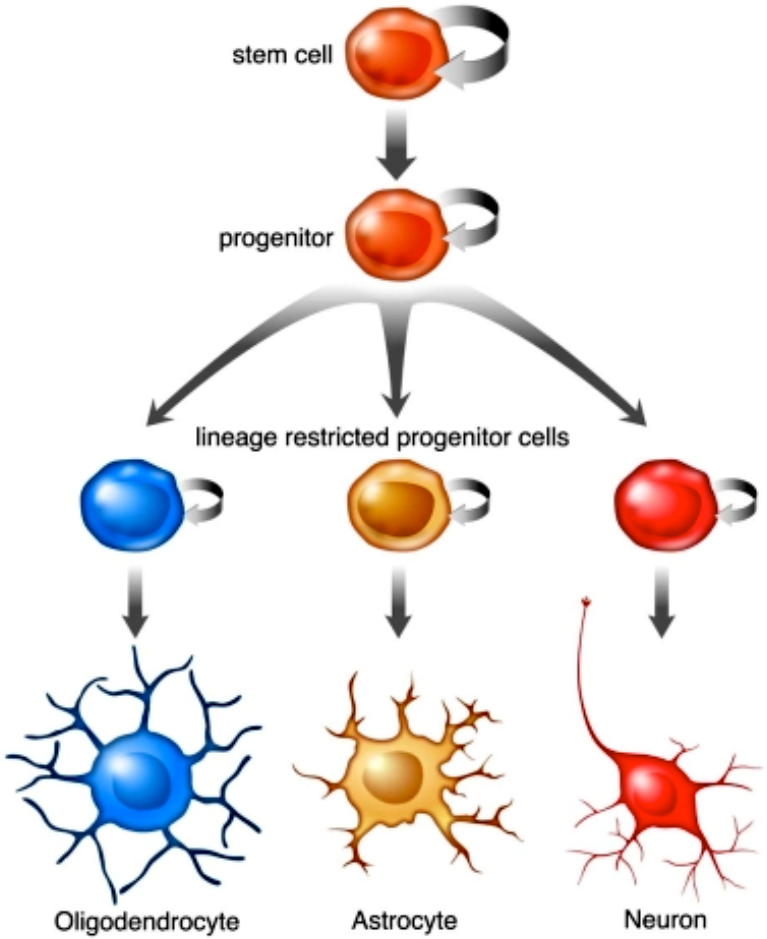
Al-Hajj (2003) PNAS 100, 3983

Stem Cell Hierarchy in Normal Mammary Gland and Breast Cancer

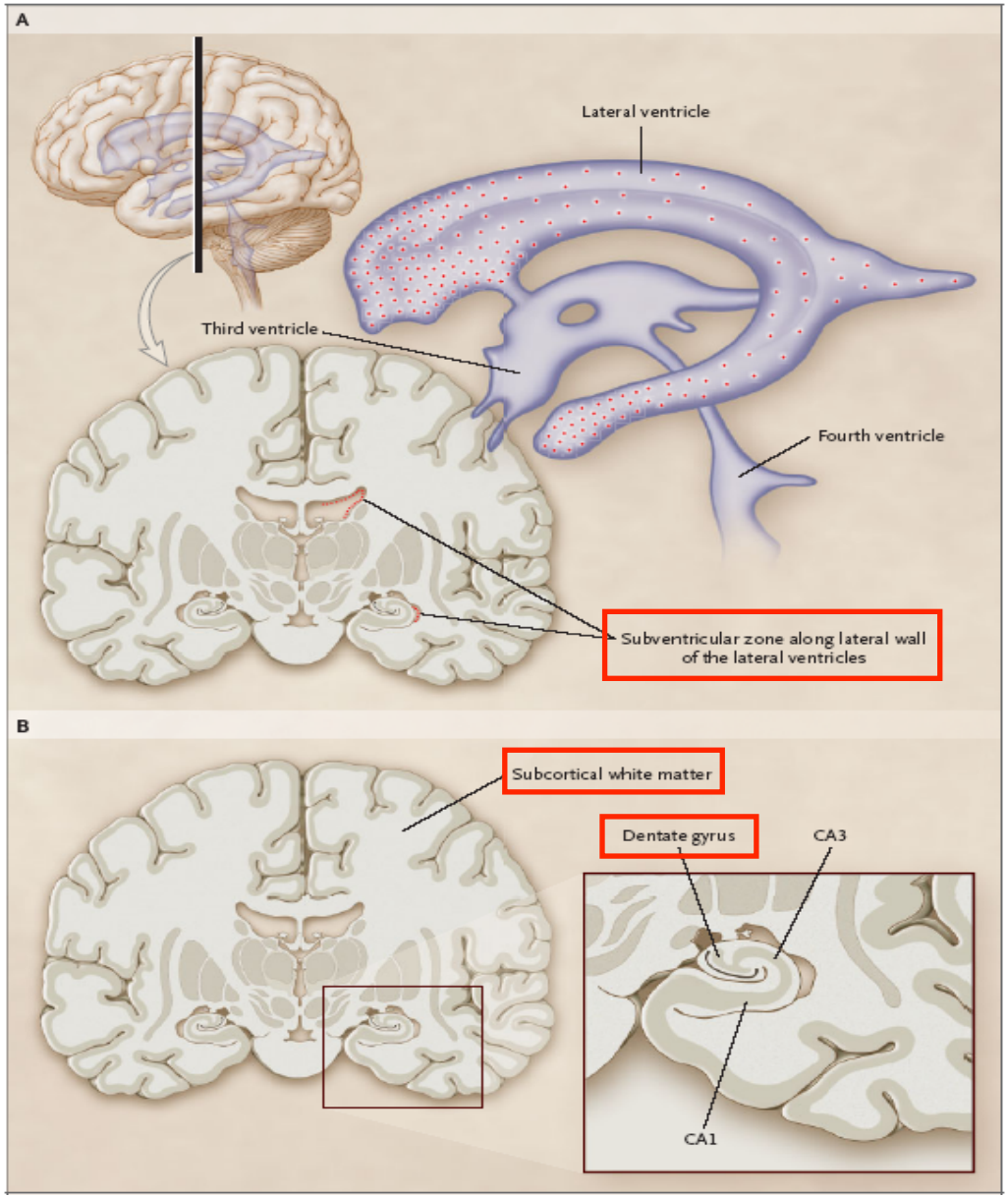


Trends in Molecular Medicine 2008 Vol.14 No.10

Neural Stem Cells in Brains

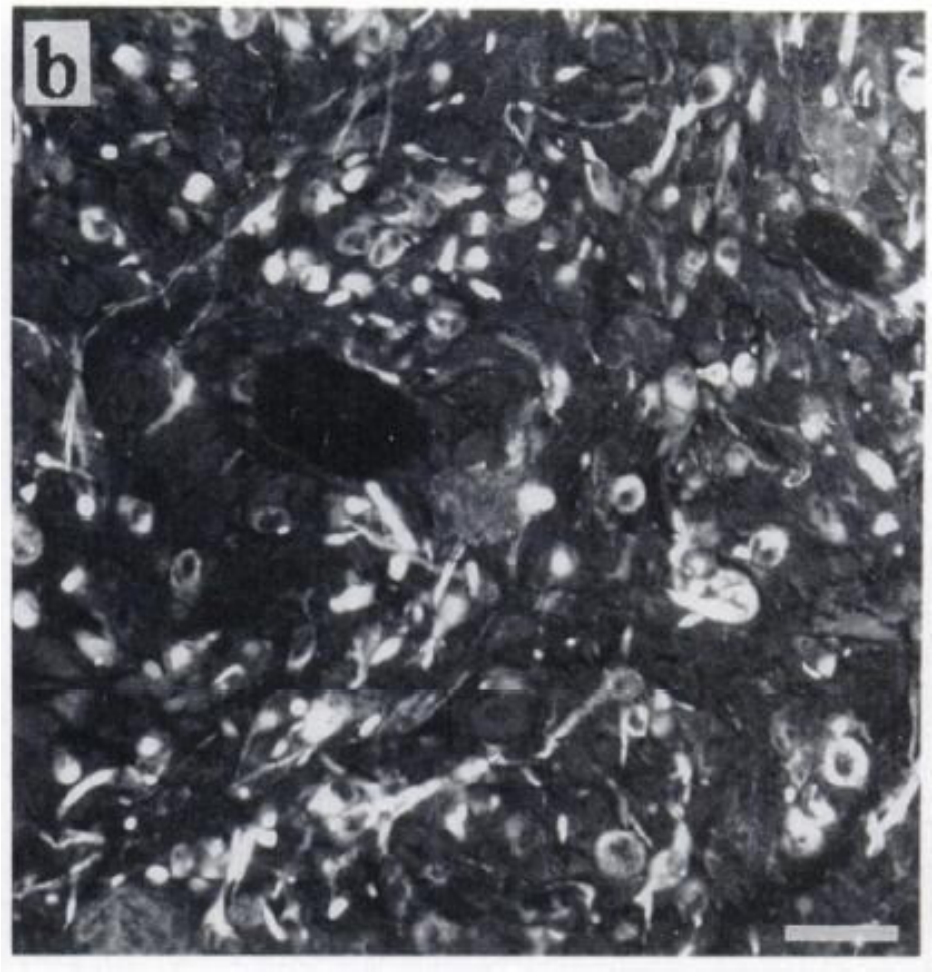


Neural stem cells and Glial progenitor cells have been found in multiple regions of the brain



Sanai et al., 2005

Characteristics of Gliomas



Nestin : Marker for neural stem cell or neural progenitor

- Many Gliomas are found in zones where neural stem cells have been found e.g. periventricular or subventricular zone

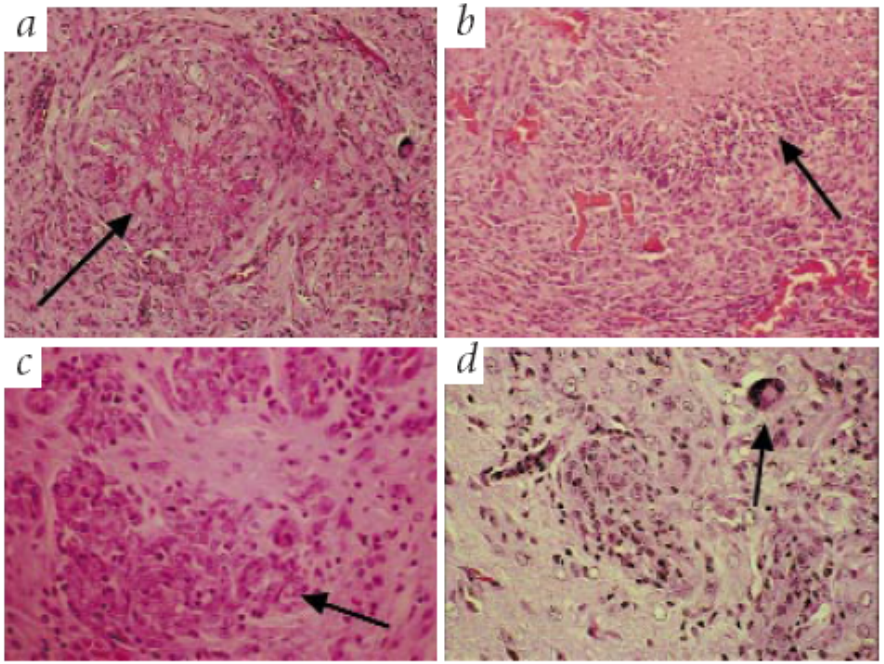
- Gliomas here have also been found to express stem/progenitor marker- Nestin

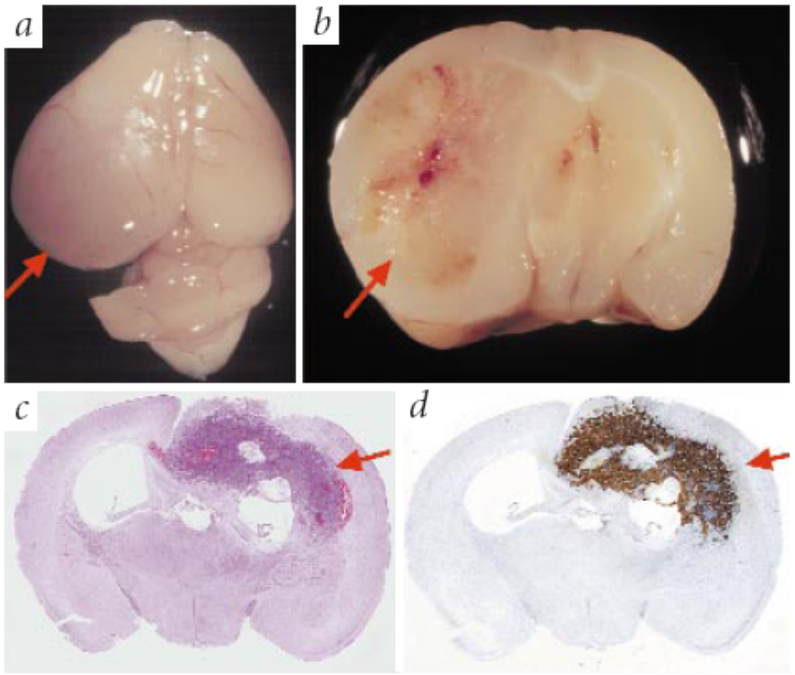
Dahlstrand et al., 1992

Expression of Activated Kras and Akt in neural progenitors induces glioblastoma

•Expression of activated form of Akt and Kras in progenitors (not in astrocytes) was able to induce high grade gliomas

•with histological features of glioblastoma

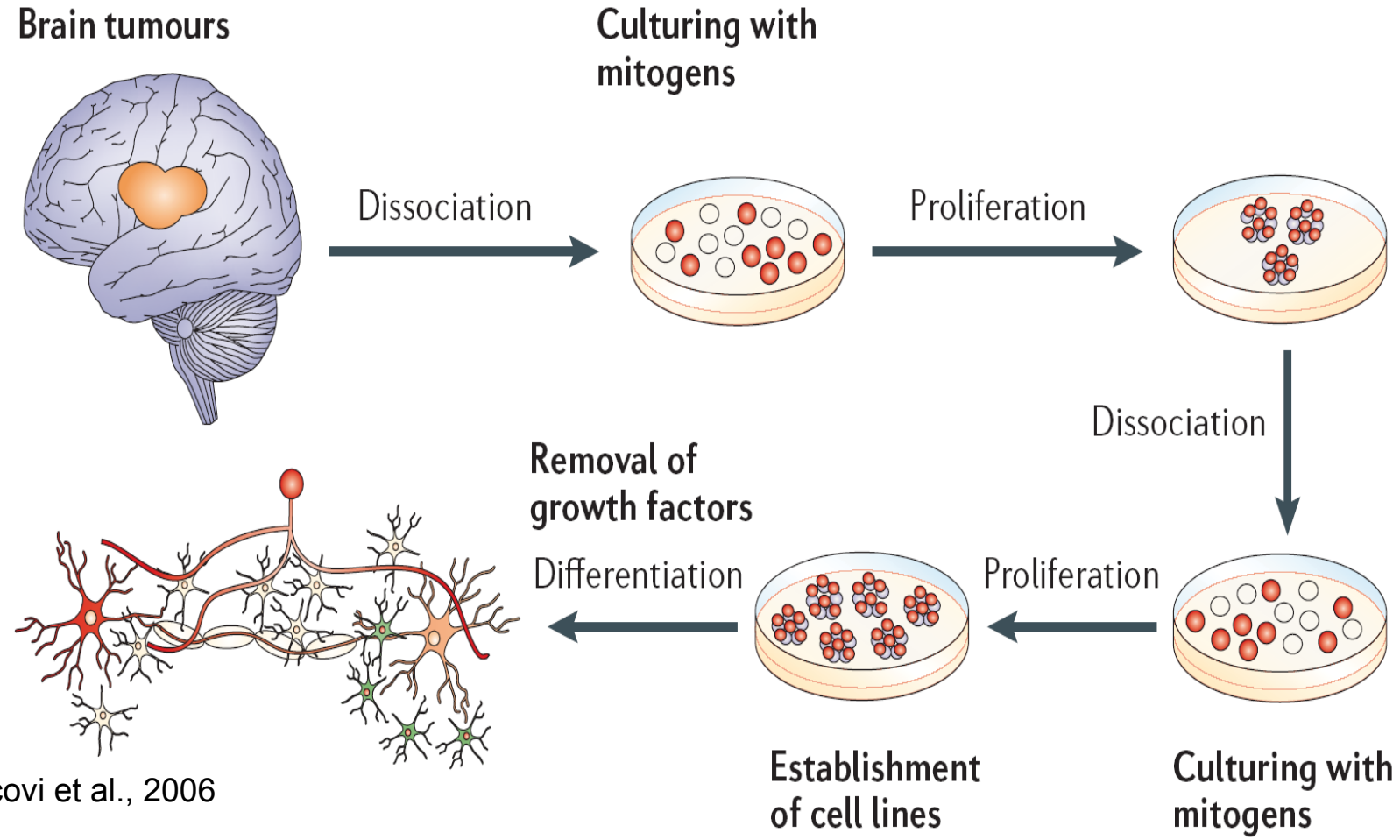




Holland et al., 2000

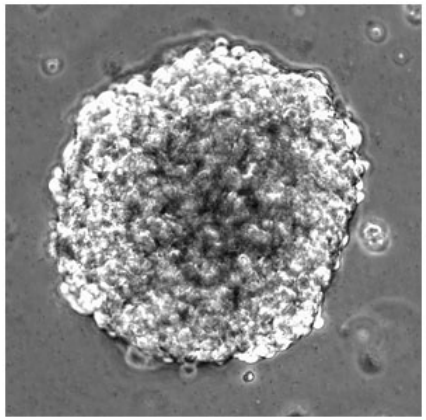
Using Neurosphere Assay to Identify Brain Tumor Stem Cells

The neurosphere assay is a simple and robust assay for the isolation, expansion and identification of neural stem cells and has now become the method to identify brain tumor stem cells



Vescovi et al., 2006

Brain tumor: “Neurosphere“ assay



- Cell culture system for normal neural stem cells

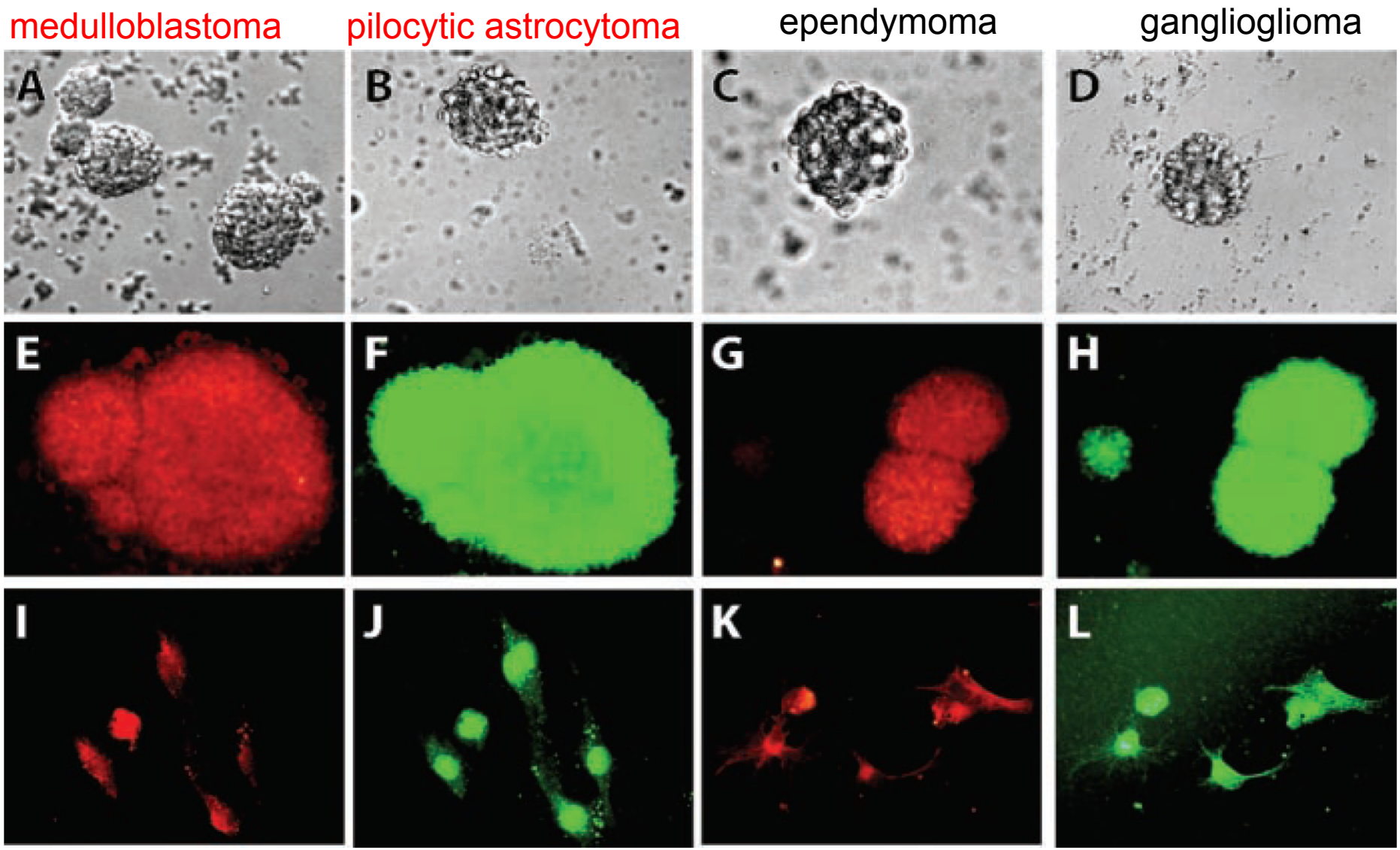
→ long-term self-renewing

→ multi-lineage-differentiating

- Galli R et al. Cancer Res. 2004;64:7011-7021:
  isolation and serial propagation of **„cancer neurospheres“**
  → long-term self-renewing
  → multi-lineage-differentiating
  → *in vivo* tumorigenicity

- Singh SK et al. Nature. 2004;432:396-401:
  Cell surface marker **CD133** identifies glioma stem cells

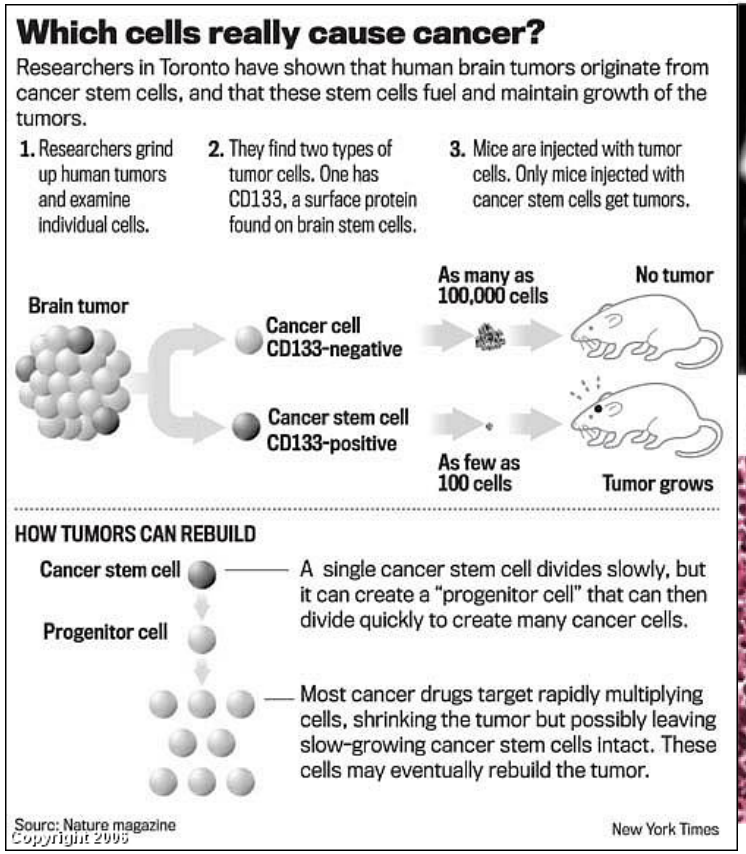
Neurospheres derived from different brain tumor expressing Nestin and CD133

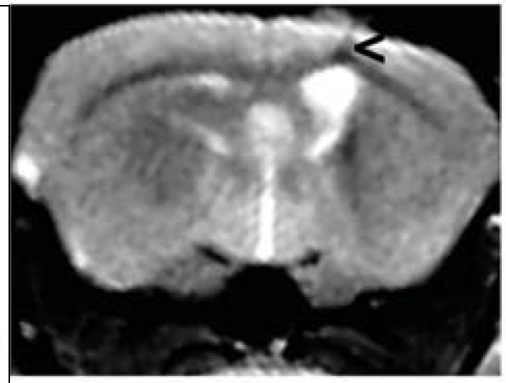


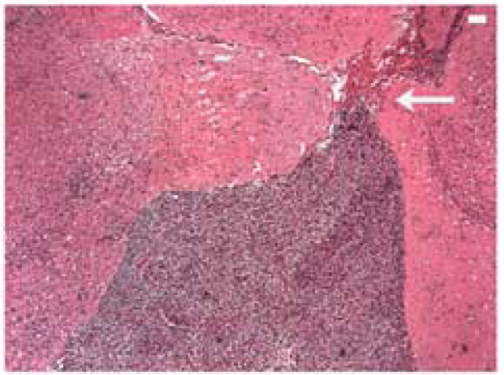
Red : Nestin / **Green : CD133**

Singh et. al 2003 Cancer Research 63: 5821-5828.

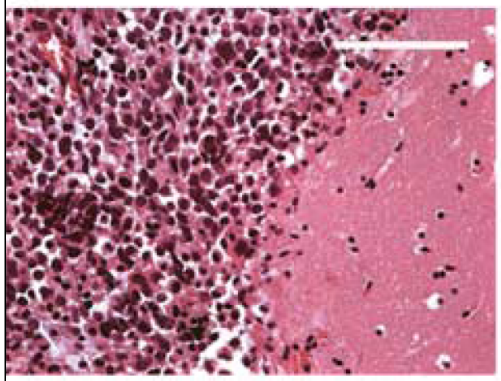
CD133+ Cells Isolated from GBM induced tumor fromation in NOD-SCID mice



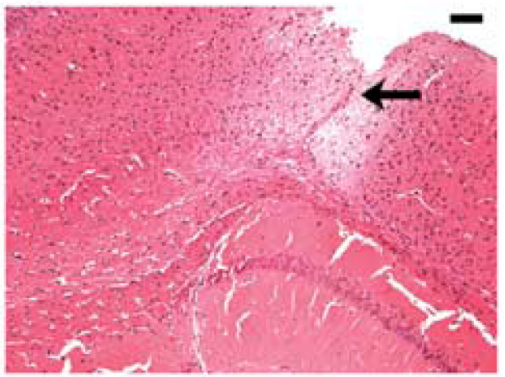




c CD133+ : 100

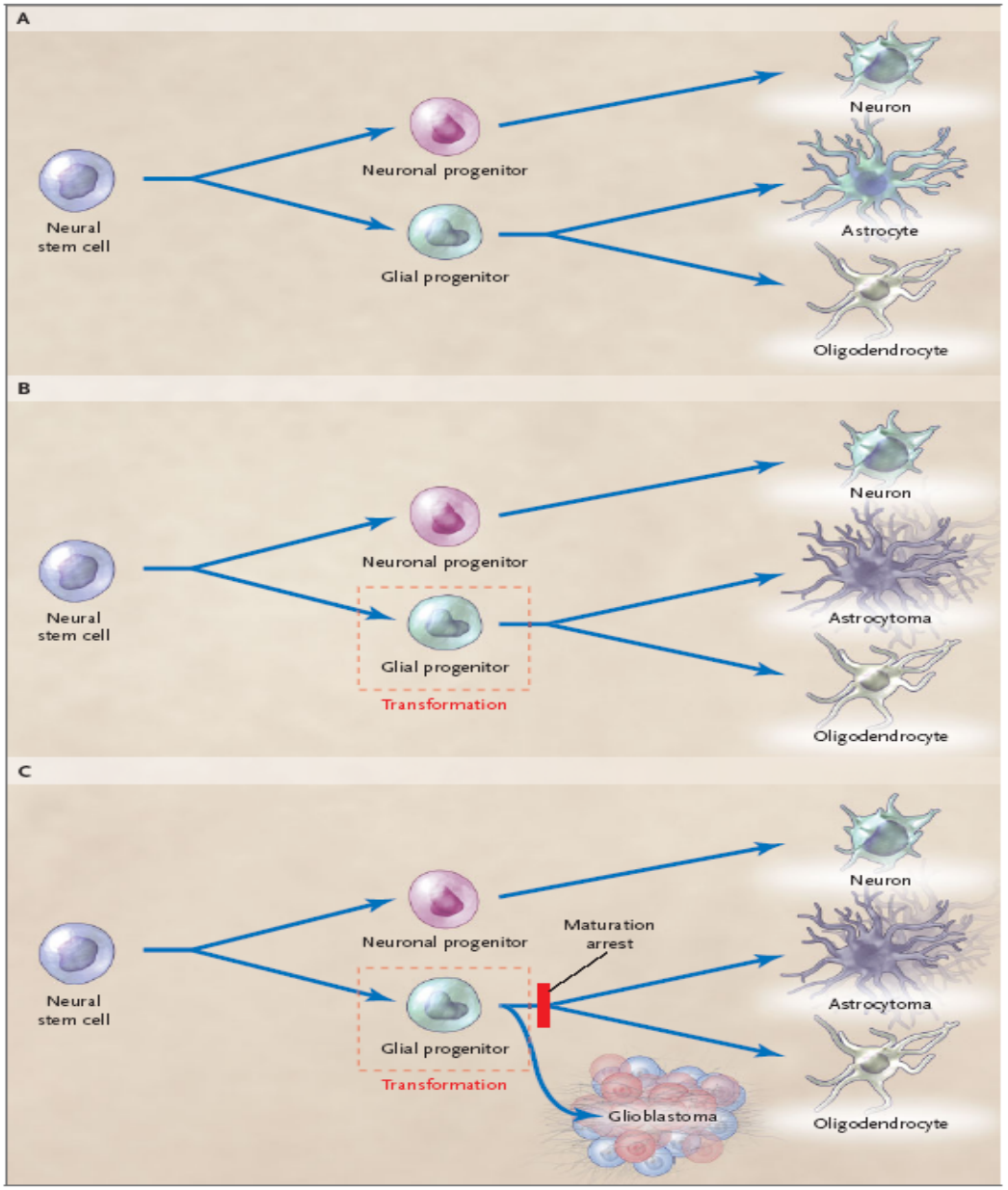


d CD133- : $0.5x10^5$ ~ $1x10^5$



Singh et al. 2004 Nature 432: 396-401

Maturation-Arrest Theory



Sanai et al., 2005

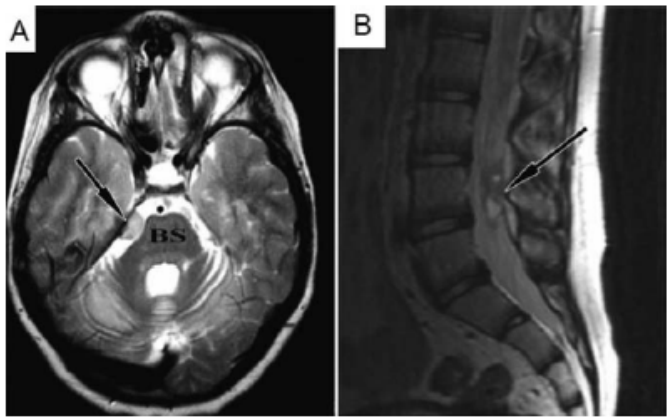
Transplants of neural stem cells led to tumors in brain & spinal cord

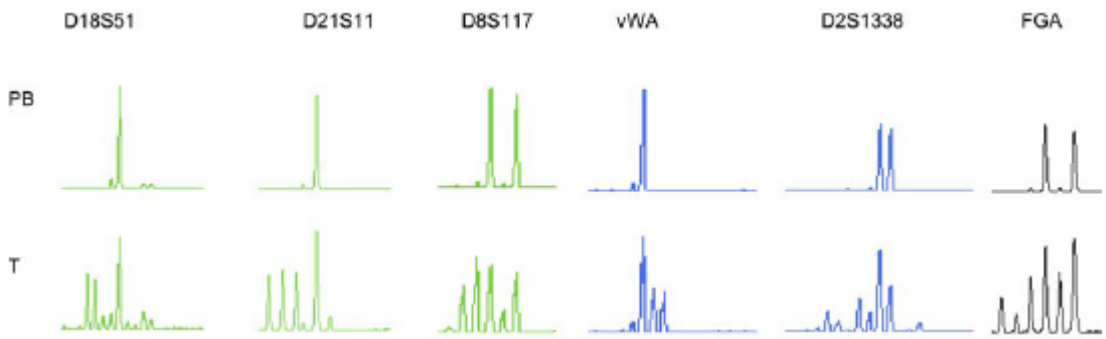
OPEN ACCESS Freely available online

PLoS MEDICINE

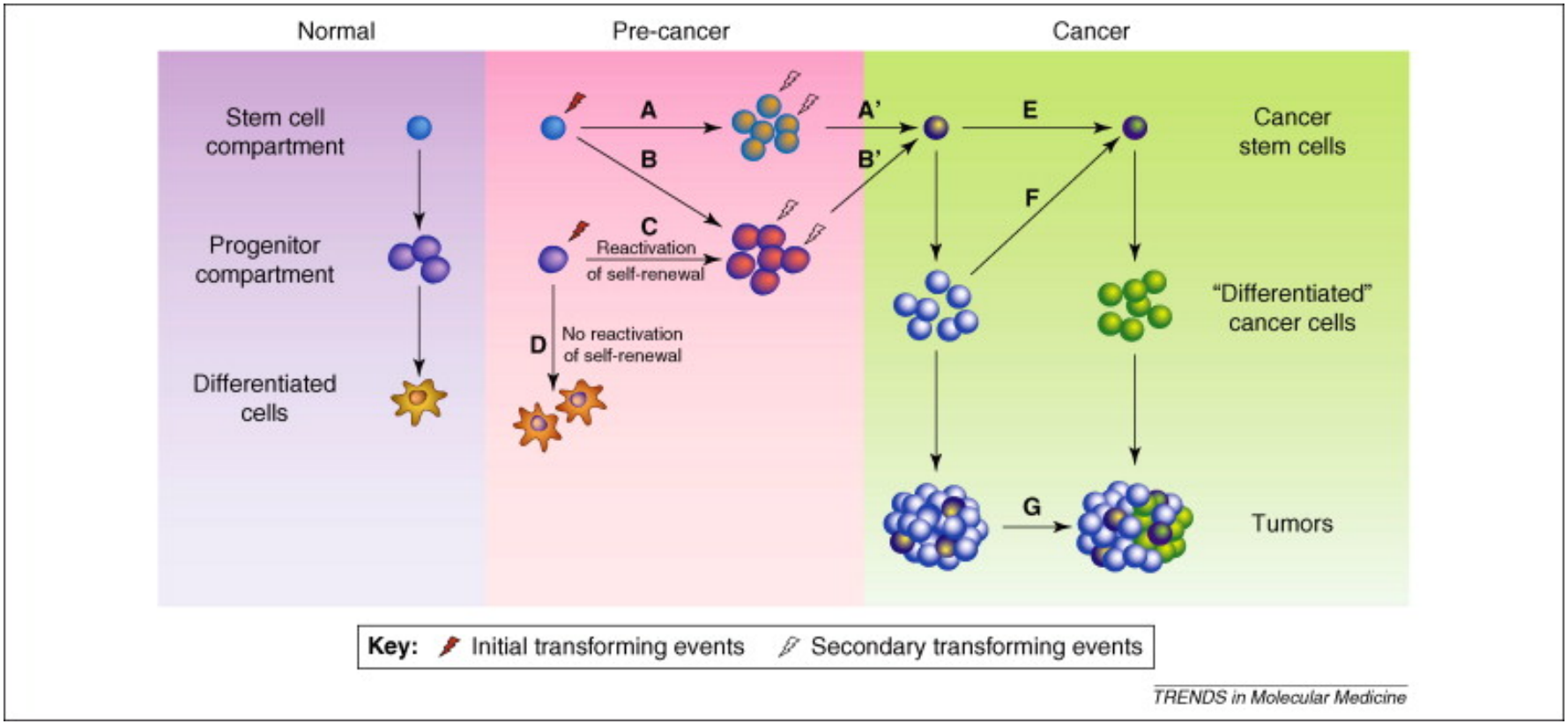
Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio[1,2], Abraham Hirshberg[3], Bernd W. Scheithauer[4], Yoram Cohen[1], Ron Loewenthal[5], Luba Trakhtenbrot[2], Nurit Paz[1], Maya Koren-Michowitz[2], Dalia Waldman[6], Leonor Leider-Trejo[7], Amos Toren[6], Shlomi Constantini[8], Gideon Rechavi[1,6*]





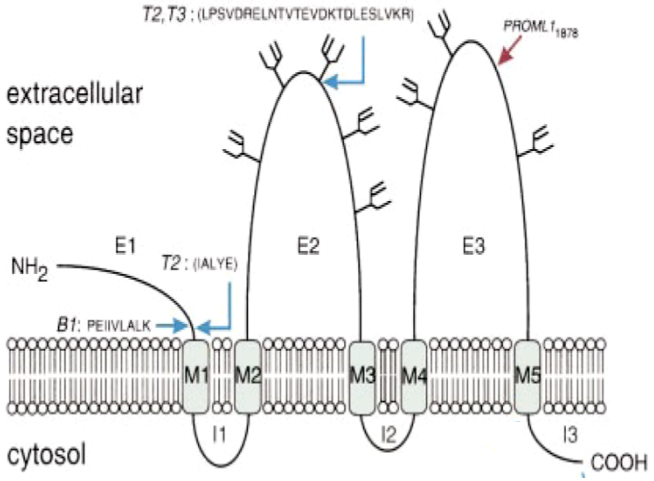
New concept of the human cancer as a a disease of stem cells



CD133 (Prominin-1)

Expression of CD133 was found in

- **primitive hematopoietic stem and progenitor cells**
- **neural and endothelial stem cells**
- **developing epithelium cells**
- **rod photoreceptor cells**



Antigenic phenotype	Origin	Stem cell action
AC133 or CD133	Human adult blood, bone marrow, cord blood, and fetal liver	Human haematopoietic reconstitution
AC133	Human peripheral blood	Myogenesis in mouse model of Duchenne's muscular dystrophy
CD133	Human peripheral blood	Endothelial and cardiomyocytic differentiation *in vitro*
CD133	Adult human kidney	Endothelial and epithelial differentiation, human renal regeneration
CD133	Human bone marrow	Human liver regeneration, mechanism unknown
CD133	Human and mouse brain	Neural differentiation in mice
CD133, SSEA4	Mouse embryonic forebrain	Neural differentiation *in vitro*
AC133-2, β1-integrin	Human neonatal foreskin	Keratinocyte differentiation *in vitro*
CD133, β1-integrin	Human prostate basal cells	Prostatic acinar differentiation in mice
$CD133^{+}CD34^{-}CD45^{-}Ter119^{-}$	Ductal epithelium neonatal mouse pancreas	Multiple lineage differentiation in mouse pancreas
CXCR4, NGN-3, nestin, CD133, Oct-4, Nanog, ABCG2, CD117	Human pancreas	Islet differentiation *in vitro*

J Pathol 2008; 214: 3–9

The origin of CD133(+) colon cancer stem cells

nature Vol 445|4 January 2007|doi:10.1038/nature05372

LETTERS

A human colon cancer cell capable of initiating tumour growth in immunodeficient mice

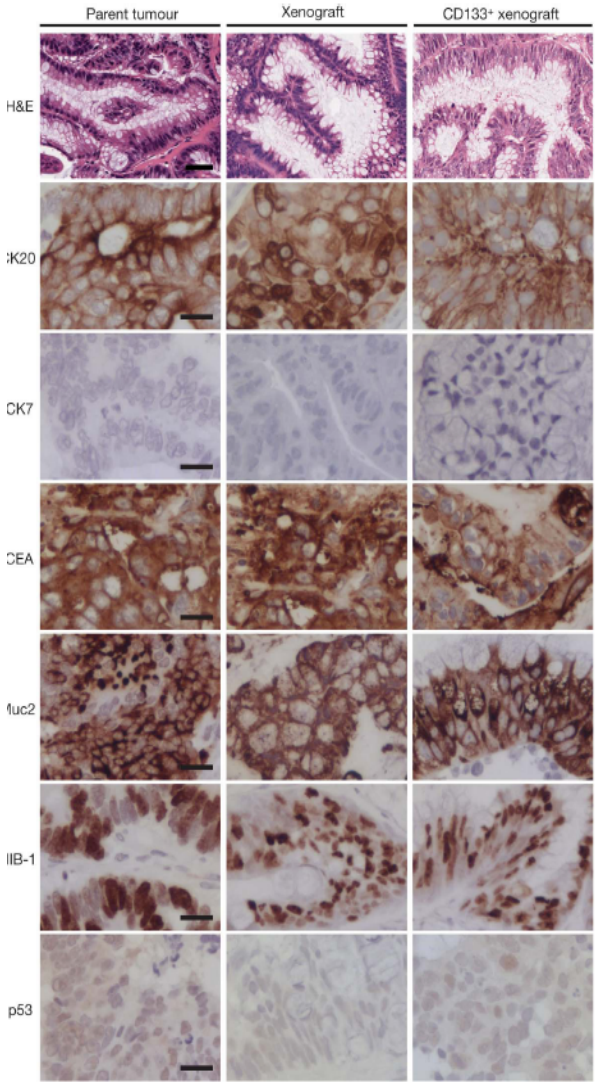
Catherine A. O'Brien[1], Aaron Pollett[2], Steven Gallinger[3] & John E. Dick[1,4]

Vol 445|4 January 2007|doi:10.1038/nature05384 nature

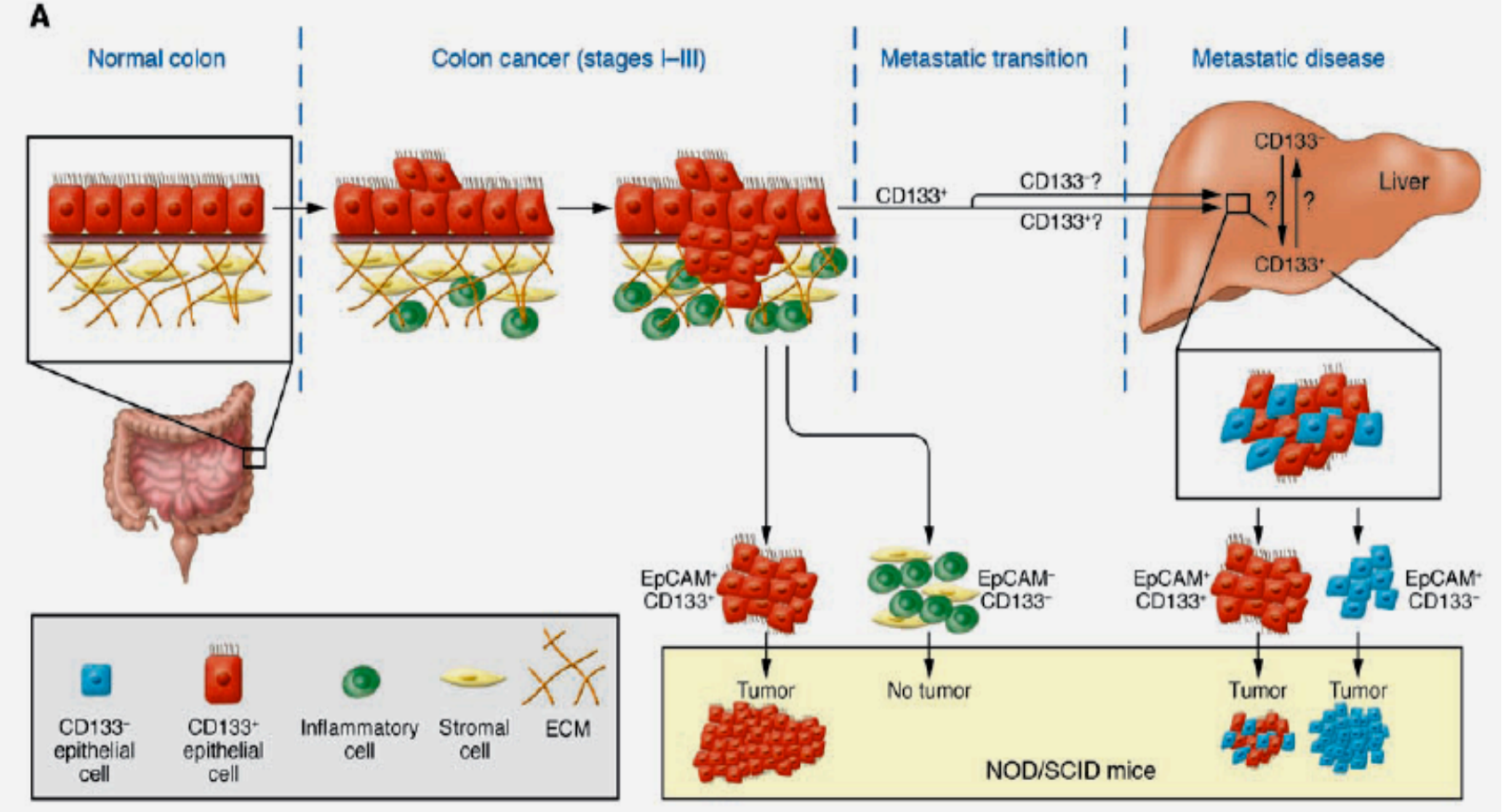
LETTERS

Identification and expansion of human colon-cancer-initiating cells

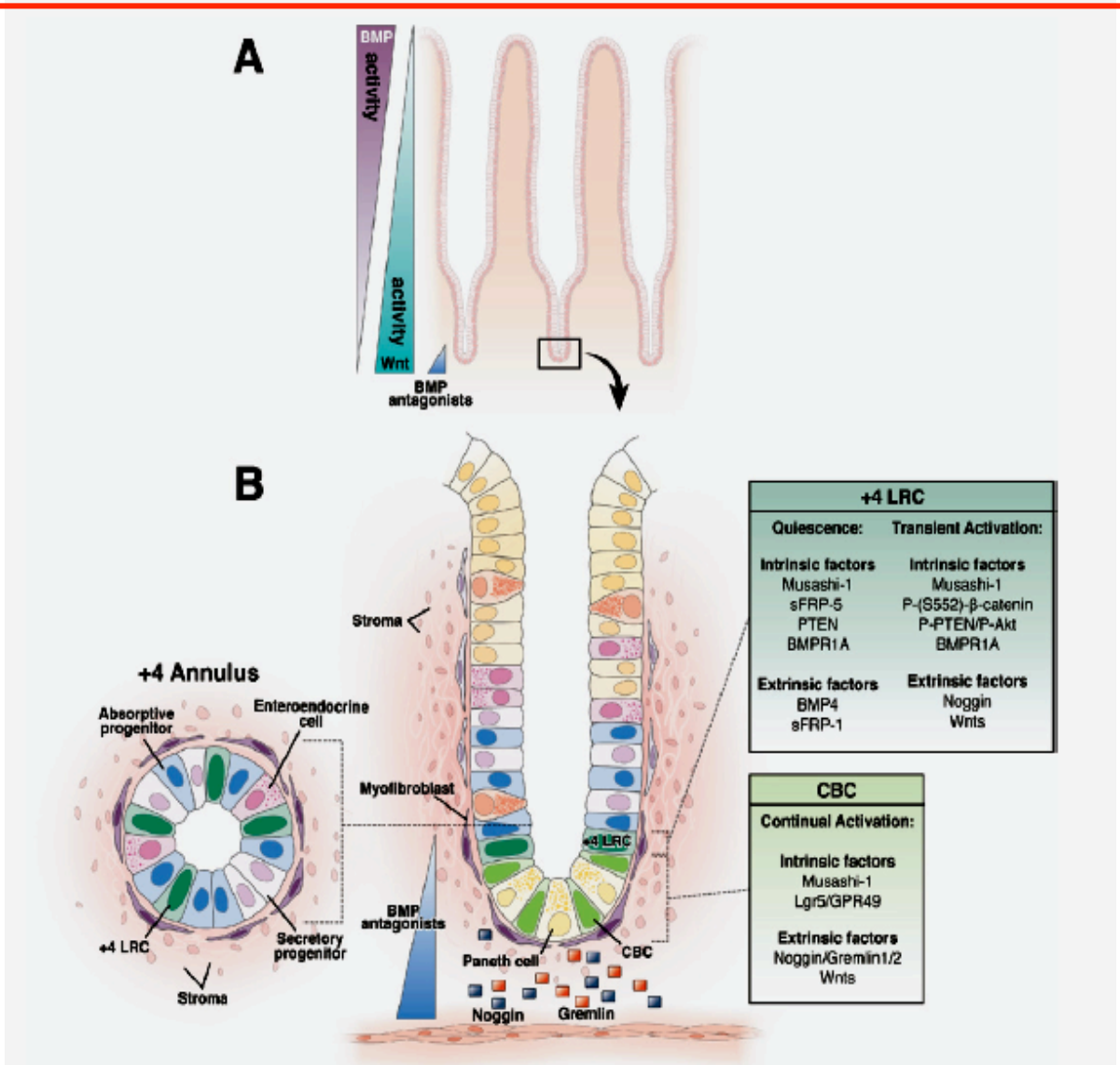
Lucia Ricci-Vitiani[1], Dario G. Lombardi[2], Emanuela Pilozzi[3], Mauro Biffoni[1], Matilde Todaro[4], Cesare Peschle[1] & Ruggero De Maria[1,2]



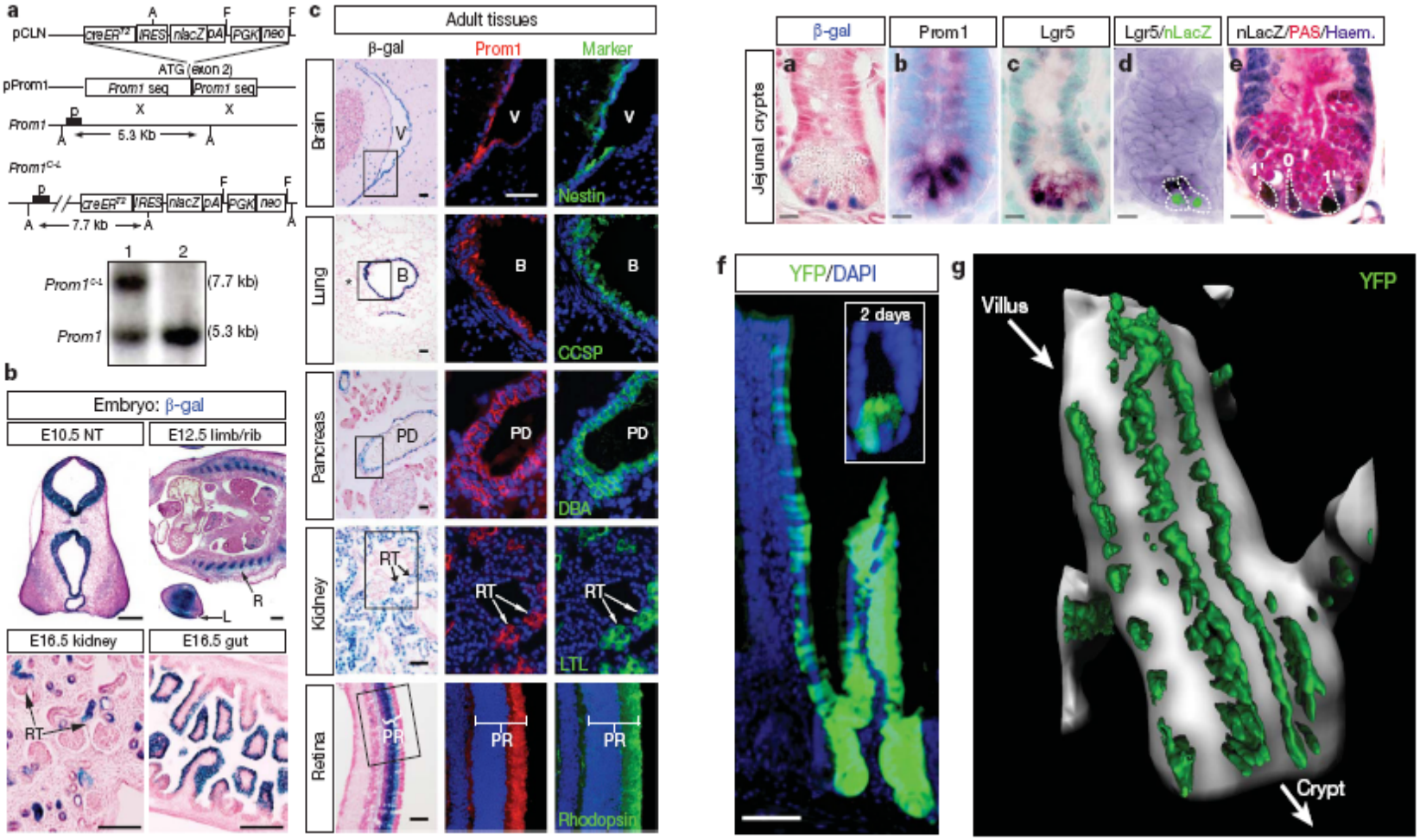
CD133(+) colon cancer stem cells



Schematic diagram illustrating two models of crypt stem cell localization

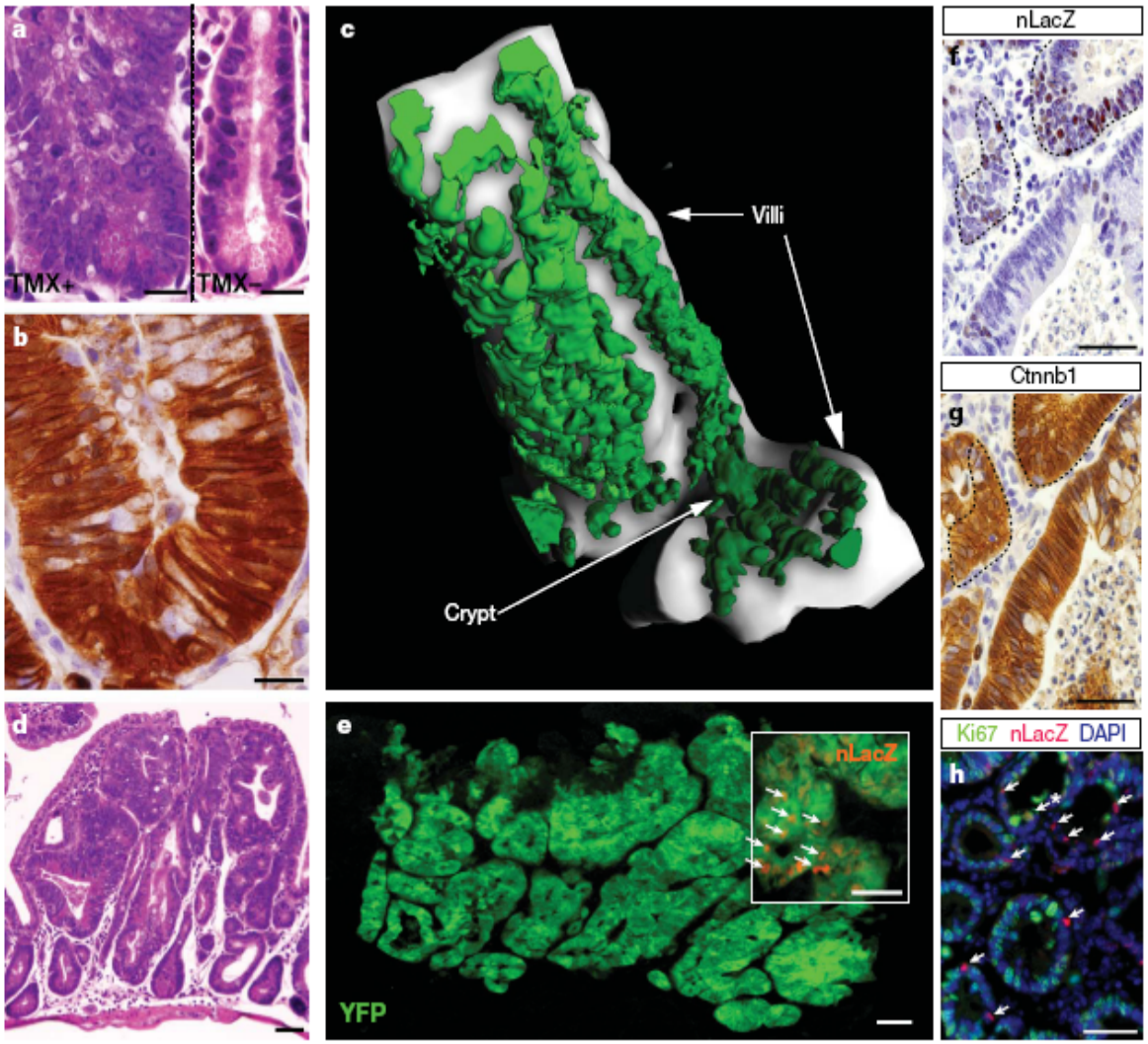


Prominin 1 marks intestinal stem cells that are susceptible to neoplastic transformation



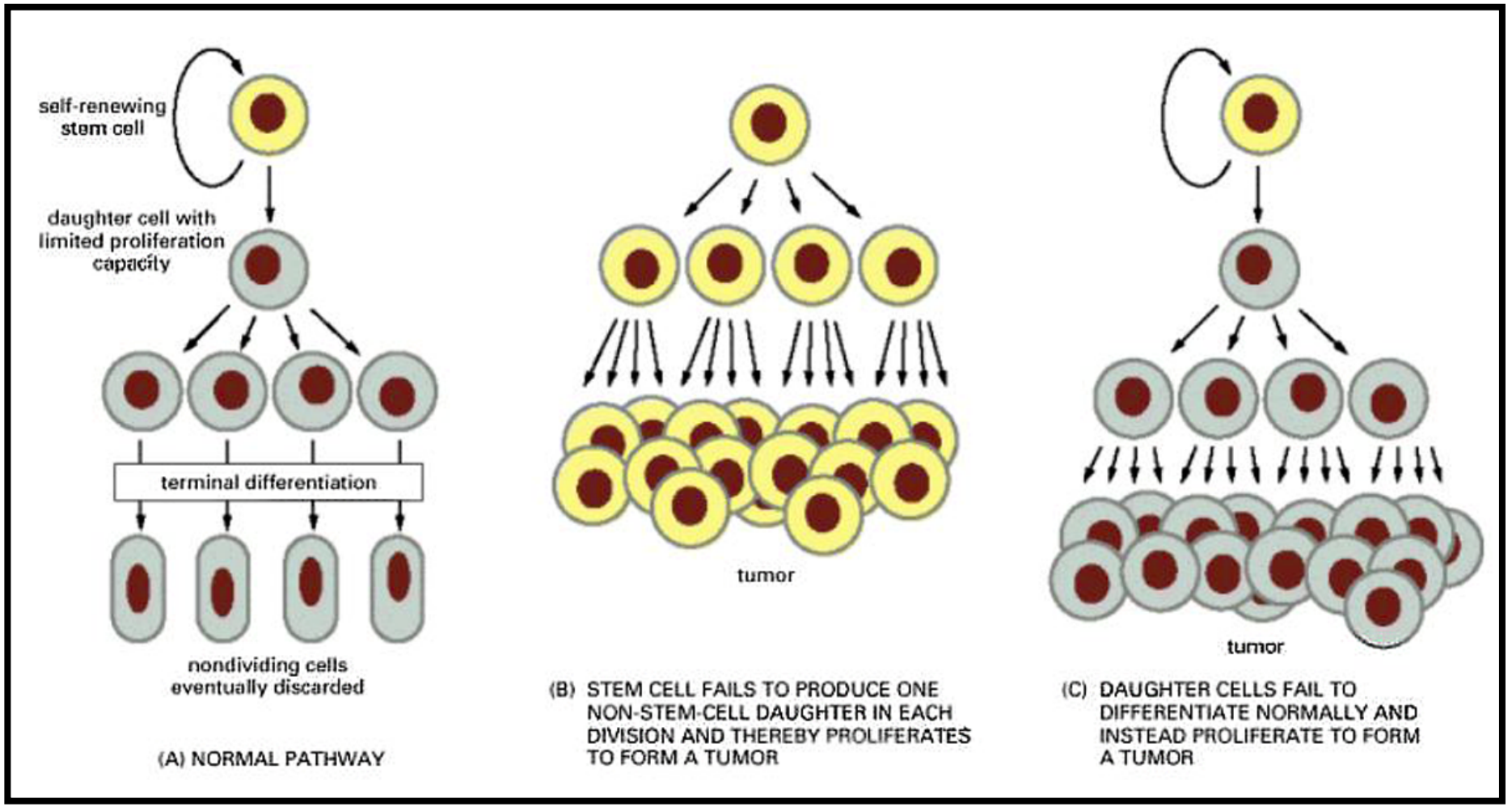
Zhu et al., 2009 Nature

Prominin 1 marks intestinal stem cells that are susceptible to neoplastic transformation



Zhu et al., 2009 Nature

Disrupting normal stem cell division can result in hyperproliferation & possibly tumor formation

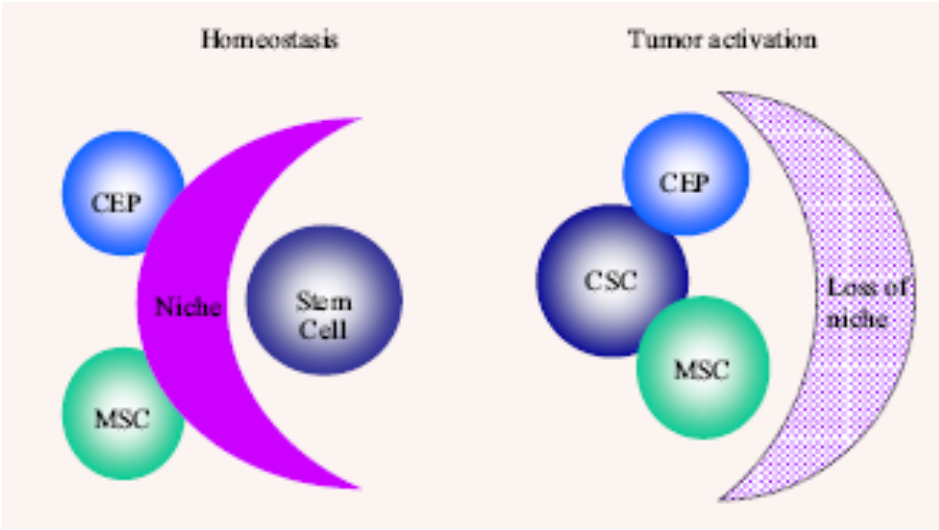


Seed & Soil hypothesis

- Paget proposed that tumour cells ('seeds') must be predisposedto arrest and proliferate only in those anatomical sites ('soil') that provide a congenial ground
- The "seed and soil" hypothesis is now widely accepted and cited.
- The "seed" may need to be renamed to progenitor cell, initiating cell, cancer stem cell, or metastatic cell,
- The "soil" to host factors, stroma cells inclduign EPC or MSC, or the organ microenvironment.

Key findings of the 1889 paper by Paget

- The pattern of metastasis is not random
- One remote organ is more prone to be the seat of secondary growth than another
- In breast cancer, the incidence of metastasis to the ovaries is higher than to the spleen and kidneys combined
- Bone metastasis cannot be explained by the theory of embolism alone
- There is a high incidence of bone metastasis from thyroid cancer, and some bones have more metastases than others



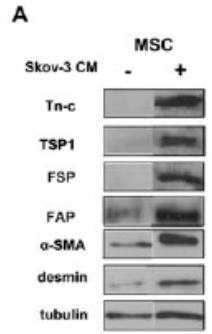
Lancet Oncol 2008; 9: 808

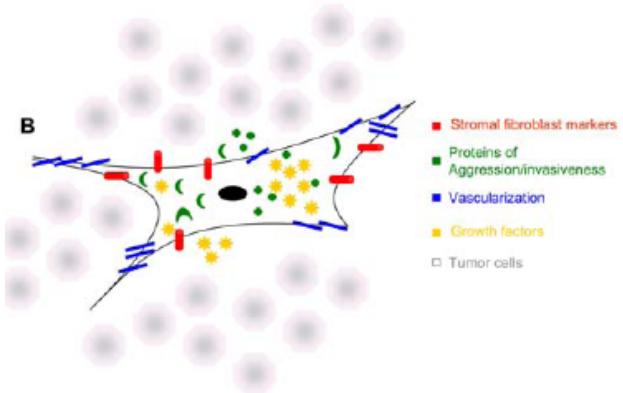
Mesenchymal stem cells contribute to tumor-associated fibroblast

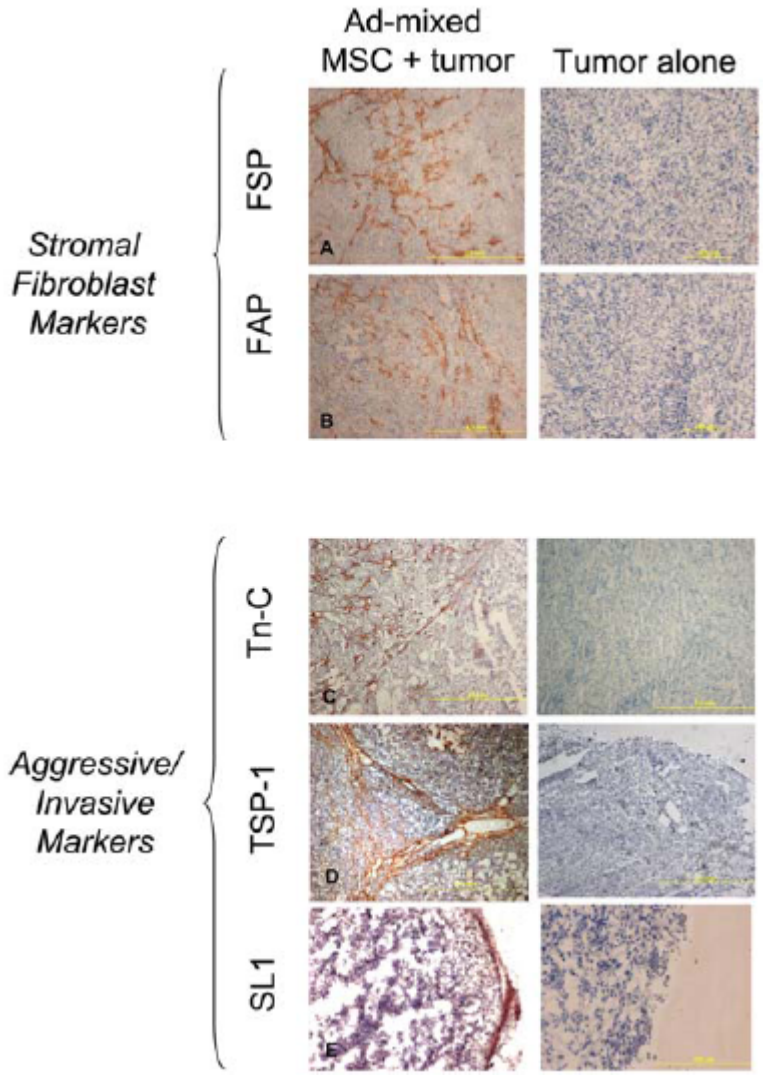
OPEN ACCESS Freely available online

Mesenchymal Stem Cell Transition to Tumor-Associated Fibroblasts Contributes to Fibrovascular Network Expansion and Tumor Progression

Erika L. Spaeth[1☯], Jennifer L. Dembinski[1☯¤], A. Kate Sasser[2], Keri Watson[1], Ann Klopp[1], Brett Hall[2], Michael Andreeff[1], Frank Marini[1*]

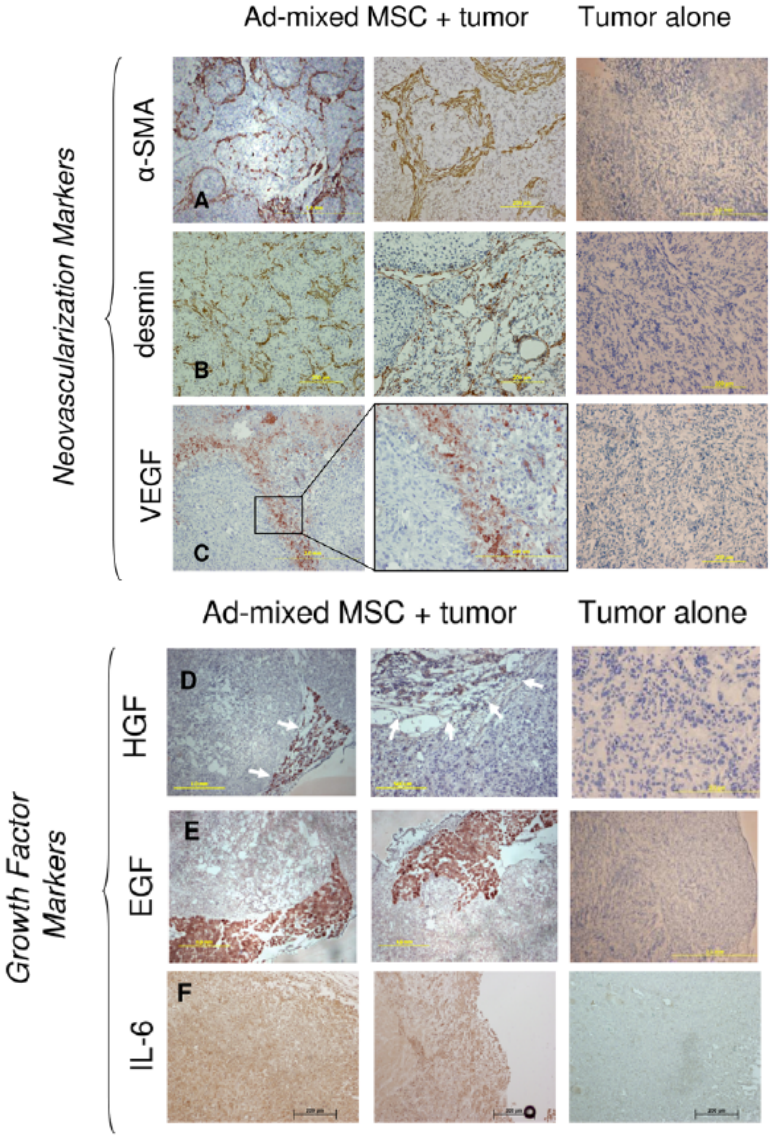


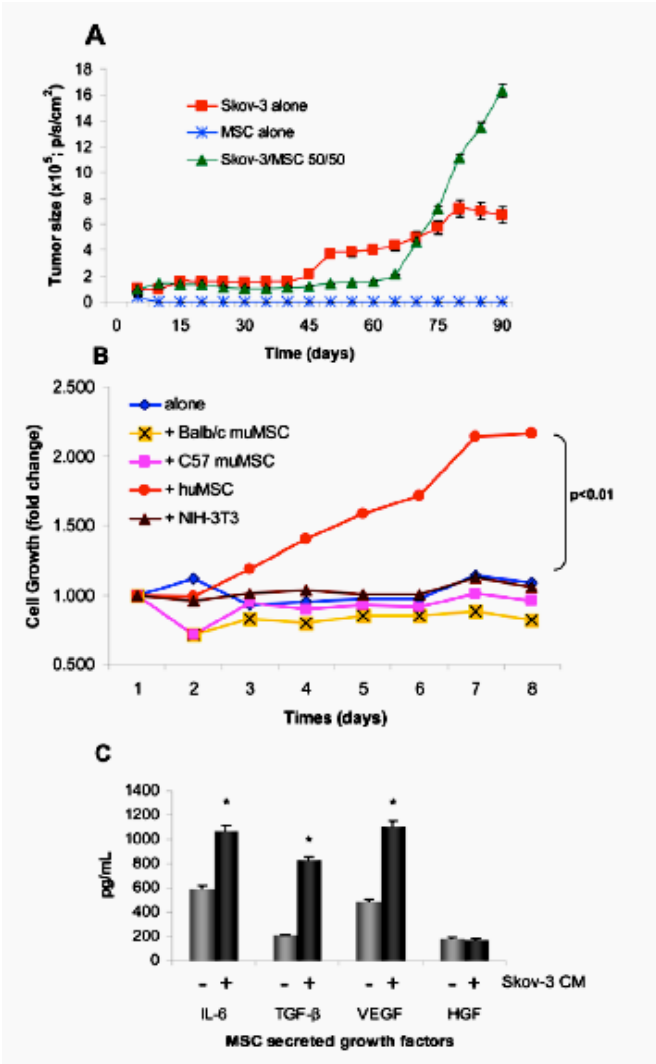




PLoS ONE 4(4): e4992. doi:10.1371/journal.pone.0004992

Mesenchymal stem cells contribute to tumor-associated fibroblast





PLoS ONE 4(4): e4992. doi:10.1371/journal.pone.0004992

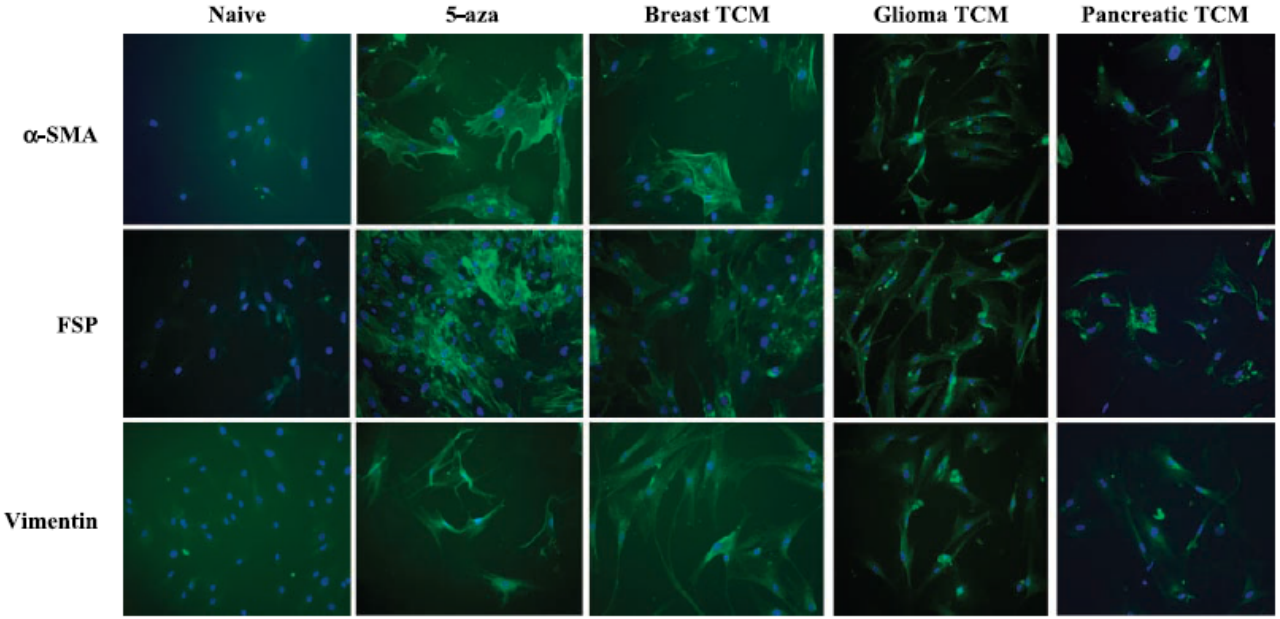
Mesenchymal stem cells contribute to tumor-associated fibroblast

Research Article

Carcinoma-Associated Fibroblast–Like Differentiation of Human Mesenchymal Stem Cells

Pravin J. Mishra,[1] Prasun J. Mishra,[1,2] Rita Humeniuk,[1,2] Daniel J. Medina,[1] Gabriela Alexe,[4] Jill P. Mesirov,[4] Sridhar Ganesan,[1,2] John W. Glod,[2,3] and Debabrata Banerjee[1,2]

Departments of [1]Medicine, [2]Pharmacology, and [3]Pediatric Oncology, The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey and [4]The Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts



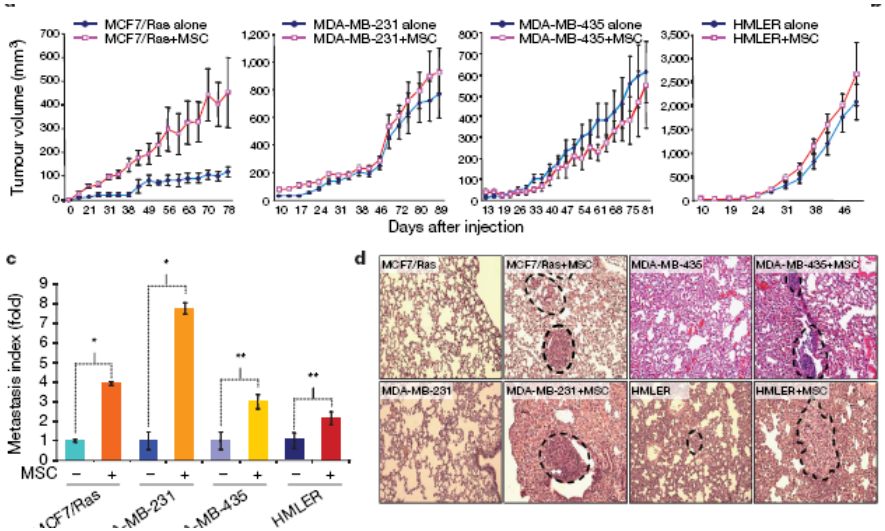
Mesenchymal stem cells promote cancer progression

Vol 449|4 October 2007|doi:10.1038/nature06188 nature

ARTICLES

Mesenchymal stem cells within tumour stroma promote breast cancer metastasis

Antoine E. Karnoub[1], Ajeeta B. Dash[2], Annie P. Vo[1], Andrew Sullivan[2], Mary W. Brooks[1], George W. Bell[1], Andrea L. Richardson[3], Kornelia Polyak[4], Ross Tubo[2] & Robert A. Weinberg[1]



Research Article

Tumor Irradiation Increases the Recruitment of Circulating Mesenchymal Stem Cells into the Tumor Microenvironment

Ann H. Klopp,[1] Erika L. Spaeth,[2] Jennifer L. Dembinski,[2] Wendy A. Woodward,[1] Anupama Munshi,[3] Raymond E. Meyn,[3] James D. Cox,[1] Michael Andreeff,[2] and Frank C. Marini[2]

Departments of [1]Radiation Oncology, [2]Stem Cell Transplantation, and [3]Experimental Irradiation Oncology, M. D. Anderson Cancer Center, Houston, Texas

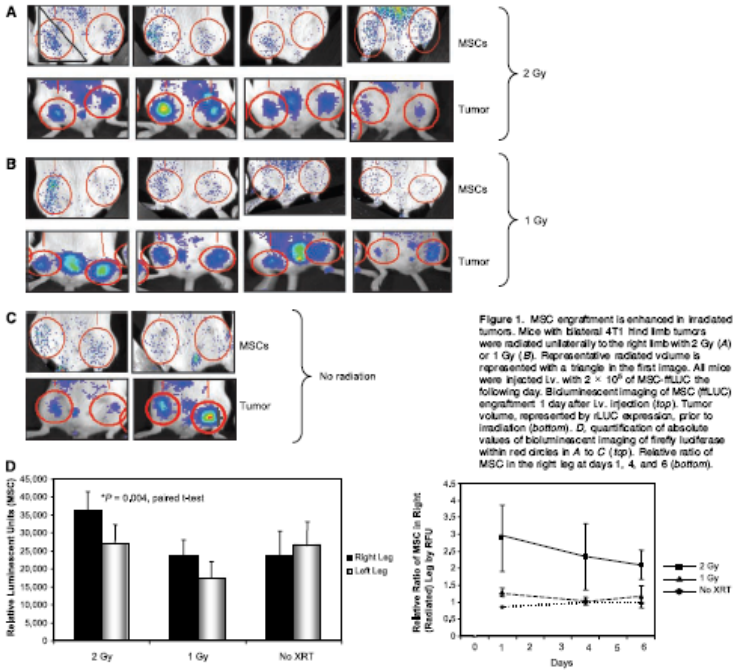
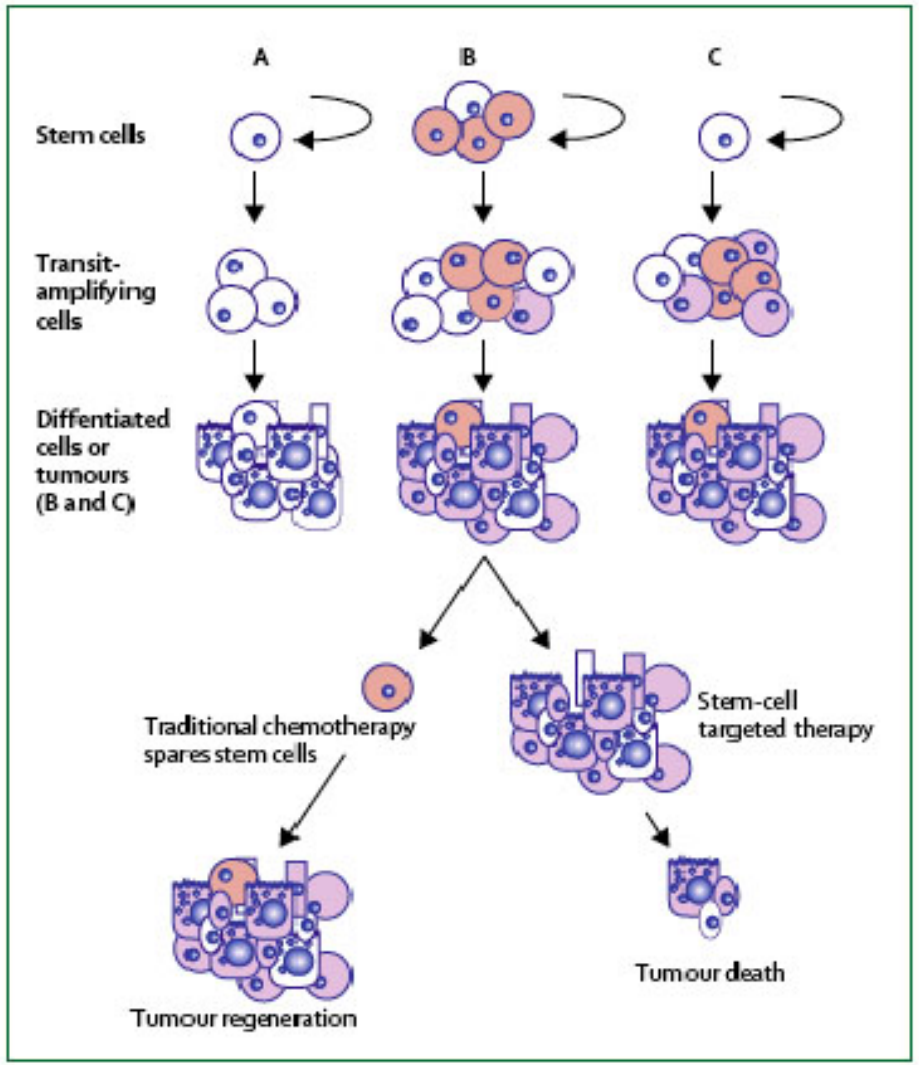


Figure 1. MSC engraftment is enhanced in irradiated tumors. Mice with bilateral 4T1 hind limb tumors were radiated unilaterally to the right limb with 2 Gy (*A*) or 1 Gy (*B*). Representative radiated volume is represented with a triangle in the first image. All mice were injected I.v. with 2×10^6 of MSC-fLUC the following day. Bioluminescent imaging of MSC (fLUC) engraftment 1 day after I.v. injection (top). Tumor volume, represented by fLUC expression, prior to irradiation (bottom). *D*, quantification of absolute values of bioluminescent imaging of firefly luciferase within red circles in *A* to *C* (top). Relative ratio of MSC in the right leg at days 1, 4, and 6 (bottom).

Summary

- Enriched for tumorigenic ability or tumor initiating activity (also named as cancer/tumor initiating cells)
- Regenerate phenotype diversity (differentiation plasticity).
- Enable serial propagation *in vivo* (self-renewal capability)
- Display resistance to conventional therapies



Inappropriate expression of stemness programs in cancer

Oncogene (2001) 20, 8085–8091

www.nature.com/onc

Human embryonic genes re-expressed in cancer cells

Marilyn Monk*,[1] and Cathy Holding[1]

[1]*Molecular Embryology Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK*

ANALYSIS

nature genetics

An embryonic stem cell–like gene expression signature in poorly differentiated aggressive human tumors

Ittai Ben-Porath[1,2,5], Matthew W Thomson[3], Vincent J Carey[4], Ruping Ge[1], George W Bell[1], Aviv Regev[3] & Robert A Weinberg[1,2]

Inappropriate expression of stemness programs in cancer

Biochemical and Biophysical Research Communications 383 (2009) 157–162

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Embryonic stem cell markers expression in cancers

Matthieu Schoenhals [b], Alboukadel Kassambara [b], John De Vos [a,b,c], Dirk Hose [d], Jérôme Moreaux [a,b], Bernard Klein [a,b,c,*]

Association Sox2, Oct4, Klf4 and c-Myc with tumor grade.

Cancer type	Sox2	Oct4	Klf4	c-Myc
Bladder	+			
Brain	+	+	+	
Breast	+	+		+
Cervix	+			
Colon	+			
Endometrium	+			
Head–Neck	+	+		
Lung				+
Lymphoma				+
Melanoma			+	+
Ovarian			+	+
Pancreas				+
Prostate			+	
Renal	+			
Sarcoma	+	+		+
Thyroid	+			

Tissue	Oct4	Sox2	KLF4	c-MYC
Lymphoma	no	no	no	yes
Leukemia	yes	no	yes	yes
Myeloma	no	no	yes	yes
Adrenal	no	no	no	no
Bladder	yes	yes	no	no
Blood	no	no	no	no
Brain	yes	yes	yes	yes
Breast	no	no	no	yes
Cervix	no	no	no	no
Chondrosarcoma	no	no	no	no
Colon	no	yes	no	yes
Endocrine	no	no	no	no
Endometrium	no	no	no	no
Esophagus	no	no	no	no
Gastric	no	no	no	no
Head–Neck	no	no	no	yes
Liver	no	yes	no	no
Lung	yes	yes	no	yes
Melanoma	no	no	no	no
Mesothelioma	no	no	no	no
Multi-cancer	no	yes	no	no
Muscle	no	no	no	no
Neuroblastoma	no	no	no	no
Oral	no	no	no	no
Others	no	no	no	no
Ovarian	yes	no	no	no
Pancreas	yes	no	no	yes
Parathyroid	no	no	no	no
Prostate	yes	yes	yes	yes
Rectum	no	no	no	no
Renal	yes	no	no	yes
Salivary-gland	no	no	no	yes
Sarcoma	no	no	no	no
Seminoma	yes	yes	no	yes
Skin	no	no	no	no
Testis	yes	yes	yes	no
Thyroid	no	no	no	no
Uterus	no	no	no	no

Inappropriate expression of stemness programs in cancer

Cell Stem Cell
Article

Module Map of Stem Cell Genes Guides Creation of Epithelial Cancer Stem Cells

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- The ESC-like transcriptional program is activated in diverse human epithelial cancers and strongly predicts metastasis and death
- In primary human keratinocytes transformed by Ras and IκBα, c-Myc increases the fraction of tumor-initiating cells by 150-fold, enabling tumor formation and serial propagation with as few as 500 cells
- Activation of an ESC-like transcriptional program in differentiated adult cells may induce pathologic self-renewal characteristic of cancer stem cells

Inappropriate expression of stemness programs in cancer

STEM CELLS
CANCER STEM CELLS

Functional Evidence that the Self-Renewal Gene *NANOG* Regulates Human Tumor Development

COLLENE R. JETER,[a] MARK BADEAUX,[a] GRACE CHOY,[a] DHYAN CHANDRA,[a] LUBNA PATRAWALA,[a] CAN LIU,[a] TAMMY CALHOUN-DAVIS,[a] HOLM ZAEHRES,[b] GEORGE Q. DALEY,[b] DEAN G. TANG[a]

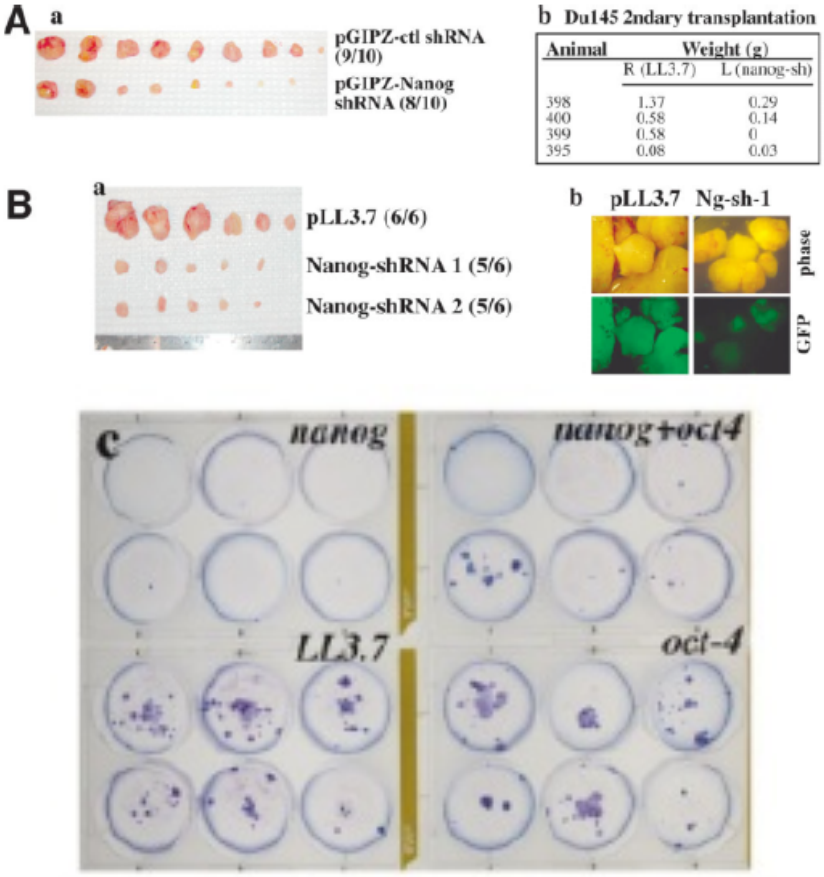


Table 1. NANOG knockdown inhibits tumor development

Experiments[a]	Tumor incidence[b]	Weight (g)[c]	*p* values[d]
Du145 (75k/injection: 56 days)			
pLL 3.7	8/8	0.25 ± 0.05	
Nanog-shRNA	8/8	0.13 ± 0.07	.02
Du145 (10k/injection; 62 days)			
pLL3.7	7/8	0.71 ± 0.45	
Nanog-shRNA	7/8	0.32 ± 0.18	.045
Du145 (25k/injection; 63 days)			
pGIPZ-control	9/10	0.50 ± 0.32	
pGIPZ-Nanog	6/10*	0.22 ± 0.27	.038
LAPC9 (1k/inj; 60 days)			
pLL 3.7	6/6	1.03 ± 0.25	
Nanog-shRNA 1*	5/6	0.04 ± 0.03	.04
Nanog-shRNA 2*	5/6	0.076 ± 0.07	.04
LAPC4 (150k/inj; 67 days)			
pLL 3.7	6/6	0.08 ± 0.05	
Nanog-shRNA	5/6	0.02 ± 0.008	.017
TRC Nanog-shRNA	2/6**	0.02 ± 0.001	.01
HPCa 18 (100k/TR; 150 days)#			
pLL 3.7	2/2	N/A	
Nanog-shRNA	0/2	N/A	
MCF7 (100k/injection; 97 days)			
pLL3.7	9/10	0.45 ± 0.13	
Nanog-shRNA	8/10	0.09 ± 0.02	.028
TRC Nanog-shRNA	9/10	0.05 ± 0.016	.012
Oct4-shRNA	9/10	0.20 ± 0.03	.1
Nanog-shRNA + Oct4-hRNA	7/10	0.06 ± 0.014	.029
Colo320 (25k/injection; 35 days)			
pLL3.7	5/5	0.11 ± 0.07	
Nanog-shRNA	3/5*	0.076 ± 0.02	.042
Colo320 (250k/injection; 35 days)			
pLL 3.7	8/8	0.82 ± 0.38	
Nanog-shRNA	4/8**	0.058 ± 0.008	.003
Oct4-shRNA	7/8	0.26 ± 0.19	.006
Colo320 (250k/injection; 34 days)			
pLL3.7-luciferase	8/8	0.77 ± 0.48	
Nanog-shRNA	2/8**	0.67 ± 0.17	.79
Oct4-shRNA	8/8	0.52 ± 0.41	.29

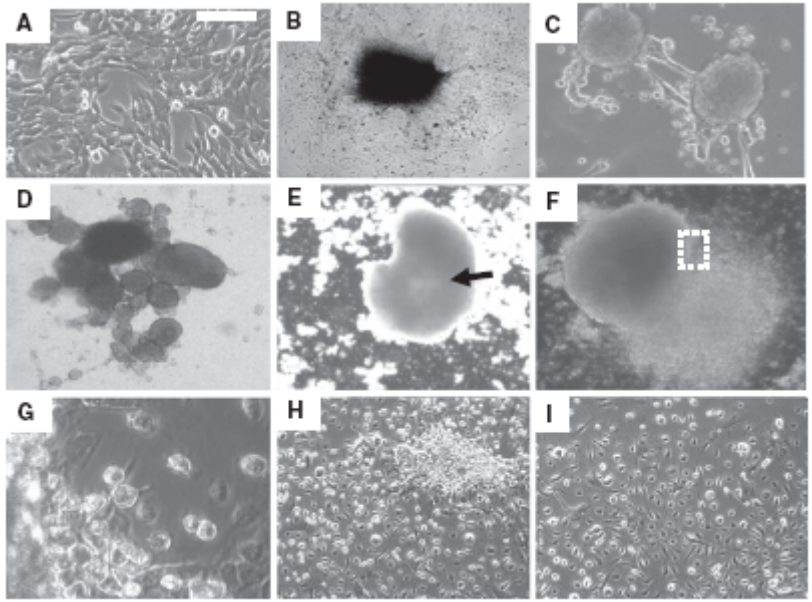
[a]Cultured cancer cells or xenograft-purified cells were infected with the indicated lentiviral vectors at an MOI of 20. 24–48 h after infection, different numbers (k) of cells were injected subcutaneously in Matrigel (50%) into NOD/SCID mice. Termination time (days) is indicated in parentheses. The asterisks (*) indicate two independent infections of LAPC9 cells in the same experiment. For HPCa (#), 100,000 infected cells were recombined with 200,000 rat urogenital sinus mesenchyme cells and transplanted under the kidney capsule and the tissue recombinants were harvested 5 months later.
[b]Number of tumors developed/number of injections. *$p < .05$; **$p < .01$ (χ^2 test).
[c]Mean ± S.D. N/A, not available.
[d]Statistical comparisons (Student *t*-test) for tumor weights were made with the control (pLL3.7, pGIPZ-control, or pLL3.7-luciferase) group.

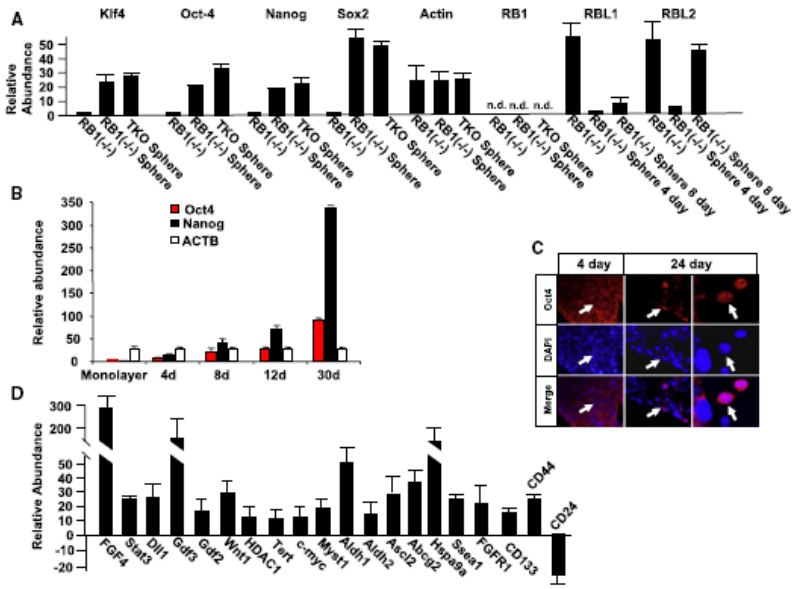
Induction of stem cell genes in RB-knockout fibroblasts

Cell Stem Cell
Article

Mouse Fibroblasts Lacking RB1 Function Form Spheres and Undergo Reprogramming to a Cancer Stem Cell Phenotype

Yongqing Liu,[1,2] Brian Clem,[1] Ewa K. Zuba-Surma,[3] Shahenda El-Naggar,[1,2] Sucheta Telang,[1] Alfred B. Jenson,[1] Yali Wang,[2] Hui Shao,[2] Mariusz Z. Ratajczak,[3] Jason Chesney,[1] and Douglas C. Dean[1,2,4,*]





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