

# Stem cell research and therapy: an overview



Michael S. Pepper  
MBChB, PhD, MD

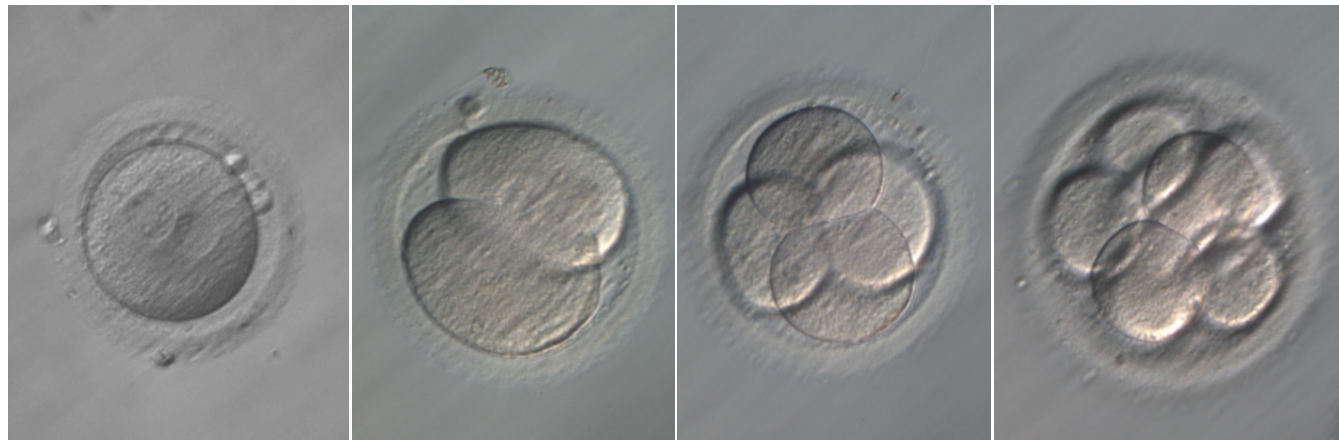


UNIVERSITEIT VAN PRETORIA  
UNIVERSITY OF PRETORIA

Institute for Cellular and Molecular Medicine

# Overview

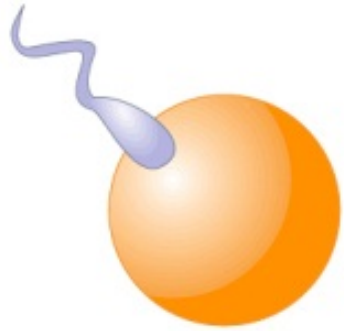
- Stem cell principles
- Therapeutic applications
- Stem cell legislation



# Stem cell principles

- Stem cell differentiation potential
- Induced pluripotent stem cells
- Embryonic stem cells
- Somatic cell nuclear transfer
- Adult stem cells

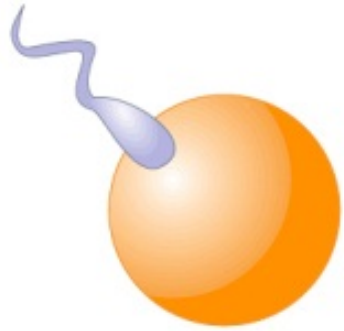
# In the beginning...



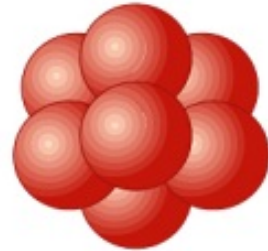
Zygote



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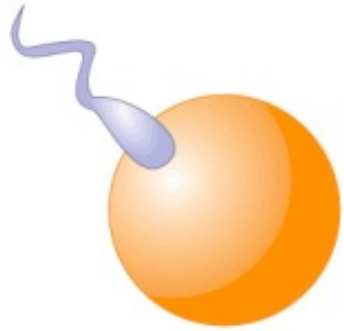
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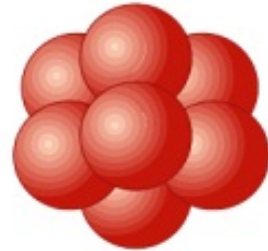
8-cell  
embryo



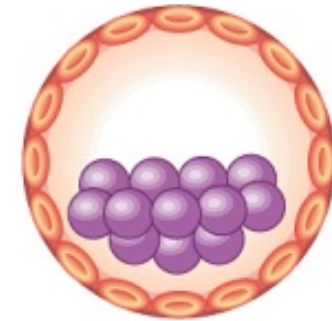
# In the beginning...



Zygote

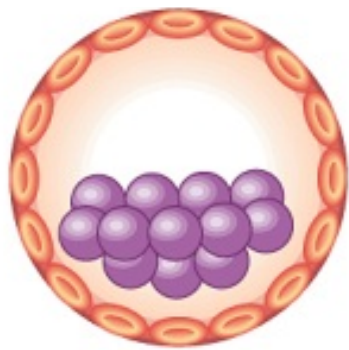


8-cell  
embryo



Blastocyst

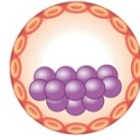
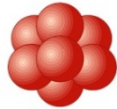
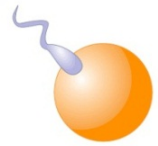




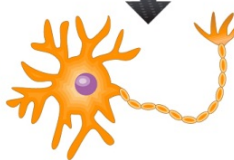
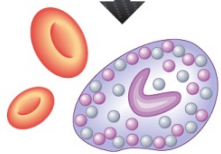
Blastocyst



Embryo



Embryo - germ layers:  
mesoderm, ectoderm,  
endoderm



## Totipotent

- post-fertilization to morula
- all the cells of the human body

## Pluripotent

- inner cell mass of the blastocyst
- cells of all three germ layers

## Multipotent

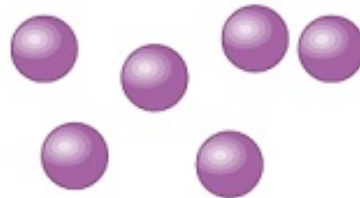
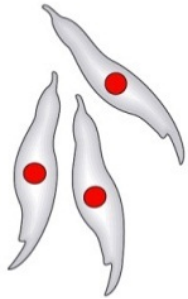
- hematopoietic stem cells
- neural stem cells
- mesenchymal stem cells
- various specialized cells in a given tissue



# Induced pluripotent stem cells

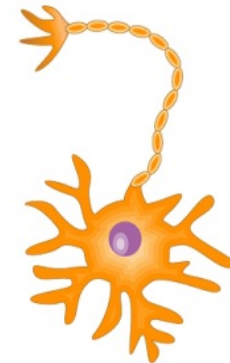
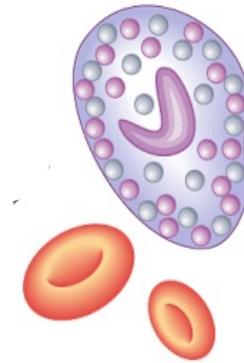
4 transcription factors:

Oct3/4  
Sox2  
Klf4  
c-Myc



Pluripotent  
stem cells

Differentiation  
factors



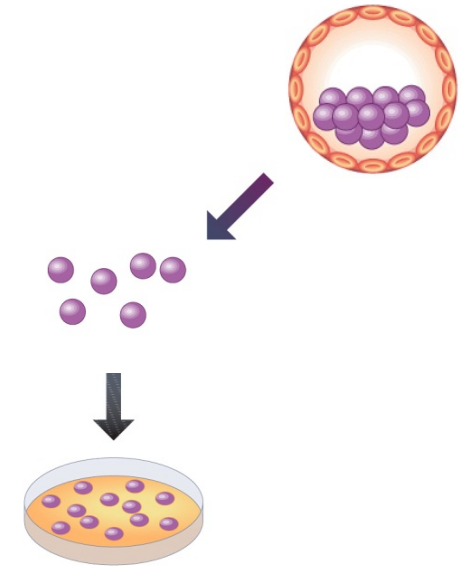
# Stem cell principles

- Stem cell differentiation potential
- Induced pluripotent stem cells
- **Embryonic stem cells**
- Somatic cell nuclear transfer
- Adult stem cells

# Embryonic stem cells

Method of obtaining ES cells:

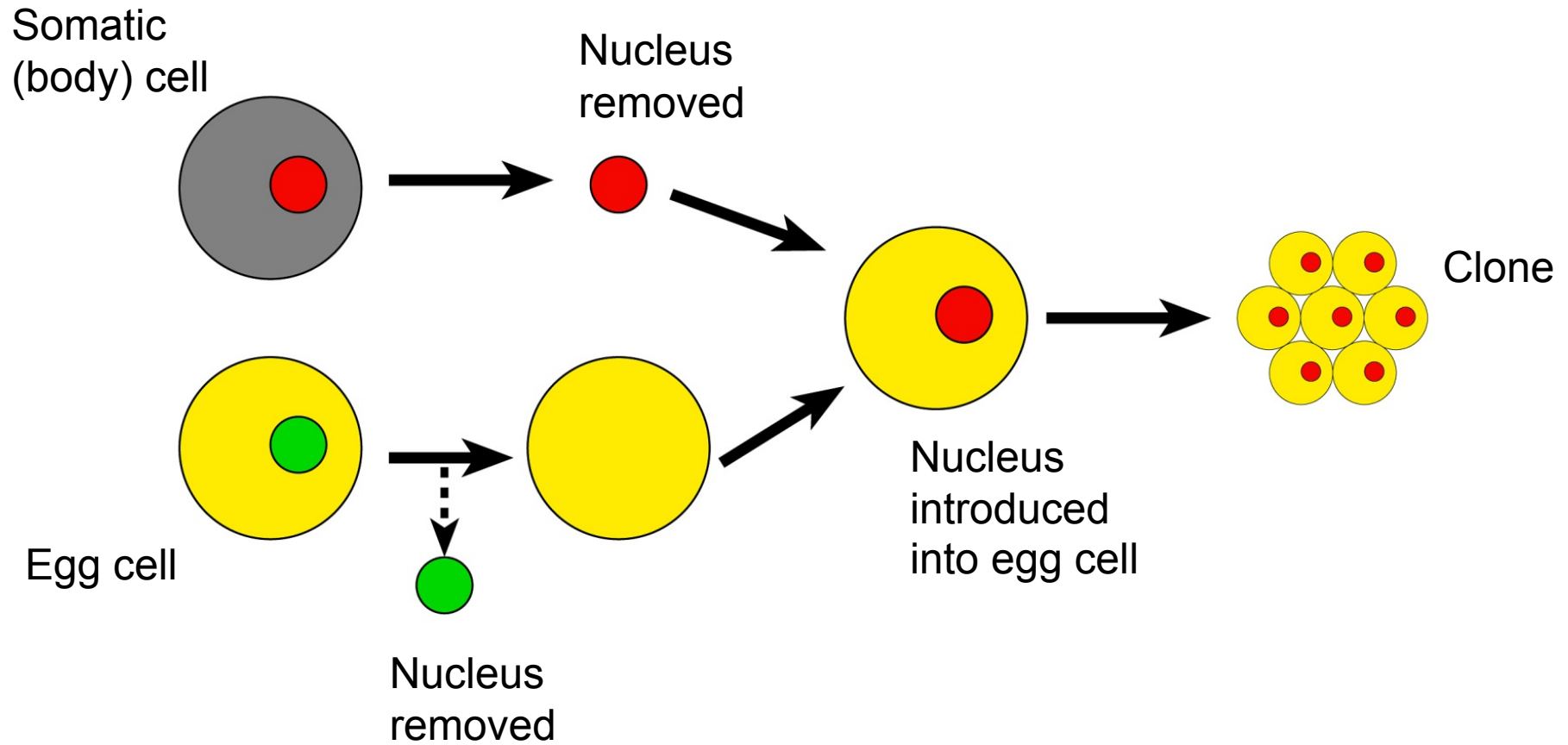
- Blastocyst
  - 5 day old embryo
  - approx 100 cells
- Remove inner cell mass
- Cultured cells = ES cells



# Stem cell principles

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# Somatic cell nuclear transfer

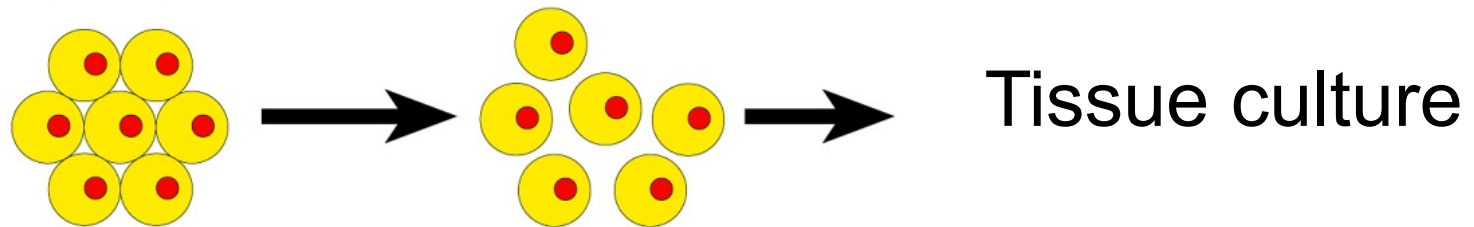


# Cloning

## Reproductive cloning



## Therapeutic cloning



# Stem cell principles

- Stem cell differentiation potential
- Induced pluripotent stem cells
- Embryonic stem cells
- Somatic cell nuclear transfer
- **Adult stem cells**

# Tissue-specific adult stem cells

- bone marrow
- gastrointestinal tract
  - liver, pancreas
- tooth
- skin, hair
- central nervous system
- kidney
- muscle (satellite stem cells)





# Pluripotent vs. adult stem cells

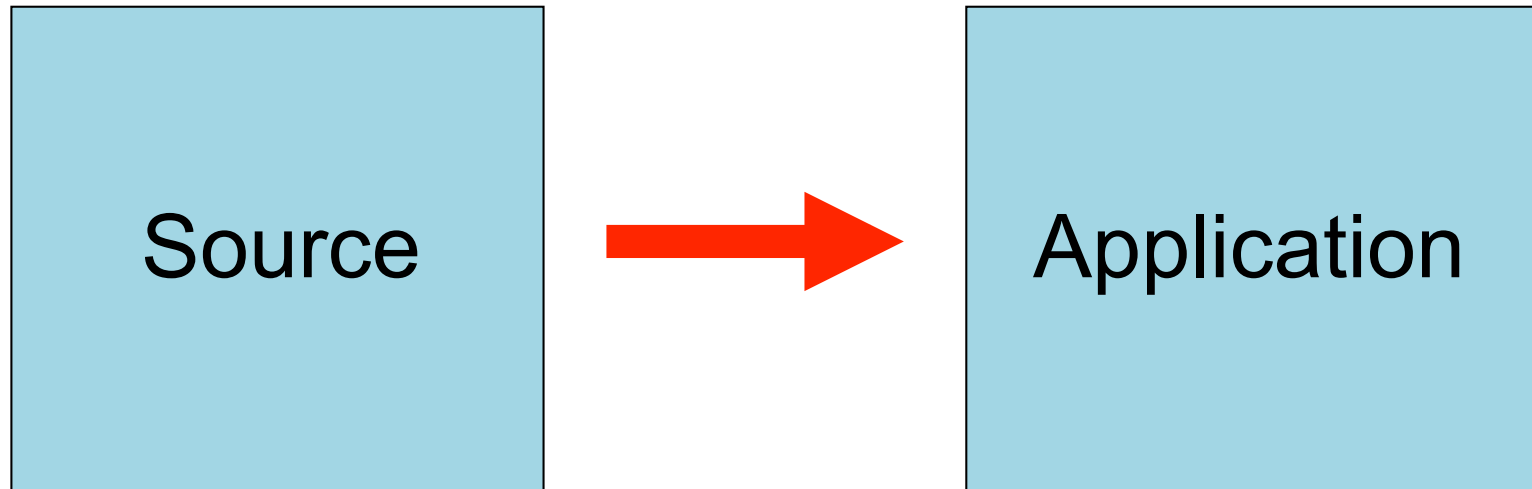
## Pluripotent

- Differentiation potential = all of the body's cell types
- Ethical issues
- Technically more difficult to obtain
- Potential for tumorigenesis
- Therapeutic value – remains to be determined
- Value: understanding disease processes, drug screening

## Adult

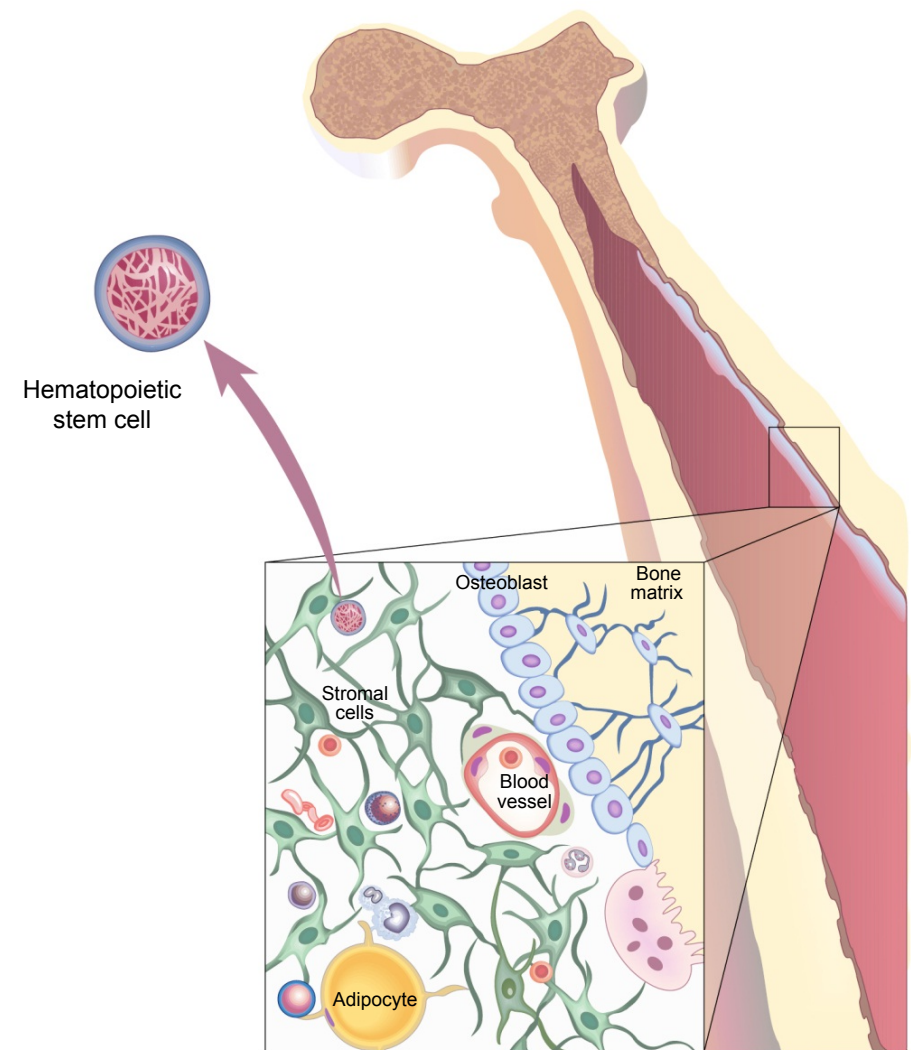
- Differentiation potential limited to cells of tissue in which they reside
- No ethical issues
- Readily available
- No evidence for tumorigenesis
- Therapeutic value well demonstrated:
  - HSCs for bone marrow transplantation
  - MSCs: approx 200 registered clinical trials

# Therapeutic applications



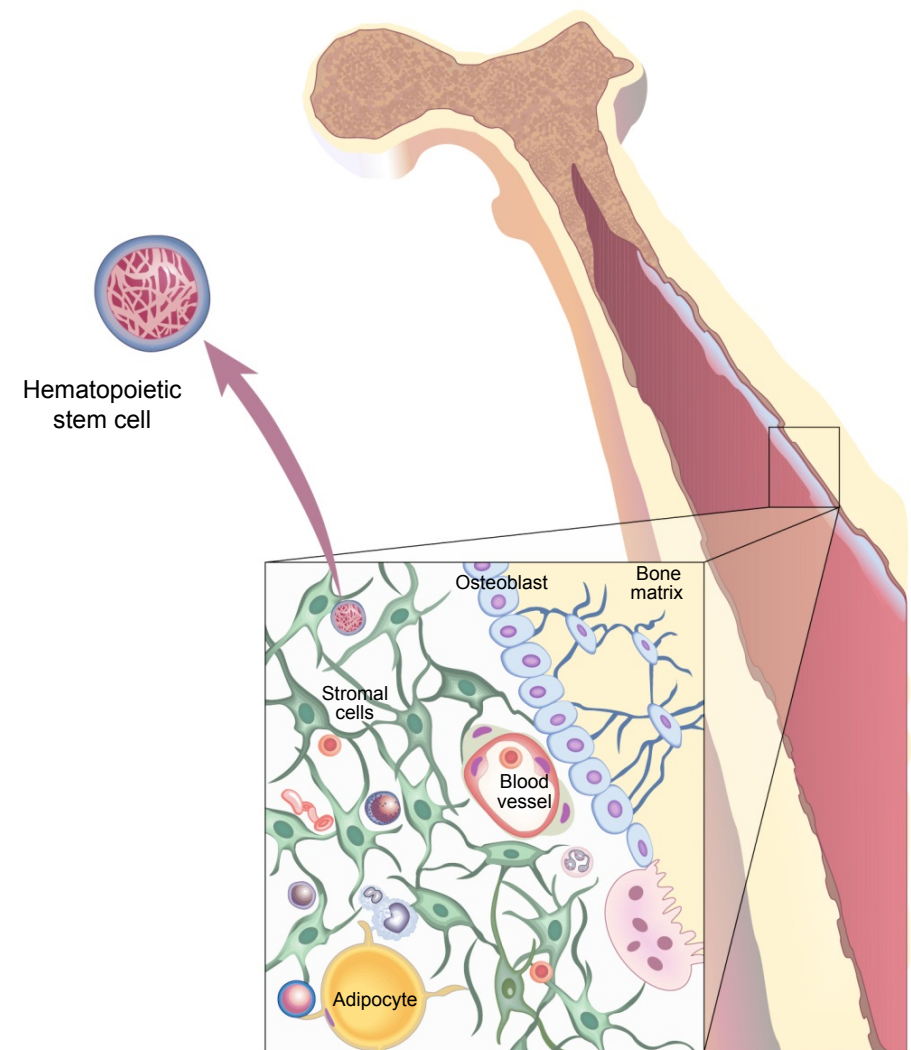
# Source

- Current
  - Bone marrow
  - Peripheral blood
  - Cord blood



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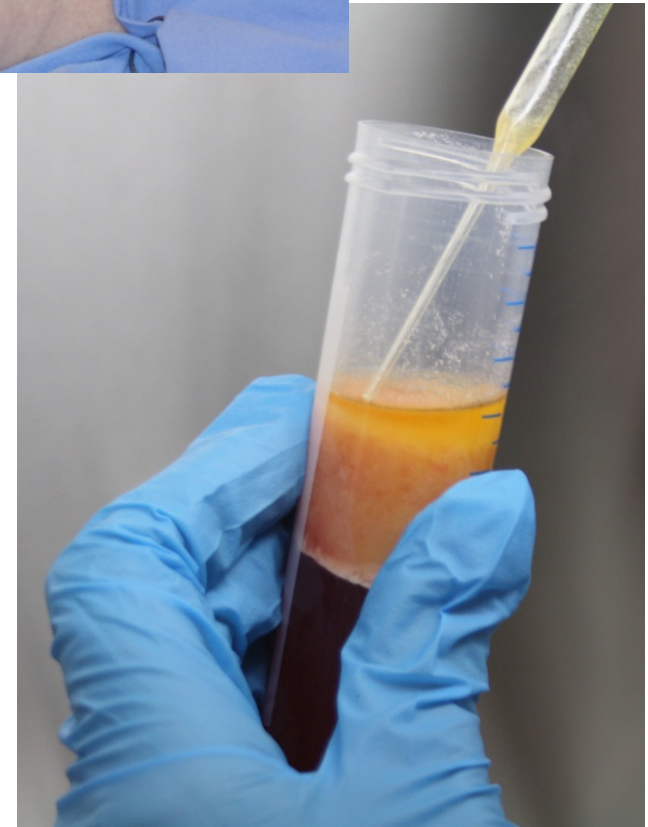


# Source

- Future
  - ES cells
  - iPS cells
  - Adipose tissue
  - Other

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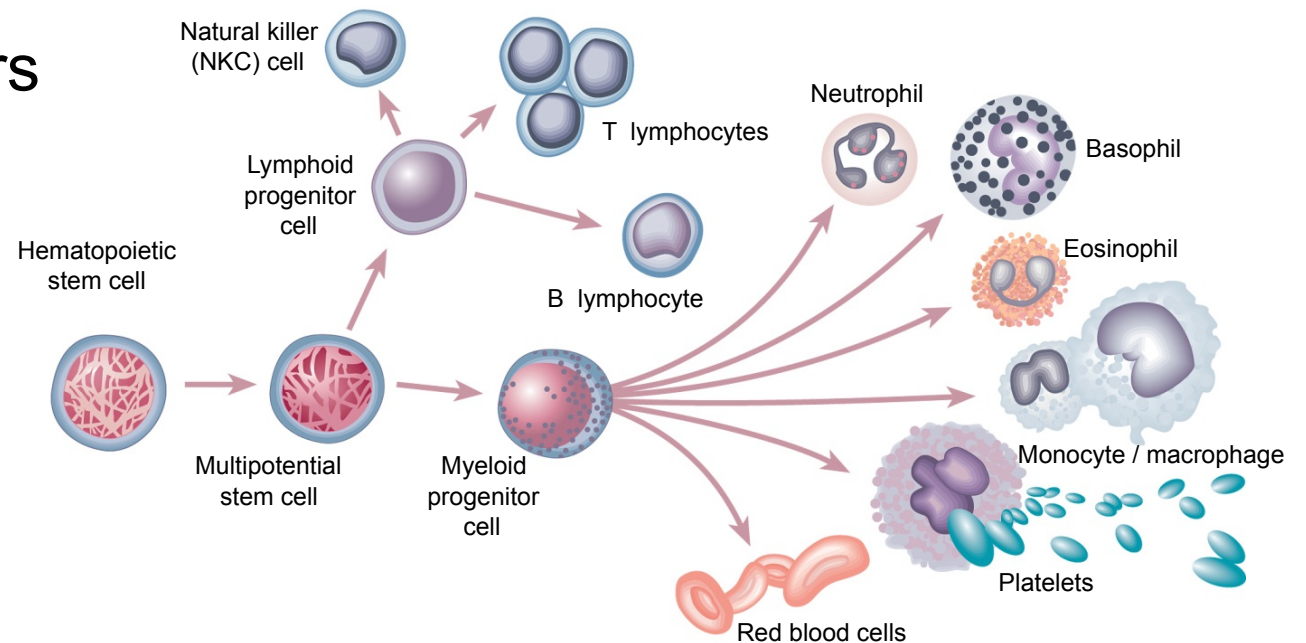


# Application

- Current
  - Bone marrow transplantation
  - Fractures, chronic wounds, burns
- Future
  - Myocardial infarction and heart failure
  - CNS disease (incl. spinal cord injury)
  - Diabetes (beta-cells)
  - Other

# Bone marrow transplantation

- Universally employed and approved
- Autologous or allogeneic
- Indications
  - cancer
  - blood disorders
  - genetic disorders





# Hematopoietic stem cell transplant – indications

## Leukemias

- Acute Leukemia
- Acute Lymphoblastic Leukemia (ALL)
- Acute Myelogenous Leukemia (AML)
- Acute Biphenotypic Leukemia
- Acute Undifferentiated Leukemia
- Chronic Leukemia
- Chronic Myelogenous Leukemia (CML)
- Chronic Lymphocytic Leukemia (CLL)
- Juvenile Chronic Myelogenous Leukemia (JCML)
- Juvenile Myelomonocytic Leukemia (JMML)

## Lymphomas

- Hodgkin's Lymphoma
- Non-Hodgkin's Lymphoma Burkitt's Lymphoma

## Plasma Cell Disorders

- Multiple Myeloma
- Plasma Cell Leukemia
- Waldenstrom's Macroglobulinemia

## Other cancers (Not originating in the blood system)

- Neuroblastoma
- Retinoblastoma

## Inherited Red Cell (Erythrocyte) Abnormalities

- Beta Thalassemia Major (also known as Cooley's Anemia)
- Blackfan-Diamond Anemia
- Pure Red Cell Aplasia
- Sickle Cell Disease

## Myelodysplastic Syndromes

- Refractory Anemia (RA)
- Refractory Anemia with Ringed Sideroblasts (RARS)
- Refractory Anemia with Excess Blasts (RAEB)
- Refractory Anemia with Excess Blasts in Transformation (RAEB-T)
- Chronic Myelomonocytic Leukemia (CMML)

## Other Disorders of Blood Cell Proliferation

- severe Aplastic Anemia
- Congenital Dyserythropoietic Anemia
- Fanconi Anemia (Note: the first cord blood transplant in 1988 was for this disease)
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Pure Red Cell Aplasia
- Amegakaryocytosis / Congenital Thrombocytopenia
- Glanzmann Thrombasthenia
- Acute Myelofibrosis
- Agnogenic Myeloid Metaplasia (Myelofibrosis)
- Polycythemia Vera
- Essential Thrombocythemia

## Inherited Immune System Disorders

### Severe Combined Immunodeficiency (SCID)

- SCID with Adenosine Deaminase Deficiency (ADA-SCID)
- SCID which is X-linked
- SCID with absence of T & B Cells
- SCID with absence of T Cells, Normal B Cells
- Omenn Syndrome

### Neutropenias

- Kostmann Syndrome
- Myelokathexis

### Other

- Ataxia-Telangiectasia
- Bare Lymphocyte Syndrome
- Common Variable Immunodeficiency
- DiGeorge Syndrome
- Leukocyte Adhesion Deficiency
- Lymphoproliferative Disorders (LPD)
- Lymphoproliferative Disorder, X-linked (also known as Epstein-Barr Virus Susceptibility)
- Wiskott-Aldrich Syndrome

### Phagocyte Disorders

- Chediak-Higashi Syndrome
- Chronic Granulomatous Disease
- Neutrophil Actin Deficiency
- Reticular Dysgenesis

# Current situation in South Africa

## Bone marrow transplantation (BMT)

- practiced successfully for many years
- many South Africans requiring a BMT remain untreated

## SA Bone Marrow Registry

- established in 1991
- >65,000 donors registered
- >250 transplants (matched unrelated donor)
- Donors: 25% local; 75% international
- majority of donors are Caucasian

# Cord blood banking in SA

## Public cord blood bank

- none at present
- genetically-diverse population
- feasibility study
  - Mandated by DoH and SANBS
  - Funded by the MRC

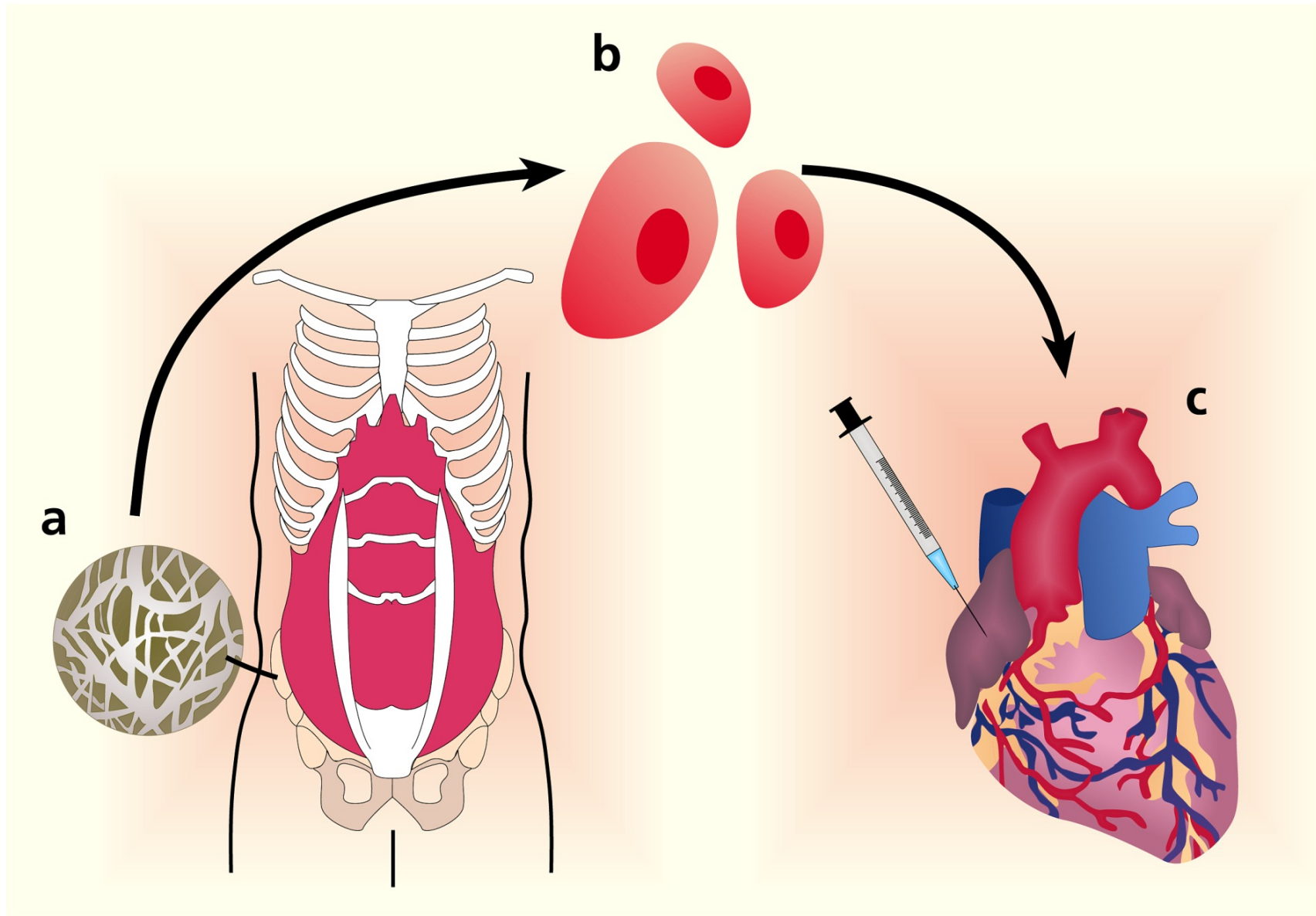
## Private cord blood banks

- 2 in South Africa

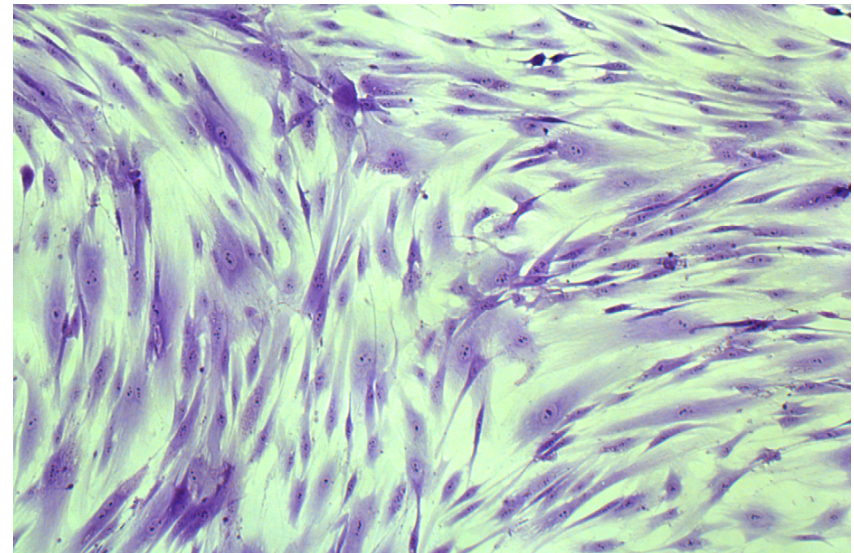
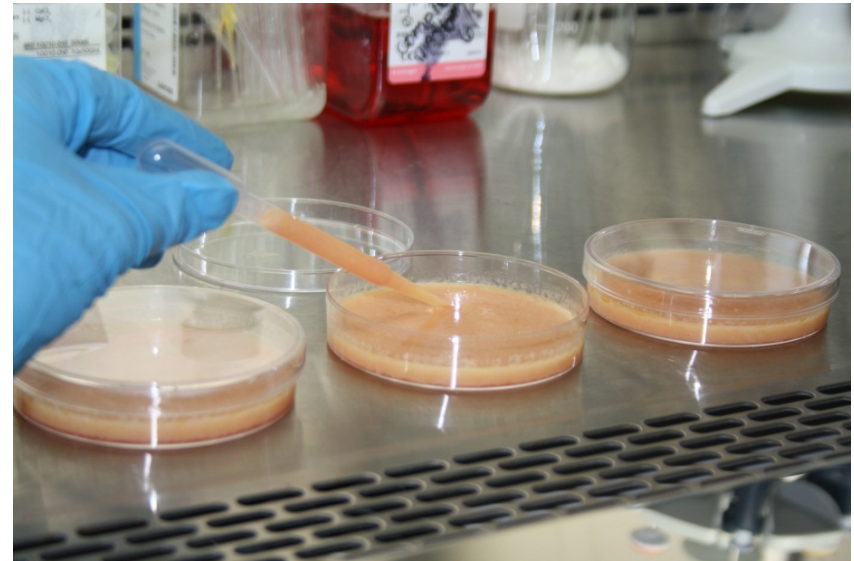
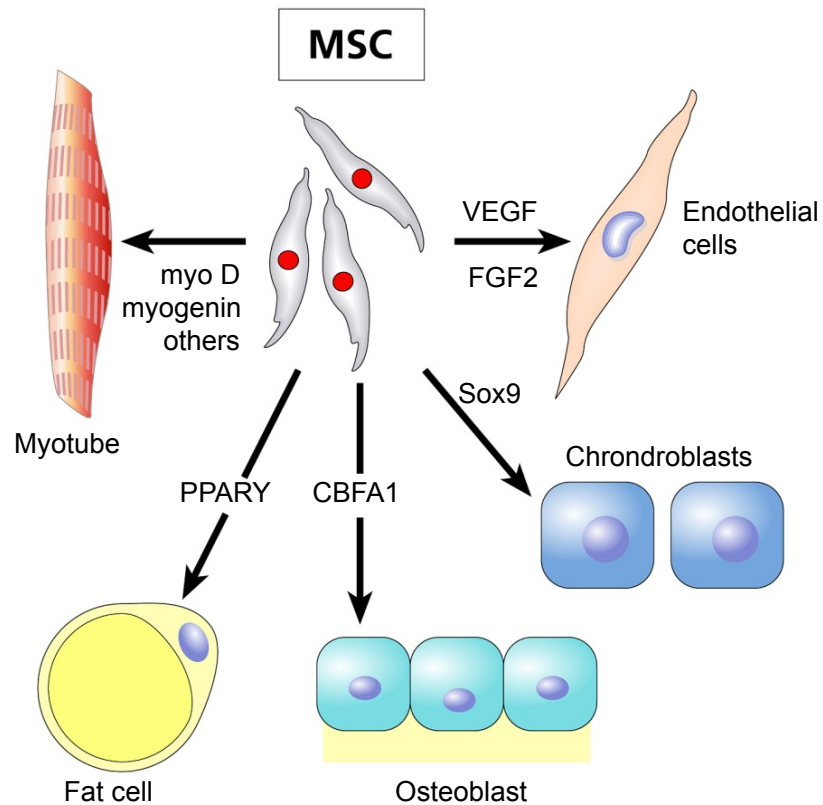
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# Future applications



# Mesenchymal stem cells



# MSC clinical trials

- ClinicalTrials.gov
- December 2011
  - 188 registered MSC clinical trials
    - 80 completed
    - 108 on-going
- Almost 100 new trials initiated in 2010 and 2011 alone

# Stem cells in SA

- Stem cell therapy and research are in their infancy in South Africa
  - potential to alleviate heavy burden of disease
  - communicable and non-communicable
- Role in cancer, hematological and inherited metabolic disorders well established but unable to meet demand
- Role in heart disease, spinal cord injury and others being assessed globally but not in SA
- Role in infectious diseases totally unexplored



# Human tissue legislation in South Africa

- Legislation incomplete and flawed
  - increasingly litigious society
  - importance of global standards
- Regulations
  - Redundancy/overlap
  - Lack of regulations
    - transplantation
    - cell-based therapy
- Definitions
  - not harmonized (NHA and regulations)

# Why legislation

## Reason no. 1

- To ensure that pre-clinical studies and well controlled clinical trials have been conducted prior to introduction of cells into patients
  - to ensure that the purported therapeutic effect is real
  - to ensure that there are no serious side effects

# Amariglio N. et al. PLoS Med, 2009

- Patient: 9 yr old boy with ataxia telangectasia
- Parents took him to Moscow
- 8-week human neural stem cells (aborted foetus?) harvested and expanded in culture for 2 weeks
- 50-100 million cells administered via intracerebellar and intrathecal injection
- 3 treatments over several years – 2001/2/4
- 2005 – recurrent headaches (Tel-Aviv)
- Developed a multifocal brain tumour
  - 2006: tumor removed surgically from cauda equina nerve roots
  - 2008: infratentorial tumour had doubled in mass
    - Patient stable and treated conservatively

# Why legislation

## Reason no. 2

- The absence of regulations permits (and even encourages) the emergence of medically-unsound and unethical practices that may be associated with the exploitation of emotionally vulnerable patients

# “Stem cells” for spinal cord injury

Melanie Skeen – MCs student

Patient Level of injury	Nature of stem cells Route of administration	Time after injury to Rx Type of injury	Treatment location	Cost Treatment (stem cells)	Travel and accomm.
Male, 47 yr T7 para	Autologous LP	10 mo Gunshot	India	R 231 000	R 36 000
Male, 32 yr T1 quad	Sheep SC (weekly x 6 mo) Orally (tds x 6 mo)	8 yr Gunshot	SA (Bloemfontein)	0	0
Male, 35 yr T8 para	Rabbit Subdural during spinal surgery	14 d Gunshot	Cells from Germany Given in SA at the time of surgery	R 200 000	0
Female, 38 yr C6/7 incomplete	Rabbit SC and LP	1 yr MVA	Germany	R 169 000 R 80 000	R 89 000
Male, 34 yr Locked-in syndrome	Rabbit SC and LP	3,5 and 5,5 yr MVA followed by CVA	Germany and SA	R 174 000 First procedure in Germany	R 54 000
Male, 34 yr C4/5 quad	Rabbit SC and LP	6 yr Fall	Germany	R 179 000 R 65 000	R 114 320
Female, 43 yr C5/6 incomplete	Sheep IM back or neck (x 8 mo)	7 yr MVA	SA (Bloemfontein)	R 8 000 (R 1 000 per treatment)	R 11 200
Male, 38 yr C6/7 quad	? type (not autologous) IV	27 mo MVA	Netherlands	R 142 000 R 76 000	R 66 000

# Human tissue legislation: towards self-regulation

Area	Professional body	Guidelines
Transplantation	Southern African Transplantation Society (SATS)	Yes <a href="http://www.sats.org.za/Guidelines.asp">http://www.sats.org.za/Guidelines.asp</a>
Assisted reproductive technology	Southern African Society of Reproductive Medicine and Gynaecological Endoscopy (SASREG)	Yes <a href="http://www.fertilitysa.org.za/TreatmentGuidelines/ReproductiveMedicine.asp">http://www.fertilitysa.org.za/TreatmentGuidelines/ReproductiveMedicine.asp</a>
Blood and blood products	National Blood Committee (not in operation since 2008)	Yes SANBS and WPBTS websites & other
Cell-based therapy	South African Stem Cell Transplantation Society (SASCTS)	Yes; none on website <a href="http://www.stemcell.org.za/index.htm">http://www.stemcell.org.za/index.htm</a>
Genetic Services	Southern African Society of Human Genetics (SAHGS)	Yes <a href="http://www.sashg.org/documents.htm">http://www.sashg.org/documents.htm</a>
Tissue banks	South African Tissue Bank Association (SATiBA)	Newly formed; in progress
Forensic pathology and medicine	National Forensic Pathology Services Committee	Yes No website
	National Clinical Forensic	In progress

# Current reality vs. future promise

- Currently only a few well-established indications for stem cell therapy
- Future applications provide a great source of hope for many patients
  - exploitation of emotionally-vulnerable patients
- Ethical considerations in pluripotent cells