

SPCE-TC

SOCIEDADE PORTUGUESA
DE CÉLULAS ESTAMINAIS
E TERAPIA CELULAR

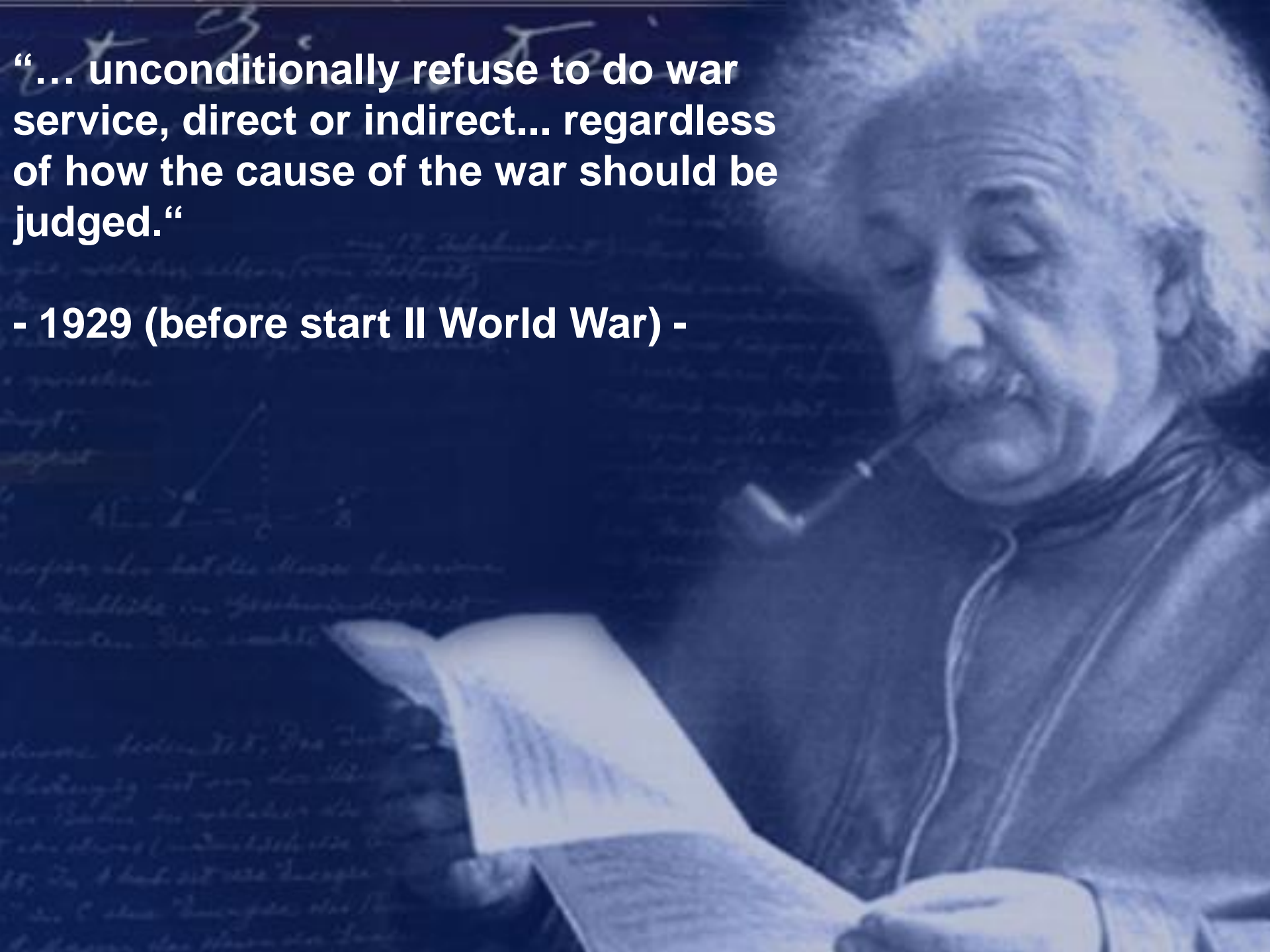
Terapias Celulares com Células Estaminais

Perpétua Pinto-do-Ó
SPCE-TC, Presidente

Simpósio CEIC - Ensaios Clínicos: novos desafios, papel social e centros de ensaio
22 novembro 2016, Lisboa

“... unconditionally refuse to do war service, direct or indirect... regardless of how the cause of the war should be judged.”

- 1929 (before start II World War) -



Albert Einstein
Old Grove Rd.
Nassau Point
Poconic, Long Island

August 2nd, 1939

F.D. Roosevelt,
President of the United States,
White House
Washington, D.C.

Sir:

Some recent work by E. Fermi and L. Szilard, which has been communicated to me in manuscript, leads me to expect that the element uranium may be turned into a new and important source of energy in the immediate future. Certain aspects of the situation which has arisen seem to call for watchfulness and, if necessary, quick action on the part of the Administration. I believe therefore that it is my duty to bring to your attention the following facts and recommendations:

In the course of the last four months it has been made probable - through the work of Joliot in France as well as Fermi and Szilard in America - that it may become possible to set up a nuclear chain reaction in a large mass of uranium, by which vast amounts of power and large quantities of new radium-like elements would be generated. Now it appears almost certain that this could be achieved in the immediate future.

This new phenomenon would also lead to the construction of bombs, and it is conceivable - though much less certain - that extremely powerful bombs of a new type may thus be constructed. A single bomb of this type, carried by boat and exploded in a port, might very well destroy the whole port together with some of the surrounding territory. However, such bombs might very well prove to be too heavy for transportation by air.

-2-

The United States has only very poor ores of uranium in moderate quantities. There is some good ore in Canada and the former Czechoslovakia, while the most important source of uranium is Belgian Congo.

In view of this situation you may think it desirable to have some permanent contact maintained between the Administration and the group of physicists working on chain reactions in America. One possible way of achieving this might be for you to entrust with this task a person who has your confidence and who could perhaps serve in an unofficial capacity. His task might comprise the following:

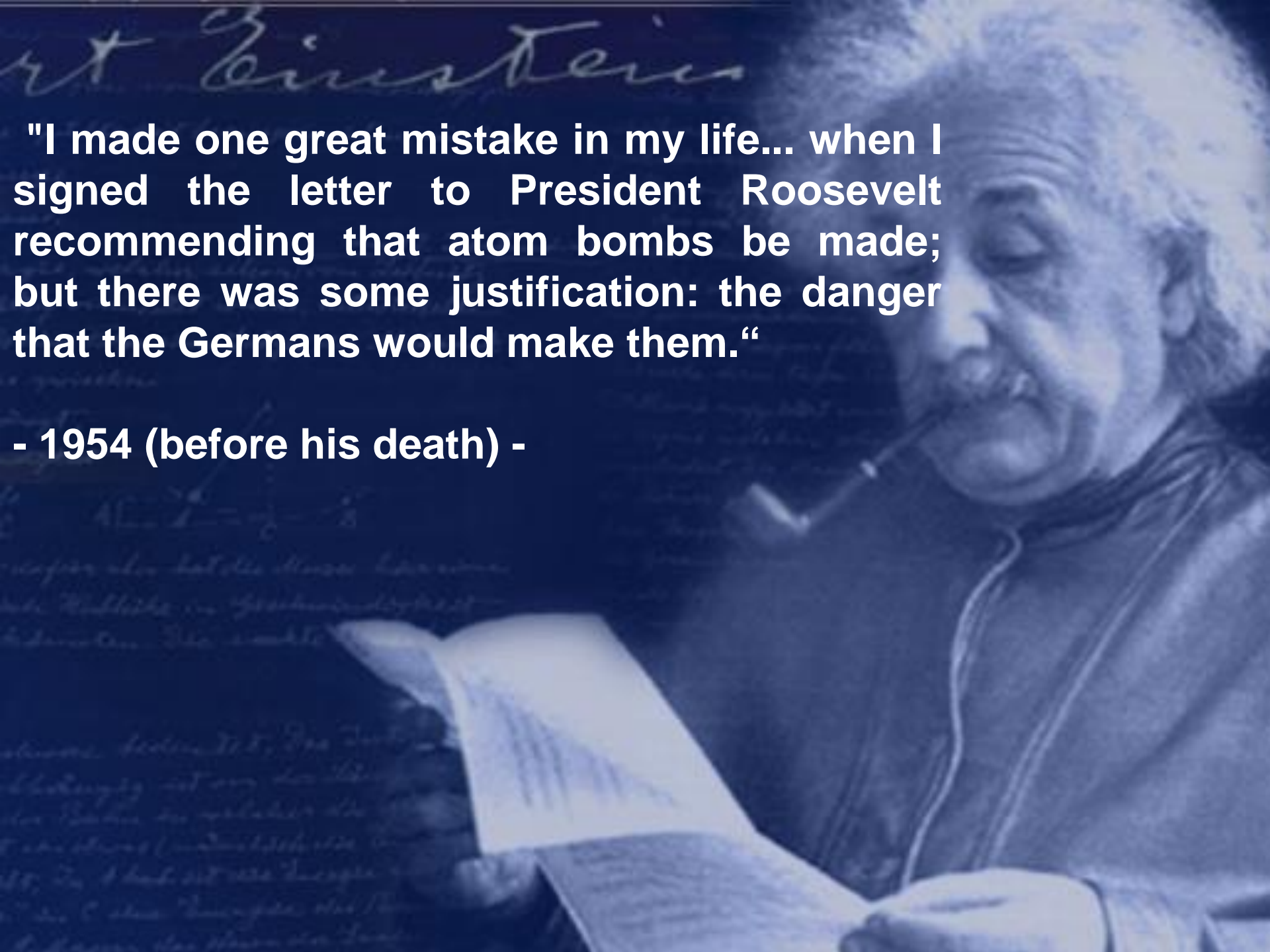
a) to approach Government Departments, keep them informed of the further development, and put forward recommendations for Government action, giving particular attention to the problem of securing a supply of uranium ore for the United States;

b) to speed up the experimental work, which is at present being carried on within the limits of the budgets of University laboratories, by providing funds, if such funds be required, through his contacts with private persons who are willing to make contributions for this cause, and perhaps also by obtaining the co-operation of industrial laboratories which have the necessary equipment.

I understand that Germany has actually stopped the sale of uranium from the Czechoslovakian mines which she has taken over. That she should have taken such early action might perhaps be understood on the ground that the son of the German Under-Secretary of State, von Weizsäcker, is attached to the Kaiser-Wilhelm-Institut in Berlin where some of the American work on uranium is now being repeated.

Yours very truly,
A. Einstein
(Albert Einstein)





"I made one great mistake in my life... when I signed the letter to President Roosevelt recommending that atom bombs be made; but there was some justification: the danger that the Germans would make them."

- 1954 (before his death) -

STEM CELL NOW

From the Experiment That Shook the World
to the New Politics of Life

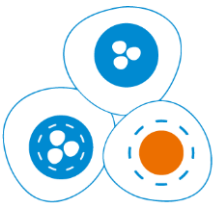


CHRISTOPHER THOMAS SCOTT

“The tragedy of the Hiroshima and Nagasaki bombings showed how effectively radiation could obliterate the rapidly dividing cells of the marrow. Most radiation victims close to ground zero died within 30 days of exposure. Follow-up research found the only way to save mice from a dose of lethal irradiation was to transplant bone marrow from a healthy donor mouse. The results led others to wonder whether radiation and chemical agents could be used against a disease of rampant cell division, cancer. Their hunch was right, and by 1965 the first cure of childhood leukaemia by a bone marrow transplant was announced. The researchers didn't know it at the time, but the marrow's rescue worker was the hematopoietic stem cell or HSC.”



Excerpt: *Stem Cell Now*, by Christopher Thomas Scott
Director of the Stem Cells & Society Programme, Stanford Univ.



The advent of the most successful stem cell-based regenerative therapy

Hematopoietic-Cell Transplantation at 50

Frederick R. Appelbaum, M.D.

September 12, 2007, marked the 50th anniversary of E. Donnall Thomas's initial report of a radical new approach to cancer treatment: radiation and chemotherapy followed by the intravenous infusion of bone marrow.¹



Top science honor
salutes pioneer
of marrow transplants

Joseph Murray, Donnall Thomas
Laureados Nobel 1990



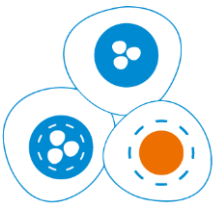
(Reprinted from Nature, Vol. 197, No. 4866, pp. 452-454, February 2, 1963)

CYTOLOGICAL DEMONSTRATION OF THE CLONAL NATURE OF SPLEEN COLONIES DERIVED FROM TRANS- PLANTED MOUSE MARROW CELLS

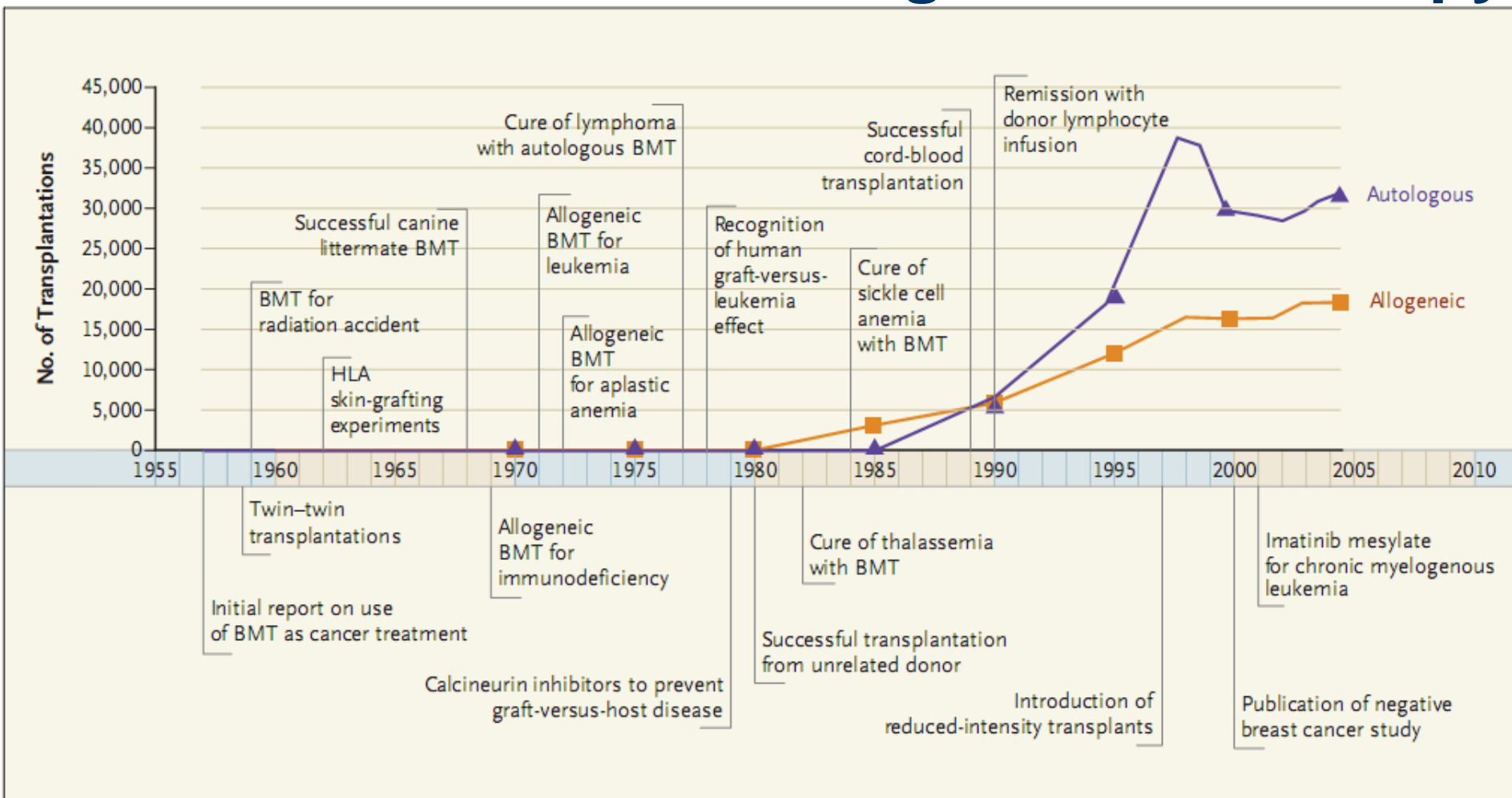
By DR. A. J. BECKER, E. A. McCULLOCH and
J. E. TILL

Department of Medical Biophysics, University of Toronto and
Ontario Cancer Institute, Toronto

1. Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 1957;257:491-6.



The most successful stem cell-based regenerative therapy



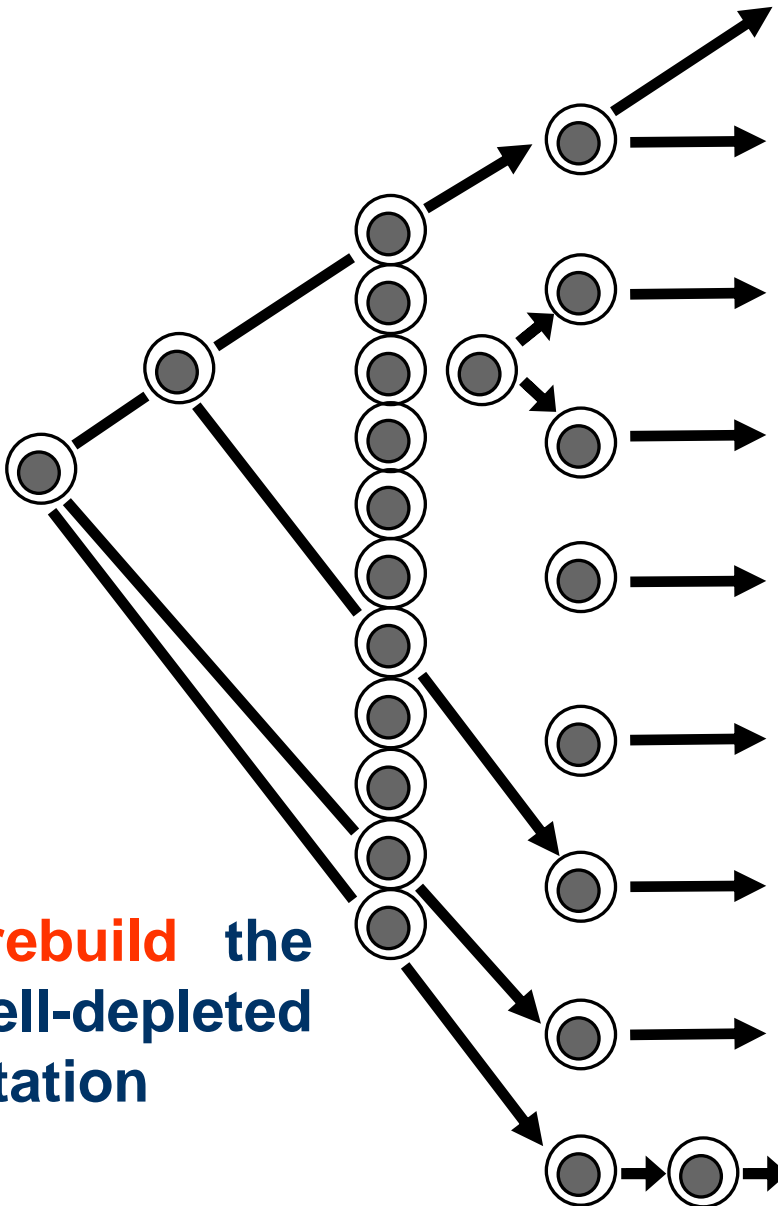
Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957–2006.

Hematopoietic stem cell: the archetype stem cell for assaying *stemness* in the adult organ-systems

Self-renewal



Differentiation



Basophil		
Eosinophil		
Neutrophil		0.1
Monocyte Macrophages		0.7
Mast cell		
Megakaryocyte Platelets		4
Erythrocyte		43
T cell		
B cell		

- A single HSC can **rebuild** the immune- and blood-cell-depleted system after transplantation

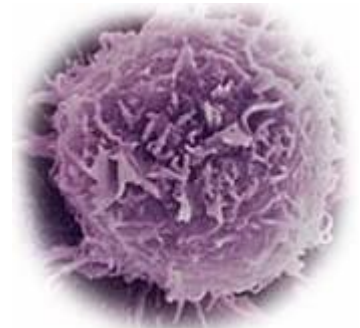
STEM CELLS

● **General definition:** *special kind of cell that has a unique capacity to renew itself and to give rise to specialized cell types (NIH, 2001).*

● **Properties:**

Self-renewal capacity

Multilineage differentiation ability
***In vivo* engraftment** ability



● **Clinical Relevance:**

➤ Treatment of degenerative disorders by **cell replacement** and/or **vehicles in gene therapy**

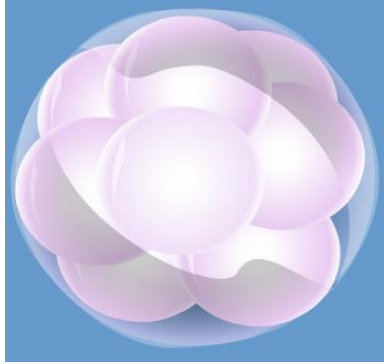
Examples: Parkinson and Alzheimer, muscular degenerative disorders, chronic liver and heart failure, type I and II diabetes, skin, eye, kidney and hematopoietic disorders

PLEASE NOTE:

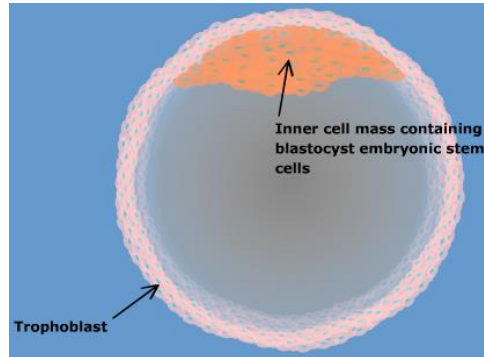
The use of stem cells as privileged vehicles for gene therapy will be best explored in the next talk by Prof. Ana P. Pêgo (i3S & INEB, ICBAS-UP)

Stem Cells

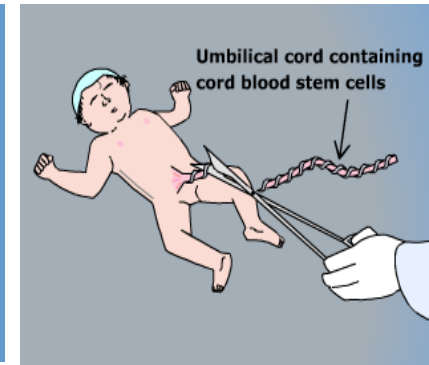
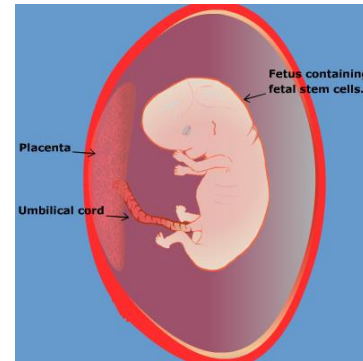
TOTIPOTENT



PLURIPOTENT



MULTIPOTENT



potential
to generate
an organism

potential to
originate all the
cells of an organism

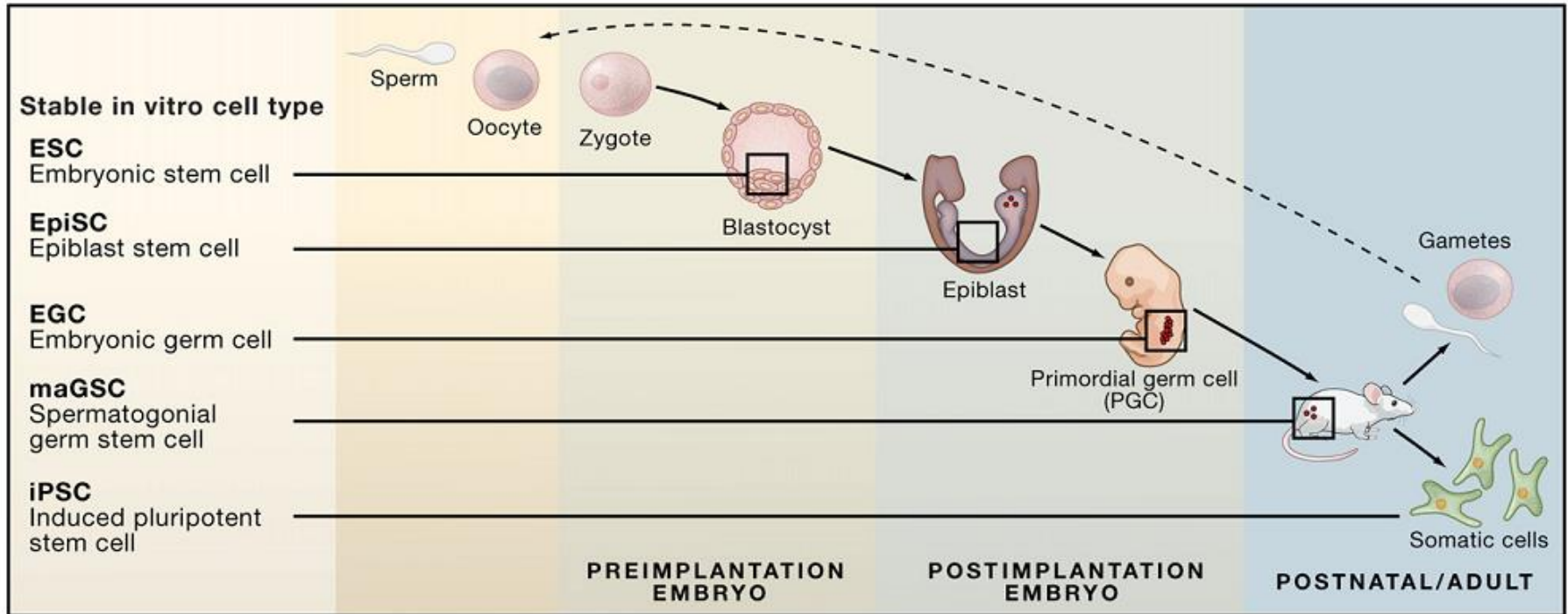
potential to originate
cells of the tissue/organs
where they are nested



- Somatic cell nuclear transfer (SCNT)
- Induced pluripotent stem cells (iPSCs)

**Somatic cell nuclei
reprogramming**

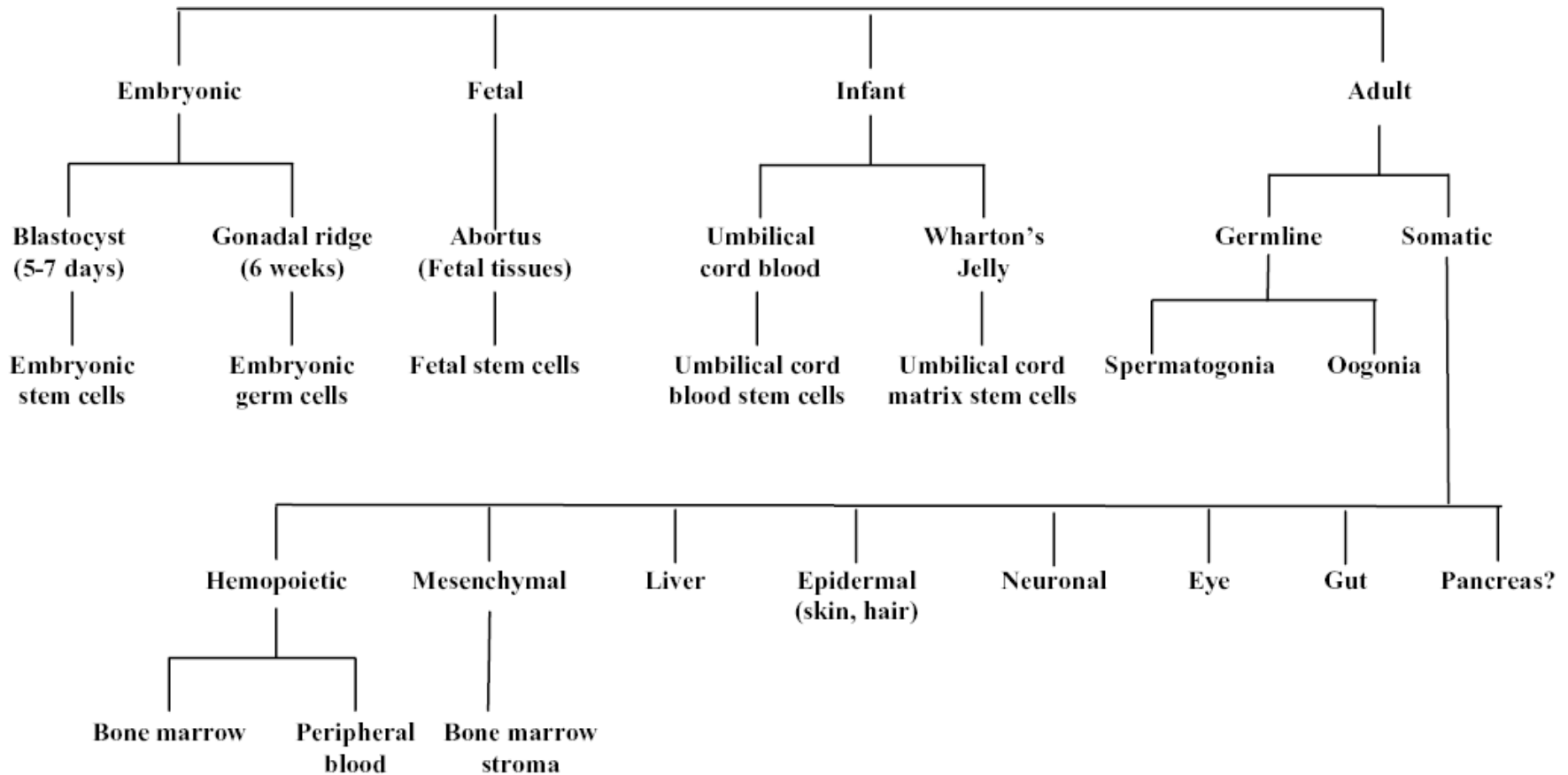
The Pluripotency State



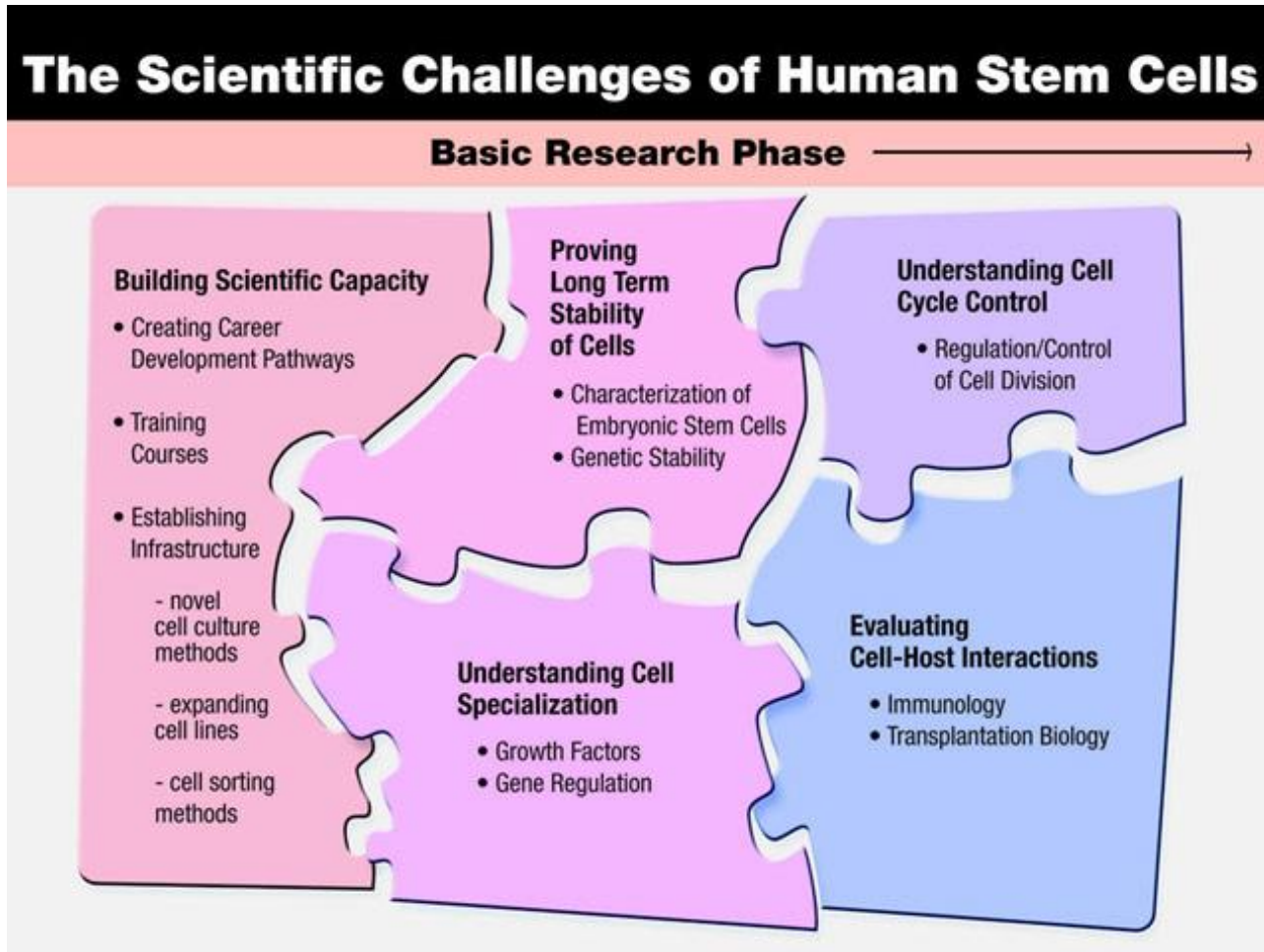
Different types of pluripotent cells can be derived by explanting cells at various stages of early embryonic development. **iPSCs** are derived by direct reprogramming of somatic cells *in vitro*

Human Stem Cells

an ever growing repertoire?...



Regenerative Medicine: 21st Century



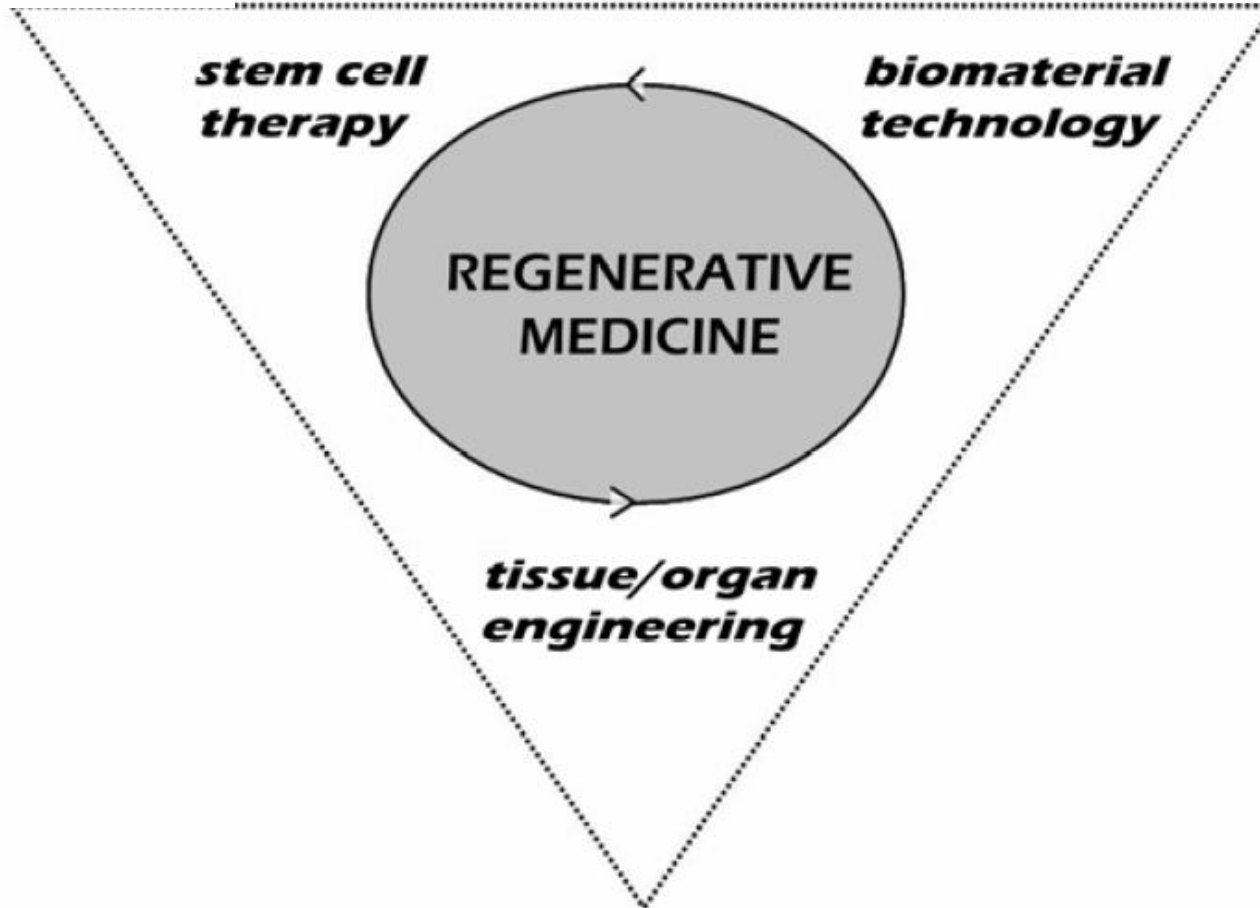
“The promise of addressing **unmet medical needs** is on the verge of being realized”

Prof. Robert Nerem,
Georgia Tech & Emory Center for Regenerative Medicine
Nerem, R.M., J. R. Soc. Interface (2010)

Regenerative Medicine

ACADEMIA

INDUSTRY



HOSPITAL

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2009

- 50 teams from 22 countries reported data on 814 patients using a dedicated survey, which were combined to additional 328 records reported by 55 teams to the standard European group for Blood and Marrow Transplantation (EBMT) database.
- **Indications** were:
 - ◆ cardiovascular (27%; 7% autologous),
 - ◆ musculoskeletal (17%; 98% autologous),
 - ◆ epithelial/parenchymal (8%; 73% autologous),
 - ◆ autoimmune (9%; 84% autologous) and
 - ◆ neurological diseases (3%; 50% autologous).
- **Autologous** cells were used predominantly for cardiovascular (42%) and musculoskeletal (30%) disorders, whereas **allogeneic** cells were used mainly for graft-vs-host-disease (58%) and cardiovascular (30%) indications.
- Reported cell types were mesenchymal stem/stromal cells (MSC) (46%), hematopoietic stem cells (27%), chondrocytes (7%), keratinocytes (5%), dermal fibroblast (13%) and others (2%).
- In 59% of the grafts, cells were delivered following expansion, in 2% of the cases cells were transduced.

PLEASE NOTE:

Stem cell- and non cell-based therapies will be updated and best explored in the next talk by Prof. Lino Ferreira (Fac. Medicina-UC, Biocant & SPCE-TC)

Stem Cells in Clinical Trials

- ✓ Stem cell therapies have been shown to be **effective** and **safe**, for **example hematopoietic stem cell transplants** for leukemia, among other hemato-oncological diseases;
- ✗ **However**, “there are some clinics around the world already exploiting patients’ hopes by purporting to offer effective stem cell therapies for seriously ill patients, typically for large sums of money, but without credible scientific, rationale, transparency, oversight, or patient protections”
- These clinical trials should follow **ethical principles** that guide all clinical research, including appropriate **balance of risks and benefits** and informed, **voluntary consent**.
- Additional ethical requirements are also warranted to strengthen trial design, coordinate scientific and ethics review, verify that participants understand key features of the trial, and ensure publication of negative findings.

Stem Cells in Clinical Trials

These measures are needed due to the highly innovative nature of the intervention, limited experience in humans, and the high hopes of patients who have no effective treatments.



Risks and Prospective Benefits in Stem Cell Clinical Trials

- ✖ The **risks of innovative stem cell-based interventions** include “tumor formation, immunological reactions, unexpected behavior of the cells, and unknown long-term health effects”;
- ✖ Evidence of **safety and proof of principle should be established through appropriate preclinical studies** in relevant animal models or through human studies of similar cell-based interventions;
- ✖ **Requirements** for proof of principle and safety should be higher if cells have been manipulated extensively in vitro or have been derived from pluripotent stem cells.



Informed consent in early stem cell clinical trials

- ✓ Participants in cancer clinical trials commonly expect that they will benefit personally from the trial (**but phase I trials target is to test safety rather than efficacy**);
- ✓ This tendency to view clinical research as providing personal benefit has been termed the **“therapeutic misconception”**. Analyses of cancer clinical trials reveal that the information in consent forms generally is adequate;
- ✓ However, in early phase I gene transfer clinical trials, researchers’ descriptions of the direct benefit to participants commonly were vague, ambiguous, and indeterminate;
- ✓ Participants in **phase I stem cell-based clinical trials** might **overestimate their benefits** and **underestimate the risks**.



Informed consent in early stem cell clinical trials

- ✓ Researchers need to communicate the **distinction** between **the long-term hope for effective treatments** and the **uncertainty** inherent to any **phase I trial**;
- ✓ Participants in phase I studies need to understand that the **intervention has never been tried before in humans** for that specific condition, that **researchers do not know whether it will work as expected**, and that the **great majority of participants in phase I studies do not receive a direct benefit.**

Informed consent in early stem cell clinical trials

- ✓ Investigators in **hESC/hiPSC clinical trials** should discuss a **broader range of information** with potential participants than in other clinical trials;
- ✓ Researchers in clinical trials of hESC transplantation should inform **eligible participants** that transplanted cells/tissues are derived **from human embryos**.

Advanced Therapy Medicinal Products [ATMPs]

● Gene Therapy Medicinal product:

COMMISSION DIRECTIVE 2009/120/EC - revised Annex I of Directive 2001/83/CE

Next Talk by Prof. Ana P Pêgo

● Somatic Cell Therapy Medicinal product:

a) Cells or tissues subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are **not intended to be used for the same essential function(s) (heterologous use)** in the recipient and the donor;

b) Administered to human beings with a view to **treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action** of its cells or tissues.

COMMISSION DIRECTIVE 2009/120/EC - revised Annex I of Directive 2001/83/CE

Advanced Therapy Medicinal Products [ATMPs]

● Tissue Engineered product:

- a) Contains or consists of **engineered cells or tissues**; = subject to substantial manipulation, so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are altered. / **heterologous use / combined products**;
- b) Administered to human beings with a view to **regenerating, repairing or replacing a human tissue**.

COMMISSION DIRECTIVE 2009/120/EC - revised Annex I of Directive 2001/83/CE

ATMPs - Examples

● Gene Therapy Products:

EU granted marketing authorization for Glybera® (2012) under exceptional circumstances as a treatment for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) confirmed by genetic testing, and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions.

● Somatic Cell Therapy Products:

Tumor vaccines (Provenge® - **autologous PB MNC**; market authorization withdrawn in 2015); **human allogeneic mesenchymal stem/stromal cells**: acute graft-versus-host disease (approved in NZ and Canada, pediatric patients)

● Tissue Engineered Products:

Expanded Chondrocytes (ChondroSelect®, MACI®); *ex vivo* expanded autologous **human corneal epithelial cells containing stem cells** (Holoclar ®, 2015).

**Coming soon in/by the
“scientist close to you”**

WORLD Precision Medicine

Congress USA 2016

FEATURED KEYNOTE

**MAKING
PRECISION
MEDICINE A
REALITY IN OUR
LIFETIME – THE
FDA’S PLANS TO
SUPPORT THE
NEW PARADIGM**

Dr. Robert Califf
FDA Commissioner

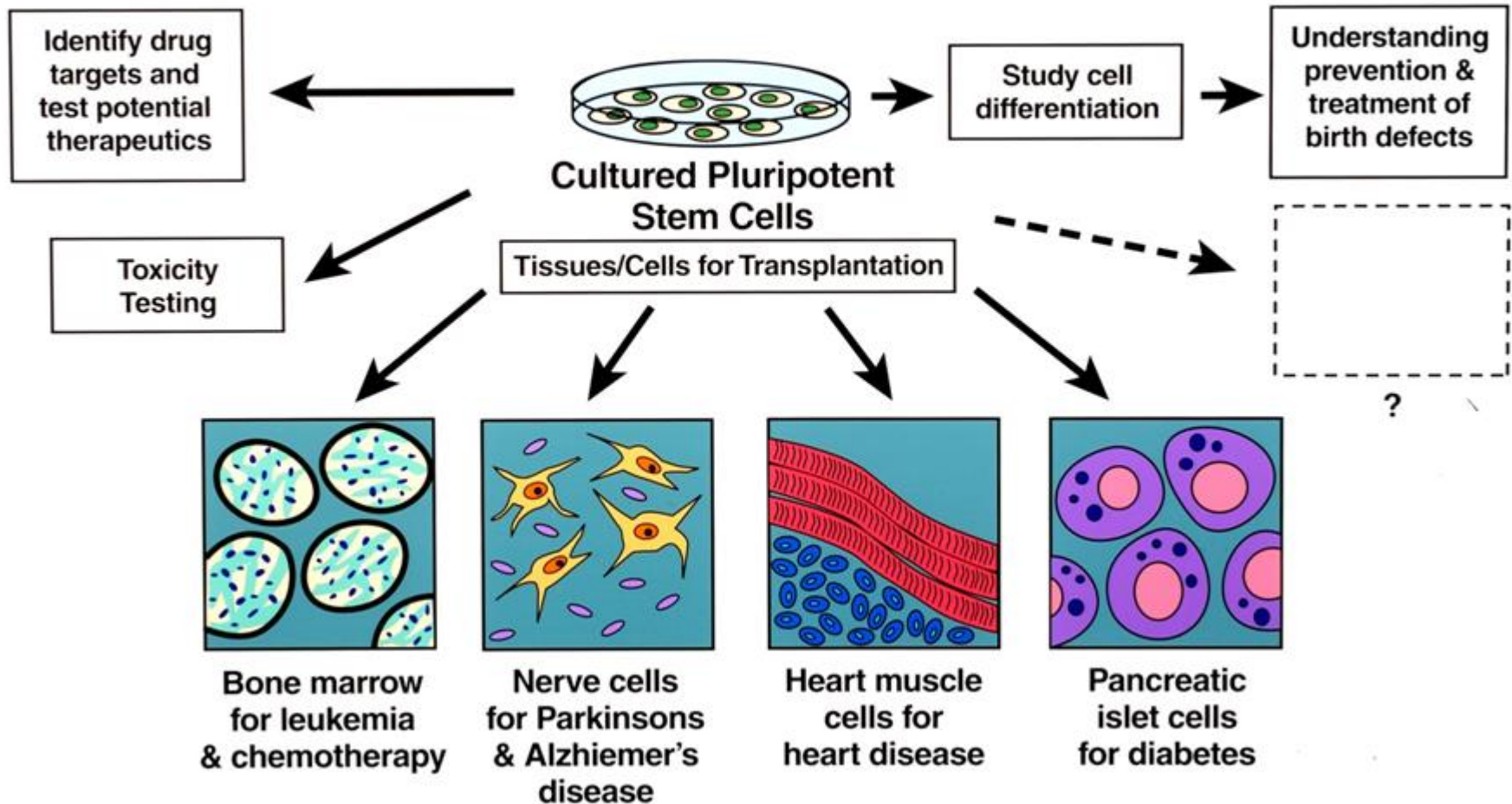
“TO ME, [THE POWER OF] GENETICS AND GENOMICS TO HELP US UNDERSTAND THE MOLECULAR BASIS OF DISEASE IS CRUCIAL FOR BEING ABLE TO TARGET THERAPIES BETTER THAN WE COULD BEFORE.”

“BUT IT GOES BEYOND GENETICS. IF YOU LOOK AT THE PRECISION MEDICINE INITIATIVE, THE EMERGING USE OF WEARABLE TECHNOLOGY AND SOCIAL MEDIA ALLOWS US TO UNDERSTAND THINGS LIKE PATIENT PREFERENCES AND CONTINUOUSLY RECORD DATA THAT WE COULDN’T MONITOR BEFORE.”



Pluripotent Human Stem Cells

- The Promise of Stem Cell Research -

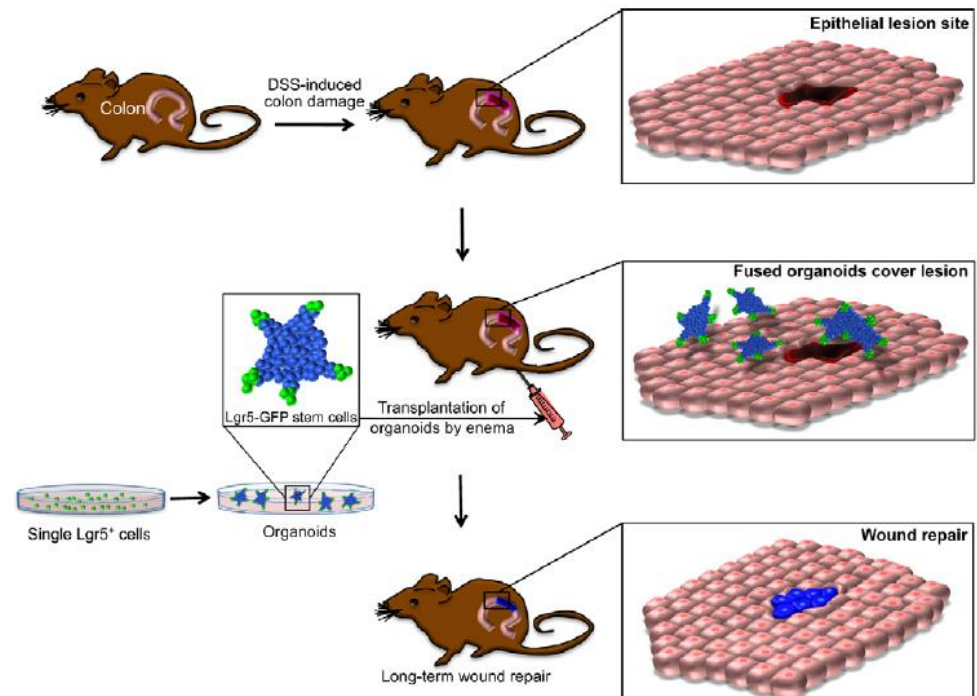
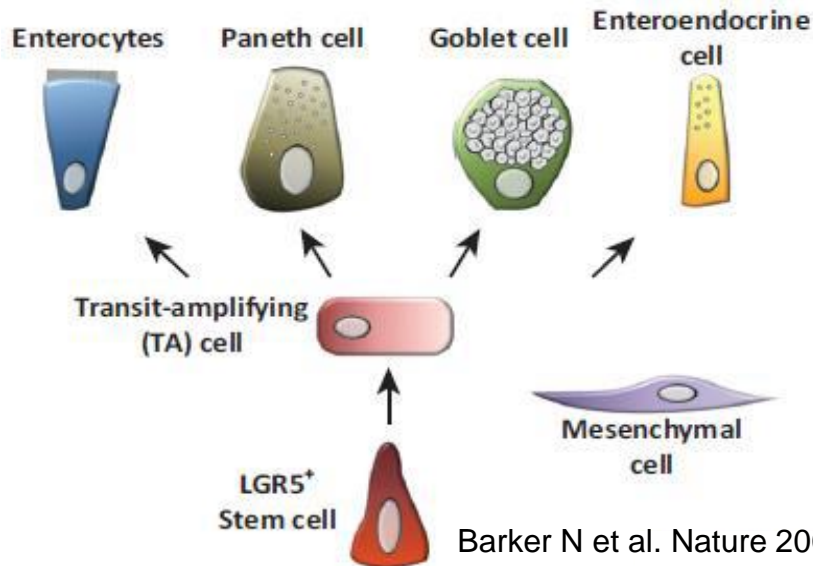
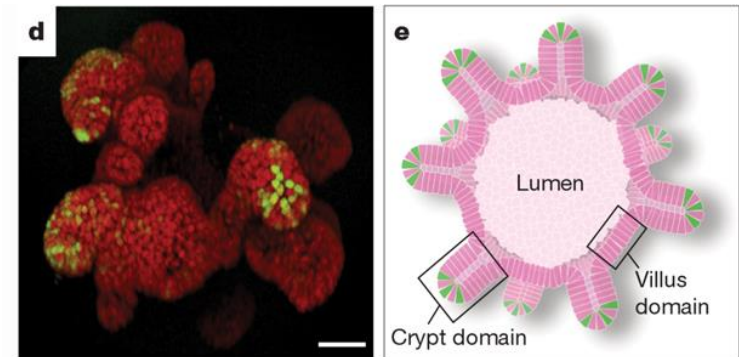
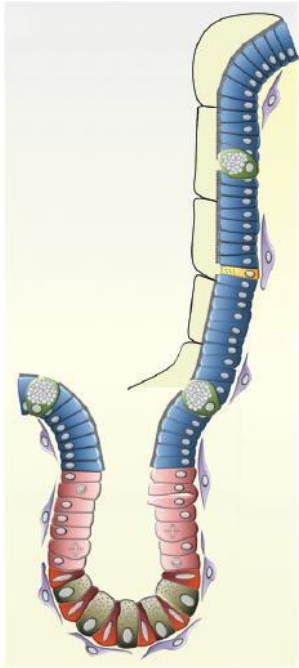


Source: Stem cell Information, NIH

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The intestinal epithelium: the Lgr5+ cell stem cell from the intestine crypt (ISC)



Barker N et al. Nature 2007 ; Sato et al., Nature, 2009 ; Fordhman, RP et al. Cell Stem Cell, 2013

Where WE ARE: Just a scent of it illustrated by the following example

- from iPSC derived Lgr5+ ISC to *in vitro* organoids for drug screening, disease modelling and human cell-replacement -



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ABOUT US



Hubrecht Organoid Technology (The HUB) is a not-for-profit organization founded by the Hubrecht Institute, KNAW and University Medical Center Utrecht, The Netherlands.

The HUB is founded on the pioneering work of Prof. Dr. Hans Clevers who discovered methods to grow stem cell-derived human epithelial 'mini-organs' (organoids) from tissues of patients with various diseases including cancer and cystic fibrosis.

In cell culture, organoids stably maintain the genotype/phenotype of the patient's diseased tissue, thereby representing an *in vitro* platform for preclinical drug discovery and validation and a tool for precision medicine.

The HUB has established a 'Living Biobank', a rapidly-growing collection of well-characterized organoids derived from patient tissues. Through a combination of the proprietary Organoid Technology and the 'Living Biobank', the HUB provides access to a unique and robust platform that links patient-specific genetic and phenotypic





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LIVING BIOBANKS



The Living Biobank consists of a rapidly growing collection of organoids from patients with various forms of cancer (colon, prostate, lung, pancreas) and cystic fibrosis. The organoids are characterized by genome sequencing,

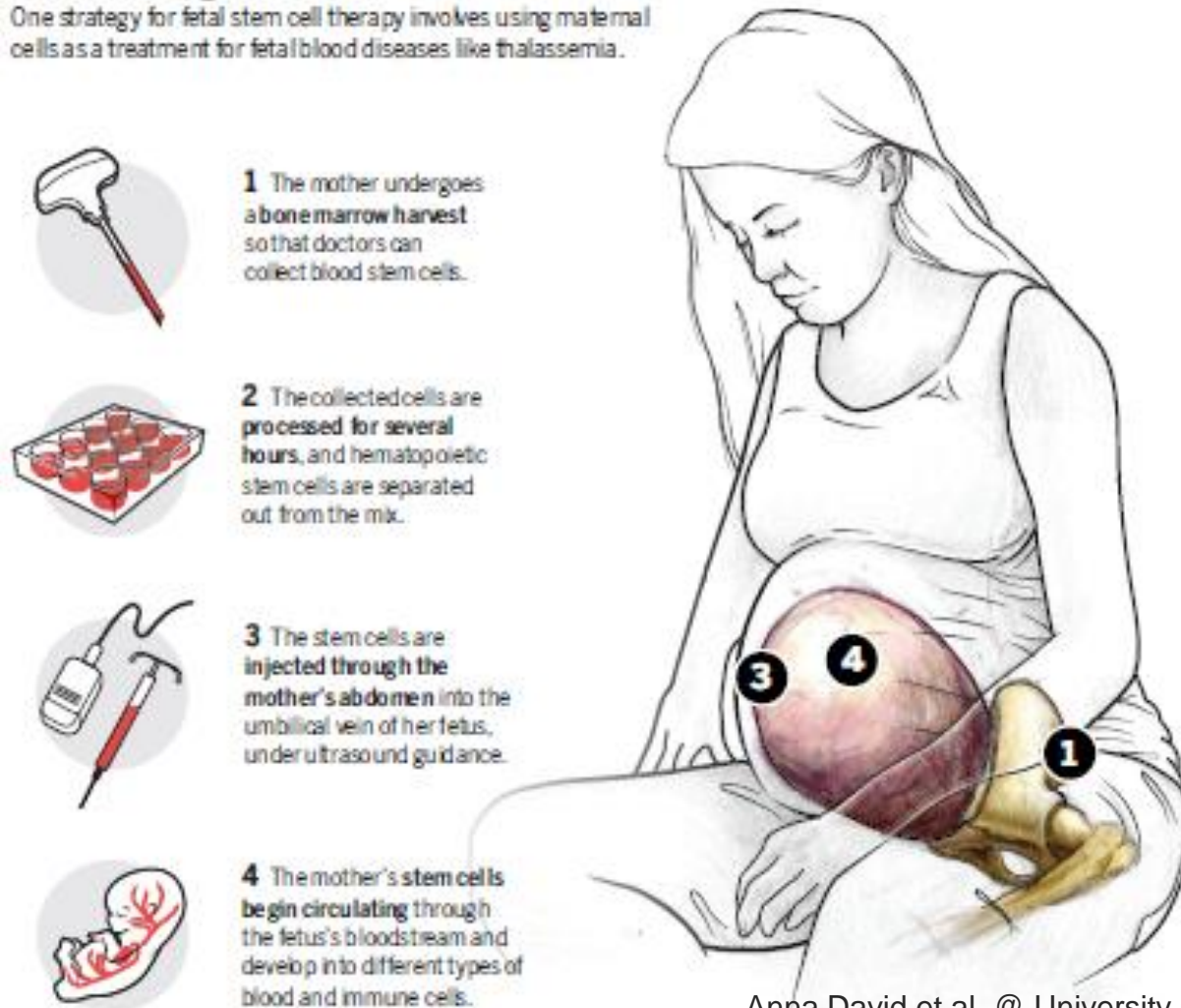
“Gene therapy gets a high-stakes test”

stem cell therapy in ailing fetuses

Fetal Growth Restriction (FGR)

A mother's gift of cells

One strategy for fetal stem cell therapy involves using maternal cells as a treatment for fetal blood diseases like thalassemia.

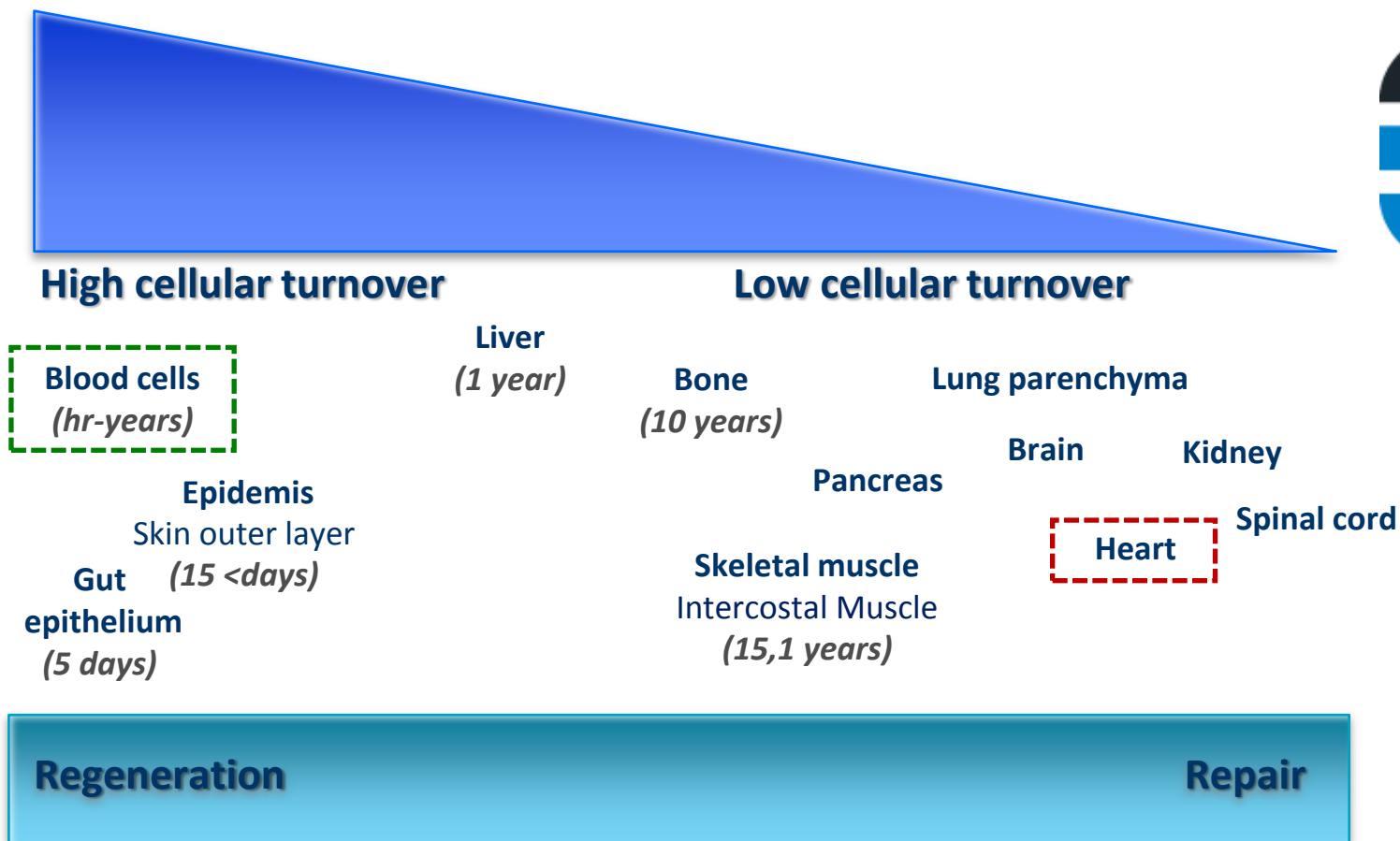




Perpétua Pinto-do-Ó Laboratory

At the Heart of Stem Cells in Regeneration and Repair

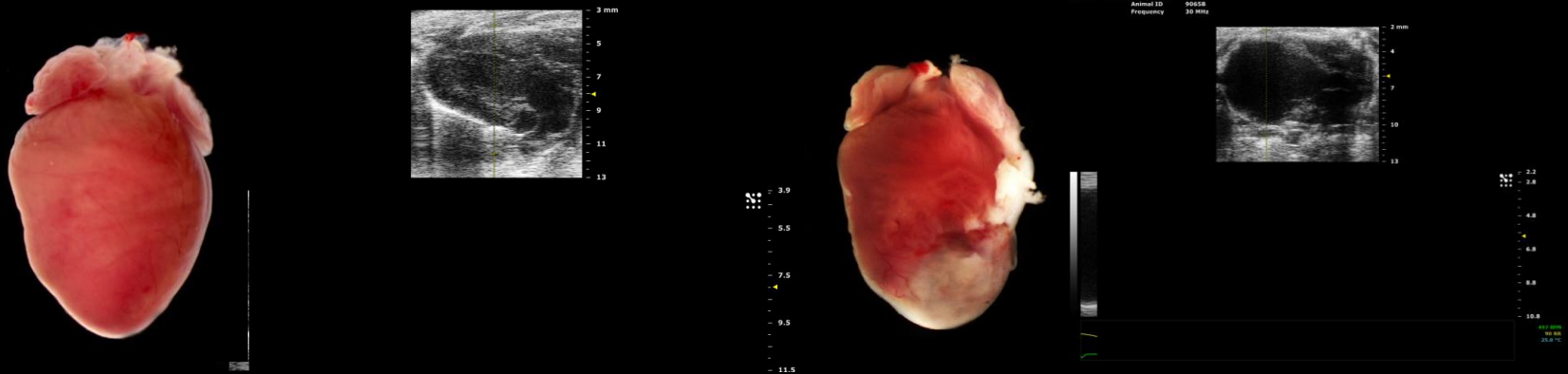




What mechanism/s define a differential stem cell contribution for homeostasis and repair in distinct organs?

RESEARCH INTEREST
Perpétua Pinto-do-Ó Laboratory

Impaired cardiac function and tissue remodelling following myocardial infarction



Evidence for Cardiomyocyte Renewal in Humans



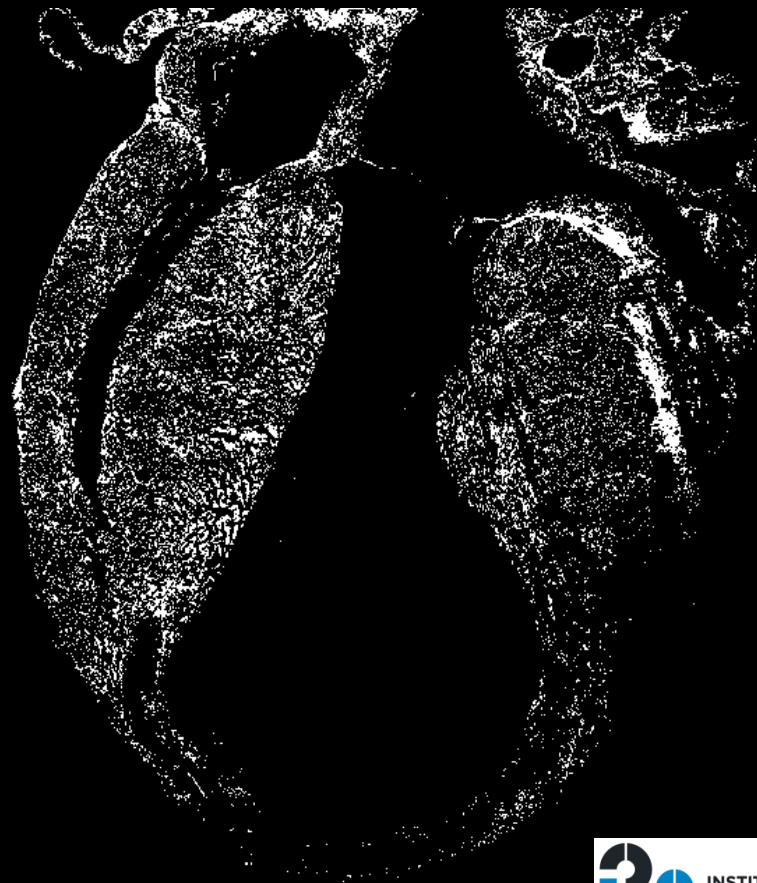
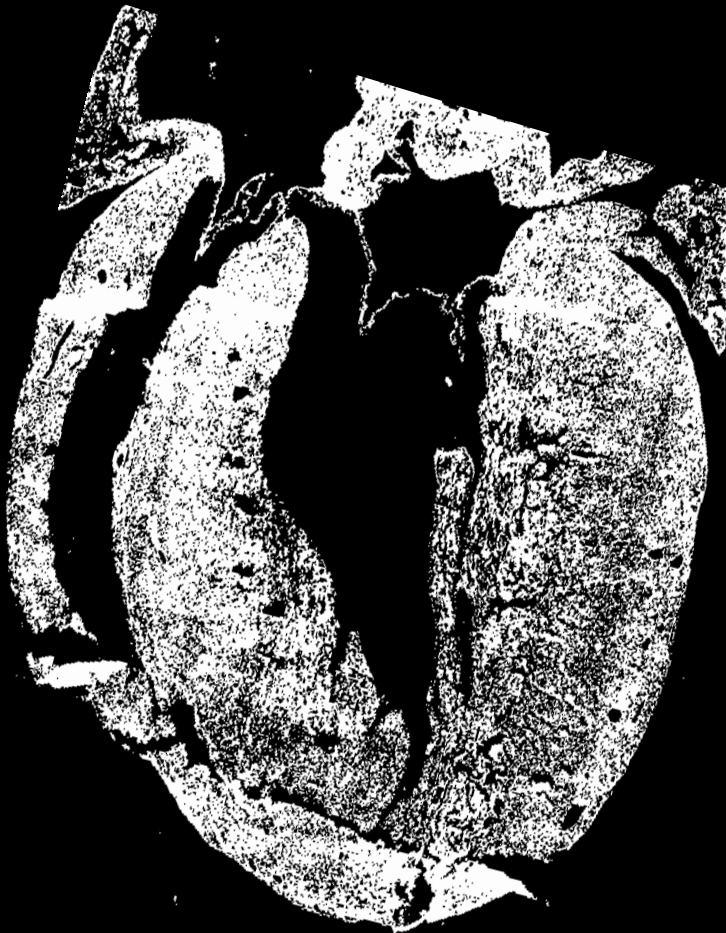
Olaf Bergmann,^{1*} Ratan D. Bhardwaj,^{1*} Samuel Bernard,² Sofia Zdunek,¹
Fanie Barnabé-Heider,¹ Stuart Walsh,³ Joel Zupicich,¹ Kanar Alkass,⁴ Bruce A. Buchholz,⁵
Henrik Druid,⁴ Stefan Jovinge,^{3,6} Jonas Frisén^{1†}

LETTERS

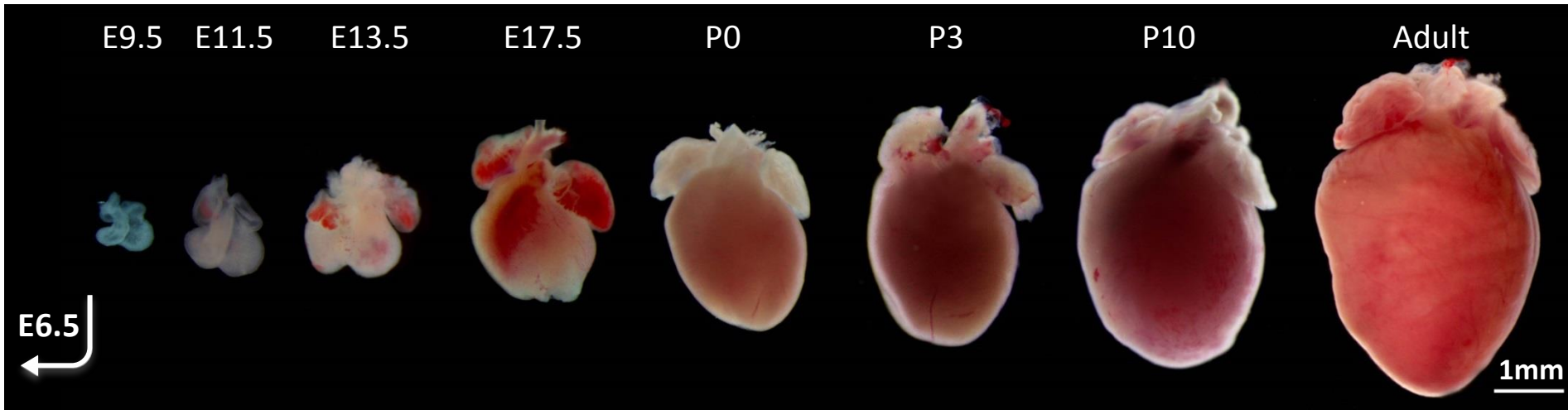
nature
medicine

Evidence from a genetic fate-mapping study that stem cells
refresh adult mammalian cardiomyocytes after injury

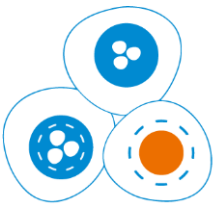
Patrick C H Hsieh^{1,3,4}, Vincent F M Segers^{1,4}, Michael E Davis¹, Catherine MacGillivray¹, Joseph Gannon¹,
Jeffery D Molkentin², Jeffrey Robbins² & Richard T Lee¹



The Cross-Talk Regeneration - Development



- Molecular mechanisms in early cardiac specification
- Unique cell surface signatures for prospective isolation of cardiovascular progenitors /heart cells along development
- Mechanisms restraining the adult heart cardiomyocyte' proliferation
- Signals in the developing heart ECM amenable to modulate the course of regeneration/repair
- Cell and non-cell based strategies to promote cardiac regeneration /repair



Thanks!
OBRIGADA E BOM TRABALHO
😊

**SLIDES PREPARED BY Cláudia Lobato da Silva (SPCE-TC, Vice-President) &
P. Pinto-do-Ó (SPCE-TC, President)**

<http://spce-tc.org/>

SPCE-TC Governing Board, Direction 2016 - 2017

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