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UNIVERSITÀ
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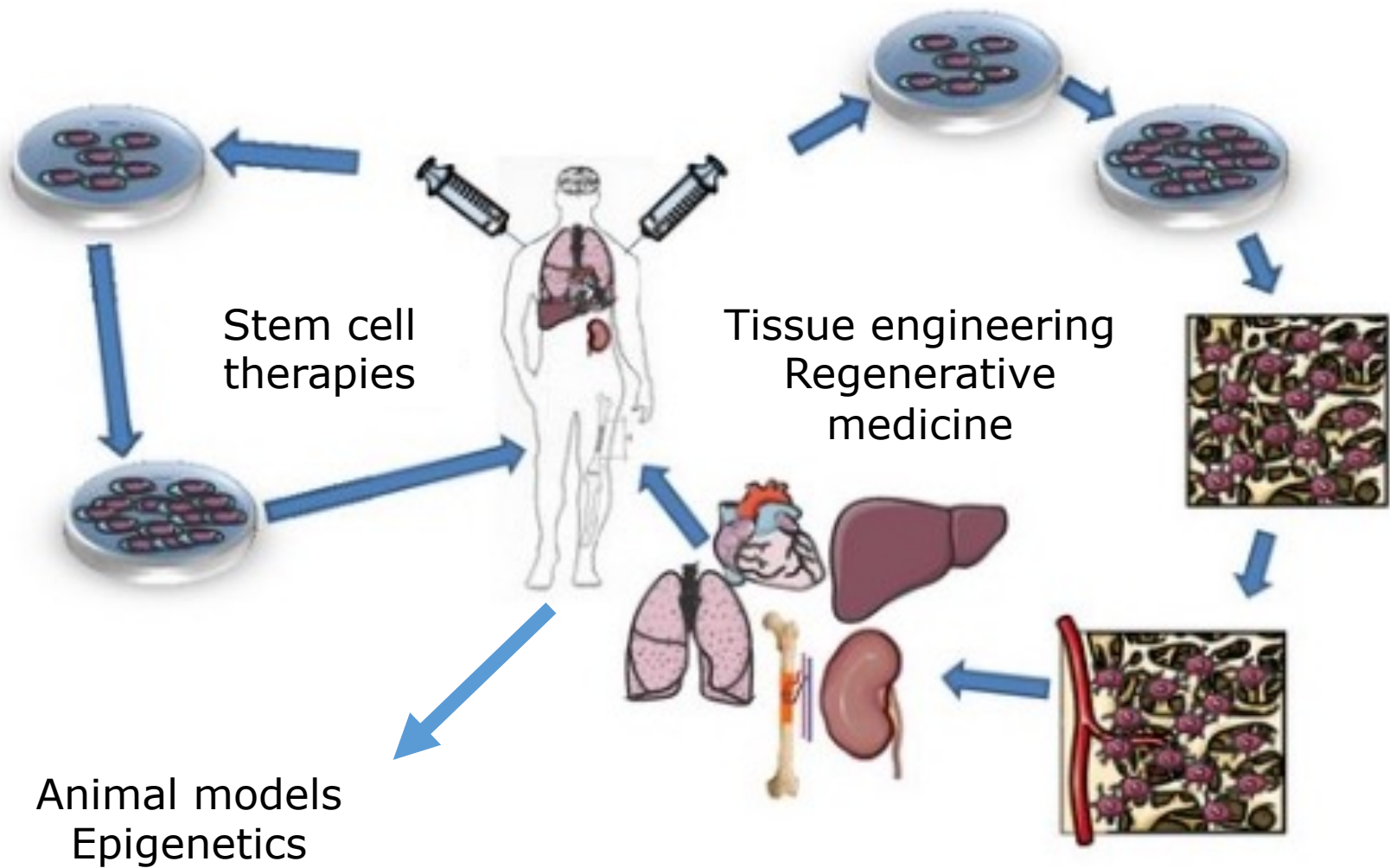
Transgenerational Aging & Gendered Life-Cycle Approach

EC2U Summer School | Pavia |
18-25 September 2022

Regenerative Medicine: where do we stand?

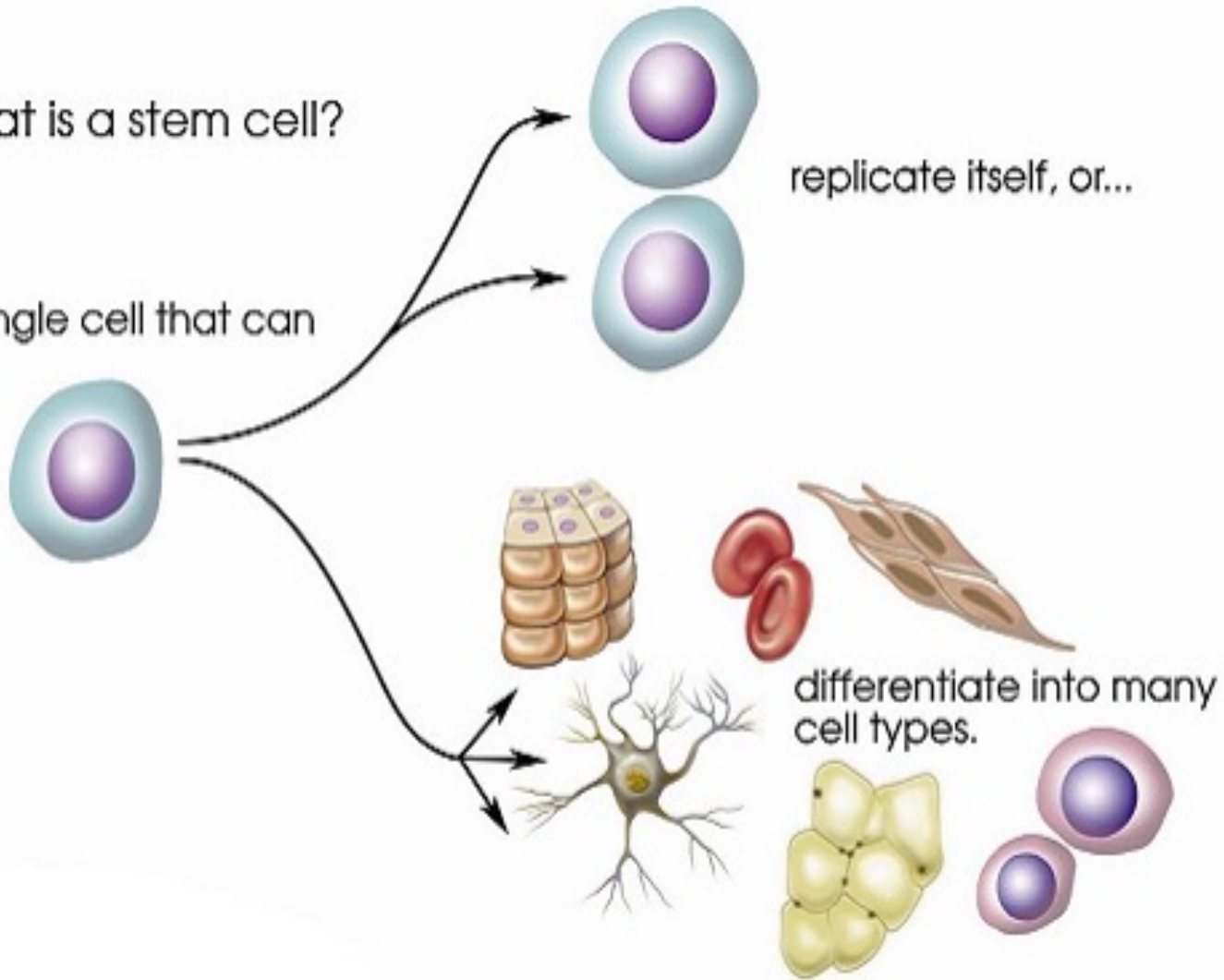
Federica Riva - Manuela Monti

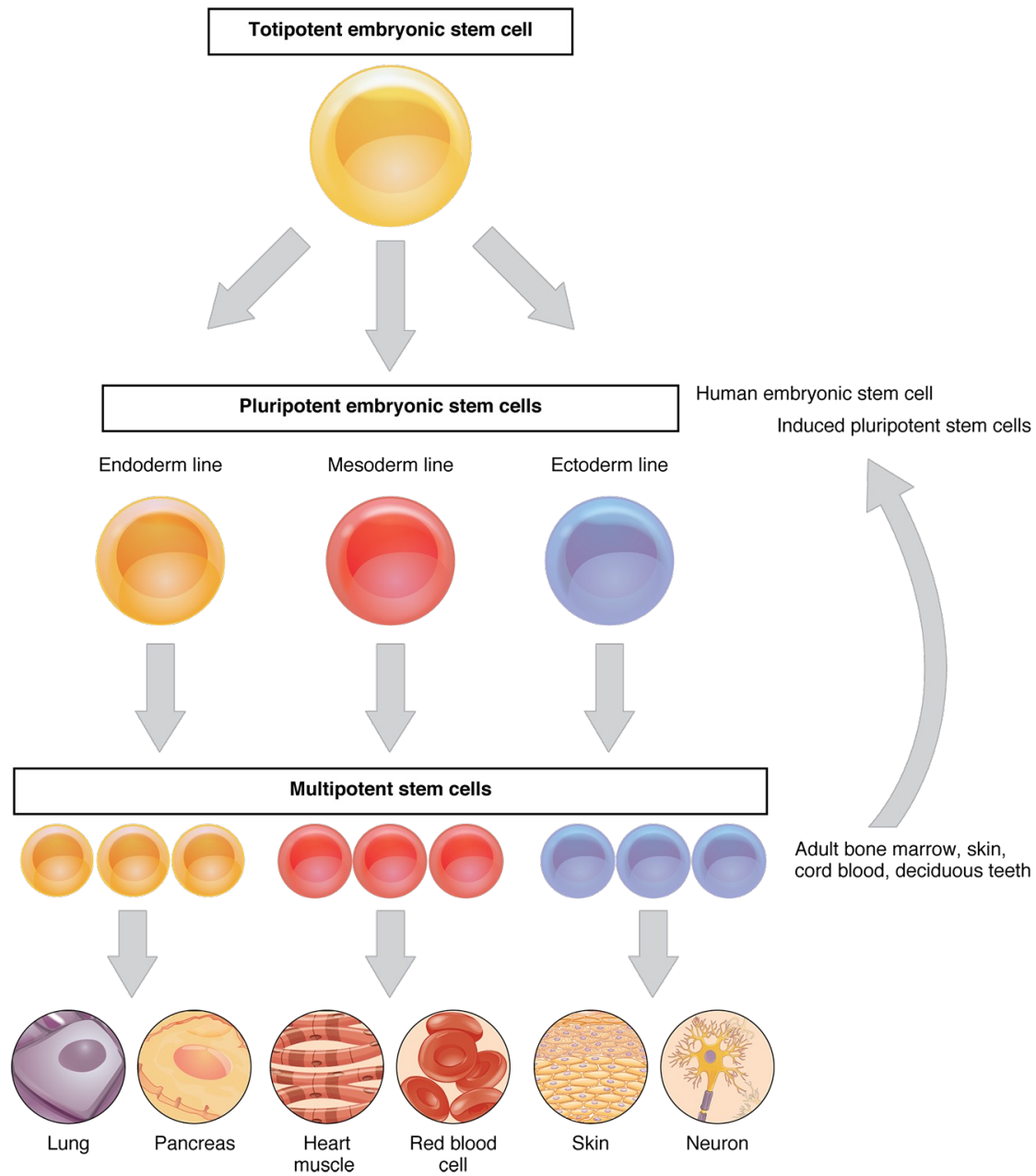
Histology and Embryology Unit
Department of Public Health, Experimental and Forensic medicine
University of Pavia



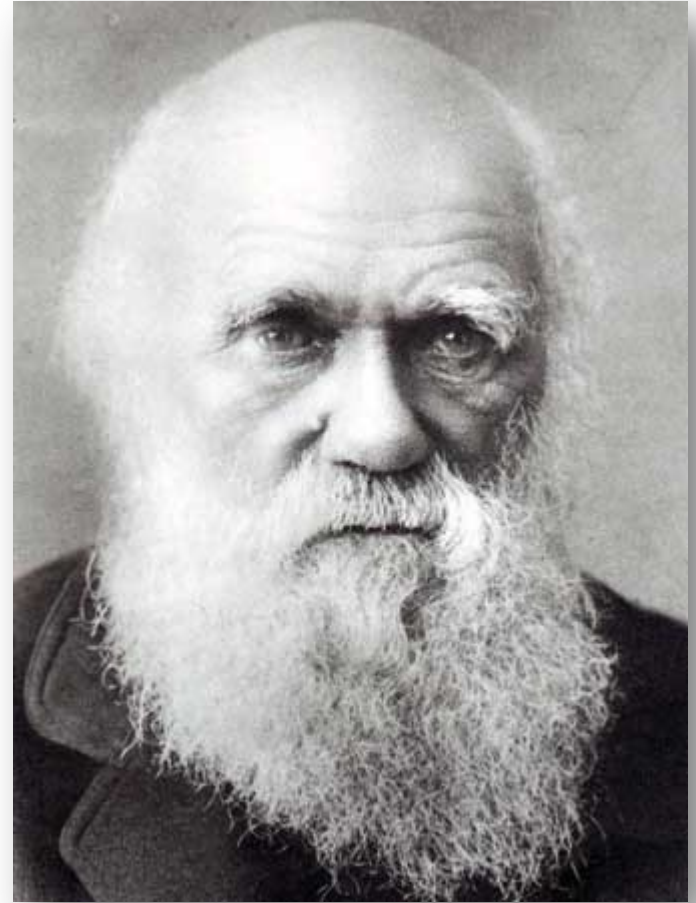
What is a stem cell?

A single cell that can





Zygote = totipotent stem cell

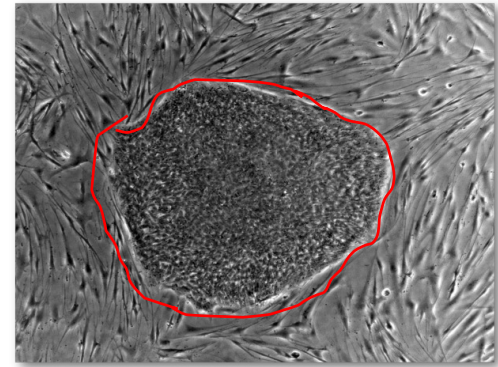
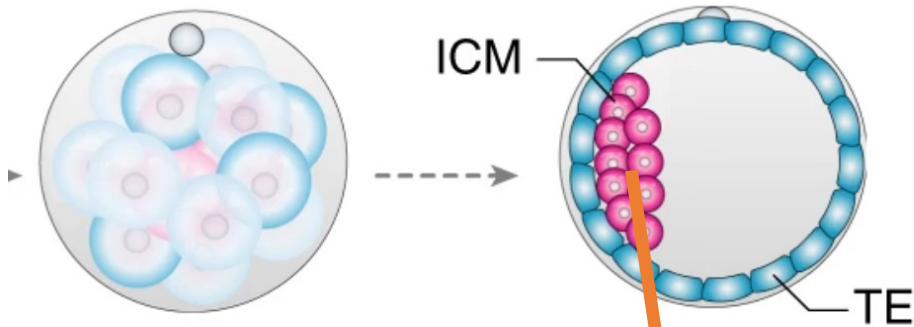
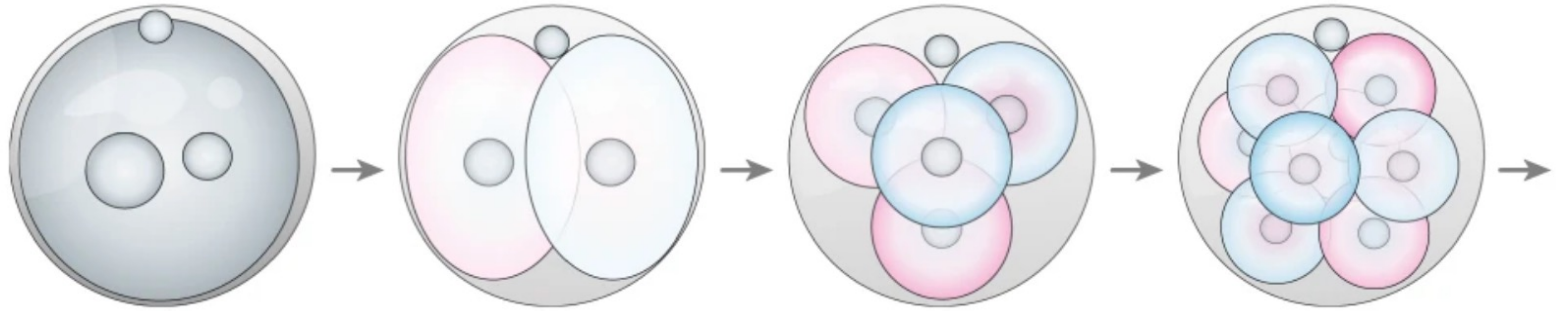


1

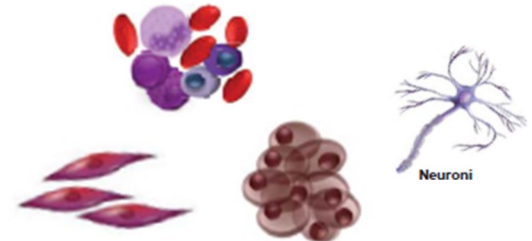
10^{17}

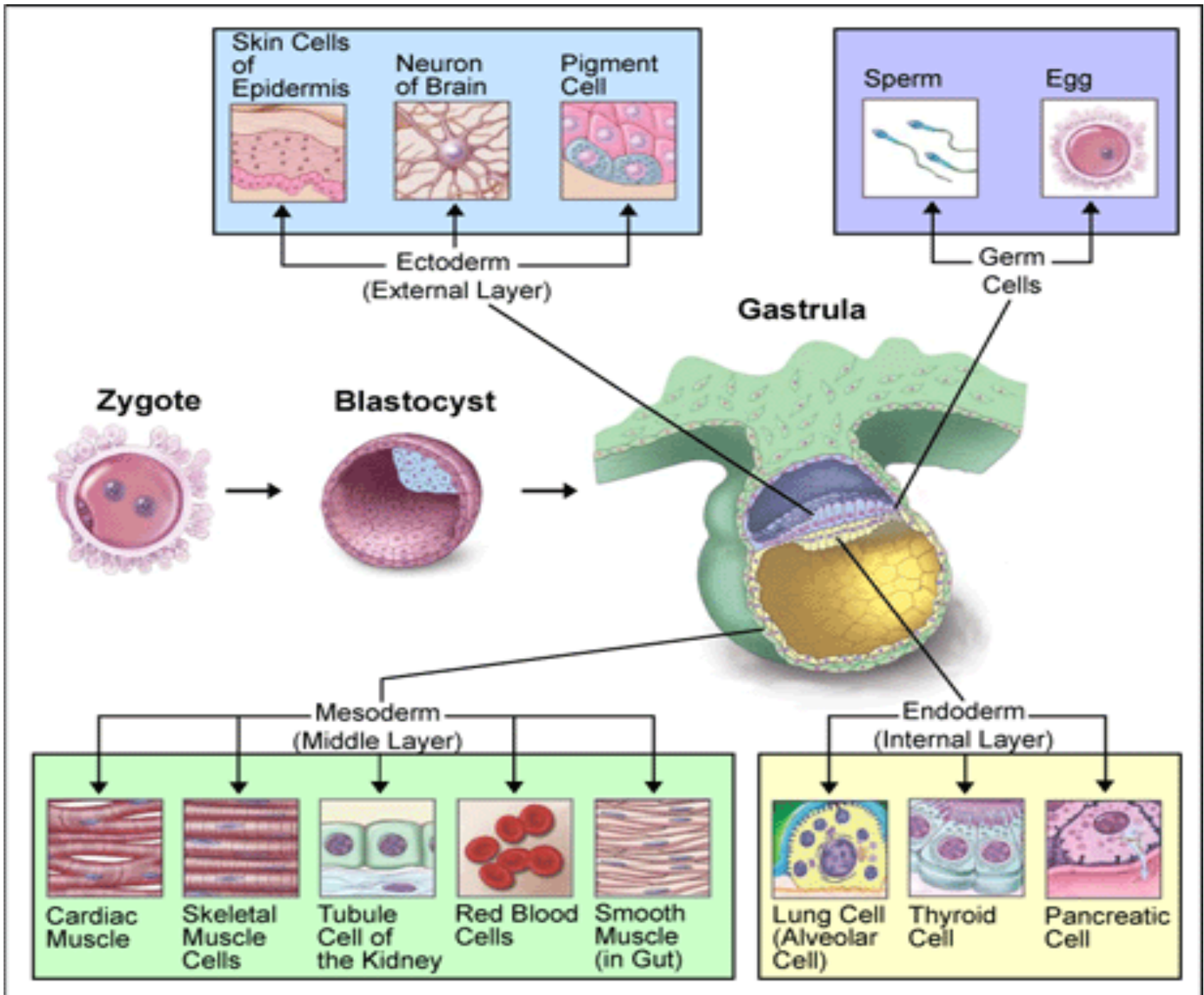
12 hrs after fertilization

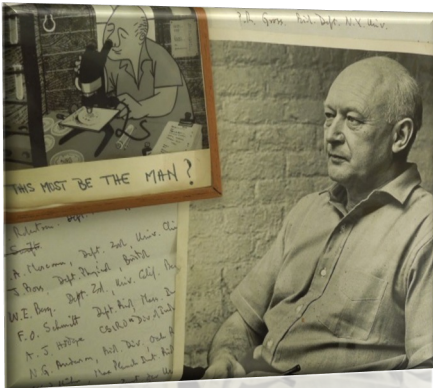
2-3 days after fertilization



pluripotent
stem cells
ES cells

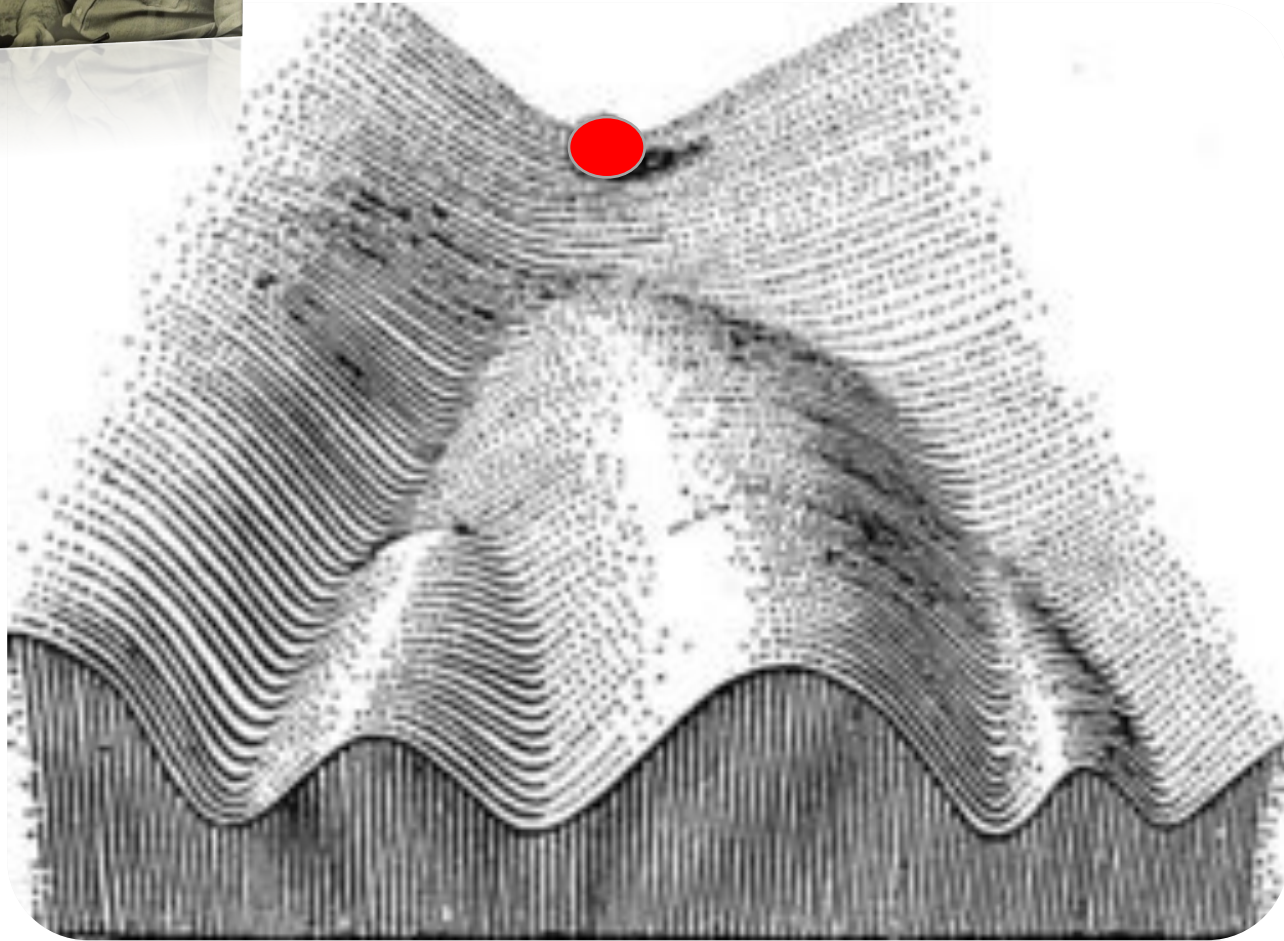


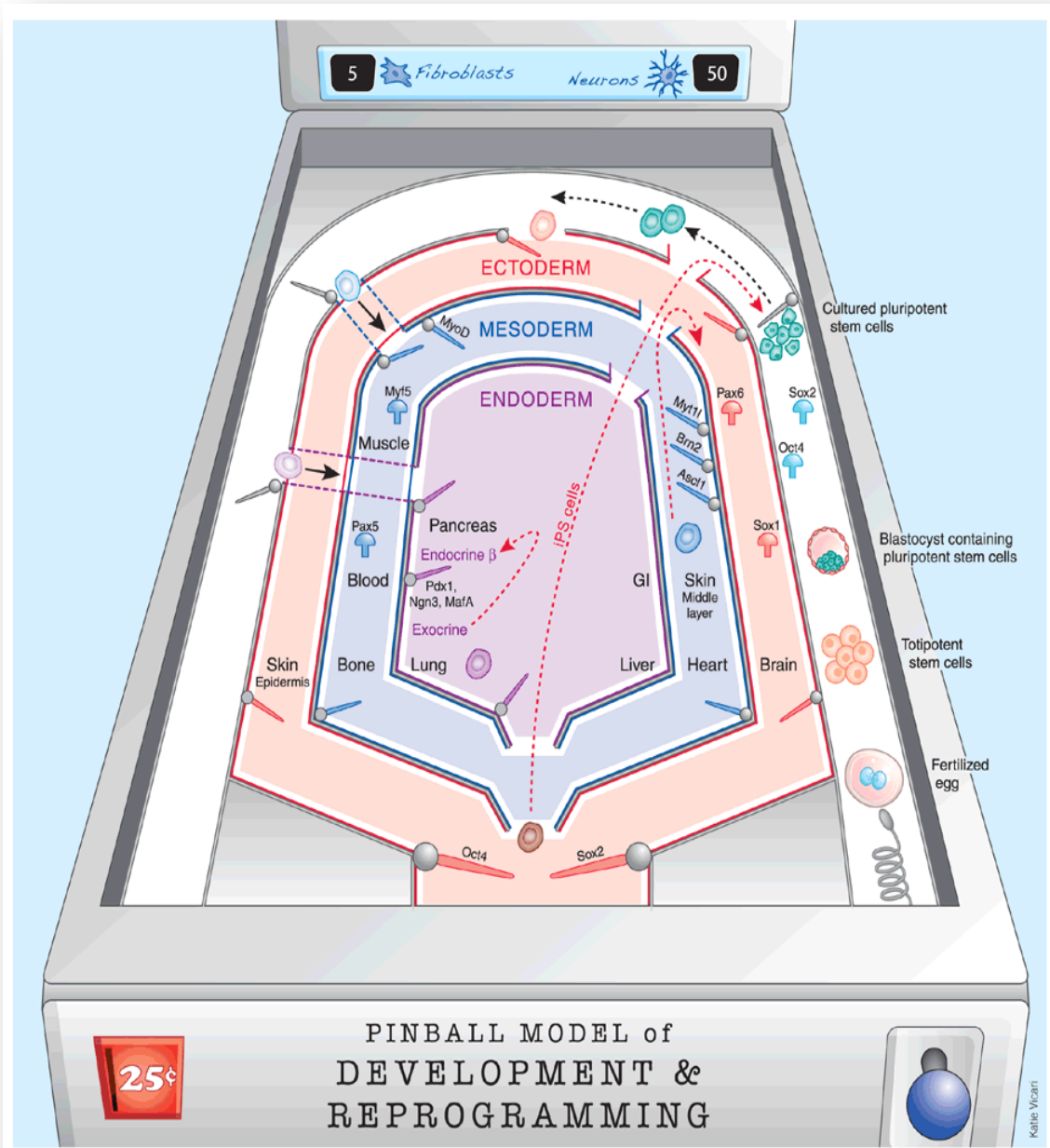




Conrad Hal Waddington (1905-1975)

epigenetic landscape





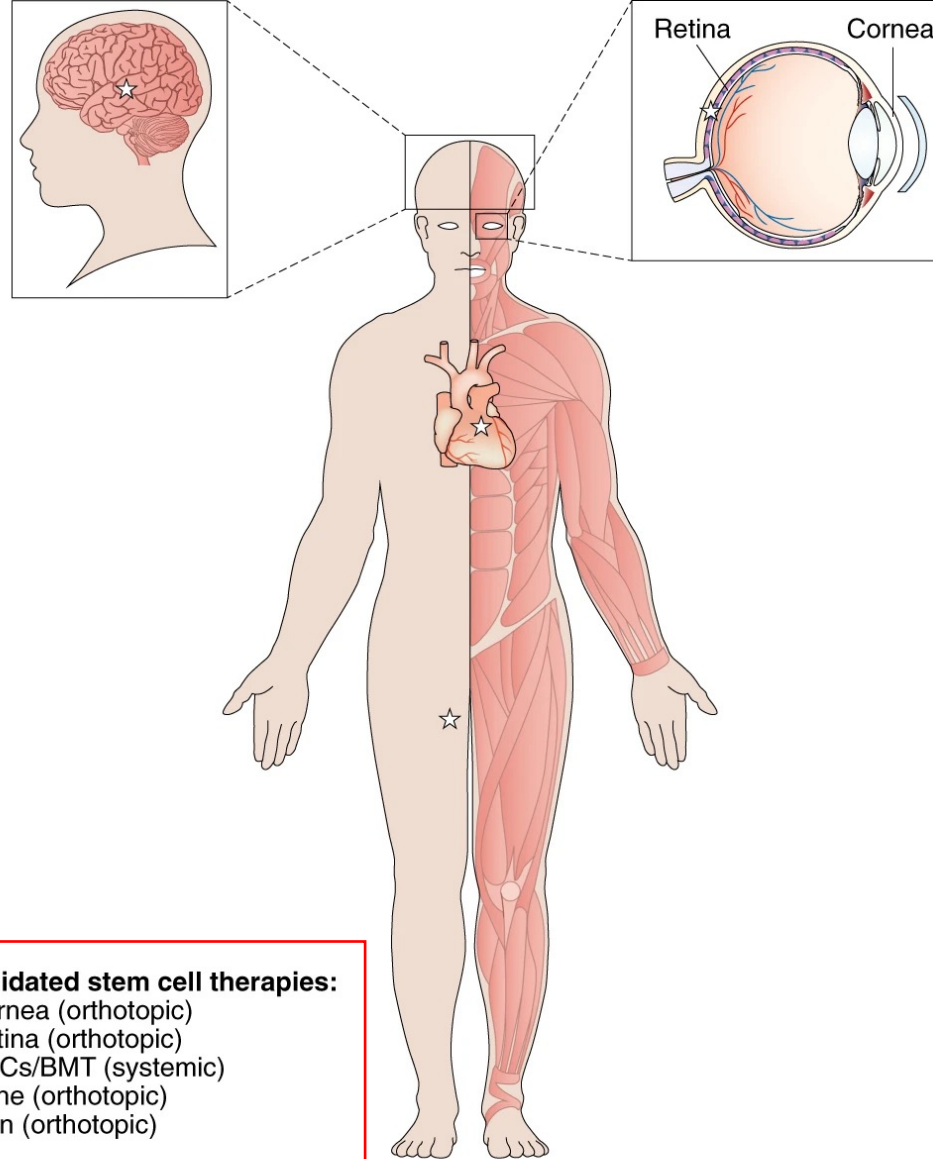
Cell

Volume 158
Number 4

August 14, 2014

www.cell.com





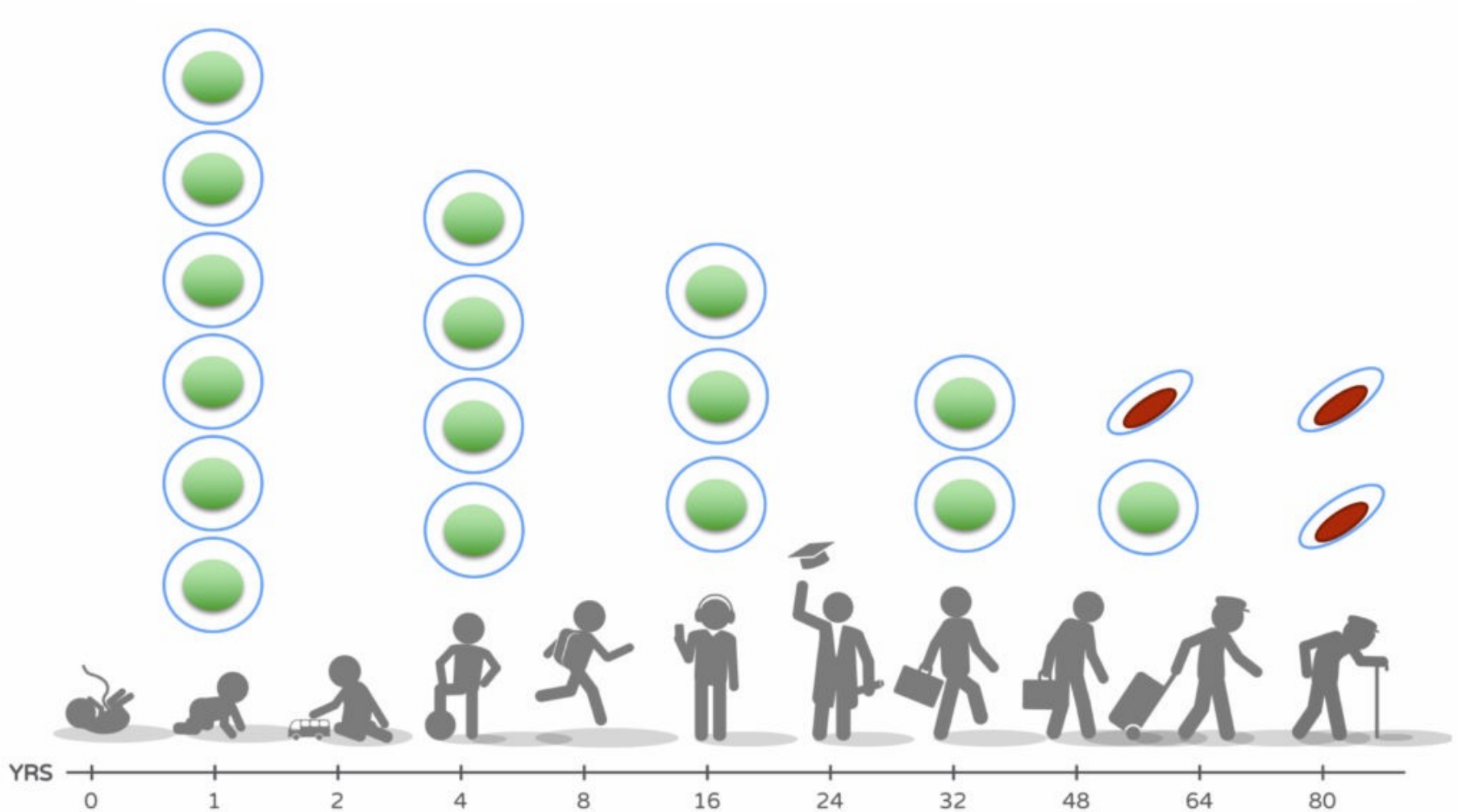
Validated stem cell therapies:
 Cornea (orthotopic)
 Retina (orthotopic)
 HSCs/BMT (systemic)
 Bone (orthotopic)
 Skin (orthotopic)

Under clinical or preclinical investigation

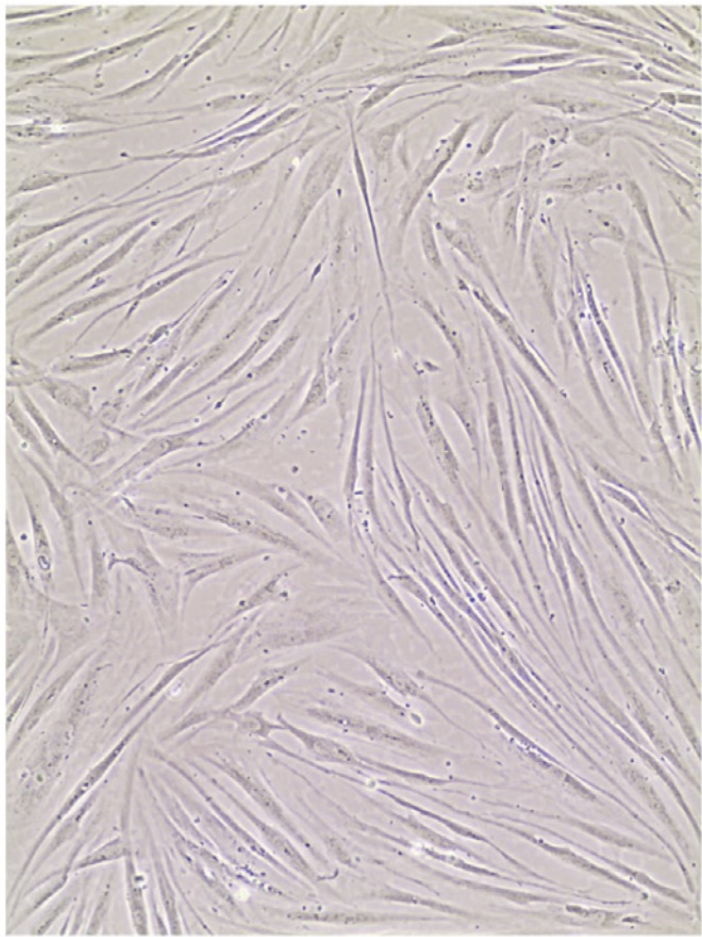
- Immunomodulation
- Musculoskeletal disorders (muscular dystrophies, bone diseases, joint injuries)
- Cardiovascular diseases (infarct, cardiac failure, peripheral artery diseases)
- Eye diseases
- Neurological disorders (Parkinson’s disease, ALS, stroke, multiple sclerosis, spinal cord injury, etc.)
- Diabetes



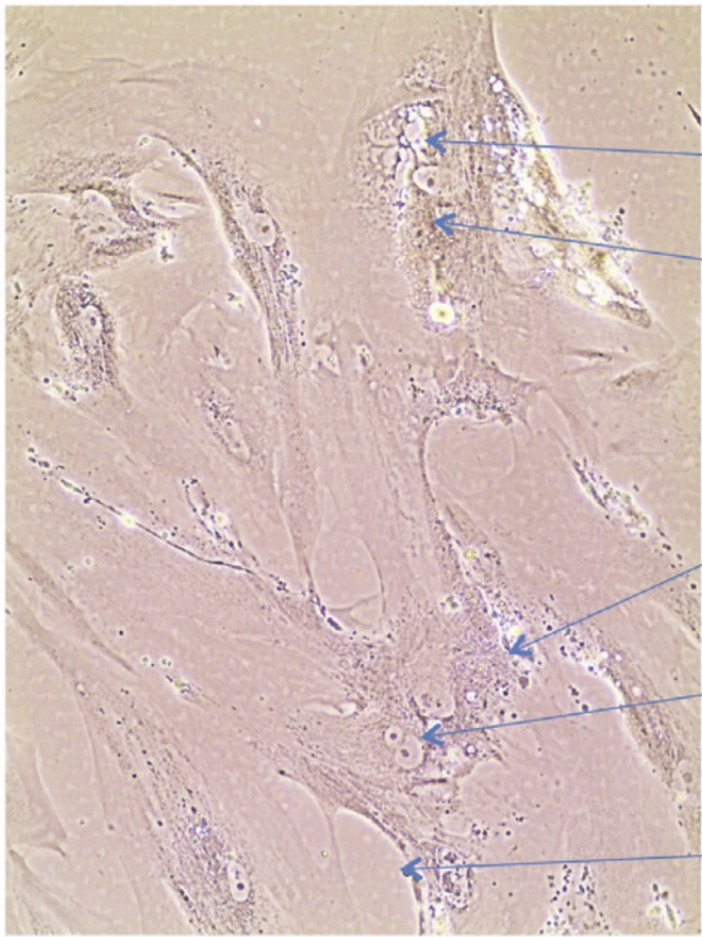
As we age our stem cell numbers diminish and begin to mutate



A proliferating



B senescent



Lipid droplets

JunQ bodies

Granular material

Multinucleate
Prominent
nucleoli

Incomplete
monolayer

Cox and Redman, Placenta (2017)

Some of the causes related to aging:

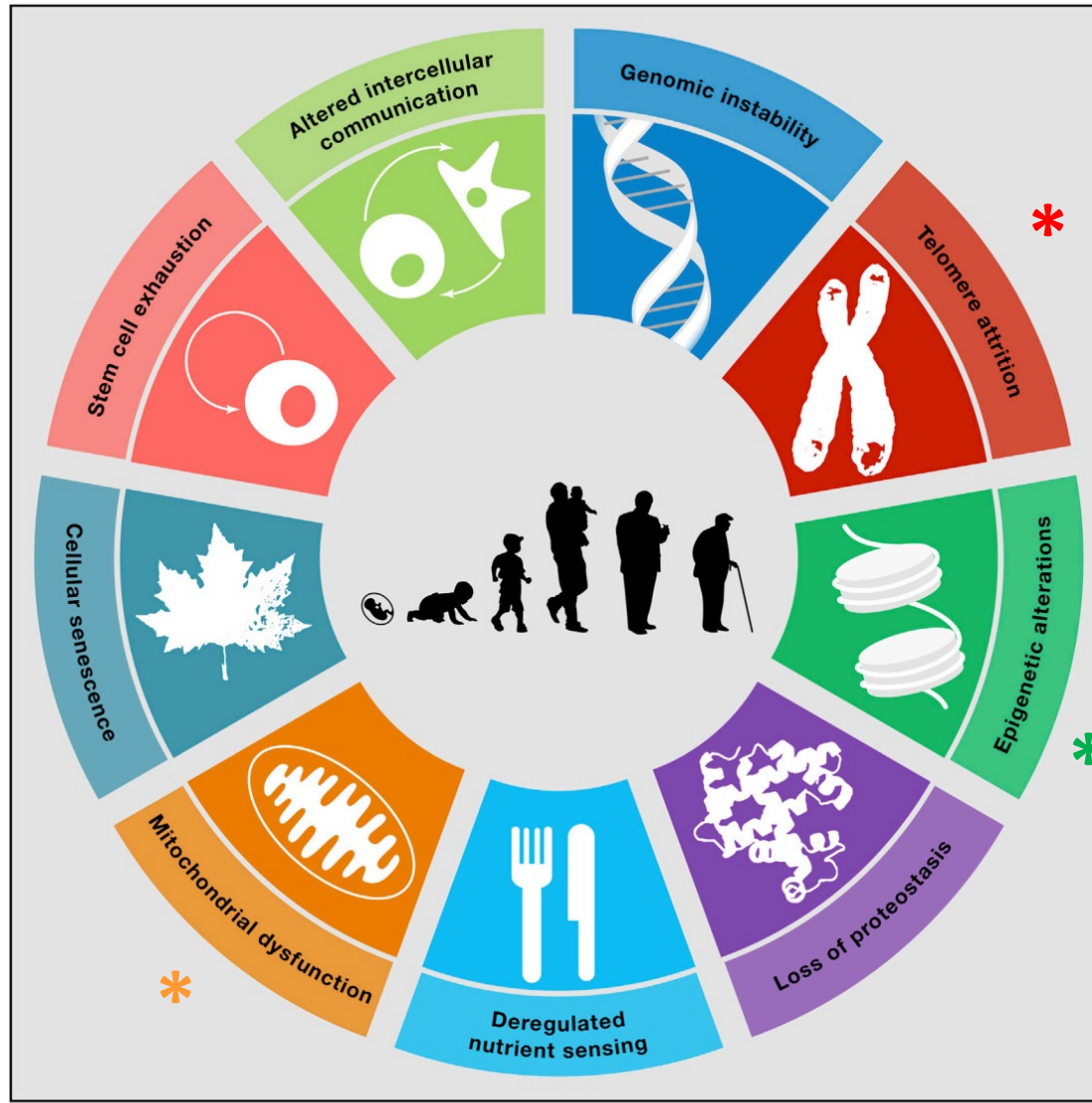
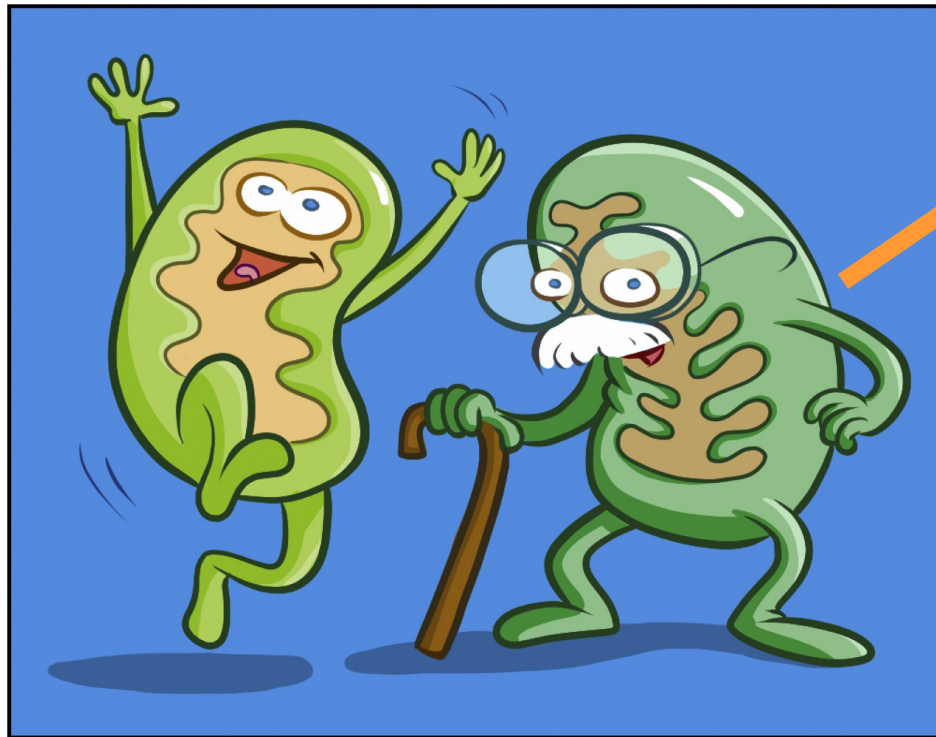
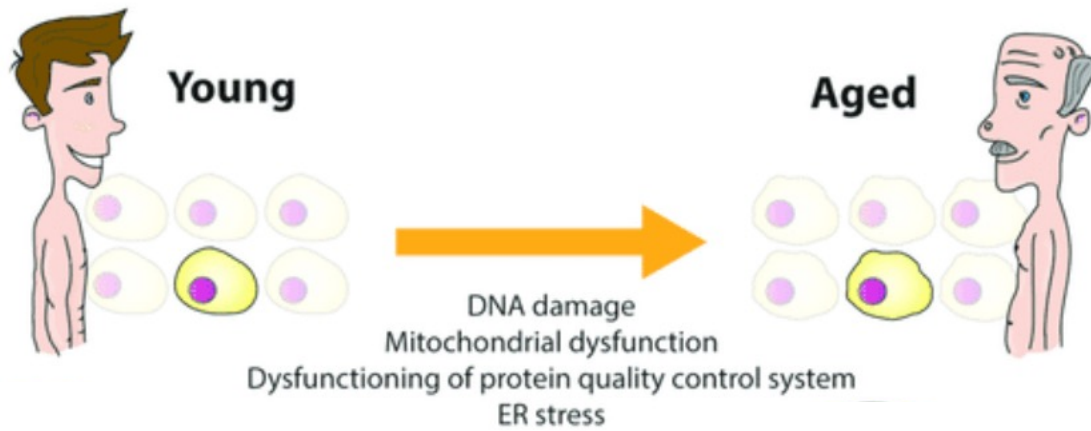


Figure 1. The Hallmarks of Aging

The scheme enumerates the nine hallmarks described in this Review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.



Vulnerability
to cell death



Prof. Minoru Ko

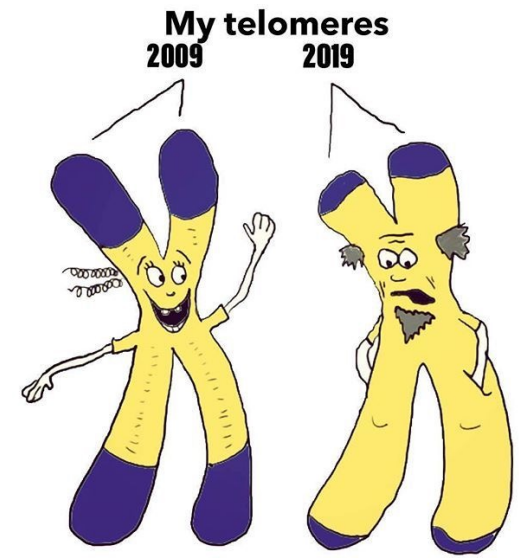
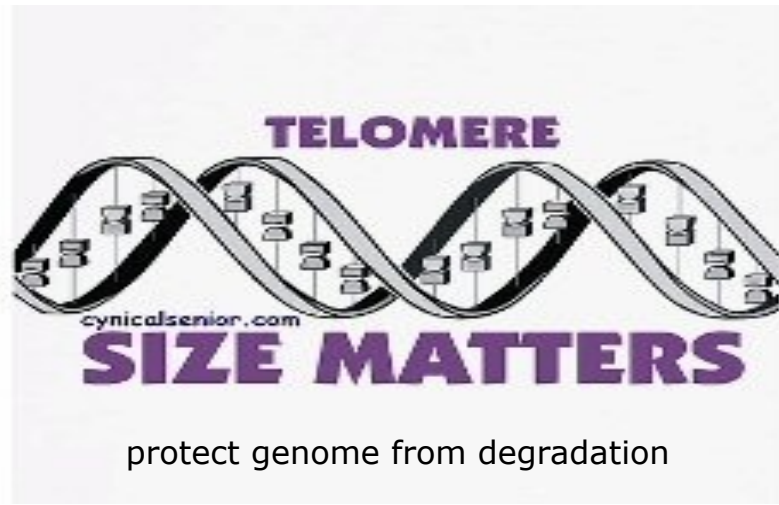
ARTICLE

Received 24 Sep 2012 | Accepted 1 May 2013 | Published 6 Jun 2013

DOI: 10.1038/ncomms2966

Zscan4 restores the developmental potency of embryonic stem cells

Tomokazu Amano¹, Tetsuya Hirata^{1,†}, Geppino Falco^{1,†}, Manuela Monti^{1,†}, Lioudmila V. Sharova¹, Misa Amano¹, Sarah Sheer¹, Hien G. Hoang¹, Yulan Piao¹, Carole A. Stagg¹, Kohei Yamamizu¹, Tomohiko Akiyama¹ & Minoru S. H. Ko^{1,2}



Epigenetics



Epigenetics is the study of how your behaviours and environment can cause changes that affect the way your genes work.

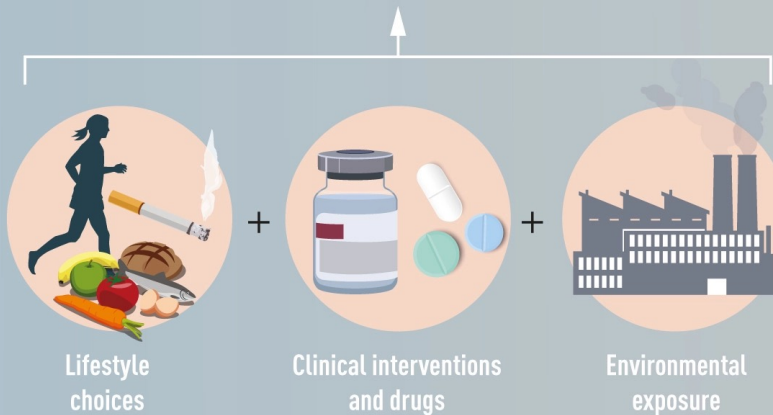
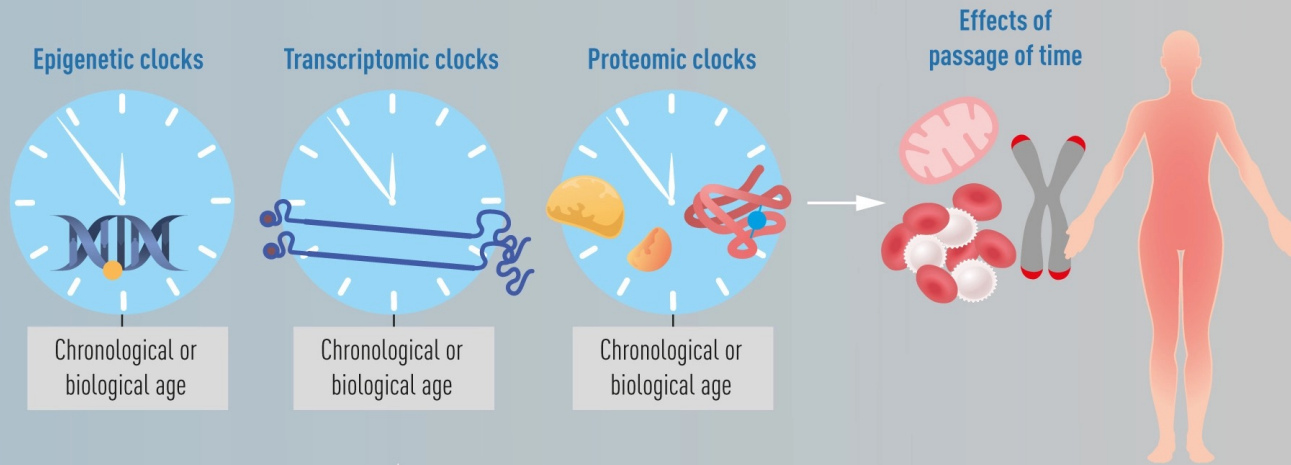
Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence.

Epigenetic aging:

Biomarkers of disease and informing a mechanistic theory of aging

Healthspan

Lifespan



JIM Journal of Internal Medicine
Founded in 1863

What is Stunting?

(It's not just about being short)



Stunting is what happens to a child's brain and body when they don't get the right kind of food or nutrients in their first 1,000 days of life.¹



Nearly 40% of children in poor countries have their growth stunted by malnutrition.²



Lack of proper nutrients stops the brain from developing properly.³



Malnourished children are less able to learn causing them to have lower earnings later in life.⁴

Sources:

(1) www.unicef.org.uk

(2, 4) <http://www.savethechildren.org.uk>

(3) www.facebook.com/savethechildreuk

BILL & MELINDA
GATES foundation

www.gatesfoundation.org





STUNTING

THE GOAL

By 2025, reduce by 40% the number of children aged under 5 years who are stunted

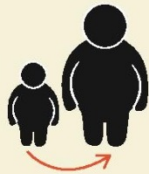
WHY IT MATTERS



Stunting is a largely irreversible outcome of **inadequate nutrition & repeated bouts of infection** during the first **1,000 days** of a child's life



Stunting has **long-term effects, including:** Diminished cognitive and physical development, reduced productive capacity and **poor health**



Stunted children have an increased risk of becoming **overweight or obese later in life**



Reduced school attendance results in diminished earning capacity; **an average of 22% loss of yearly income in adulthood**



RECOMMENDED ACTIONS

SCALE UP PREVENTION

WHAT? Scale up coverage of stunting-prevention activities

HOW? Improve the identification, measurement and understanding of stunting



MATERNAL NUTRITION

WHAT? Improve the nutrition of women of reproductive age

HOW? Enact policies and/or strengthen interventions to improve maternal nutrition and health, beginning with adolescent girls



SUPPORT BREASTFEEDING

WHAT? Support optimal breastfeeding practices

HOW? Implement interventions for improved exclusive breastfeeding and complementary feeding practices



COMMUNITY SUPPORT

WHAT? Provide community-based strategies to prevent infection-related causes of stunting

HOW? Strengthen community-based interventions, including improved water, sanitation and hygiene



Short-term

Impaired brain development

Lower IQ



Weakened immune system

149 millions in 2019

Long-term

Lost productivity & healthcare costs

Smaller stature



Premature death

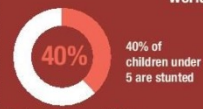
Greater risk of diabetes and cancer

Globally, approximately **162 million children** under the age of 5 years are stunted

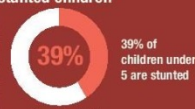


SCOPE OF THE PROBLEM

Sub-Saharan Africa and South Asia are home to **three quarters** of the world's stunted children



Sub-Saharan Africa



South Asia



Environment Special:
The oceans—why 70%
of our planet is in danger

The Facebook Movie:
The secret history of
social networking

TIME

How the first nine months shape the rest of your life

The new science
of fetal origins
BY ANNIE MURPHY PAUL





We Are Building a Future Free of Age-Related Disease

SENS Research Foundation works to develop, promote, and ensure widespread access to therapies that cure and prevent the diseases and disabilities of aging by comprehensively repairing the damage that builds up in our bodies over time. We are redefining the way the world researches and treats age-related ill health, while inspiring the next generation of biomedical scientists.

Support our Mission

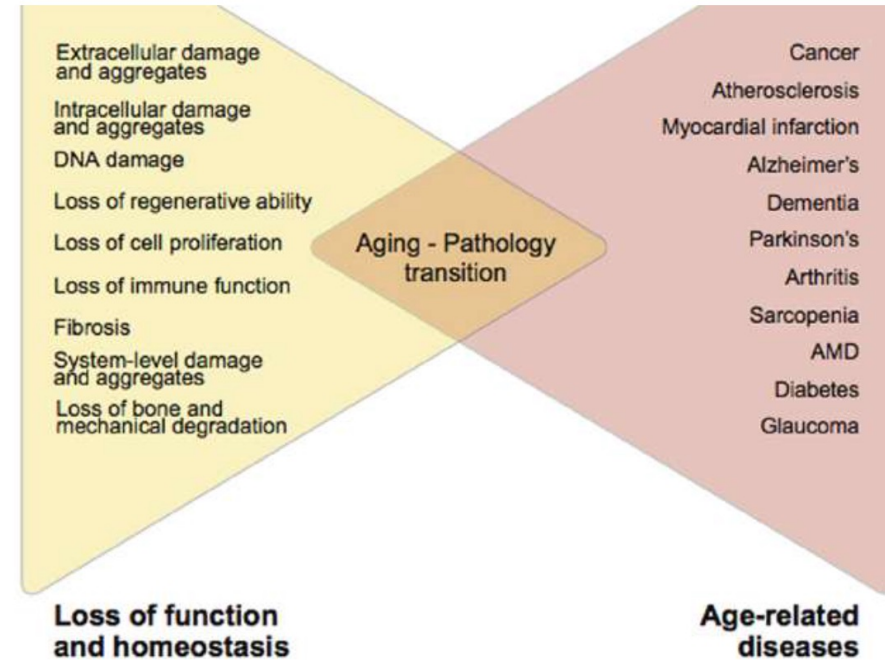
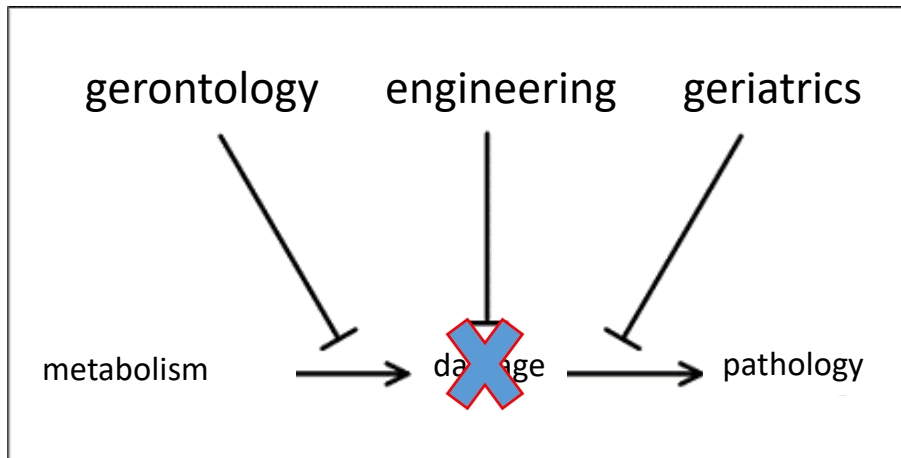
Biogerontology:
the science of understanding
aging and longevity










Aging is a pathology and thus it
can be treated



AI + medicine



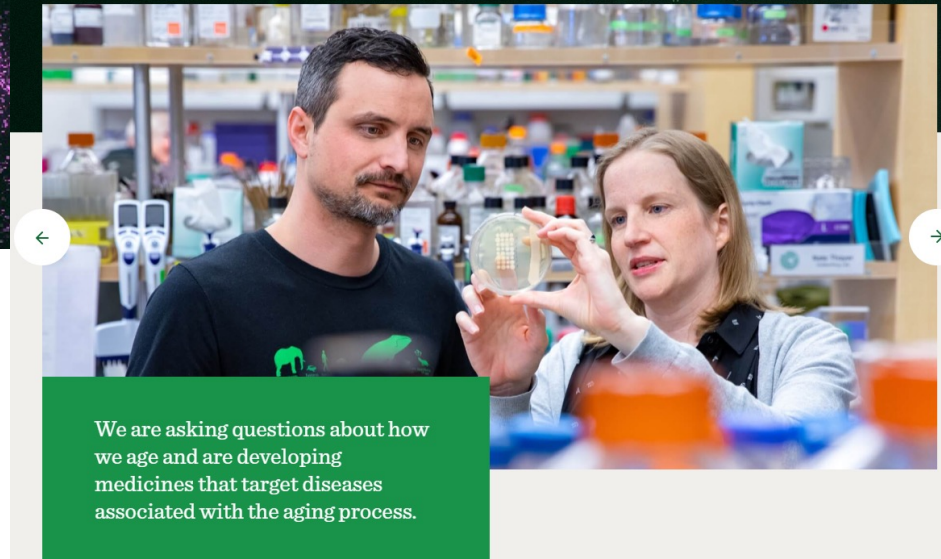
Through groundbreaking research in rejuvenation biotechnology, SENS Research Foundation is catalyzing the development of new medical therapies to comprehensively address the disabilities and diseases of aging, leading to a reimagined aging. Please [help advance and expand](#) our critical scientific research.

Program	Rejuvenation Biotechnology	Aging Damage	Year Discovered
 AmyloSENS	Immunotherapeutic clearance	Extracellular aggregates	1907 ⁸
 ApoptoSENS	Targeted ablation	Death-resistant cells	1965 ⁶
 GlycoSENS	AGE-breaking molecules; tissue engineering	Extracellular matrix stiffening	1958 ⁶ , 1981 ⁷
 LysoSENS	Novel lysosomal hydrolases	Intracellular aggregates	1941 ⁹ , 1842 ¹⁰
 MitoSENS	Allotopic expression of 13 proteins	Mitochondrial mutations	1972 ⁴
 OncoSENS	Removal of telomere-lengthening machinery	Cancerous cells	1959 ² , 1982 ³
 RepleniSENS	Stem cells and tissue engineering	Cell loss, tissue atrophy	1955 ¹



What if we could better understand how we age?

www.calicolabs.com



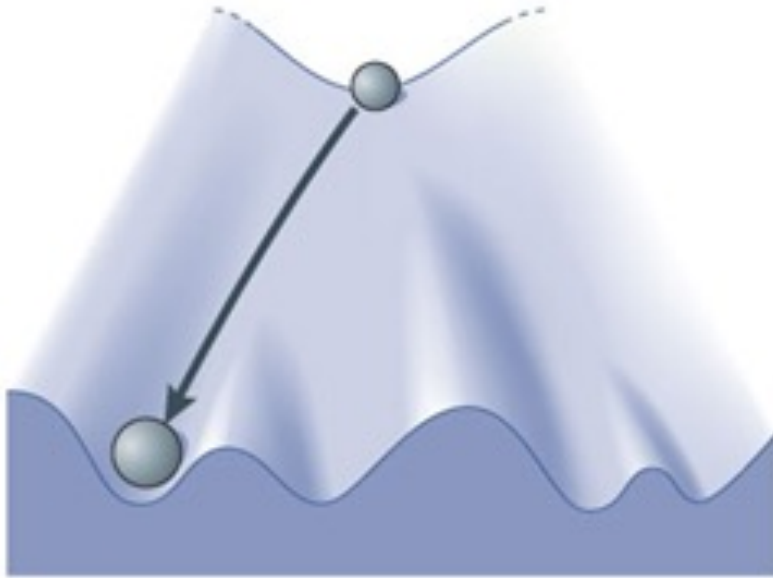
We are asking questions about how we age and are developing medicines that target diseases associated with the aging process.



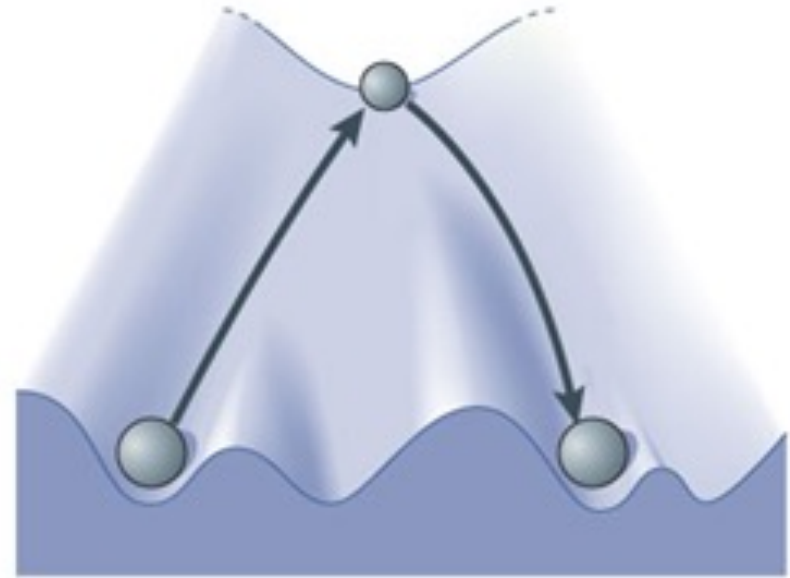
What are
we doing today?

1

ES cell



iPS cell



Nature Reviews | Molecular Cell Biology

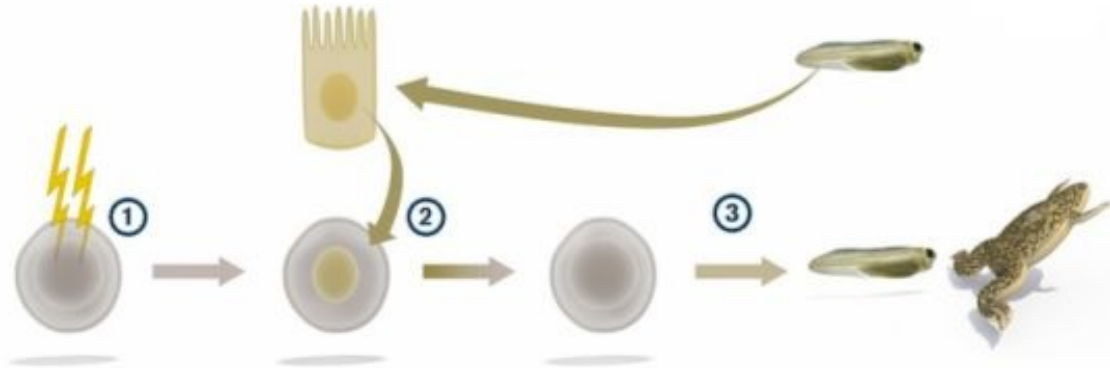
Leveling Waddington: the emergence of direct programming and the loss of cell fate hierarchies (2013)

Julia Ladewig, Philipp Koch and Oliver Brüstle

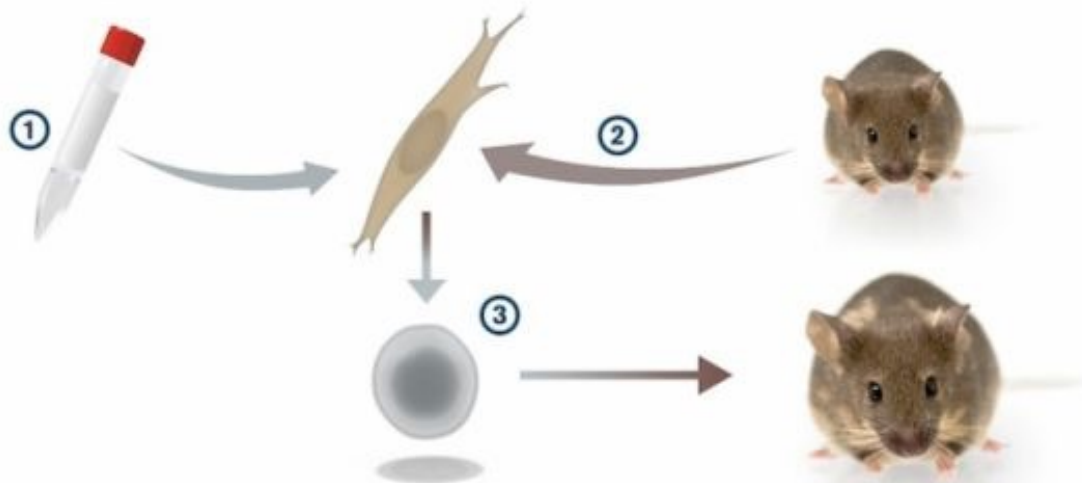
Nobel prize in physiology or medicine 2012



John B. Gurdon

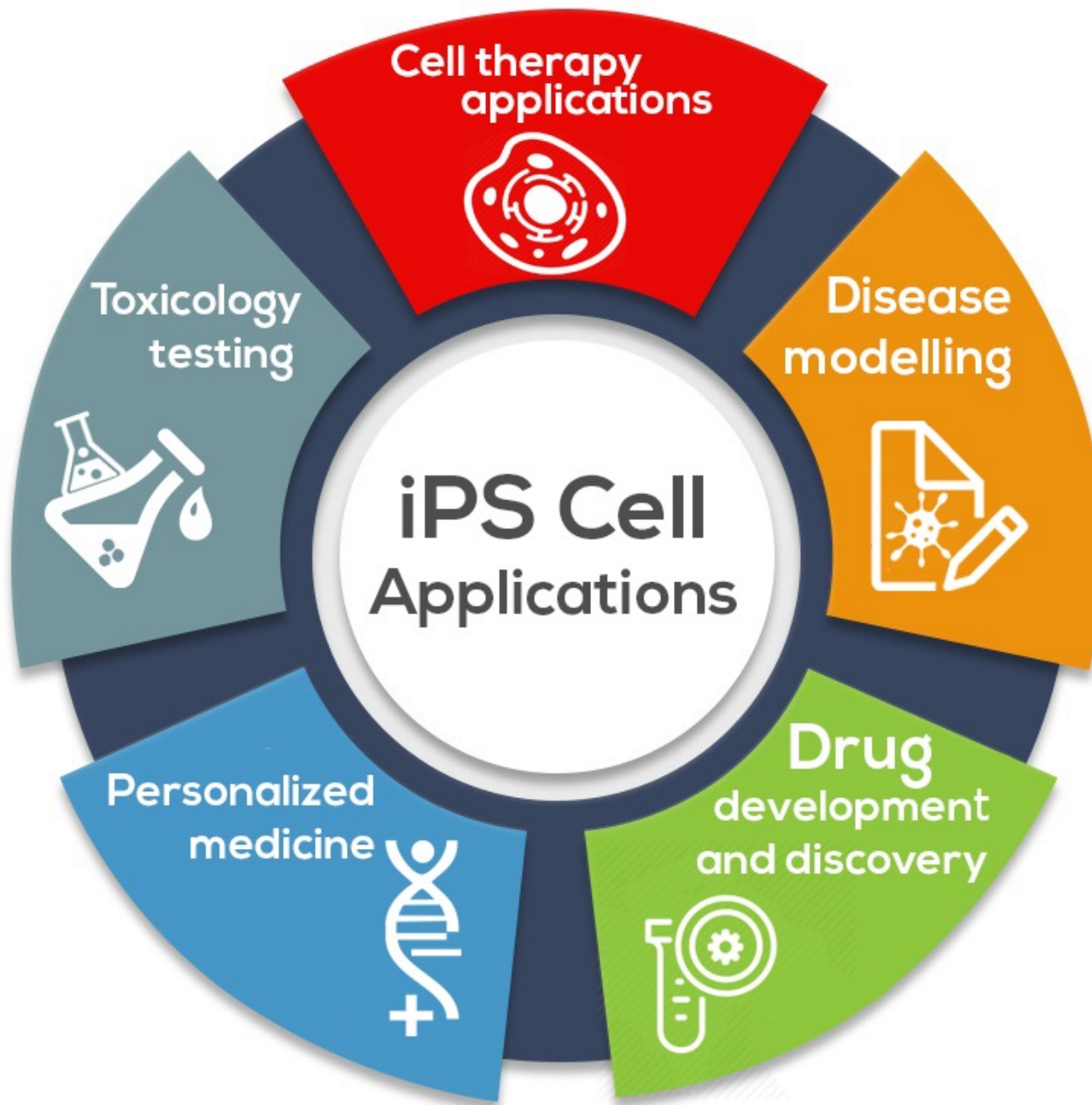


John B. Gurdon eliminated the nucleus of a frog egg cell (1) and replaced it with the nucleus from a specialised cell taken from a tadpole (2). The modified egg developed into a normal tadpole (3). Subsequent nuclear transfer experiments have generated cloned mammals (4).

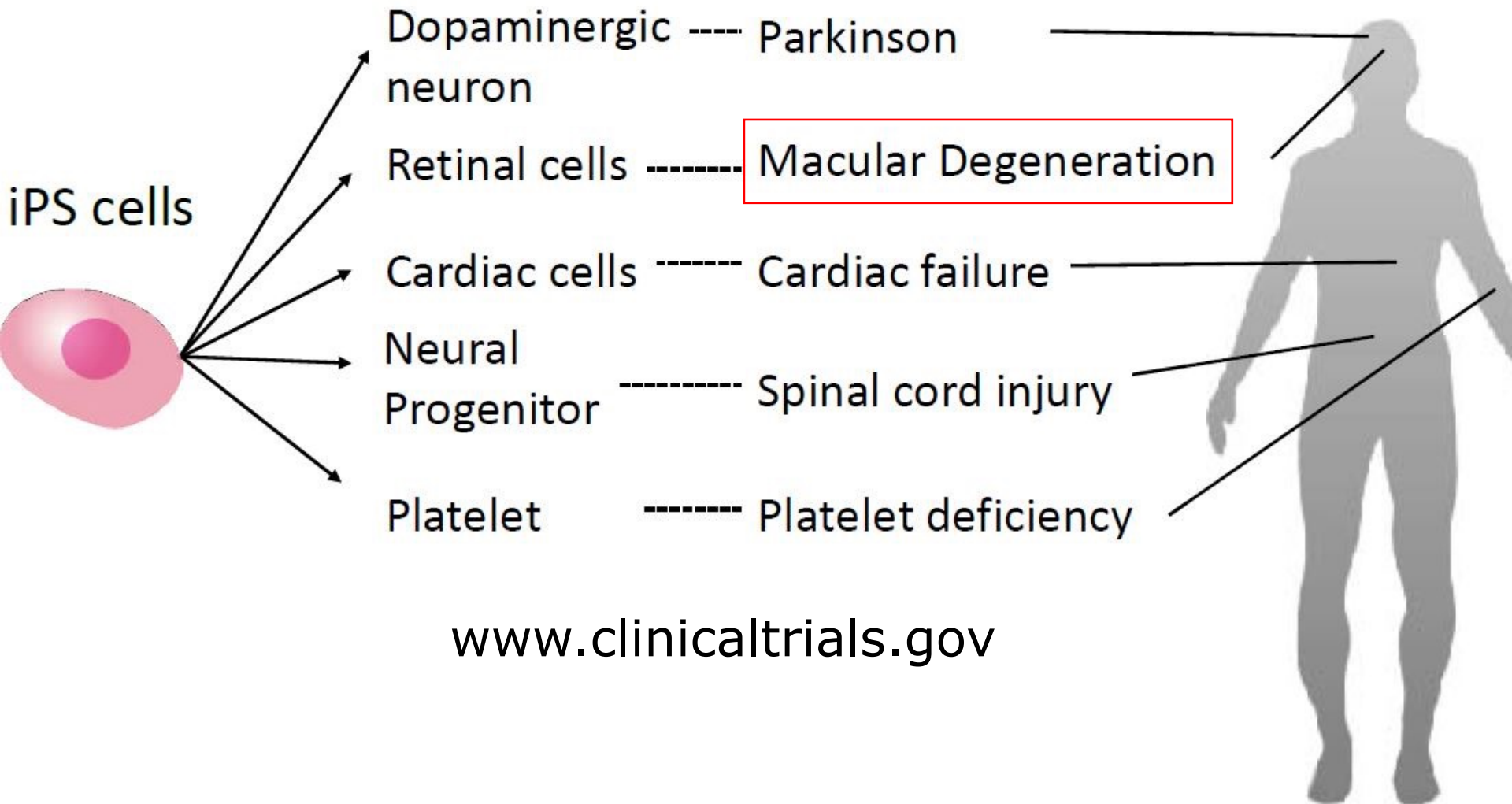


Shinya Yamanaka

Shinya Yamanaka studied genes that are important for stem cell function. When he transferred four such genes (1) into cells taken from the skin (2), they were reprogrammed into pluripotent stem cells (3) that could develop into all cell types of an adult mouse. He named these cells induced pluripotent stem (iPS) cells.



Ongoing preclinical studies in Japan



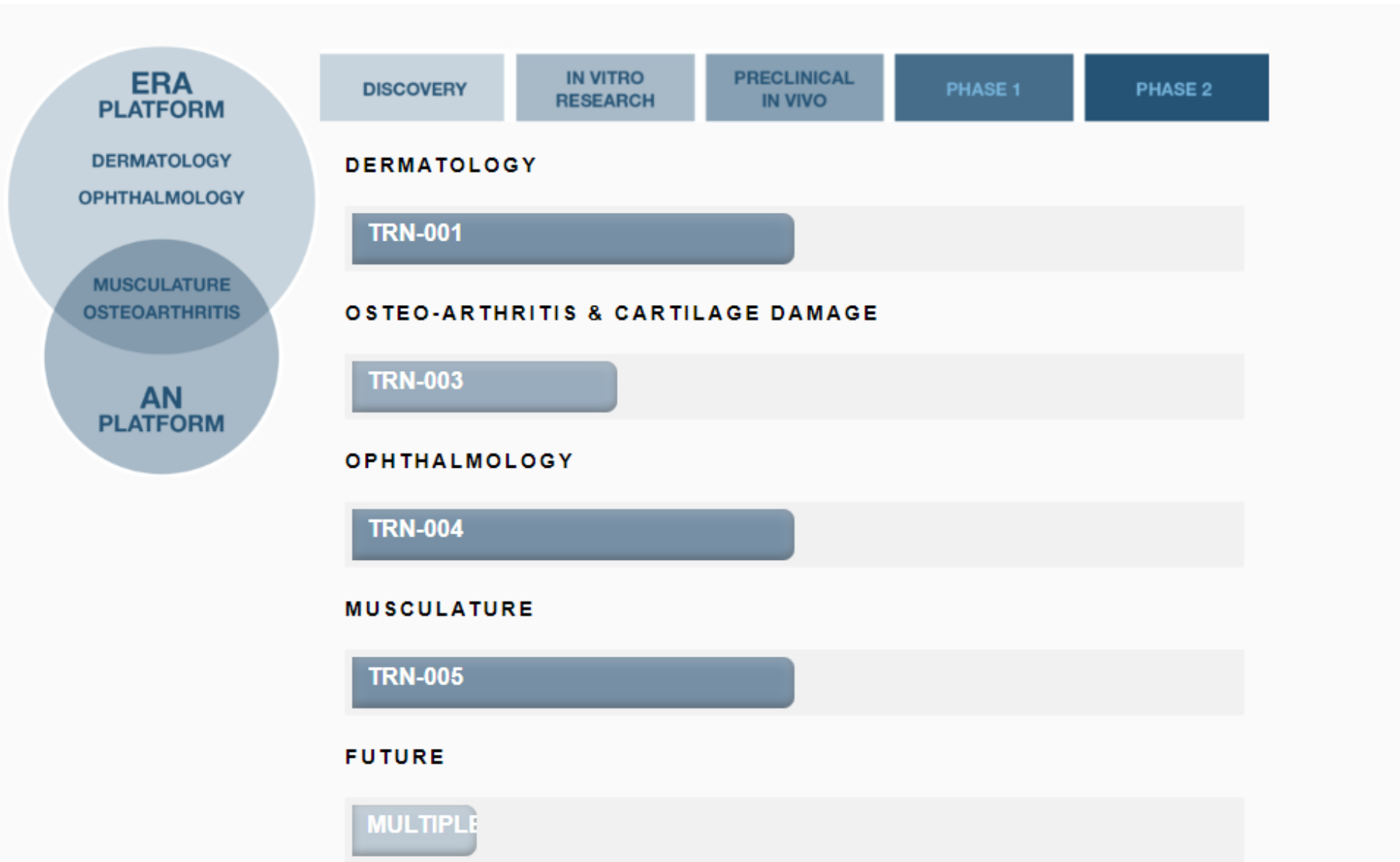
www.clinicaltrials.gov



Turn's proprietary Epigenetic Reprogramming of Age (ERA™) methodology is the latest step in the evolution of cellular reprogramming. It restores specific cells' youthful functionality and their ability to fight age-related disease, while maintaining cellular identity.



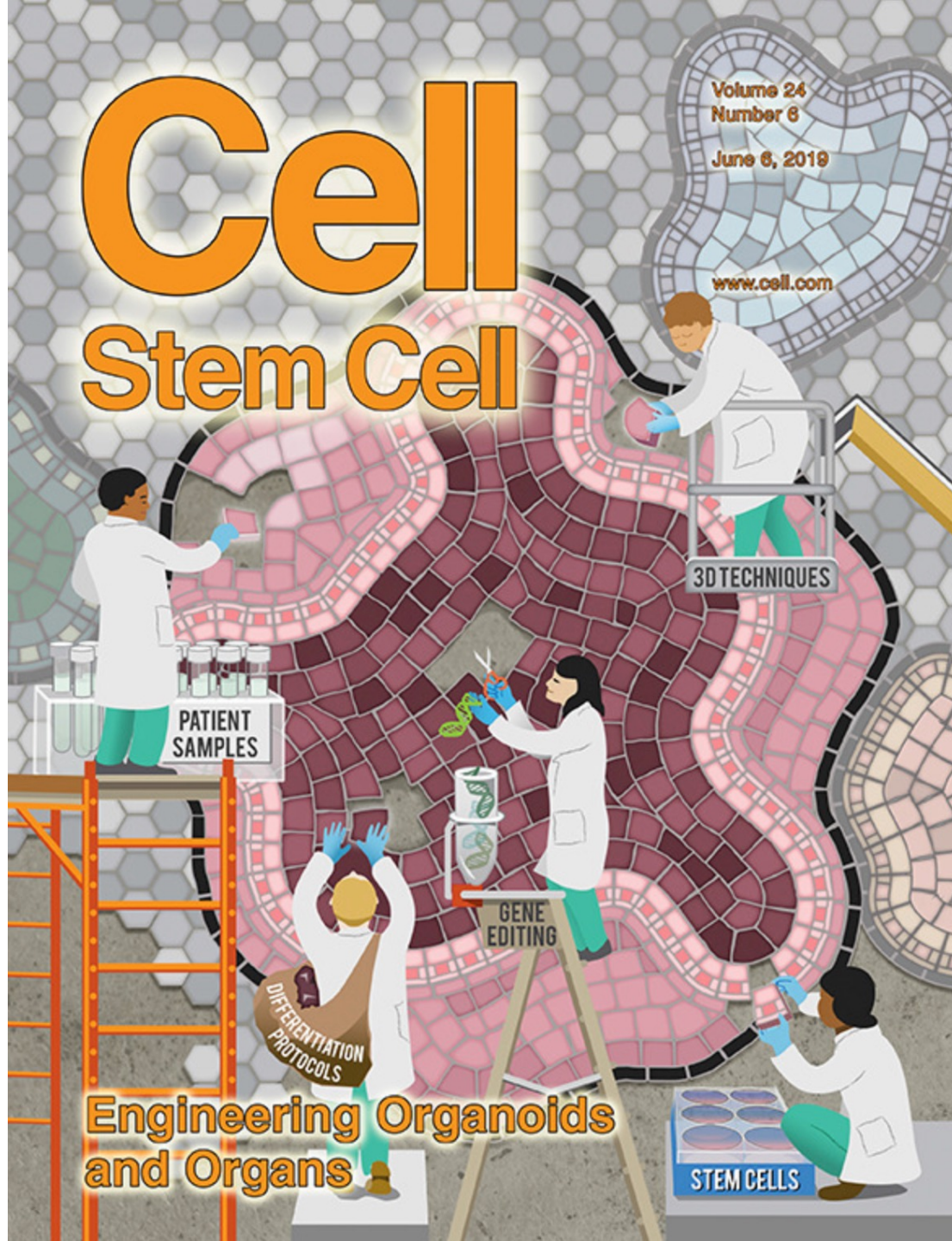
Pipeline



Cell Stem Cell

Volume 24
Number 6
June 6, 2019

www.cell.com

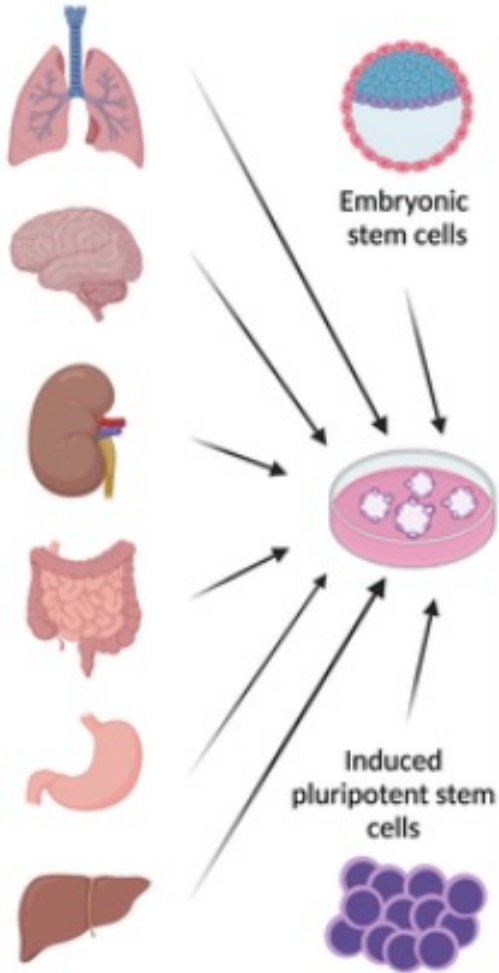


Engineering Organoids and Organs

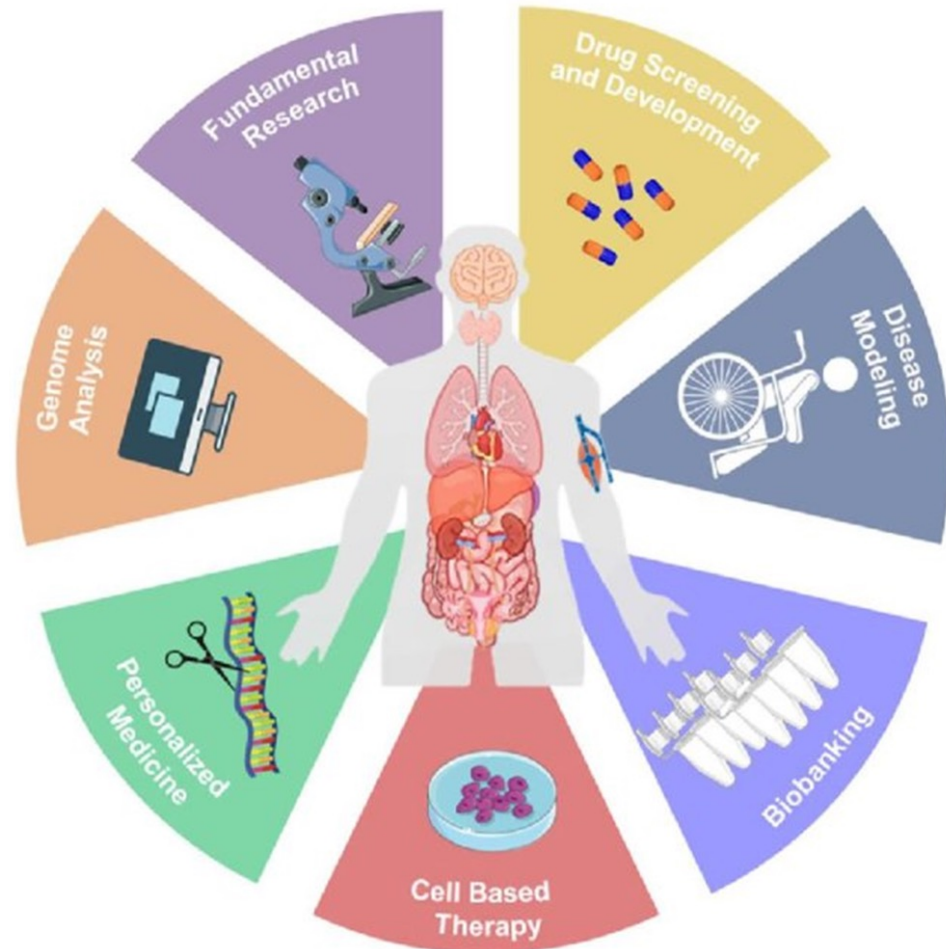
STEM CELLS

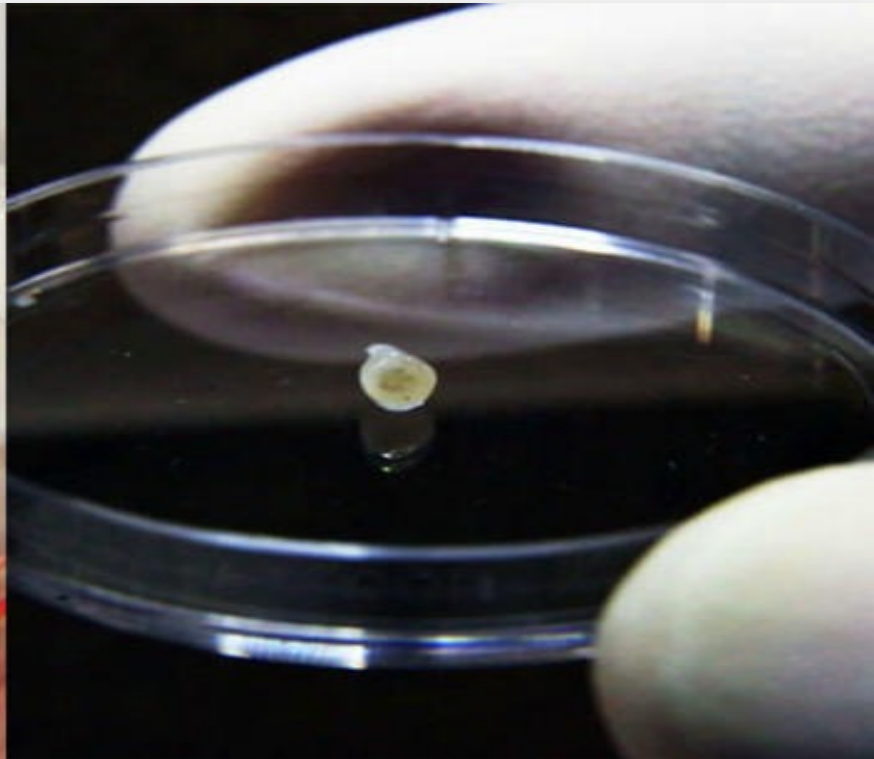
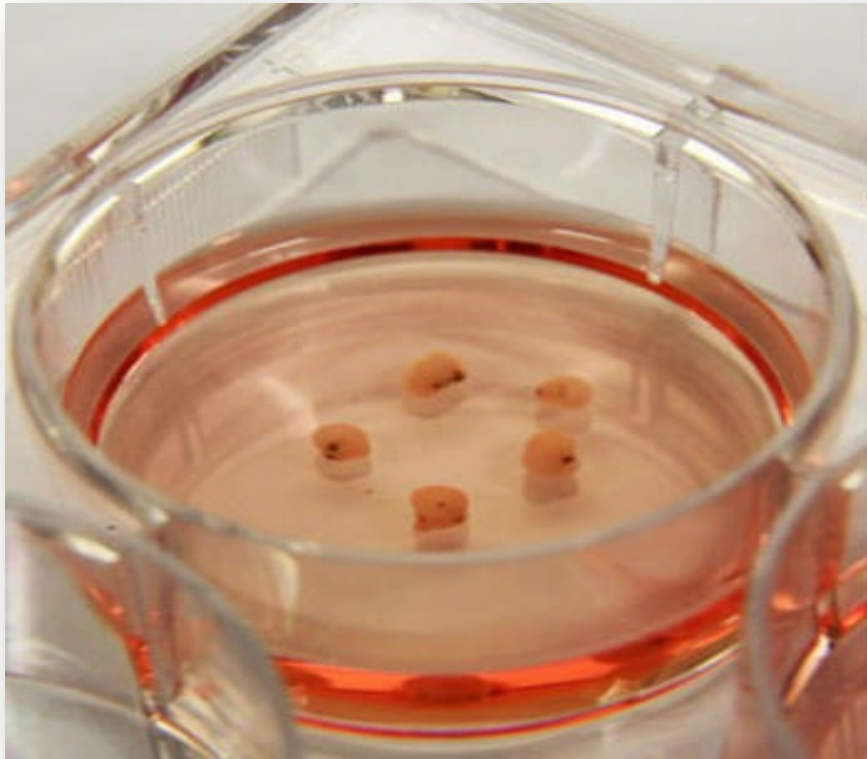
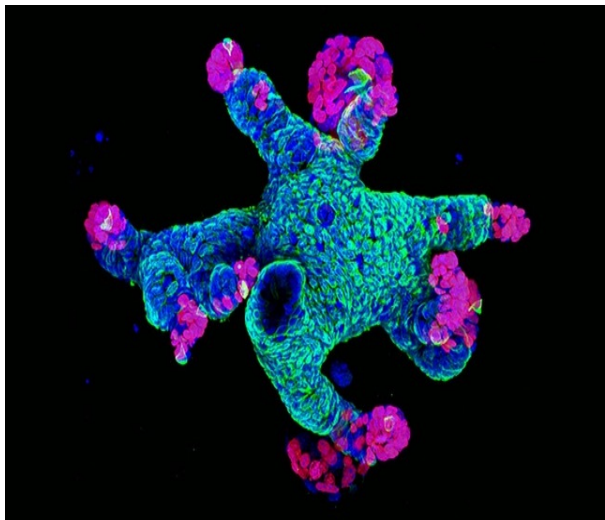
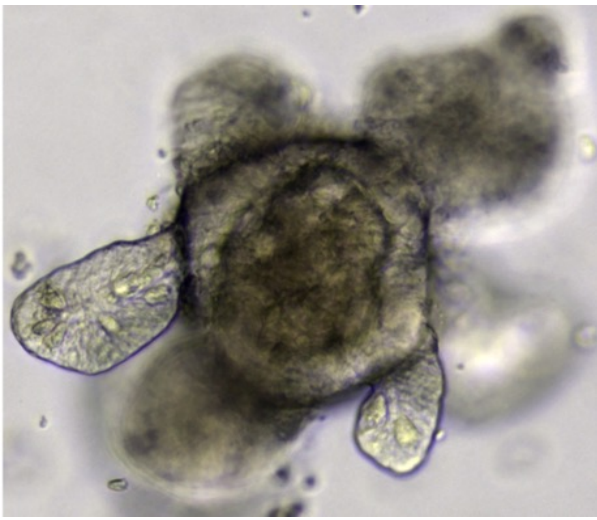
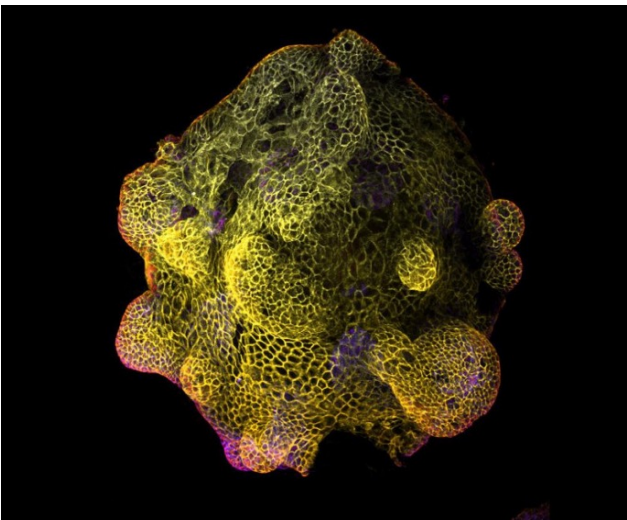
Healthy cells Diseased cells

A. Tissue sources for organoids



B. Organoid cultured *in vitro*





3

- Look deep into nature, and then
you will
understand everything better –



Pavia, covered bridge

Review Article

A biomimetic natural sciences approach to understanding the mechanisms of ageing in burden of lifestyle diseases

Lu Dai¹, Leon Schurgers^{2,3},  Paul G. Shiels⁴ and  Peter Stenvinkel¹

¹Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; ²Department of Biochemistry, Cardiovascular Research School Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands; ³Institute of Experimental Medicine and Systems Biology, RWTH Aachen University, Aachen, Germany; ⁴Institute of Cancer Sciences, Wolfson Wohl Translational Research Centre, University of Glasgow, Bearsden, Glasgow, U.K.

Correspondence: Peter Stenvinkel (peter.stenvinkel@ki.se)



The worldwide landscape of an ageing population and age-related disease brings with it huge socio-economic and public healthcare concerns across nations. Correspondingly, monumental human and financial resources have been invested in biomedical research, with a mission to decode the mechanisms of ageing and how these contribute to age-related disease. Multiple hallmarks of ageing have been identified that are common across taxa, highlighting their fundamental importance. These include dysregulated mitochondrial metabolism and telomeres biology, epigenetic modifications, cell–matrix interactions, proteostasis, dysregulated nutrient sensing, stem cell exhaustion, inflammageing and immuno-senescence. While our understanding of the molecular basis of ageing is improving, it remains a complex and multifactorial process that remains to be fully understood. A key aspect of the shortfall in our understanding of the ageing process lies in translating data from standard animal models to humans. Consequently, we suggest that a ‘biomimetic’ and comparative approach, integrating knowledge from species in the wild, as opposed to inbred genetically homogenous laboratory animals, can provide powerful insights into human ageing processes. Here we discuss some particularities and comparative patterns among several species from the animal kingdom, endowed with longevity or short lifespans and unique metabolic profiles that could be potentially exploited to the understanding of ageing and age-related diseases. Based upon lessons from nature, we also highlight several avenues for renewed focus in the pathophysiology of ageing and age-related disease (i.e. diet-microbiome-health axis, oxidative protein damage, adaptive homeostasis and planetary health). We propose that a biomimetic alliance with collaborative research from different disciplines can improve our understanding of ageing and age-related diseases with long-term sustainable utility.



Arctica islandica

- ❑ longest lived non-colonial metazoan known on earth, with a recorded lifespan of >500 years



Sea urchin

- ❑ marine invertebrates that maintain huge regenerative and reproductive capacity throughout their lifespan (up to 200 years)

- ✓ low **proteasome activity**: it delays the entry of their final life zone
- ✓ adaptive **homoeostasis** in response to acute or chronic stress during their life course



bears



squirrel

❑ 'diseasome of ageing' including chronic kidney disease diabetes, cardiovascular disease, osteoporosis, muscle wasting, arteriosclerosis and organ dysfunction

✓ changes in **white adipose** tissue and skeletal muscle are likely to be responsible for the metabolic shift in these animals

✓ diversity in the **gut microbiota** during hibernation is involved in metabolic changes

✓ despite a long period of **immobilisation**, muscle mass and strength are well maintained during hibernation

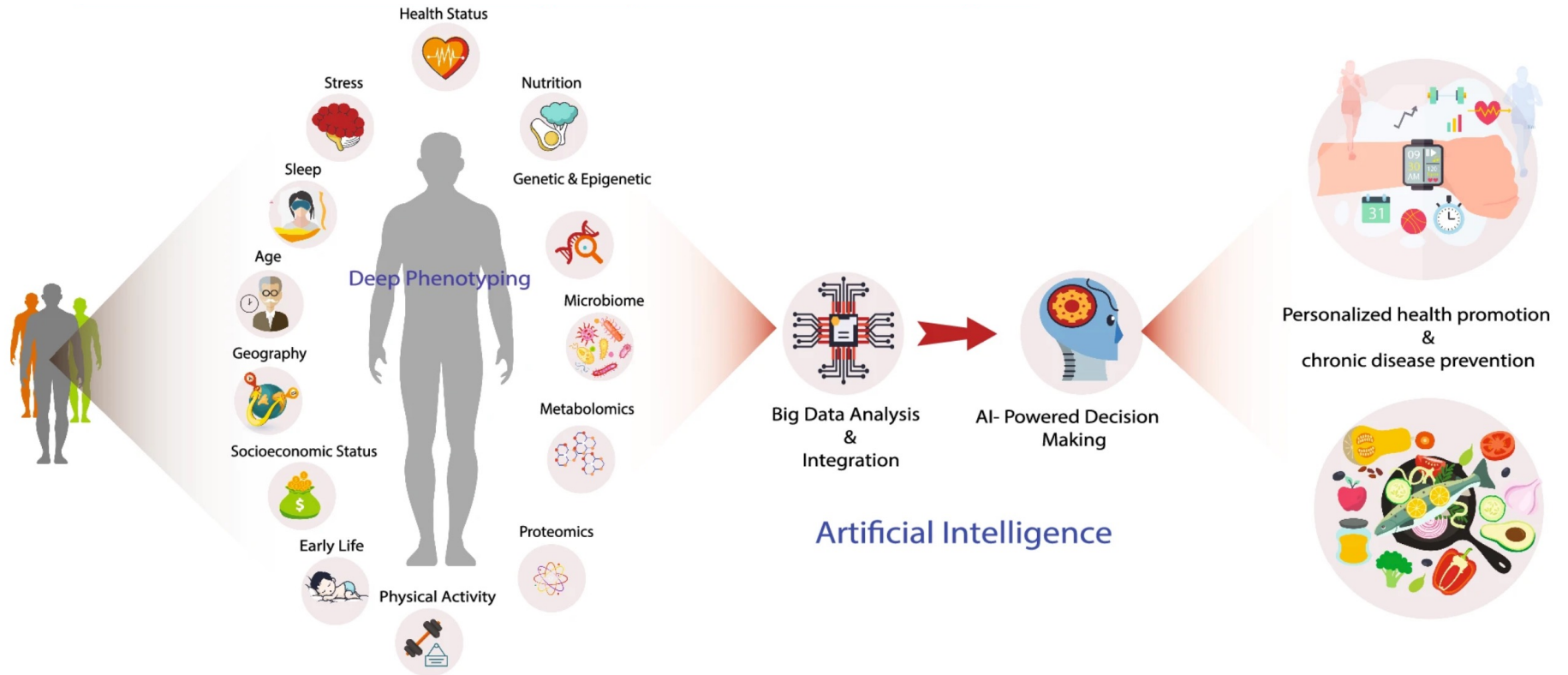
✓ **mitochondrial** biogenesis involved during hibernation

TARDIGRADES



4

Personalized medicine



Subramanian et al. J. Translational Medicine (2020)

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All of Us: Release of Nearly 100,000 Whole Genome Sequences Sets Stage for New Discoveries

Posted on March 29th, 2022 by Joshua Denny, M.D., M.S., and Lawrence Tabak, D.D.S., Ph.D.



Nearly four years ago, NIH opened national enrollment for the [All of Us Research Program](#). This historic program is building a vital research community within the United States of at least 1 million participant partners from all backgrounds. Its unifying goal is to advance precision medicine, an emerging form of health care tailored specifically to the individual, not the average patient as is now often the case. As part of this historic effort, many participants have offered DNA samples for whole genome sequencing, which provides information about almost all of an individual's genetic makeup.

Recent Items

- All of Us: Release of Nearly 100,000 Whole Genome Sequences Sets Stage for New Discoveries March 29, 2022
- Unraveling the Role of the Skin Microbiome in Health and Disease March 22, 2022
- Finding the 'Tipping Point' to Permanent Kidney Damage March 15, 2022
- Biology of Aging Study Shows Why Curbing Calories Counts March 8, 2022
- How COVID-19 Immunity Holds Up Over Time March 1, 2022

Blog Archives

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NATIONAL INSTITUTES OF HEALTH (NIH, USA)



NIH National Institutes of Health
Office of Research on Women's Health

Cardiovascular Risk



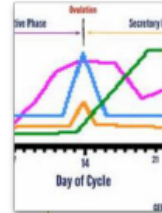
Risks differ between women and men



In women, aspirin reduces risk of ischemic stroke
In men, low-dose aspirin reduces risk of heart attack



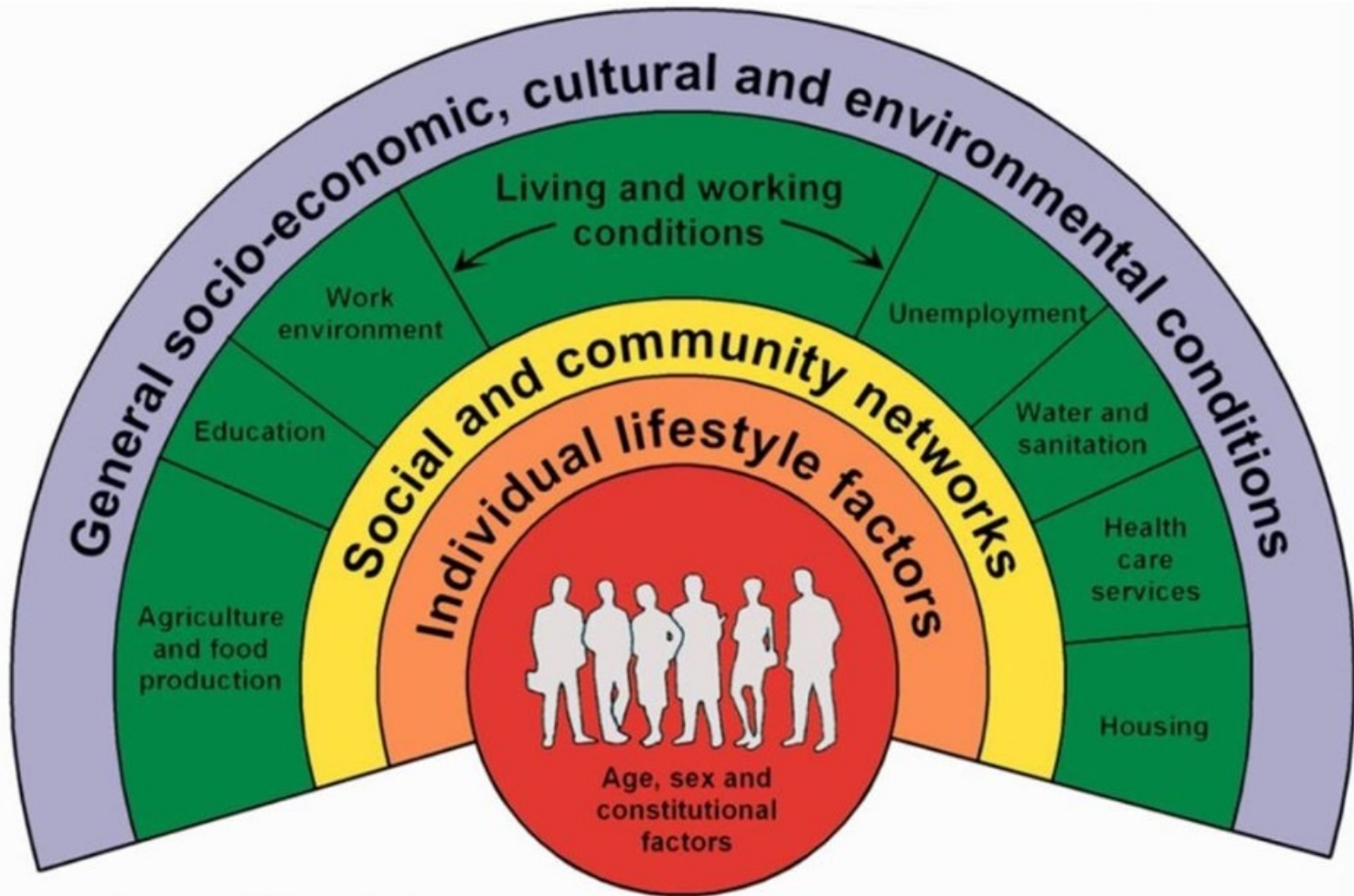
In women, cholesterol plaque spreads evenly throughout the artery wall



Cholesterol levels vary over the course of a menstrual cycle

This means that artery blockages can be more difficult to diagnose in women, who may not have outright symptoms but are still at high risk for heart attack





Source: Dahlgren and Whitehead, 1991

not impossible

Home Blog Not Impossible Awards Music: Not Impossible
Build: Not Impossible Project: C.O.D.I. Hunger: Not Impossible

Technology for the Sake of Humanity

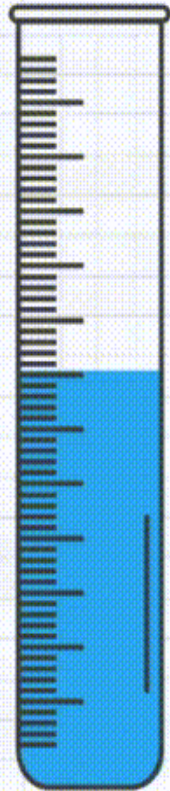
LEARN MORE ABOUT LABS

<http://www.notimpossible.com/>

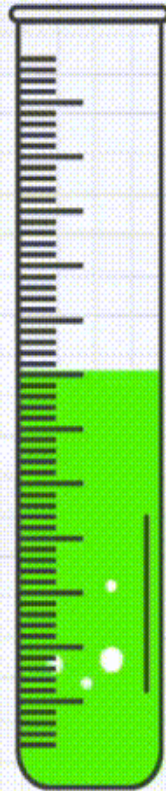


98years old yoga teacher

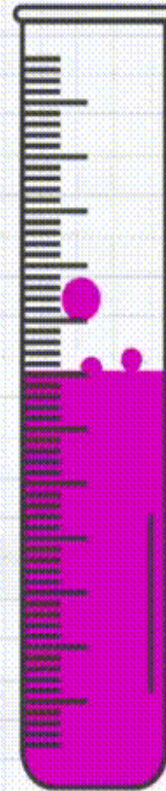
Aging and the manifestations of age-associated disorders can be delayed by regular exercise, caloric restriction AND.....



DOPAMINE



SEROTONIN



OXYTOCIN