How to be a healthy centenarian?

Mayana Zatz
Human Genome and Stem-cell center
University of São Paulo, São Paulo, Brazil

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Human characteristics

Interaction
Genes/ environment

Only
Environment

Only
Genetics

Healthy aging ?

80% Environment
20% Genetics

How to be young at 100 years-old and beyond?

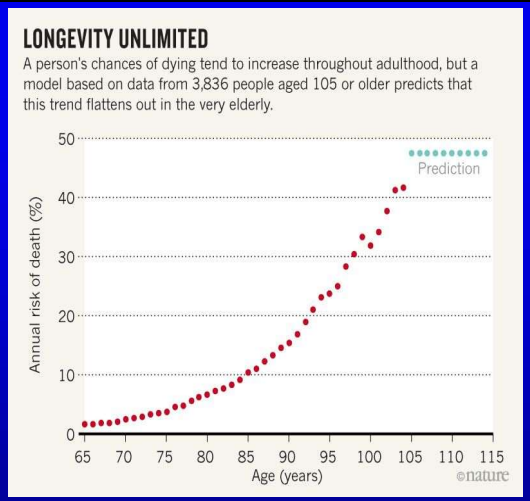
Eugenia- 103

Protective genes ?

Is there a limit for longevity?

According to a recent study

Italian Emma Morano who died at age 117



The risk of death would levels off after age 105, creating a 'mortality plateau'. At that point, the odds of someone dying from one birthday to the next are roughly 50:50

The secret is to endure until 105……

Barbi E, et al. Science. 2018

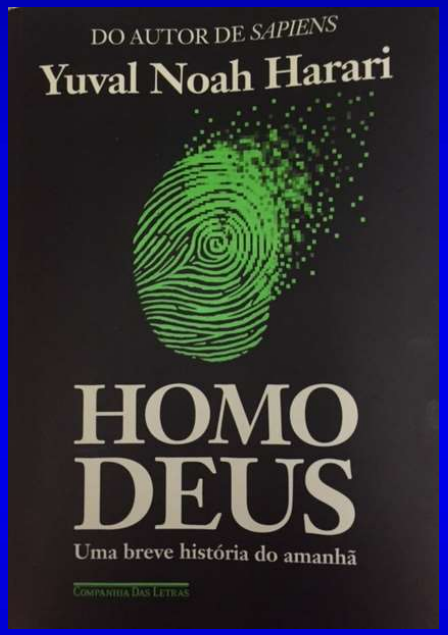
Transhumanism : NBIC

Dr. Laurent Alexandre

Transhumanism believes in the continuation and acceleration of the evolution of intelligent life beyond its currently human form
Max More (1990)

Nanotecnology
Biology
Informatics
Cognitive science

According to Yuval Harari



Death is just a technical problem

How can we control environment?

Physical activity

Diet

Red wine

Caloric restriction

Physical exercise: Why is it beneficial?

It improves autophagy

In animal models, autophagy protects against cancer, neurodegenerative disorders, infections, inflammatory diseases, ageing and insulin resistance

Yoshinori Ohsumi
Nobel, 2016

Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. He C et al. Nature. 2012

Mediterranan diet: More recent studies

A higher intake of vegetables, nuts, and whole grains were associated with a significantly decreased hazard of mortality. Zaslavsky et al., J Nutr Gerontol Geriatr. 2018

MeDi was associated with a 41% reduced risk of incident advanced age related macular degeneration. Merle BM et al., Ophthalmology. 2018

Resveratrol

Present in grapes and red wine

Resveratrol and Alzheimer disease

Resveratrol (Res), acts on Alzheimer disease (AD) in numerous *in vivo* and *in vitro* models.

Res decreases the cleavage of the amyloid precursor protein (APP), enhances clearance of amyloid beta-peptides, and reduces Aβ aggregation.

Res also protects neuronal functions through its antioxidant properties.

Jia et al.,Resveratrol and Amyloid-Beta: Mechanistic Insights Nutrients. 2017.

Alicia Kowaltowski

Caloric restriction?

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What is the fun to live long if you cannot eat?

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In short, better to drink red wine and exercise than starving.....

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What will be the genetics contribution?

What can we expect in the future?

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The future: Medicine P4

Predictive

Preventive

Personalized

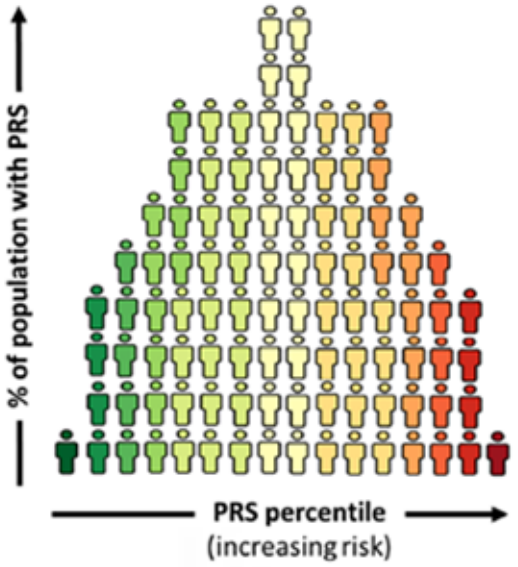
Participative

PREDICTIVE

Polygenic scores: future disease susceptibility

PRS percentile	Risk of disease vs. reference group
0-1	Lowest
1-5	
5-10	
10-20	
20-40	
40-60 (reference)	1
60-80	
80-90	
90-95	
95-99	
99-100	Highest

Source: RGA



Increased risk for diabetes? Heart condition? Hipertension? Cancer?

PREVENTIVE

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PERSONALIZED (PRECISION) MEDICINE

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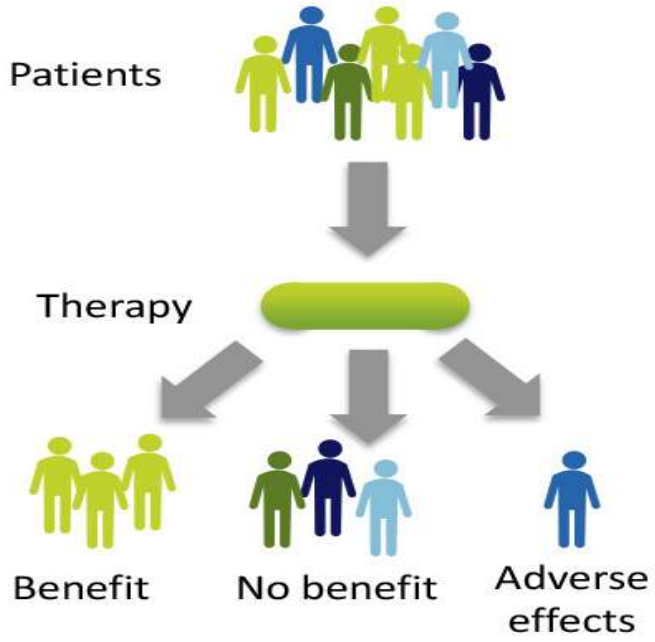
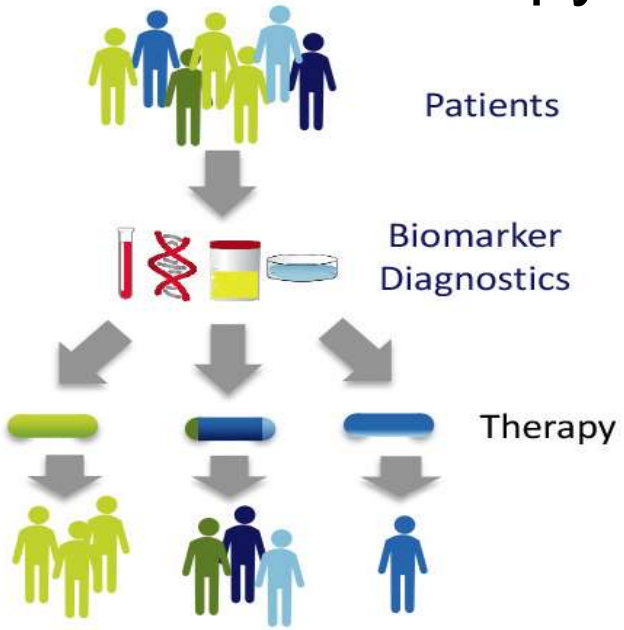
Non Personalized Medicine

One size fits all



Personalized Medicine

Tailor made therapy



No adverse effects

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PARTICIPATIVE

What are we investigating?

Organs' "repair"

Xenotransplantation

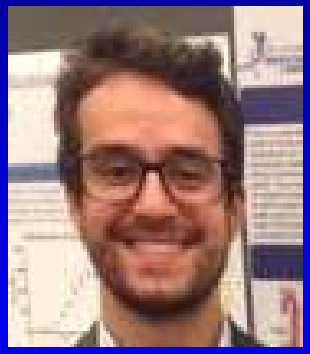
The search for protective genes

Neurons from healthy 90+ and 100+

The organs approach

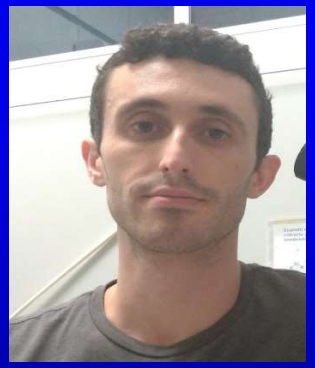
Silvano Raia

Luiz Caires



Ernesto Goulart

Maria Rita Passos-Bueno

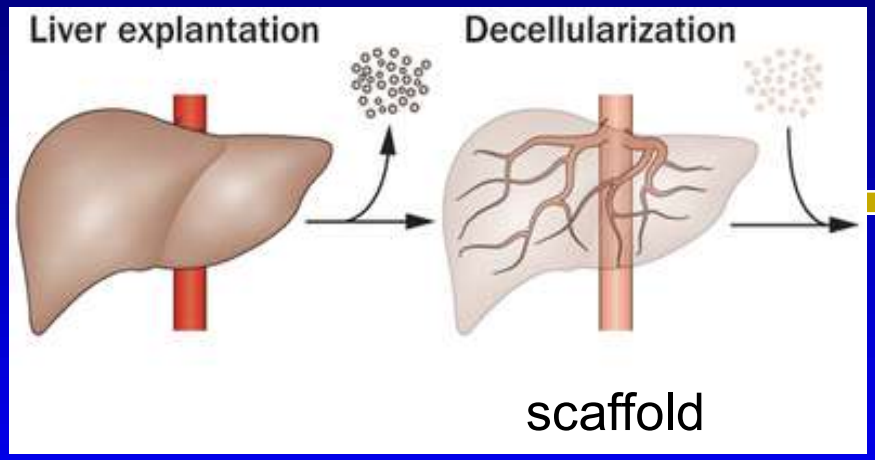


Luciano Brito

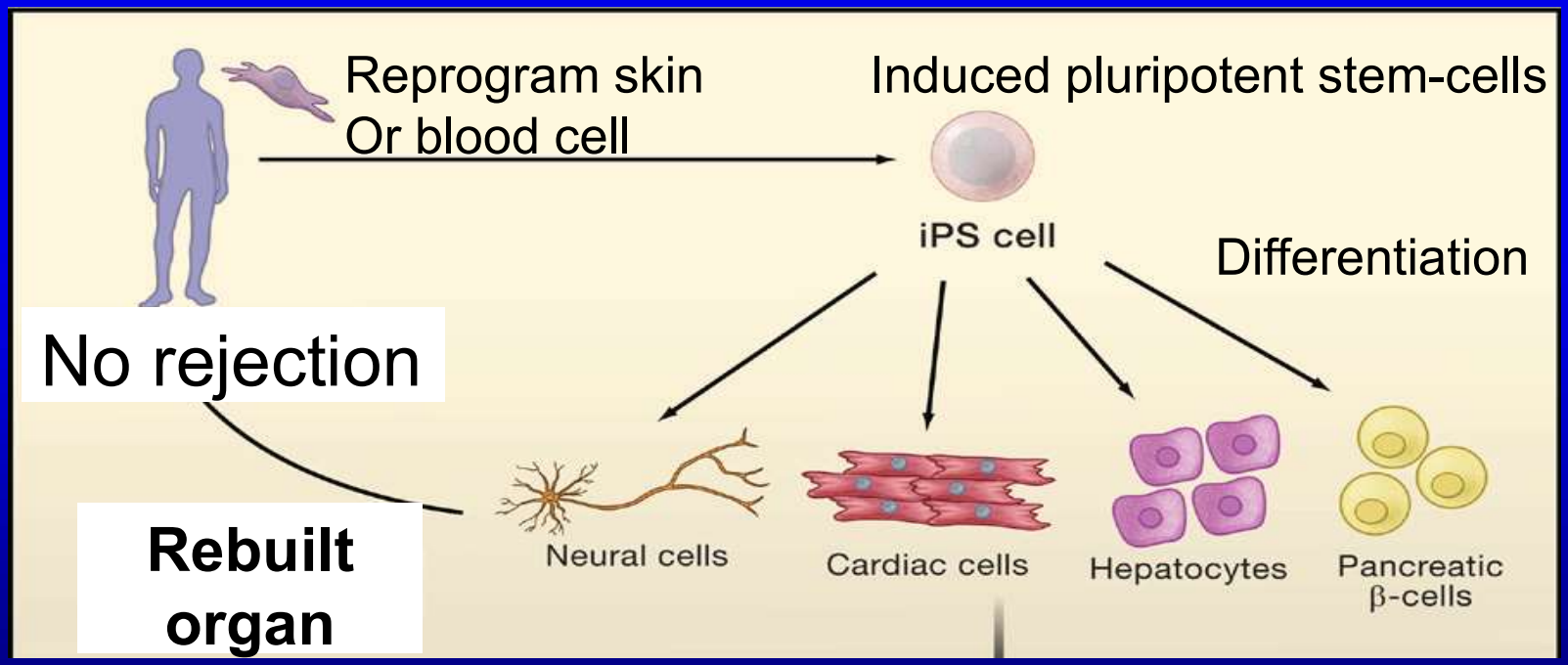
Jorge Kalil

Kayque Silva

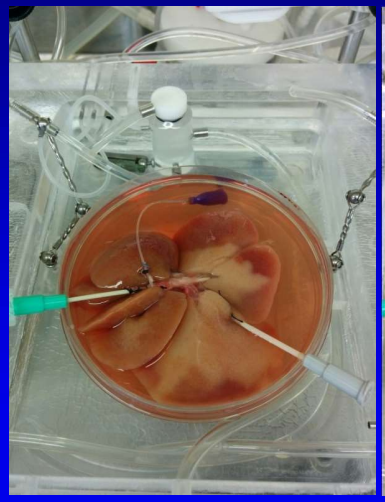
Organs reconstruction



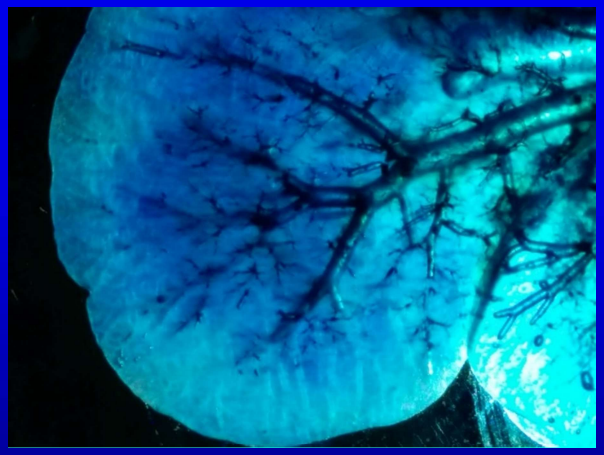
Recellularization with patient' derived IPS liver cells



Decellurization: rat liver



Recellularization: Human IPS derived cells



Scaffold
3D printer

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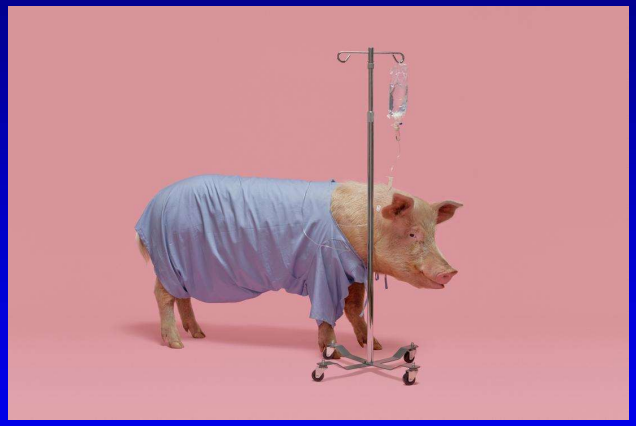
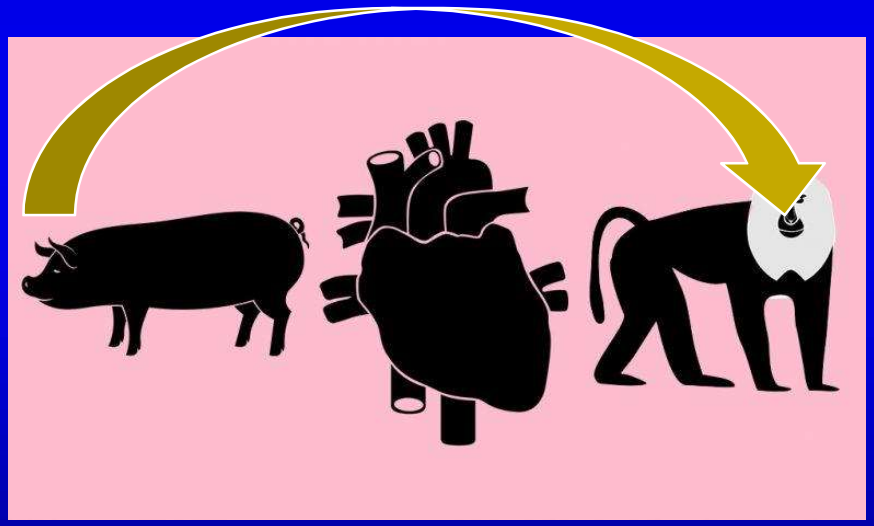
Xenotransplantation with pigs' organs



Pigs' genes wil be edited to avoid organs rejection when transplanted in humans



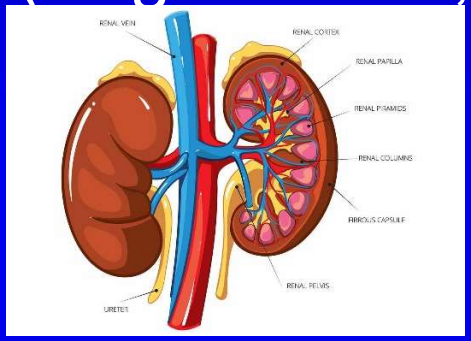
Pigs' heart transplantation successful in baboons

Längin M et al. Consistent success in life-supporting porcine cardiac **xenotransplantation**. Nature. 2018

Project: Partnership EMS/FAPESP

Brazil has 32.716 patients in the waiting list for : kidney, liver, heart, lung, pancreas and cornea. (August 2018, ABTO)

21.962 ☞ for kidney



130.000 individuals undergo hemodialysis

We will start with kidneys

The search for protective genes/variants

Asymptomatic patients carrying pathogenic mutations

Lessons from centenarians

Today there are ~ 500.000 centenarians around the world)

What are their secrets?

Diet?

Protective genes?

Life style?

Extraordinarily low levels of adrenomedullin, a hormone that widens blood vessels.

Helping the optimal development of capillary circulation.

Could this also explain the benefits of exercise?

Could adrenomedullin be a biomarker of longevity?

Study of 477 centenarians

Nir Barzilai

101, 103, 109, 110

"60% of men and 30% of women smoked during a long period of their lives. Almost 50% were overweigth and less than 50% did physical exercise.

Protective genetic variants ?

Kahn brothers had a variant associated to higher levels of LDL (good colesterol)

Protected against Alzheimer disease?

Rajpathak & Crandall, 2011

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Some “candidate” variants/polymorphisms

CETP(Cholesteryl ester transfer protein) is involved in the regulation of high density lipoprotein (HDL) and may affect susceptibility to age-related diseases: atherosclerosis and AD

Apolipoprotein C-III is a component of very low density lipoprotein (VLDL)

Adiponectin has a protective role against the development of obesity, type 2 diabetes and cardiovascular disease

MTP (microsomal triglyceride transfer protein):metabolism of lipoproteins and fat transportation

What was oberved in 900 centenarians in Okinawa?

Evidence of rare HLA variants

HLA, DR, and DQ Phenotype Distribution of Okinawan Centenarians

HLA Antigen	Control (n=159)		Centenarian (n=82)		p value
	n	frequency (%)	n	frequency (%)	
DR1	0	0	5	6.1	0.0042
DRw9	49	30.8	7	8.5	0.00004
DRw10	0	0	4	4.9	0.01276
DQw3	135	84.9	56	68.3	0.00258

From H. Takata et al. Lancet 1987;2:824-6.

Decreased risk of inflamatory and autoimmune diseases

The genomes of super centenarians

Both lived more than 114 years

Genes for common diseases: Alzheimer, cancer, cardiac diseases etc.. Comparable to common genomes

Sebastiani et al. (2012). Frontiers in Genetics..

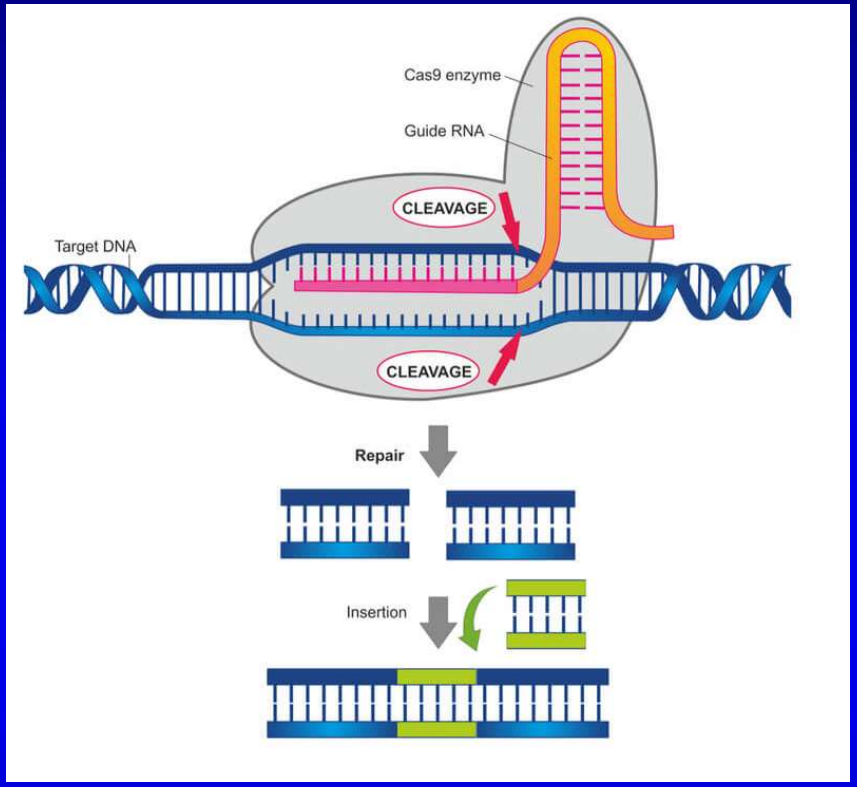
Protective variants

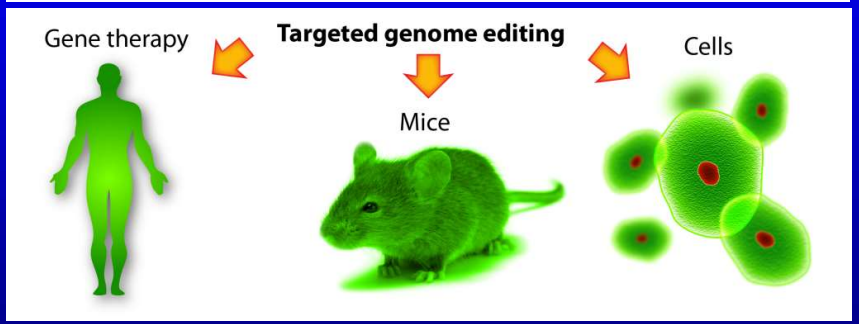
What is their function?

How to use this information to protect everyone?

What other approach could we plan in the future?

CRISPR-Cas9 technology





Correct/edit defective genes or responsible for rapid aging

Transform common genes into “protective”genes

Our 80 plus project

In 2008 we started
A collection of healthy octagenarians

Search for “protective”genes and mechanisms responsible for healthy aging

Serve as a databank of the Brazilian population to interpret next generation sequencing

The advantages of our population

Racial admixture

Project SABE
(Saude, Bem estar e envelhecimento)
Health, well-being and aging

Maria Lucia Lebrão and Yeda Duarte
Saude Publica-USP

Follow-up of a cohort of people from S. Paulo population
older than 60 since 2000

Michel Naslavsky
HUG-CELL/IB-USP

Dr. Maria Lucia Lebrão

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Survey
(150 pages)

Genomics

Blood analyses

Healthy volunteers

Dr. Yeda Duarte
USP

Guilherme Yamamoto, MD
HUG-CELL/IB-USP

Dr. Edson Amaro
USP/HIAE

Brain MRI

Biometry & Functional tests

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What was achieved until now?
From 80plus ☞ AbraOM

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Online Archive of Brazilian mutations

Michel Naslavsky

Guilherme Yamamoto

609 Whole exome sequencing (WES)

200.000 variants not reported in other databanks

Naslavsky et al., Human mutation, 2017

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Whole genome sequencing

1324 individuals

Partnership with Human Longevity Institute (HLI)

More than 7 million variants never reported before

Data is under investigation and opened for collaborations

Ten had pathogenic mutations for 6 cancer genes:

Breast cancer: *BRCA1, BRCA2*

Lynch syndrome *MLH1, MSH2, MSH6* and *PMS2*

Eigth were recontacted

2 reported cancer: (*MSH6* ~ Digestive tract + *BRCA2* ~ Lung)

6 reported no history of cancer

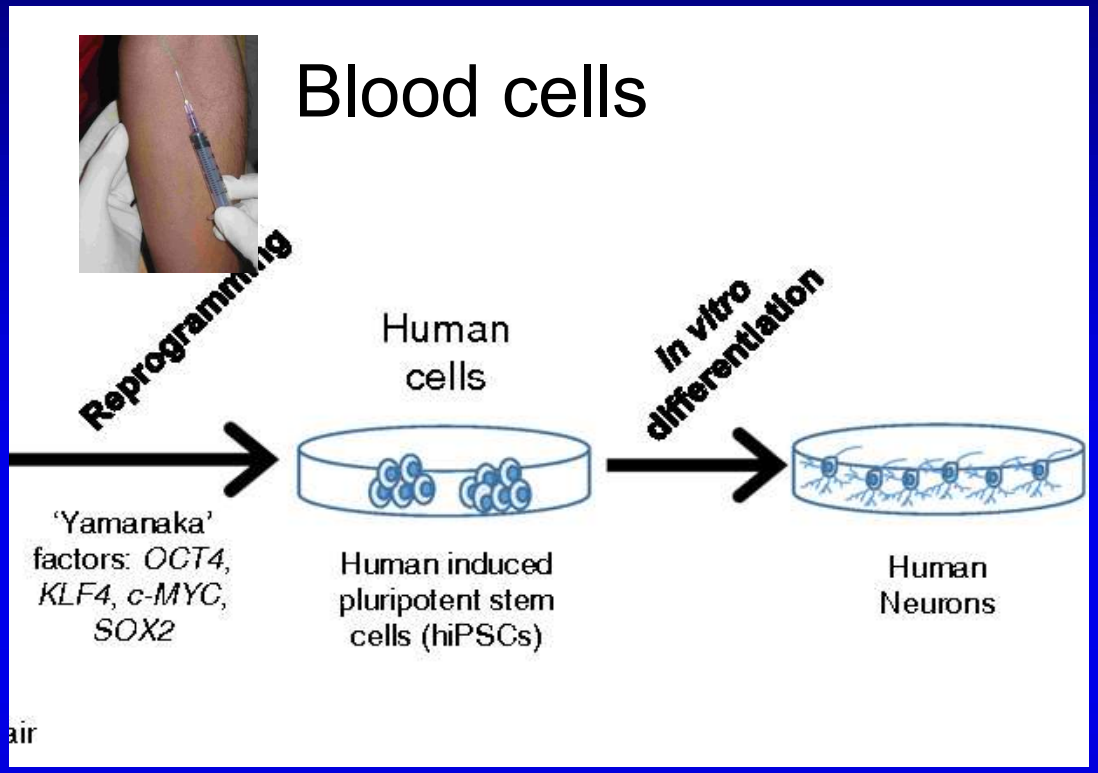
One 93 years old lady had a pathogenic BRCA1 mutation. She had not manifested cancer nor her offspring

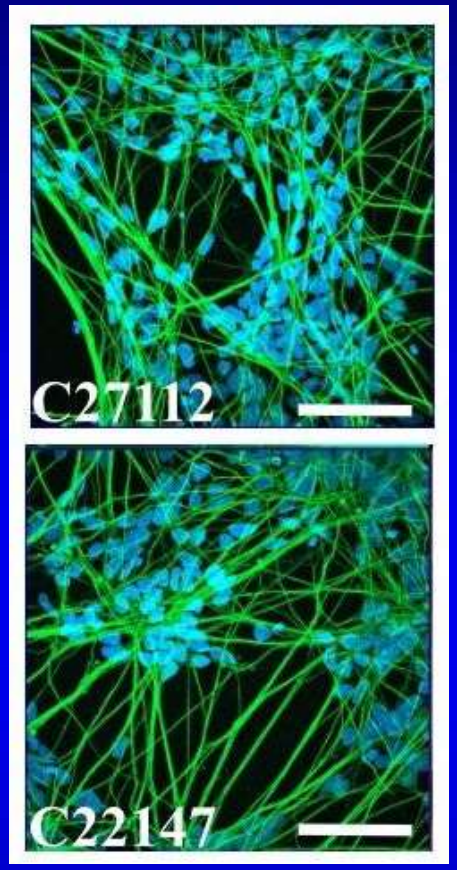
Genetic background? Protective variants? Life style?

What can we learn from IPS-derived neurons In healthy nonagenarians/ centenarians

And

Asymptomatic carriers of mutations of neurodegenerative disorders?





Mitochondria functioning? Biogenesis ?

What are their life style secrets?

Rita Levi-Montalcini
103
Medicine Nobel Prize

Passion for sciences

Alice Herz-Sommer
107
Pianist Holocaust survivor

Passion for music
Love for people
Optimism

And our Brazilian centenarians ?

Optimism, “joie de vivre”
Sense of humor

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While we are trying to learn how to live longer and better

What are the recommendations ?

Healthy food

And passion.....of course

THANK YOU SO MUCH

Centro de Pesquisa sobre o Genoma Humano e Células-Tronco

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inct institutos nacionais de ciência e tecnologia

CNPq