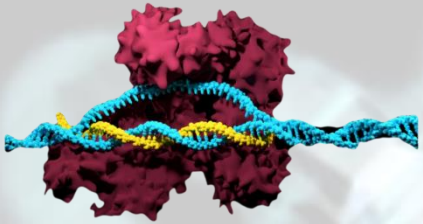
19th June 2018

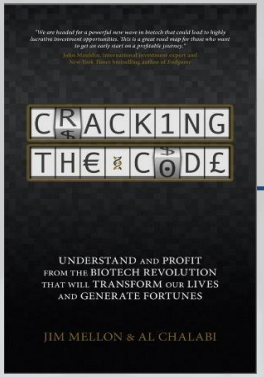
Mortality and Longevity Seminar 2018

Institute and Faculty of Actuaries

“All men are cre**m**ated equal.”

-Spike Milligan



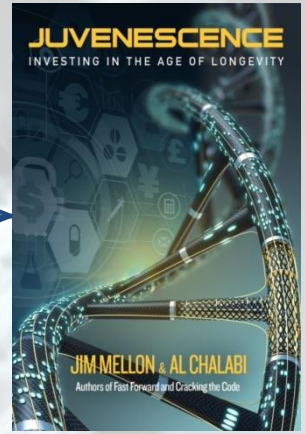


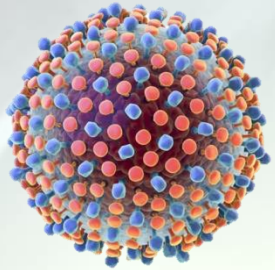
Artificial Intelligence

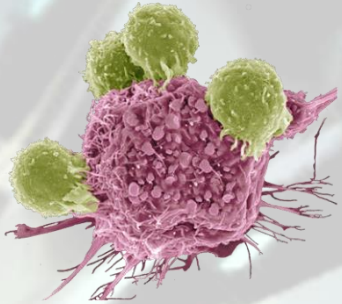
HCV Cure

CRISPR

Cancer Immunotherapy








“Quietly, over the past few decades, remarkable discoveries have been made about the biology of ageing.”
-Cynthia Kenyon, Calico LLC


PORTO
VALDOURO
RUBY
PORT

The following article was published in one of Britain's largest newspapers called *The Telegraph* on November 29, 2015:

November 29, 2015

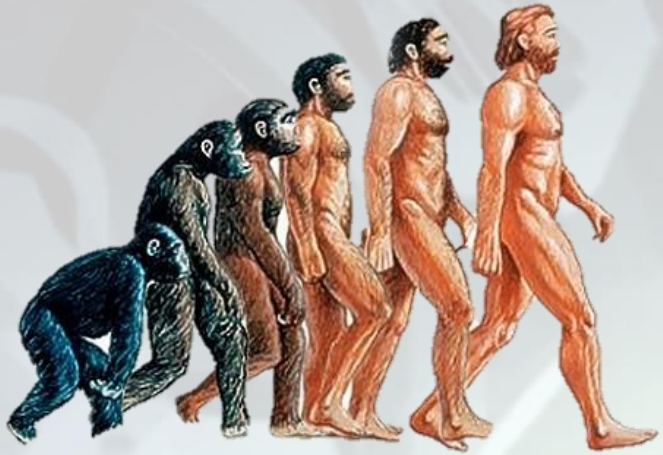
The Telegraph

World's First Anti-Ageing Drug Could See Humans Live to 120

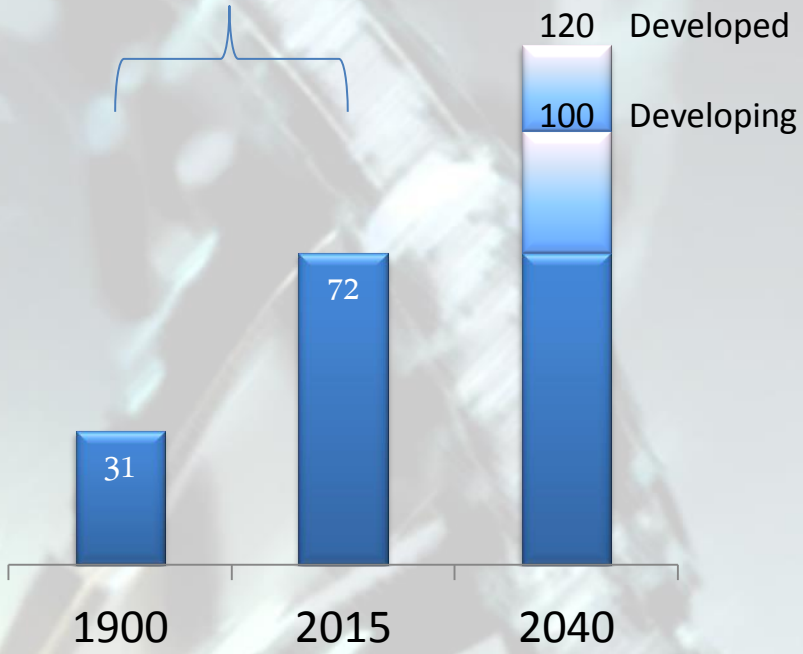
BY SARAH KNAPTON

WORLDWIDE LIFE EXPECTANCY

Four million years produced an
11-year increase from 20 to 31



115 years produced
a 41 year increase



WHAT IS AGEING?

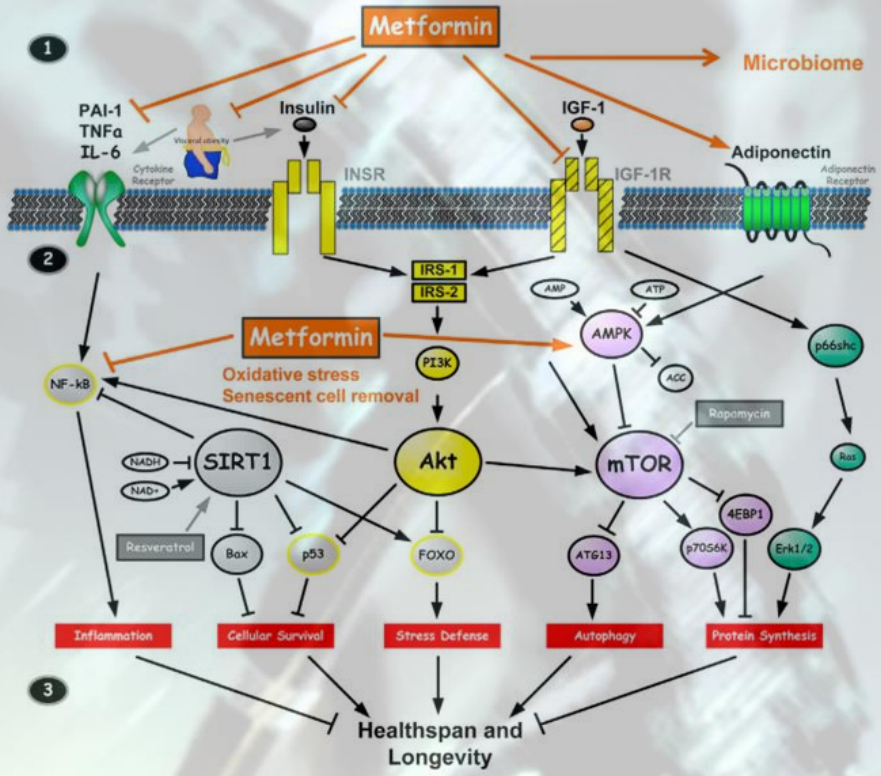
When wear and tear outruns repair.

NEGLIGIBLE SENESCENCE

An organism is considered to display negligible senescence if it does not exhibit ***any*** measurable decline in survival characteristics such as strength or mobility with age, does not have a gradually increasing death rate with age, and also does not exhibit any measurable reduction in reproductive ability with age.

VERTEBRATE OF THE YEAR 2013!

AGEING IS VERY COMPLEX



AGEING THEORIES

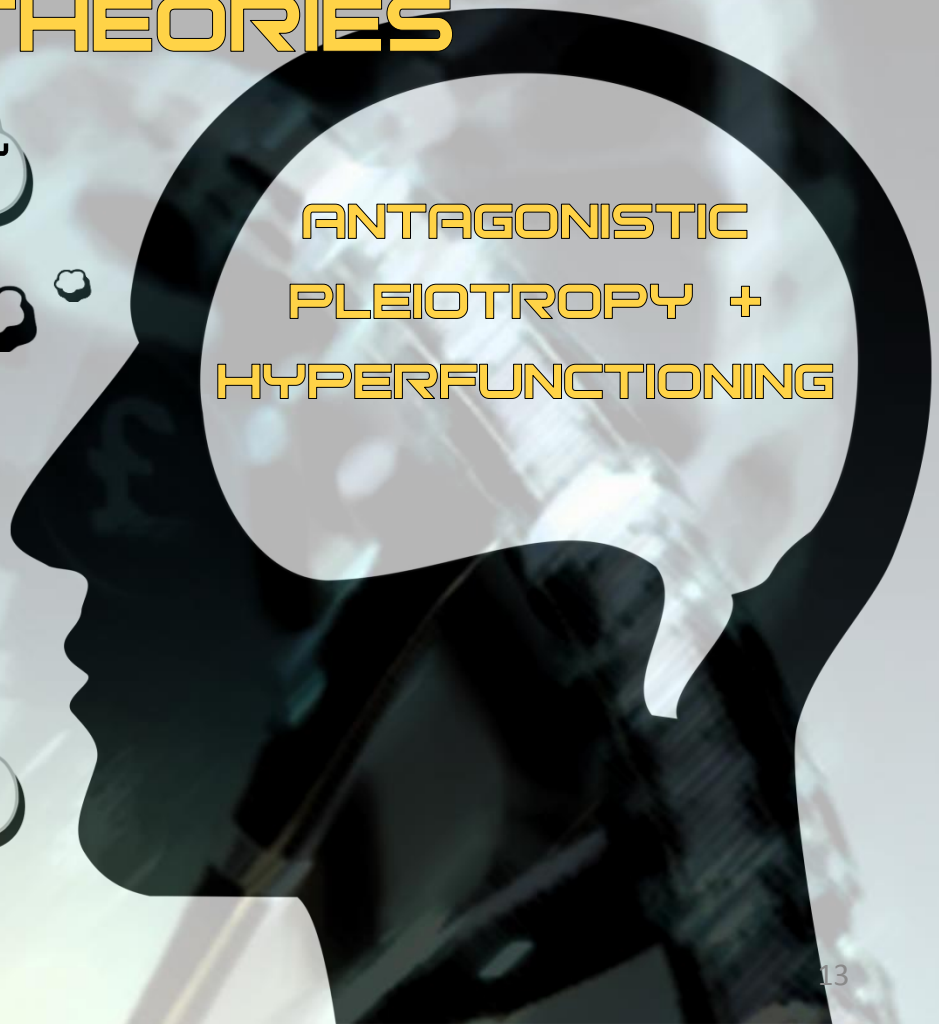
DISPOSABLE SOMA

OXIDATIVE THEORY OF AGEING

EVOLUTIONARY THEORY OF AGEING

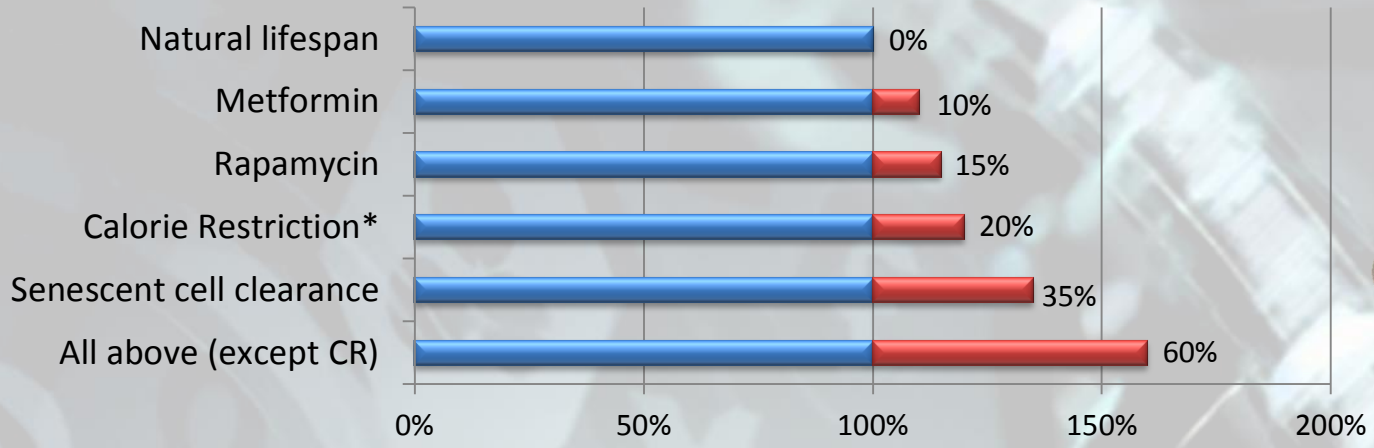
SECOND LAW OF THERMODYNAMICS

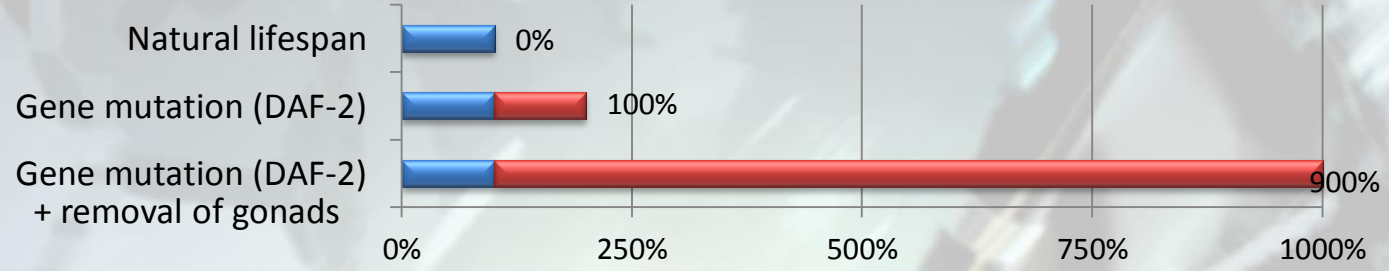
RATE OF LIVING THEORY



MODELS OF AGEING

WE CAN ALREADY MANIPULATE LIFESPAN

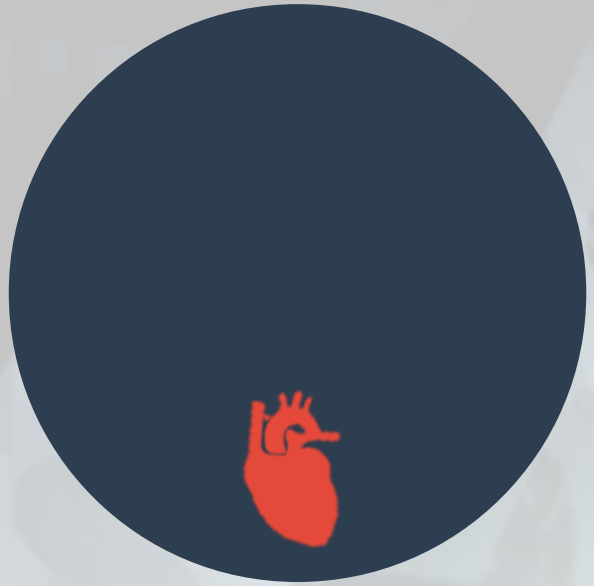




Source: Journal of Nutrition, April, 116(4), pages 641-54.

**Depending on level of caloric restriction*

Age is the single biggest risk factor in the deadly quintet of diseases accounting for 70% of all deaths



747k (28%)

592k (23%)

147k (6%)

94k (5%)

76k (3%)

Source: Figures for United States - 2014

THERAPIES IN DEVELOPMENT

afar

AGEX THERAPEUTICS

ELYSIUM

Elevian

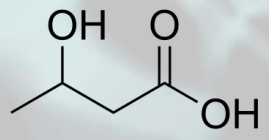
resTORbio™

LYGENESIS

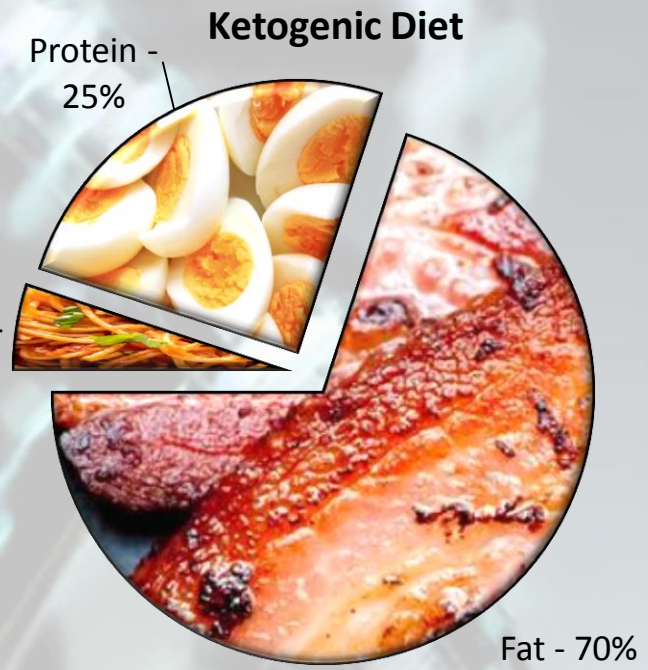
UNITY BIOTECHNOLOGY

CALORIC RESTRICTION

- Eating consistently less without starvation and malnutrition
- Increases life expectancy and lessens disease burden in aged mammals but unclear whether findings translate into humans
- CR mimetics being investigated include resveratrol, oxaloacetate, rapamycin, rimonabant
- CR increases the production of keytone bodies that are produced when liver uses fat stores rather than sugars – e.g. ketogenic diet
- Mimetic of ketogenic diet is beta-hydroxybutyrate



Beta-hydroxybutyrate



Certainly makes life <u>FEEL</u> a *lot longer!*

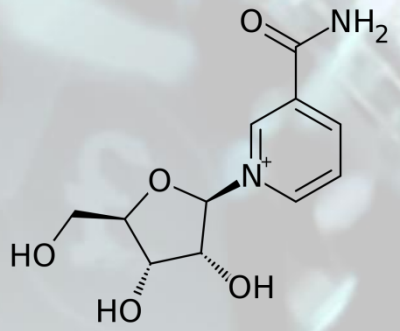
Follow me on twitter! JIMMHK

METFORMIN & TAME

- 60 year old drug derived from French Lilac
- Excitement - diabetics taking metformin showed 15% mortality advantage over matched non-diabetic population
- Targeting Ageing with Metformin (TAME) – first FDA approved trial looking at delaying onset of age related diseases
- Nir Barzilai, Albert Einstein College of Medicine is proponent of the TAME trial

NAD+ PRECURSORS

- NAD+ (Nicotinamide adenine dinucleotide) - coenzyme found in all living cells that decreases with age
- NAD is a critical co-factor, or helper molecule, to a family of proteins called *sirtuins*
- Two approaches:
  - Increase NAD+ in cells
  - Prevent decline in NAD+ - CD38 inhibition
- Eric Verdin, President and CEO of the Buck Institute for Research on Aging a key opinion leader in this area

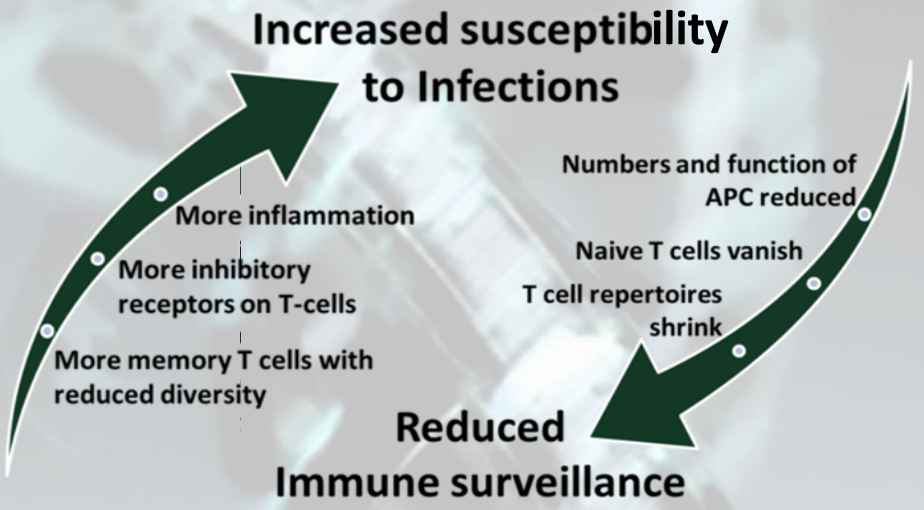


Nicotinamide riboside

A Potent and Specific CD38 Inhibitor Ameliorates Age-Related Metabolic Dysfunction by Reversing Tissue NAD+ Decline

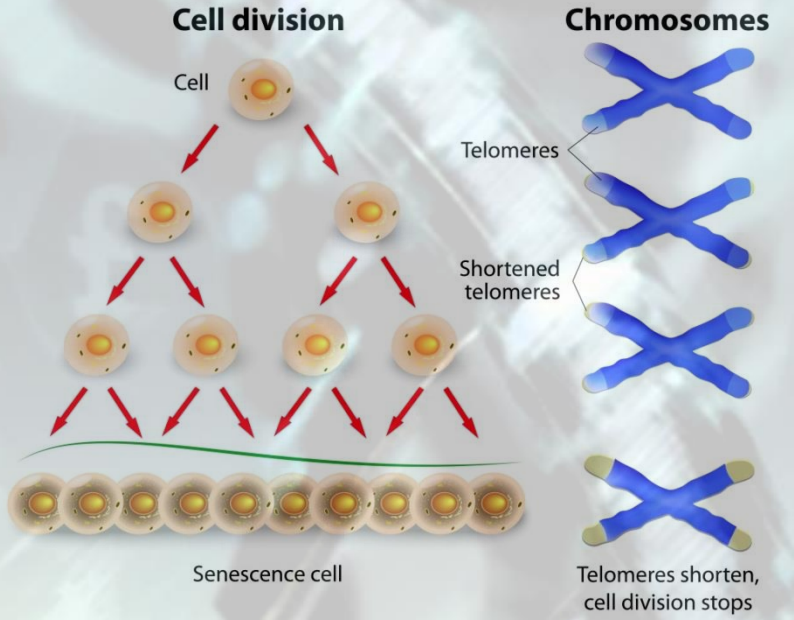
RAPAMYCIN / RAPALOGS

- Rapamycin is the only compound to extend life in all species studied to date
- Being tested in middle aged dogs in the *Dog Aging Project*
- Advanced human clinical trials being run by resTORbio (NASDAQ:TORC)
- phase 2b clinical trials with RTB-101 in combination with everolimus (a rapalog)
  - Enhanced response to influenza vaccine by ~20%
  - Ameliorated immunosenescence in elderly volunteers
  - Reduced % of CD4 and CD8 T lymphocytes expressing PD-1 receptor, which inhibits T cell signalling



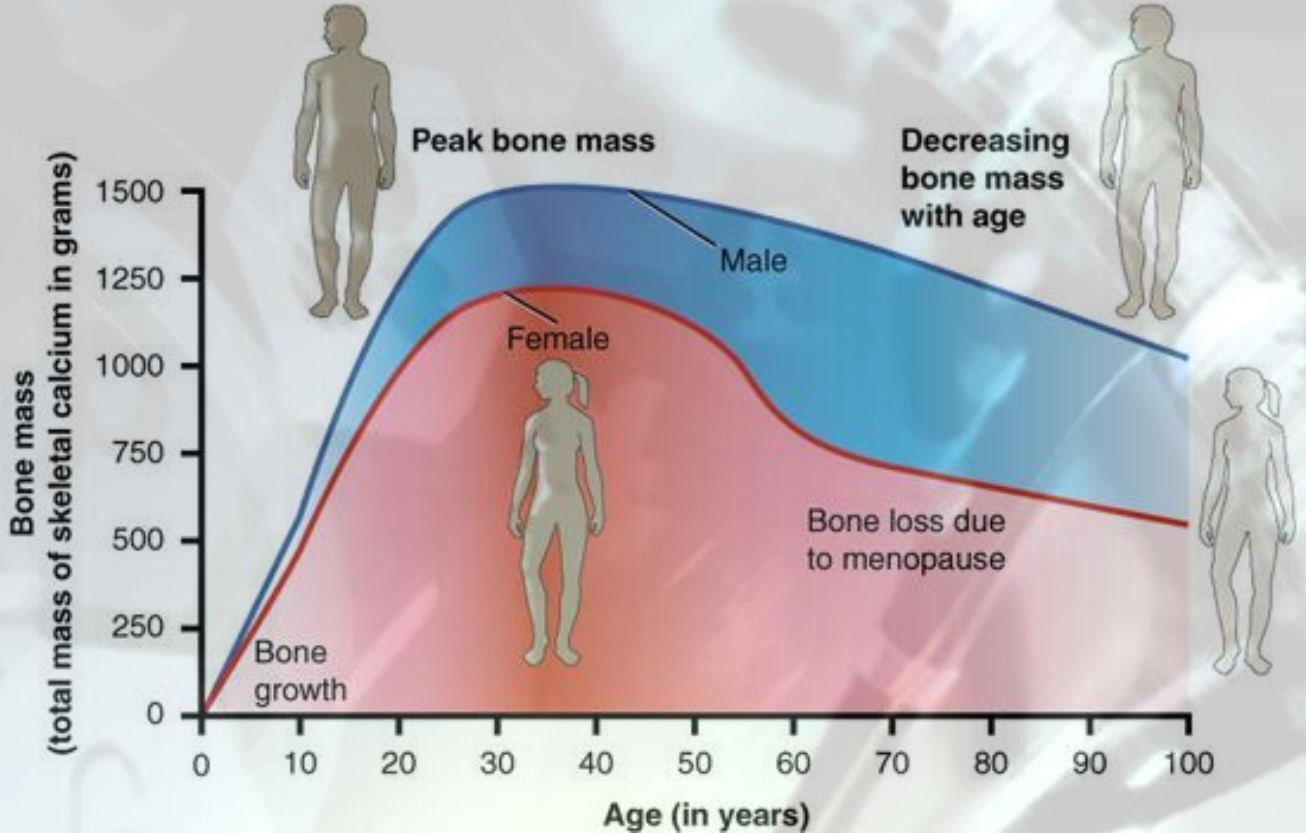
SENOLYTIC DRUGS

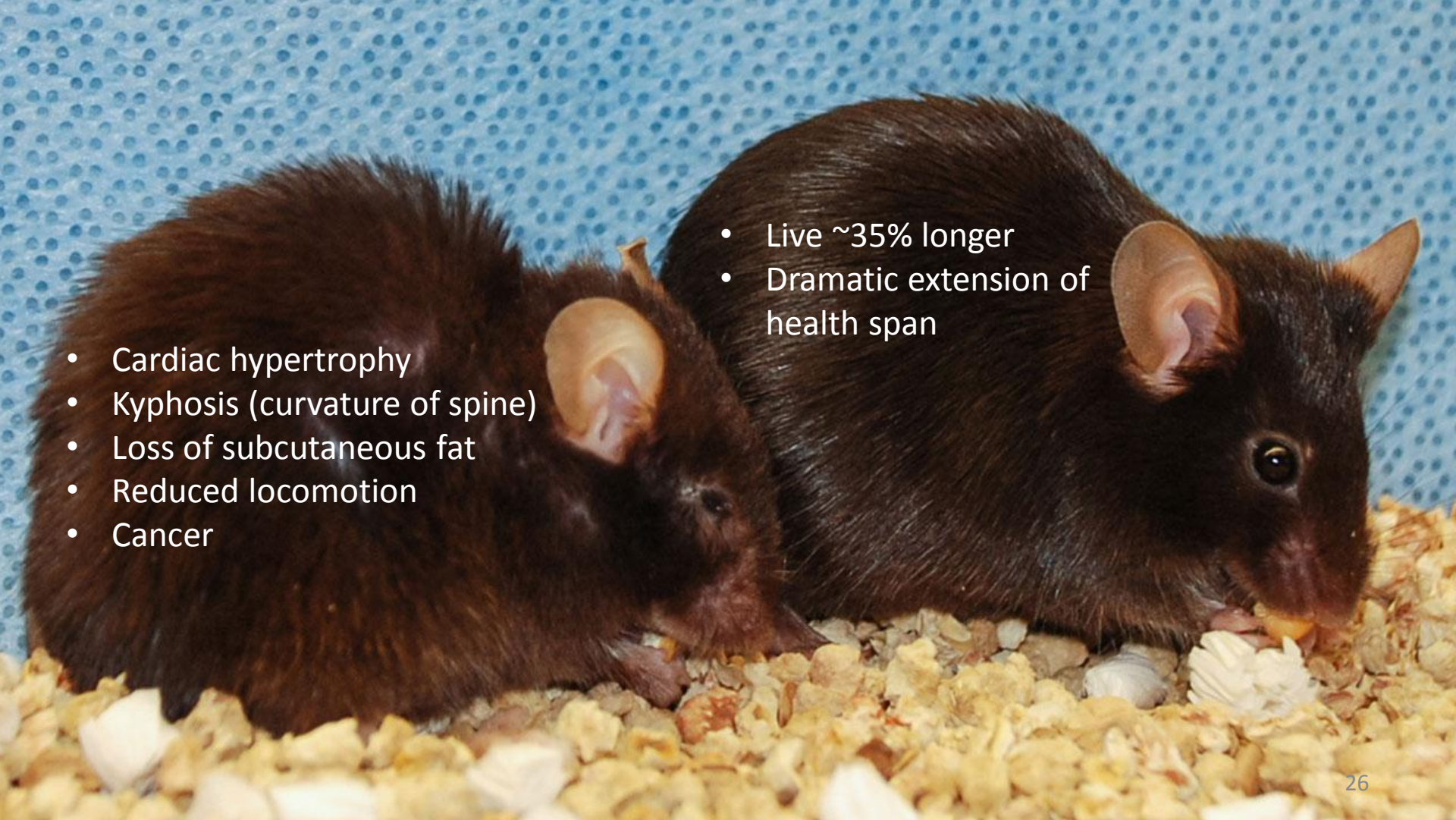
- Cellular senescence
  - Phenomenon by which normal cells cease to divide
  - Dormant but metabolically active state
  - Promotes inflammation and accelerates ageing
- Leonard Hayflick observed replicative senescence in 1960s – the Hayflick Limit
- Caused by endogenous and exogenous DNA damage



Senolytic drugs increase maximum lifespan by 35% in mice

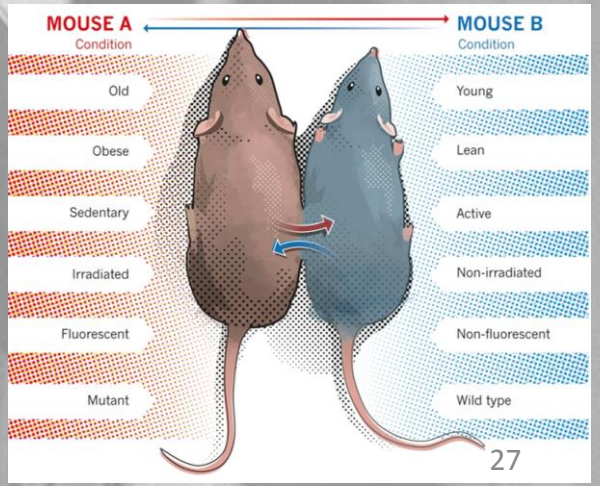
TARGETING SENESCENT CELLS INCREASES BONE MASS



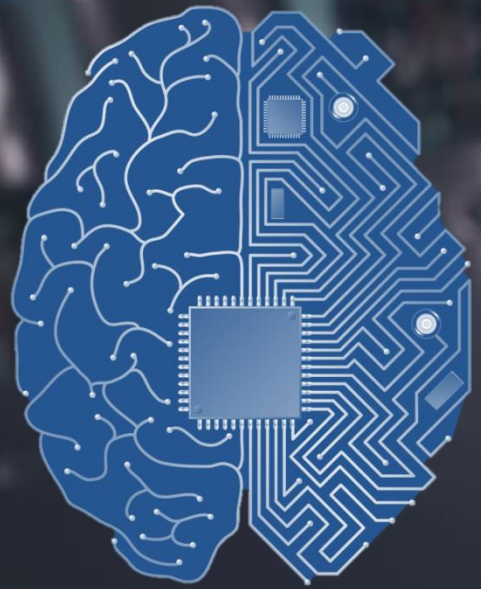

• Live ~35% longer
• Dramatic extension of health span
• Cardiac hypertrophy
• Kyphosis (curvature of spine)
• Loss of subcutaneous fat
• Reduced locomotion
• Cancer

PARABIOSIS

- Oldest known attempt to extend lifespan
- Circulatory systems of animals surgically joined
- Used by Kim Il sung to the extend it changed his blood type from AB to B; he died age 82
- Modern version looks at specific “factors” in blood that provide the benefits and administering by transfusion
- Ambrosia sells blood from younger people for USD 8,000 a pop!

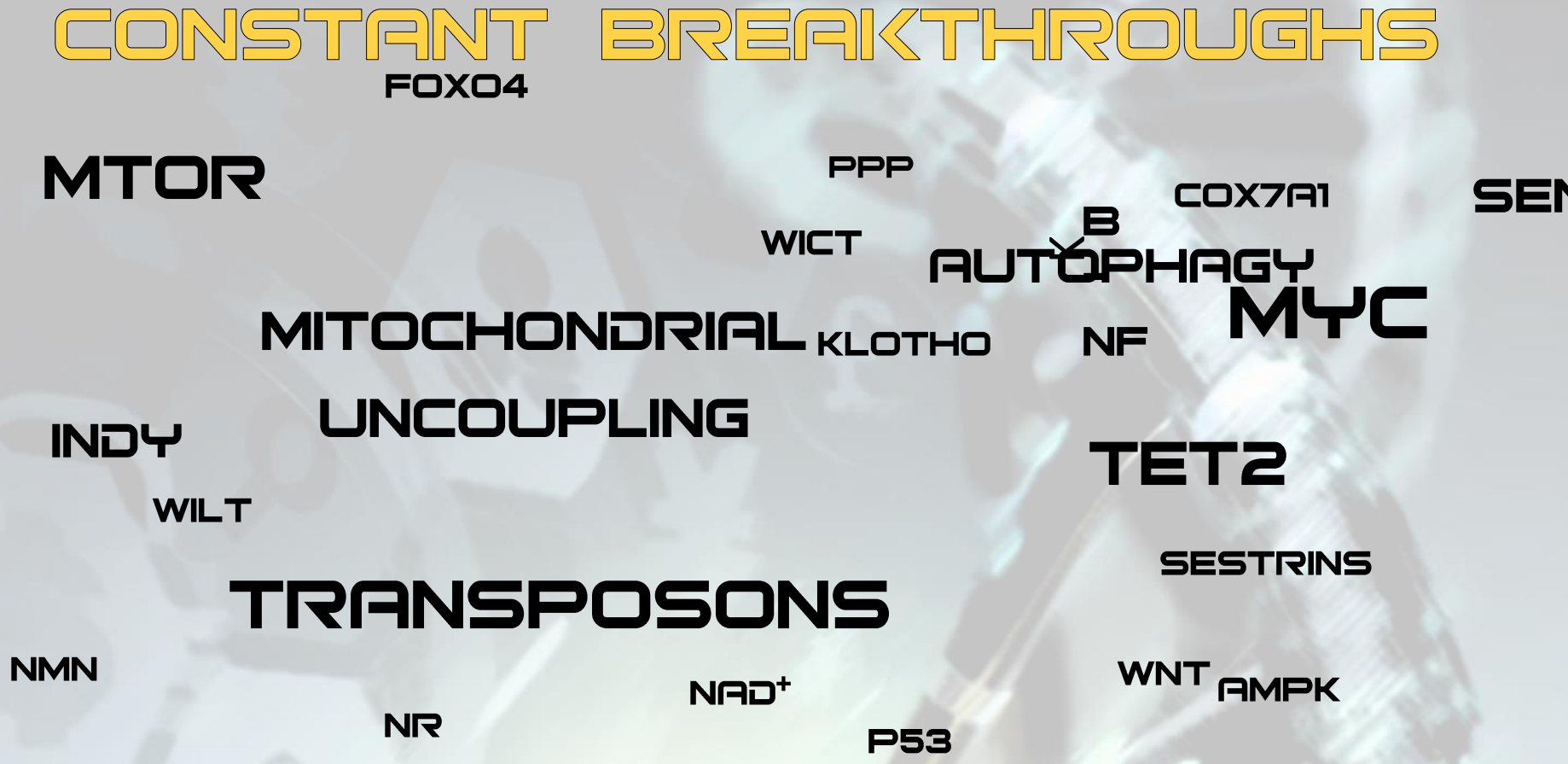


THE AGE OF ACCELERATION



INSILICO MEDICINE

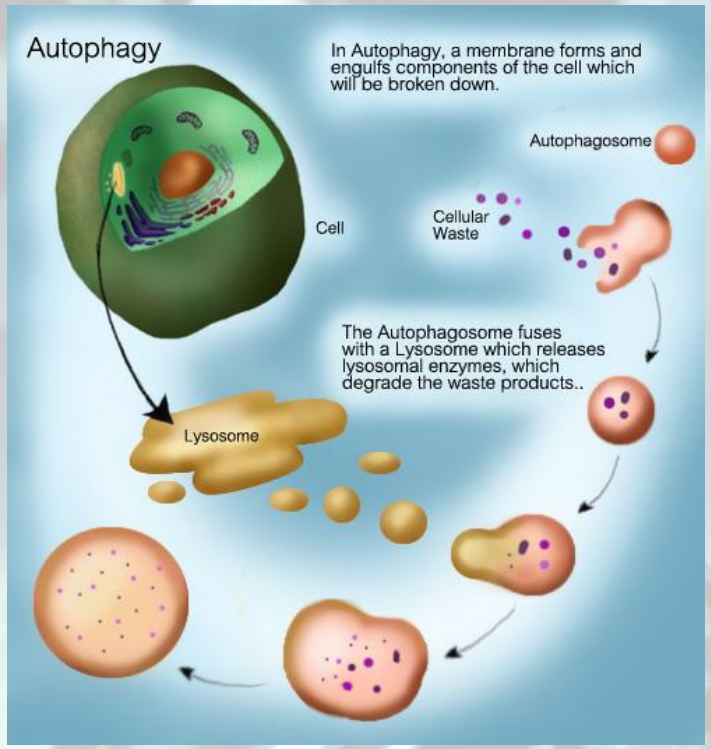
CONSTANT BREAKTHROUGHS



CONSTANT BREAKTHROUGHS

Autophagy

- Cellular disposal system that clears unwanted components to lysosome such as dysfunctional mitochondria
- System becomes less efficient with age
- Mice with high expression of autophagy-associated protein beclin-1 live 10% longer, and have a lower incidence of cancer and heart disease than wildtype
- Metformin induces autophagy under certain conditions
- Inhibition of CoX7a1 leads to increased autophagy



CONSTANT BREAKTHROUGHS

WNT Pathway

- Wingless-related integration site
- Signalling pathway that regulates self-renewal and differentiation of adult stem cells
- Dysregulation of WNT in a specific tissue almost always leads to disease
- Implicated in cancer and degenerative conditions
- Significant capital raised by Samumed (US $12b private market valuation) with lead indications in osteoarthritis and alopecia

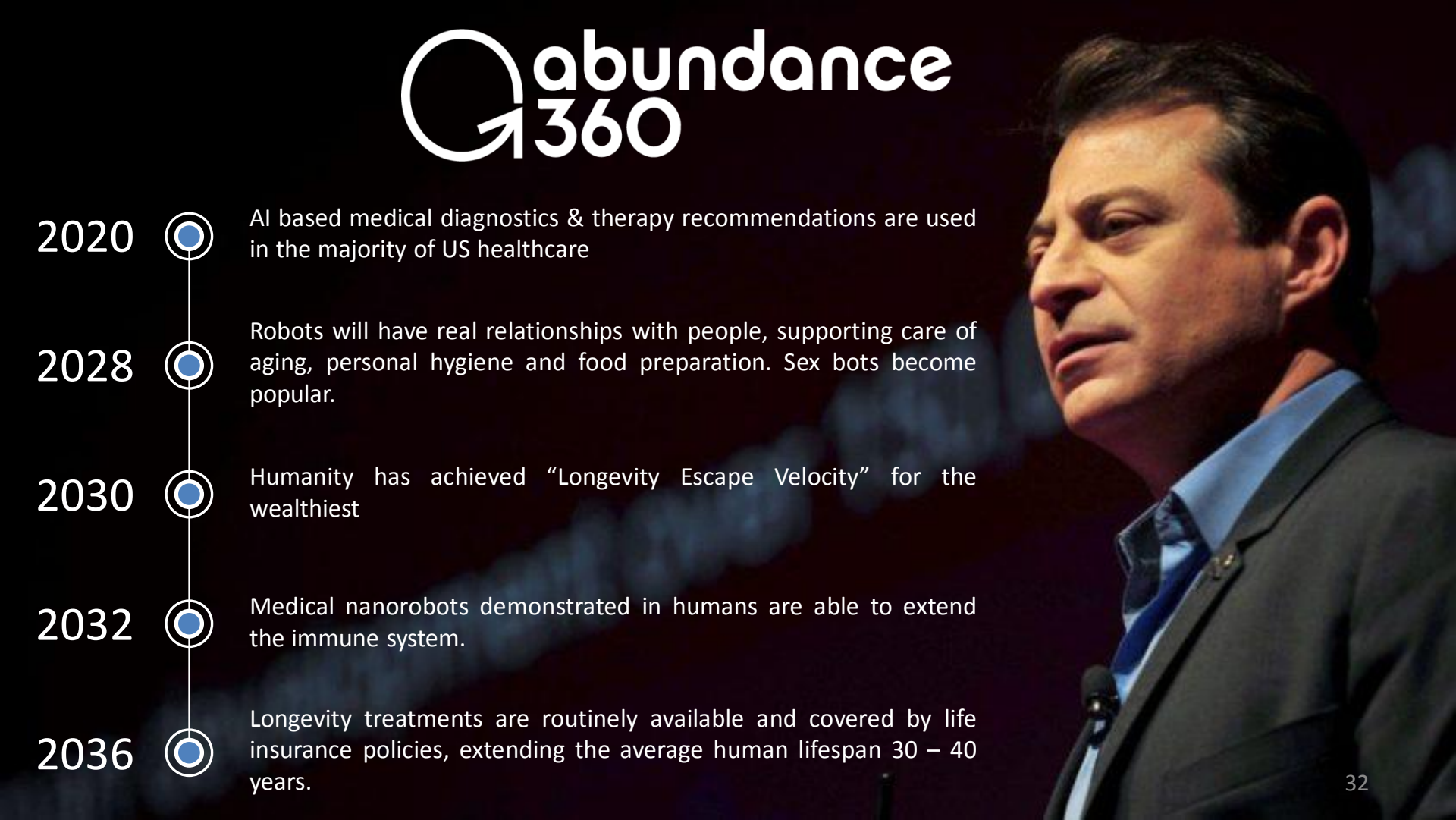
samumed

FOXO

- Forkhead box family of transcription factors
  - FOXO1 – insulin signalling
  - FOXO3 – tumour genesis
  - FOXO4 – Judith Campisi
- Play a role in expression of genes involved in cell growth, proliferation, differentiation and longevity
- Believed to contribute significantly to the immortality of the hydra
- Evolutionarily conserved in humans

UNITY BIOTECHNOLOGY

abundance 360



2020 AI based medical diagnostics & therapy recommendations are used in the majority of US healthcare

2028 Robots will have real relationships with people, supporting care of aging, personal hygiene and food preparation. Sex bots become popular.

2030 Humanity has achieved “Longevity Escape Velocity” for the wealthiest

2032 Medical nanorobots demonstrated in humans are able to extend the immune system.

2036 Longevity treatments are routinely available and covered by life insurance policies, extending the average human lifespan 30 – 40 years.

INDUCED TISSUE REGENERATION

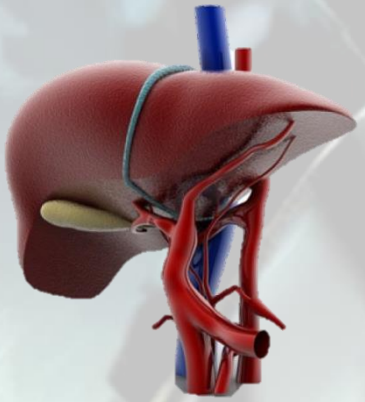
Cox7a1 Gene:

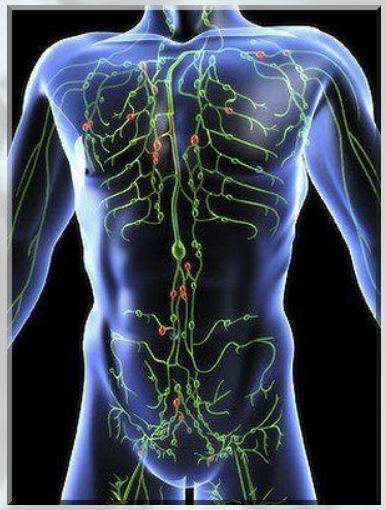
- Expression after the embryonic-foetal transition inhibits regeneration of organs
- Not expressed in liver which allows it to regenerate
- Inhibition leads to reversion to embryonic state and increased autophagy
- 90% of cancers inhibit its expression
- Mexican salamander stuck in developmental larval state does not express

ORGAN REGENERATION

- Lygenesis, Inc. novel technology to use lymph nodes as mini-bioreactors
- When lymph nodes are seeded with purified hepatocytes (liver cells), the cells engraft and grow into small, functional ectopic livers
- Livers only grow to size required by body
- Bridge patients to transplant or completely supplanting the need for a transplant
- Applications in other organs including the thymus and pancreas

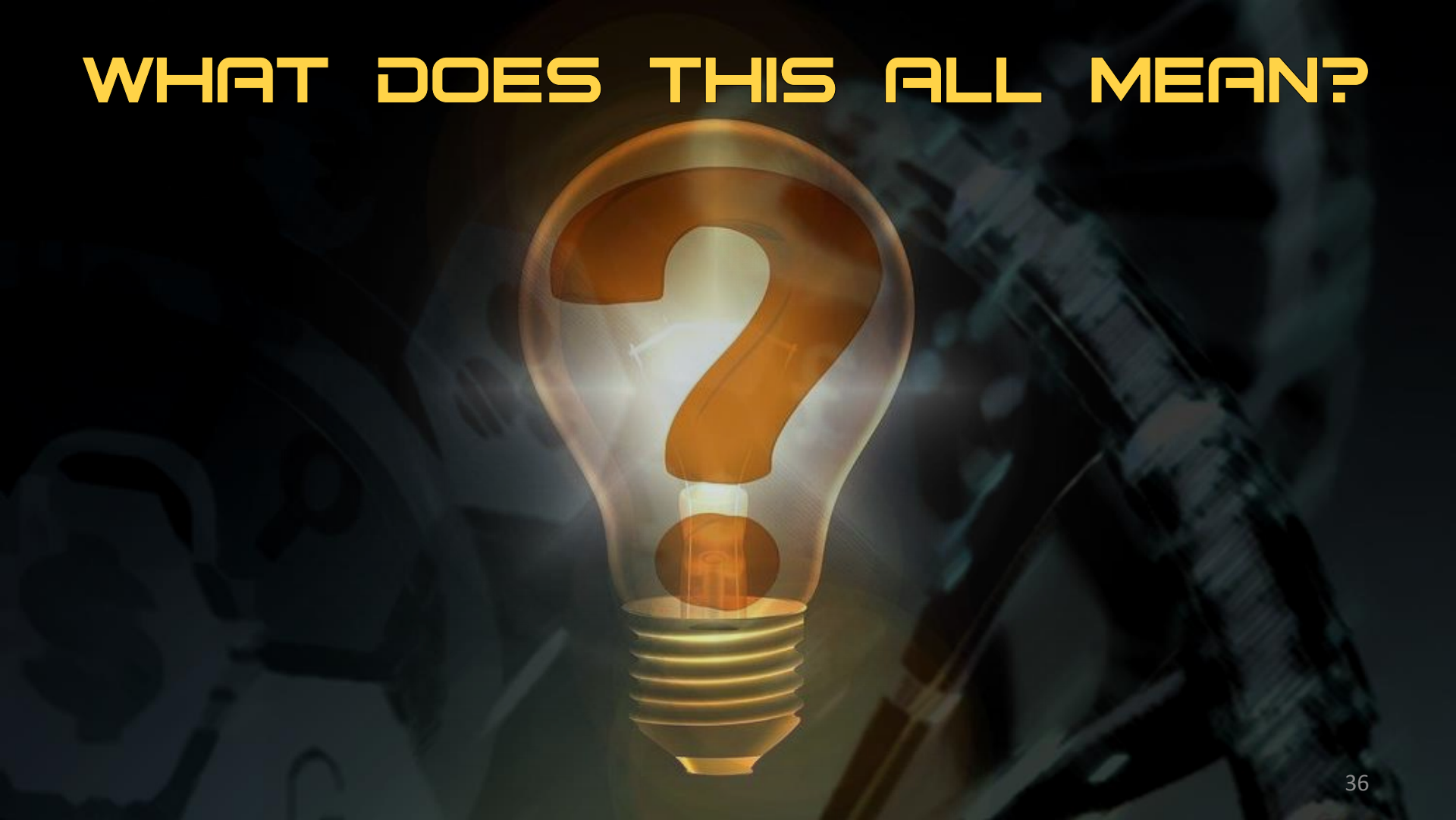
LYGENESIS

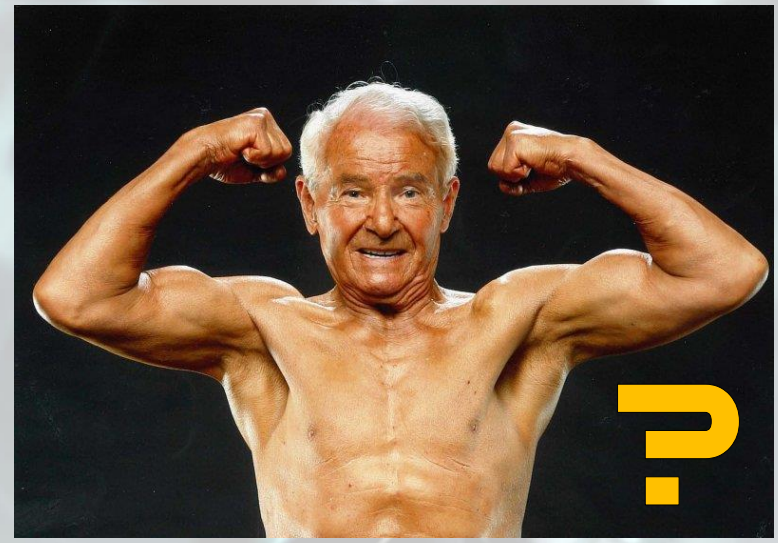




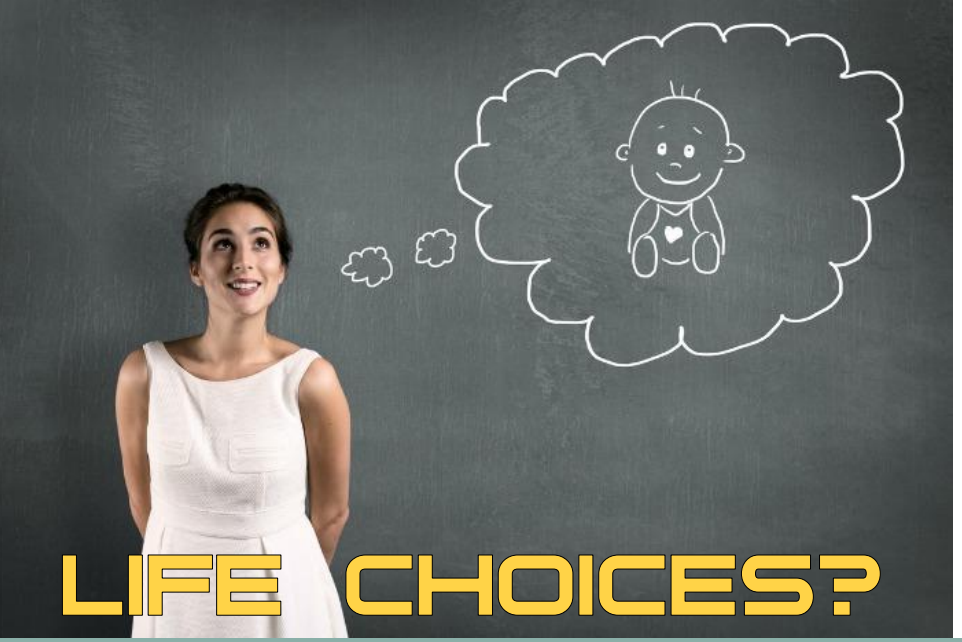
GENE THERAPY

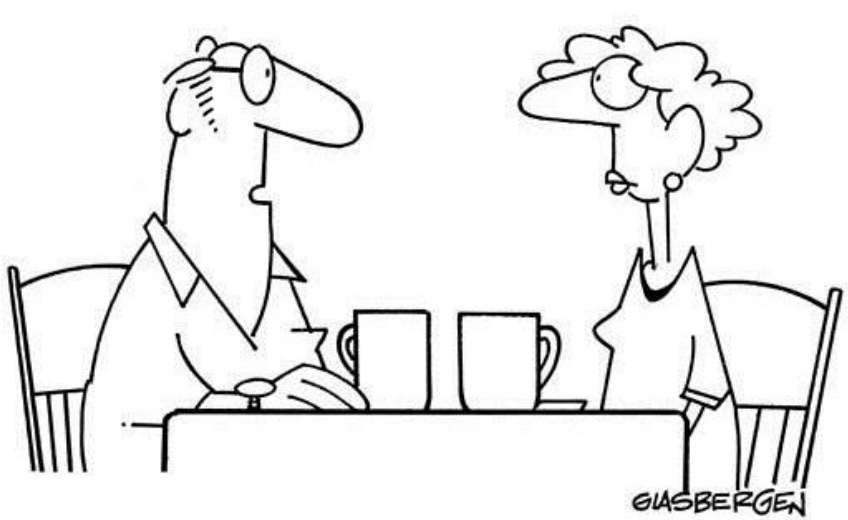
WHAT DOES THIS ALL MEAN?



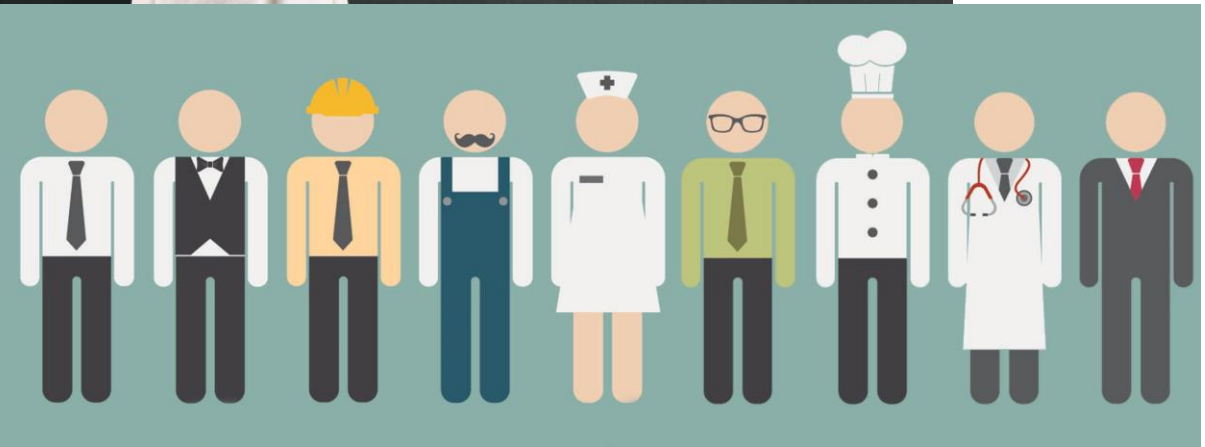


Gone are the days when you're born, learn, earn, burn out, retire and expire!



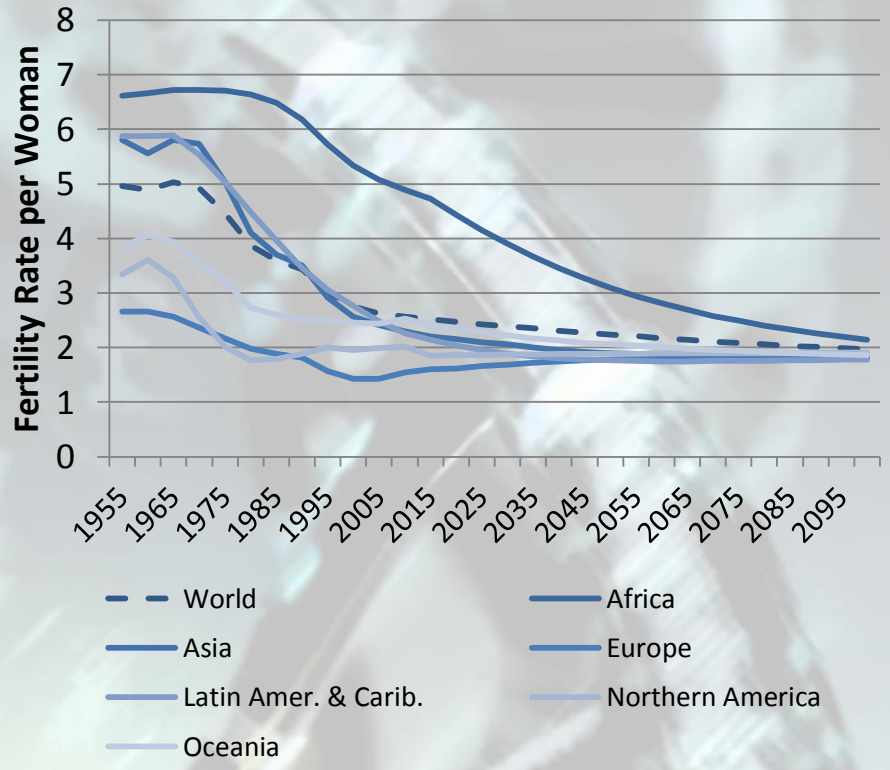


"I finally put something aside for my retirment.
I put aside my plans to retire."



GLOBAL POPULATION

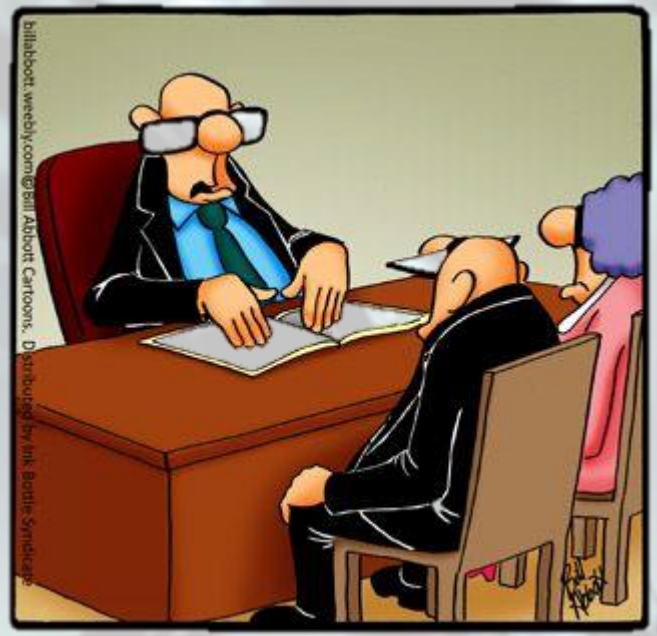
- Plateau and decline
- In 2015, 46% of world's pop. (in 86 countries) below replacement level of 2.1
- 2017 – 2050
  - half the world's population growth will occur in 9 countries
- "Peak Children"
  - 1960 / 1 billion / 35%
  - 2011 / 1.9 billion / 27%
  - 2050 / 1.9 billion / 20%



Source: UN World Population Prospects

INDUSTRIES TO BE DISRUPTED

- Pensions
- Life insurance
- Healthcare – BUT burden of care likely to decline
- Leisure industry
- Social care
- Education



"I've crunched the numbers in your retirement account. It's time to figure out who will be wearing the mask and who will be driving the getaway car."

sens research foundation
reimagine aging

SALK INSTITUTE FOR BIOLOGICAL STUDIES

UNSW SYDNEY

The Institute of HEALTHY AGEING

BROAD INSTITUTE

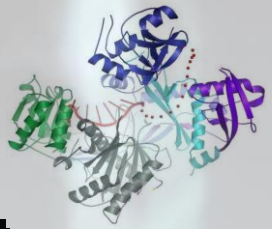
MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING

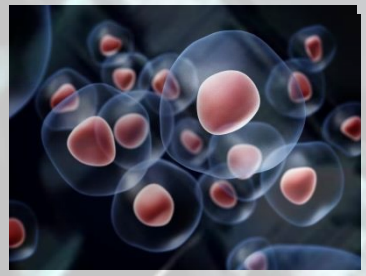
BUCK INSTITUTE FOR RESEARCH ON AGING

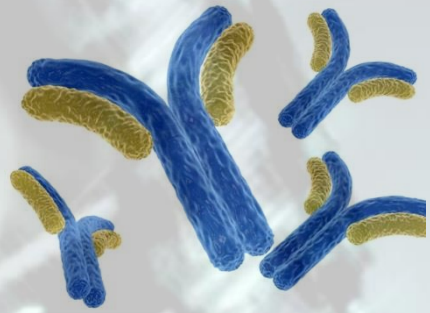
HARVARD

EINSTEIN
Albert Einstein College of Medicine

UNIVERSITY OF OXFORD





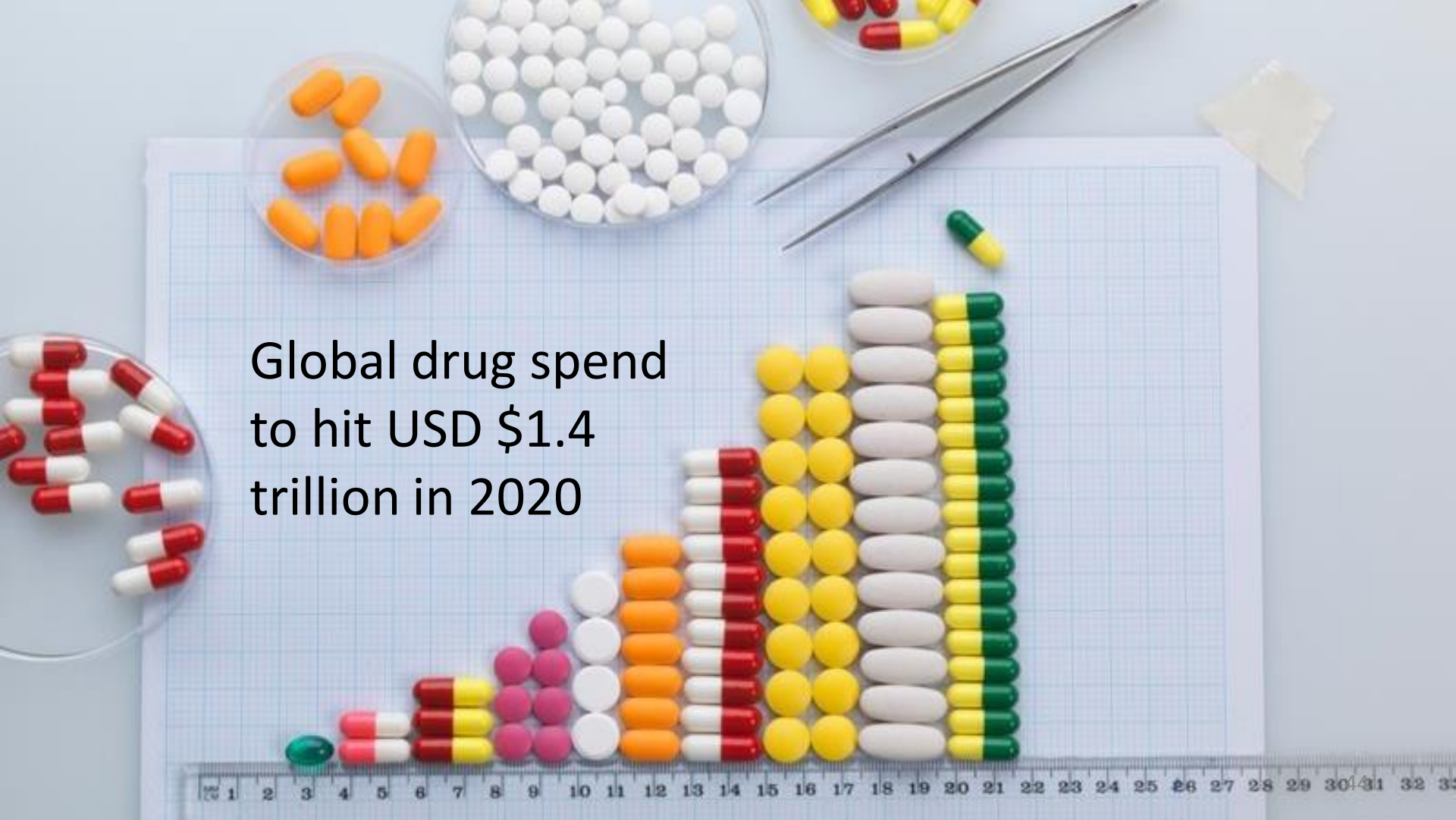


DAWN OF INDUSTRIES

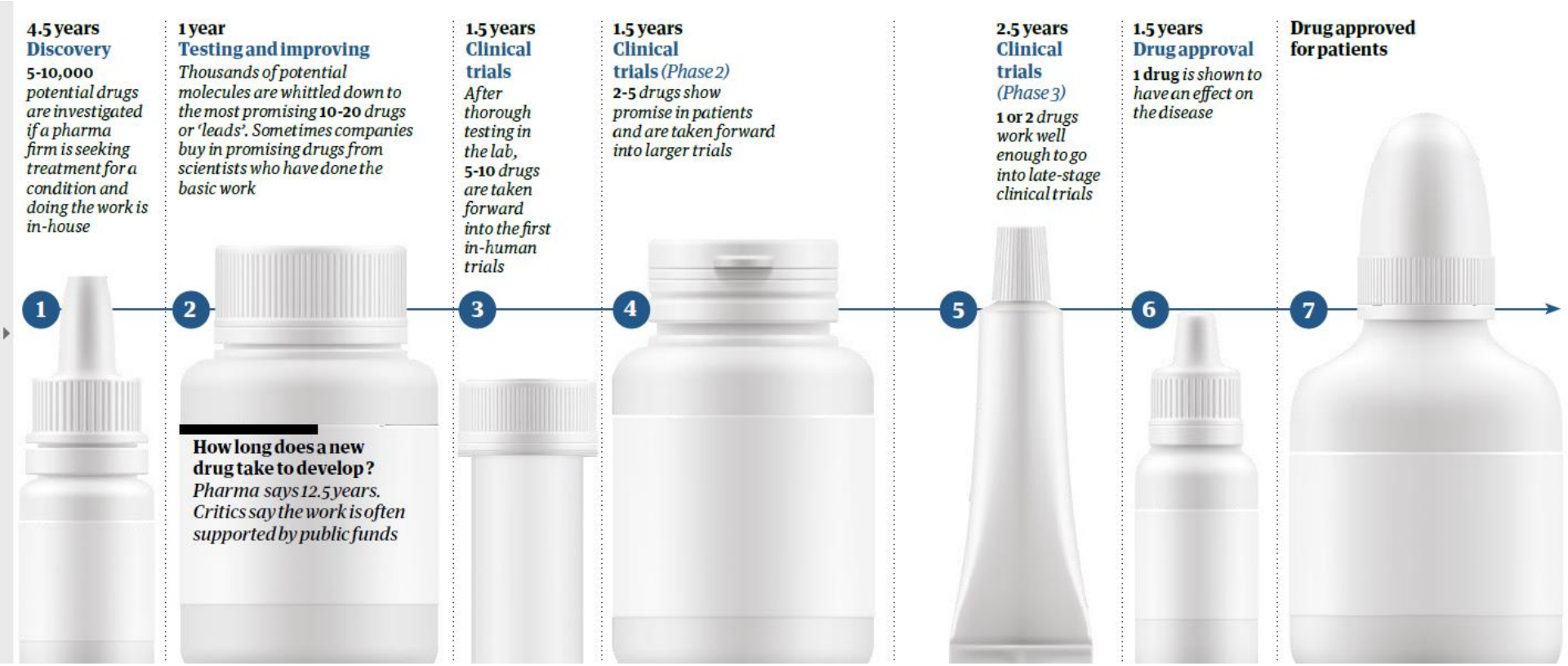
Computing

Internet

Longevity

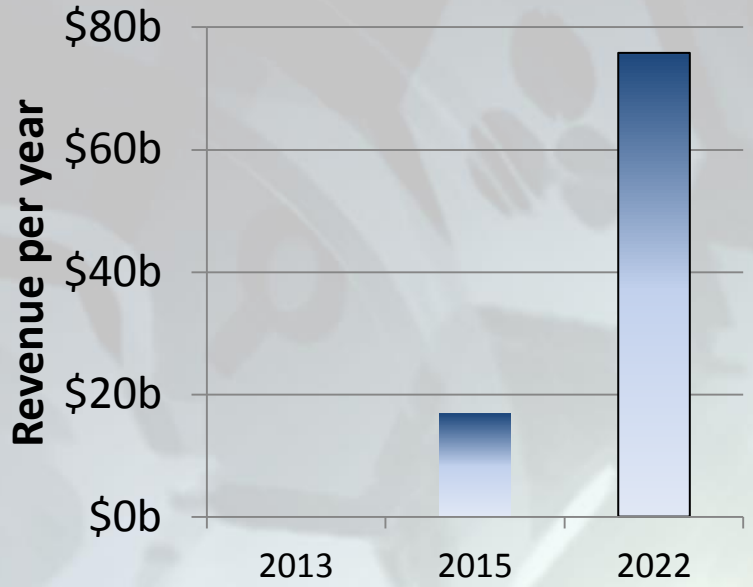

Global drug spend
to hit USD $1.4
trillion in 2020

LONG ROAD TO APPROVAL



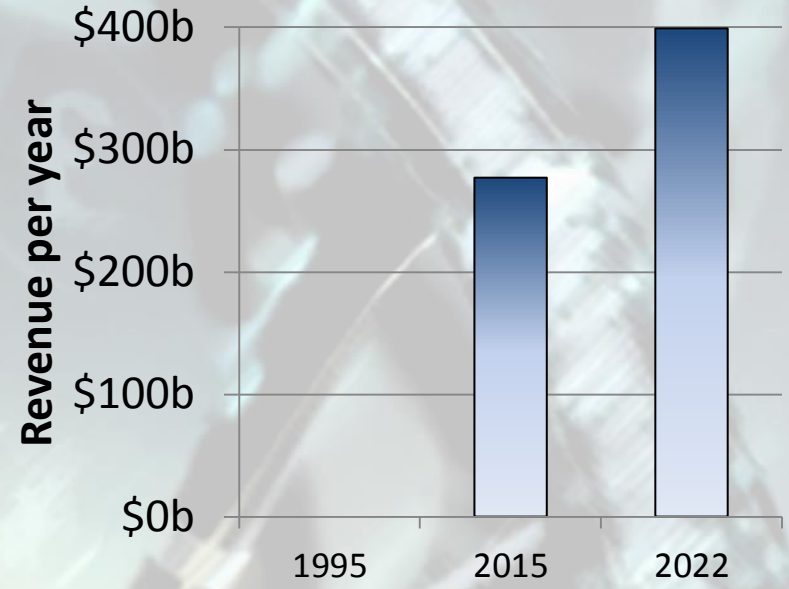
MARKETS DEVELOP QUICKLY

Cancer Immunotherapy



Source: GBI Research

Biologics



Source: Grand View Research

TOTAL ADULT POPULATION

5.70

BILLION

~15%

EARN MORE THAN

GLOBAL MEDIAN INCOME

$9,733

PER YEAR

@ $1

PER DAY

GLOBAL MARKET FOR LONGEVITY

$312

BILLION PER YEAR

JUVENESCENCE THE COMPANY

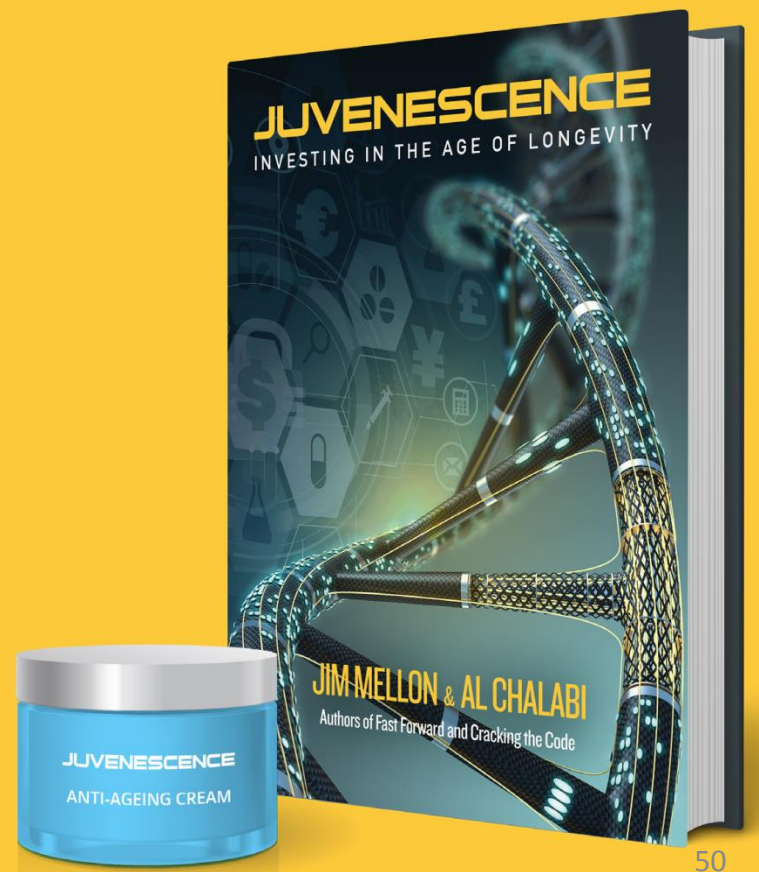
- Founded by Jim Mellon, Greg Bailey and Declan Doogan
- Highly experienced investors, entrepreneurs and drug developers
- Combination of artificial intelligence and classical drug development
- Company has raised US $63m to date – US $50m Series A
- Contemplating IPO in 2019

- Portfolio and collaborations includes:
  - Insilico Medicine, Inc.
  - Juvenescence AI
  - NetraPharma
  - Lygenesis, Inc.
  - AgeX Therapeutics, Inc.
  - Buck Institute for Research on Aging
- Multiple deals in pipeline


JUVENESCENCE.AI
ICHOR THERAPEUTICS
freenome
Calico
EVERON BIOSCIENCES
celularity
GRAIL
OISÍN™ BIOTECHNOLOGIES
ANTOXERENE

The market for anti-ageing treatments is currently worth USD 140 billion annually.

Imagine how much they'll be worth when they actually work.



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