afar american federation for aging research

THE GEROSCIENCE PROMISE:

How we age and what we can do about it

Richard G.A. Faragher, Bsc, ARCS, DPhil
AFAR Board Member

Professor Richard Faragher

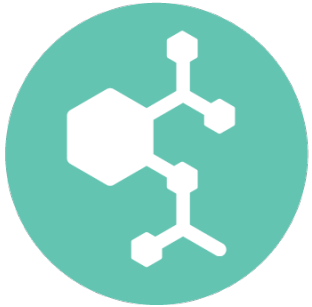
- Professor of Biological Gerontology
  - Board Member, American Federation for Aging Research
  - Scientific Advisory Board of the Longevity Vision Fund
  - Expertise primarily in cellular senescence

- Honors and Awards
  - Royal Pharmaceutical Society Conference Science Medal for outstanding scientific achievement.
  - Paul F Glenn Foundation Award for Biomedical ageing research.
  - Help the Aged ‘Living Legend’ award for championship of older people.
  - Lord Cohen Medal for outstanding contributions to gerontology.

My talk in one slide

Old age has historically been accompanied by ill health

It doesn't have to be that way



Understanding the biology of ageing is changing things for the better

But challenges remain

Life expectancy: a brief history

Old age: a time of satisfaction or struggle?

Satisfied innovators

17%

Middle/upper-middle class
Good health, socially active
Gym, wine club or similar
Interested in change
Keeping up to date

Bored and depressed

9%

Former manual workers
Dependent on state pension
Poor health, multiple medicines
Socially isolated
Lots of TV

The situation today

Some old people are so happy, healthy and wealthy they should be helping **me**

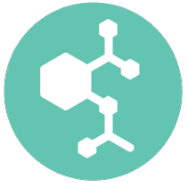
But many others are not

Health is a key determinant of happiness

Poor health costs money and causes misery

Things don’t have to be this way

Age dramatically increases vulnerability to disease and functional impairment. We have known this happens for a long time. But we did not know why.



We now know enough about the physiology of ageing to extend healthspan.

Important breakthroughs for older people are happening now and transformative things will happen later - if we act boldly

Mechanisms that maintain health are shared between species

Invertebrates

Insects

Mice

Humans

nature
international weekly journal of science

A *C. elegans* mutant that lives twice as long as wild type.

Cynthia Kenyon et al.

Science
AAAS

Extension of Life-Span by Loss of CHICO, a Drosophila Insulin Receptor Substrate Protein.

David J. Clancy et al.

The FASEB Journal

Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice.

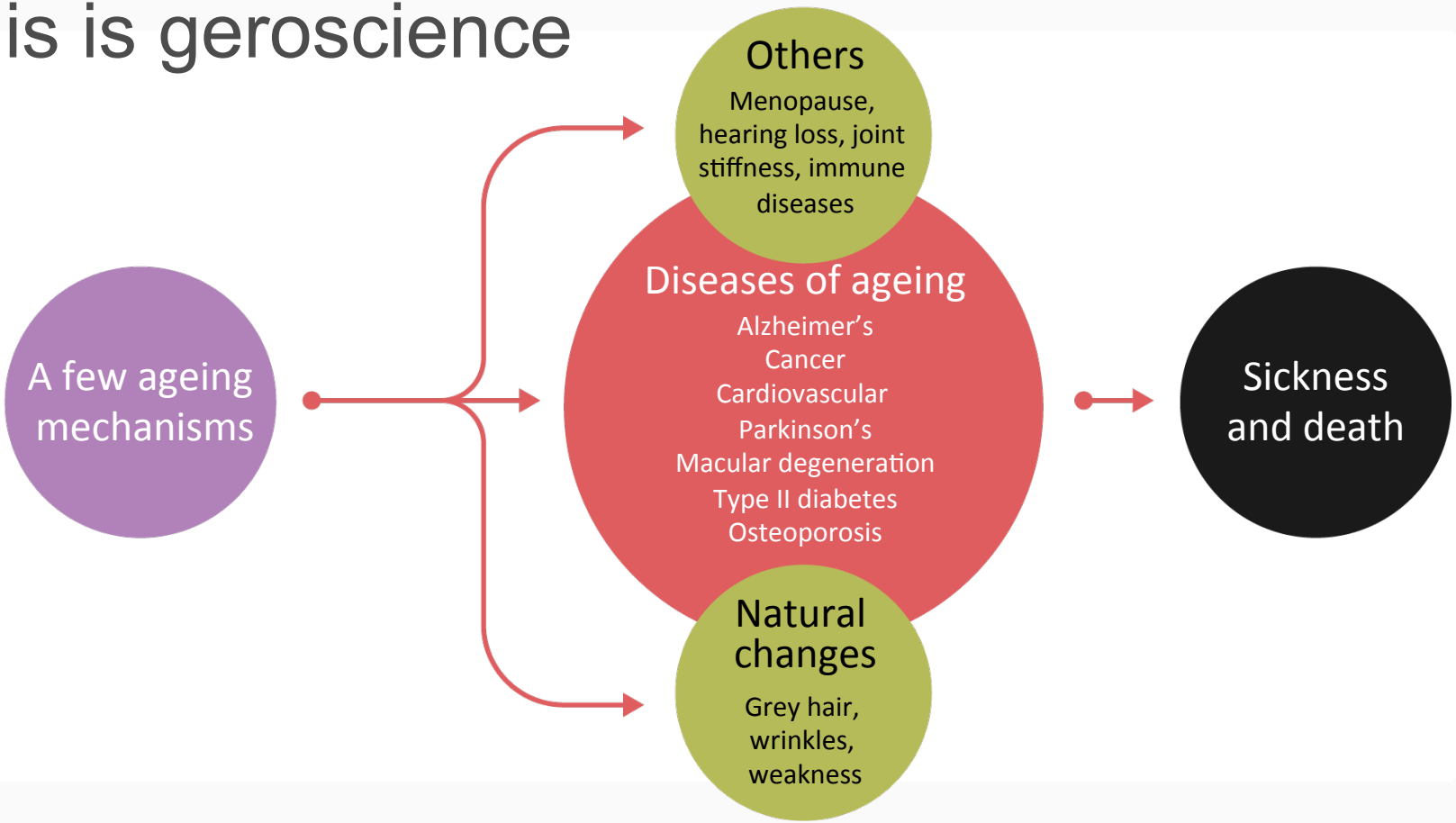
Colin Selman et al.

PNAS

FOXO3A genotype is strongly associated with human longevity.

Bradley J. Willcox et al.

This is geroscience



Some established health maintenance mechanisms

And why we know they are real

In 2009 *Science* identified healthy lifespan extension by rapamycin as one of the most significant breakthroughs that year.

IT'S NOT PONCE DE LEÓN'S VISION of the fountain of youth: the secretion of a dirt-dwelling bacterium from Easter Island. But this year researchers showed that the compound, called rapamycin, boosts longevity in mice, the first time any drug has stretched a mammal's life span.

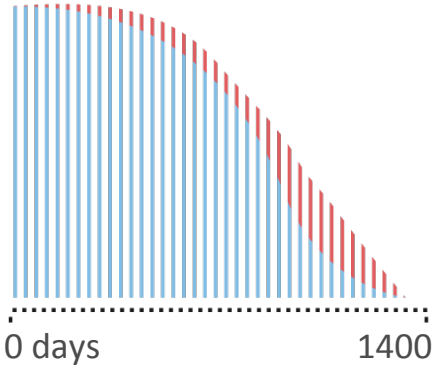
Doctors prescribe rapamycin to battle kidney cancer and to stymie rejection of transplanted organs. After the U.S. National Institute on Aging added the drug to its list of molecules that might increase rodent life span, the three U.S. labs that test such candidates

Methuselah mice. Longevity soared as much as 14% in rodents fed the drug rapamycin.

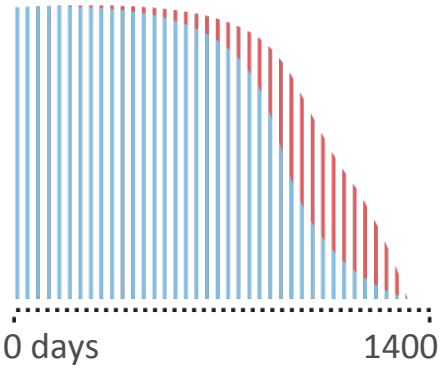
Altering nutrient sensing improves healthspan

Control Rapamycin-treated mice

Survival rate of male mice



Survival rate of female mice



AGEING

A midlife longevity drug?

Matt Kaeberlein and Brian K. Kennedy

The small molecule rapamycin, already approved for clinical use for various human disorders, has been found to increase lifespan in mice significantly. Is this a step towards an anti-ageing drug for people?

Journal of Gerontology

Rapamycin, but not resveratol or simvastatin, extends life span of genetically heterogeneous mice.

Richard A. Miller et al.

Rapamycin improves health in animals

nature genetics

Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington's disease.

Brinda Ravikumar et al.

Aging Cell

We report here that many forms of age-dependent change occur more slowly in rapamycin-treated mice.

John E. Wilkinson et al.

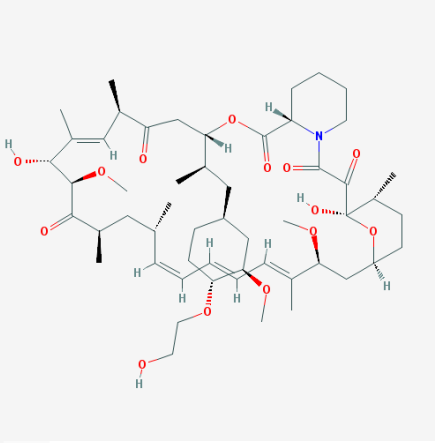
PLOS | ONE

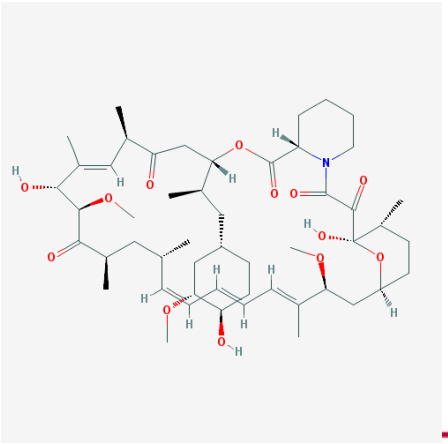
Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces Amyloid-β levels in a mouse model of Alzheimer's Disease.

Patricia Spilman et al.

First human trials based on geroscience

mTOR inhibition improves immune function in the elderly
Mannick *et al. Science Translational Medicine* 24 Dec 2014:





RAD001 enhanced the response to the influenza vaccine by about 20% at doses that were relatively well tolerated. RAD001 also reduced the percentage of CD4 and CD8 T lymphocytes expressing the programmed death-1 (PD-1) receptor, which inhibits T cell signaling and is more highly expressed with age. These results raise the possibility that mTOR inhibition may have beneficial effects on immunosenescence in the elderly

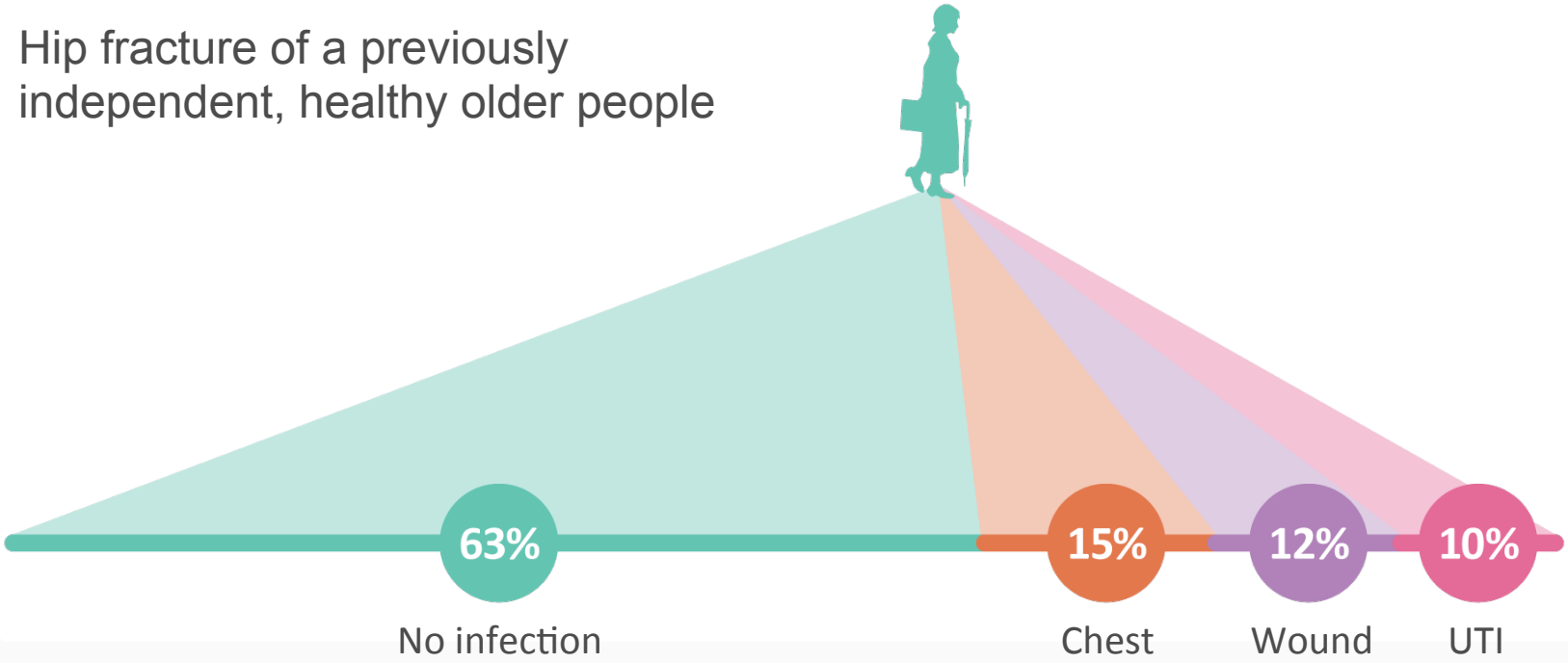
But not a panacea!

Targeting the biology of ageing with mTOR inhibitors to improve immune function in older adults: phase 2b and phase 3 randomised trials

Joan B Mannick, Grace Teo, Patti Bernardo, Dean Quinn, Kerry Russell, Lloyd Klickstein, William Marshall, Sarb Shergill

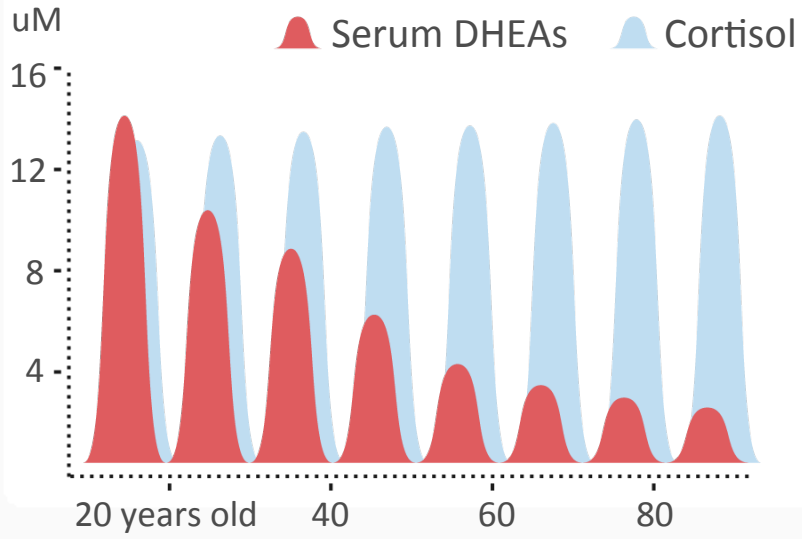
Infection after hip fracture

Hip fracture of a previously independent, healthy older people

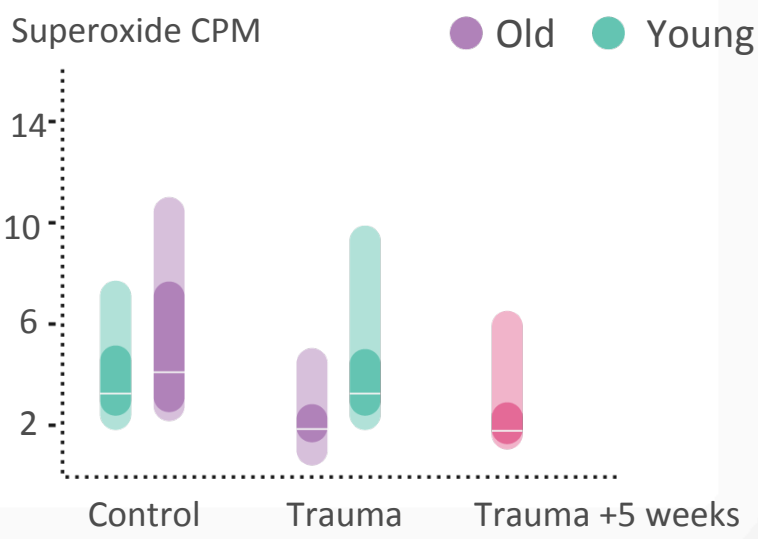


Simple interventions could stop this

DHEA levels decline with age



Trauma suppresses neutrophil bactericidal function in older people



Removing senescent cells improves health

nature

Removal of senescent cells improves multiple markers of health (e.g. wheel running).

Darren J. Baker et al.

EXPERIMENTAL EYE RESEARCH

Senescent keratocytes fail to produce IL-6 compromising corneal defences.

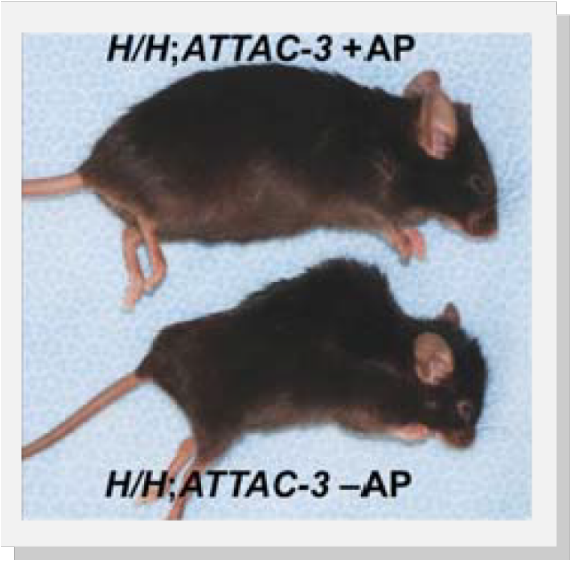
David Kipling et al.

Experimental Gerontology

Senescent VSMC secrete inflammatory cytokines and promote vascular calcification.

Dominick G. A. Burton et al.

Removing senescent cells in mice increases exercise capacity



Old mouse with senescent cells removed

Old mouse

Distance travelled at time of exhaustion

+175%

Running time to exhaustion

+100%

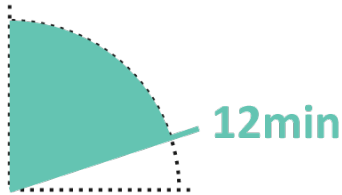
Mice today, independent elders tomorrow?

Distance travelled at time of exhaustion

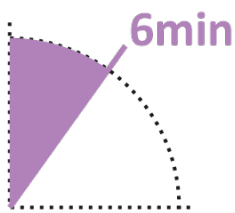
Time to exhaustion

Speed

Old person
'with senescent cells removed'



Old person



Rapid progress in removing senescent cells in humans is already being made

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Research paper

Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study

Jamie N. Justice [a,*,1], Anoop M. Nambiar [b,1], Tamar Tchkonia [c], Nathan K. LeBrasseur [c], Rodolfo Pascual [d], Shahrukh K. Hashmi [c], Larissa Prata [c], Michal M. Masternak [e], Stephen B. Kritchevsky [a], Nicolas Musi [f,g], James L. Kirkland [c]

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease

DKD shortens life expectancy by 16 years…

But we could simply reverse senescence instead

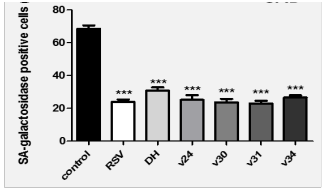
Latorre *et al. BMC Cell Biology* (2017) 18:31
DOI 10.1186/s12860-017-0147-7

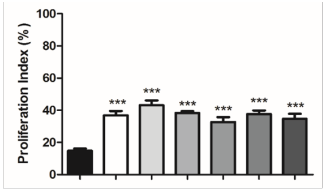
BMC Cell Biology

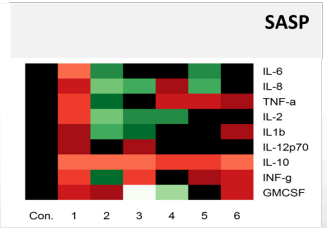
RESEARCH ARTICLE Open Access

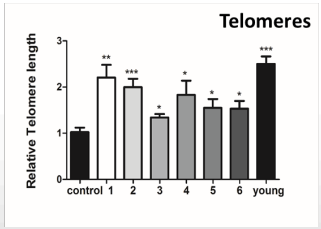
Small molecule modulation of splicing factor expression is associated with rescue from cellular senescence

Eva Latorre[1], Vishal C. Birar[2], Angela N. Sheerin[2], J. Charles C. Jeynes[3], Amy Hooper[1], Helen R. Dawe[4], David Melzer[1], Lynne S. Cox[5], Richard G. A. Faragher[2], Elizabeth L. Ostler[2*] and Lorna W. Harries[1*]









Gerontology

Gerontology
DOI: 10.1159/000504845

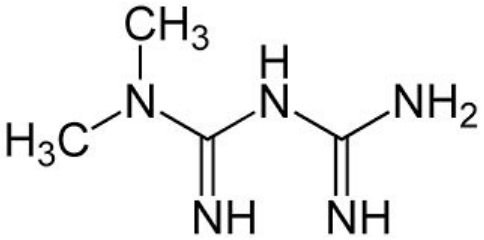
Resveralogues: From Novel Ageing Mechanisms to New Therapies?

Richard G.A. Faragher Elizabeth L. Ostler

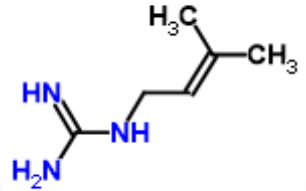
School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, UK

Drug repurposing: Metformin

- Derived from the natural product galegine.
- 1918, galegine shown to lower blood glucose
- 1957 first use of metformin
- Lowers blood glucose by very complex mechanisms
- A classic ‘dirty drug’ like resveratrol



Metformin



Galegine

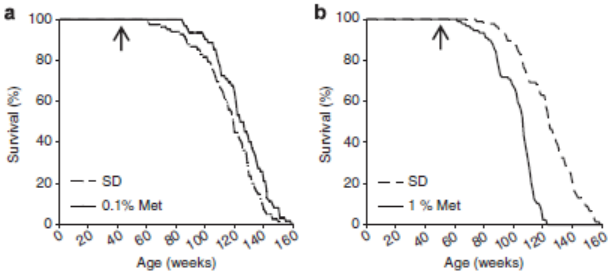
ARTICLE

Received 2 Nov 2012 | Accepted 26 Jun 2013 | Published 30 Jul 2013

DOI: 10.1038/ncomms3192

Metformin improves healthspan and lifespan in mice

Alejandro Martin-Montalvo[1,*], Evi M. Mercken[1,*], Sarah J. Mitchell[1,2,3], Hector H. Palacios[1], Patricia L. Mote[4], Morten Scheibye-Knudsen[5], Ana P. Gomes[6], Theresa M. Ward[1], Robin K. Minor[1], Marie-José Blouin[7], Matthias Schwab[8], Michael Pollak[7], Yongqing Zhang[9], Yinbing Yu[10], Kevin G. Becker[9], Vilhelm A. Bohr[5], Donald K. Ingram[11], David A. Sinclair[6], Norman S. Wolf[12], Stephen R. Spindler[4], Michel Bernier[1] & Rafael de Cabo[1]



Ageing Research Reviews 40 (2017) 31–44

Contents lists available at ScienceDirect

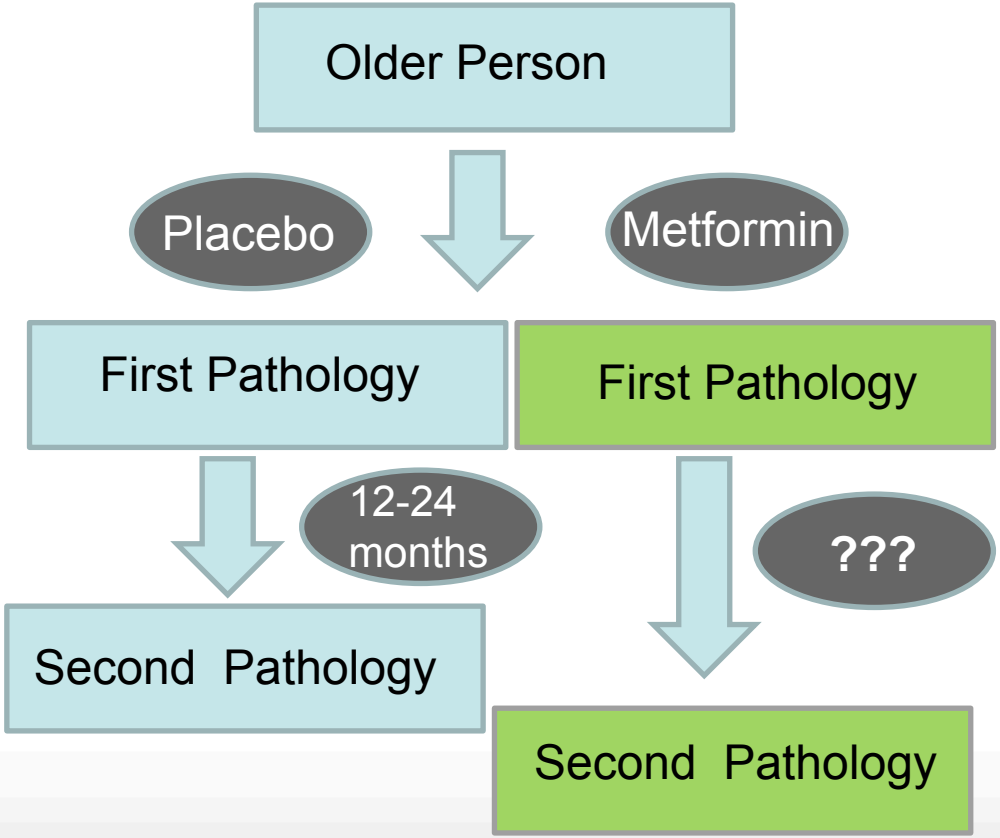
Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis

Jared M. Campbell[a,b,*], Susan M. Bellman[a], Matthew D. Stephenson[a], Karolina Lisy.[c]

Targeting **A**ging **W**ith **M**etformin

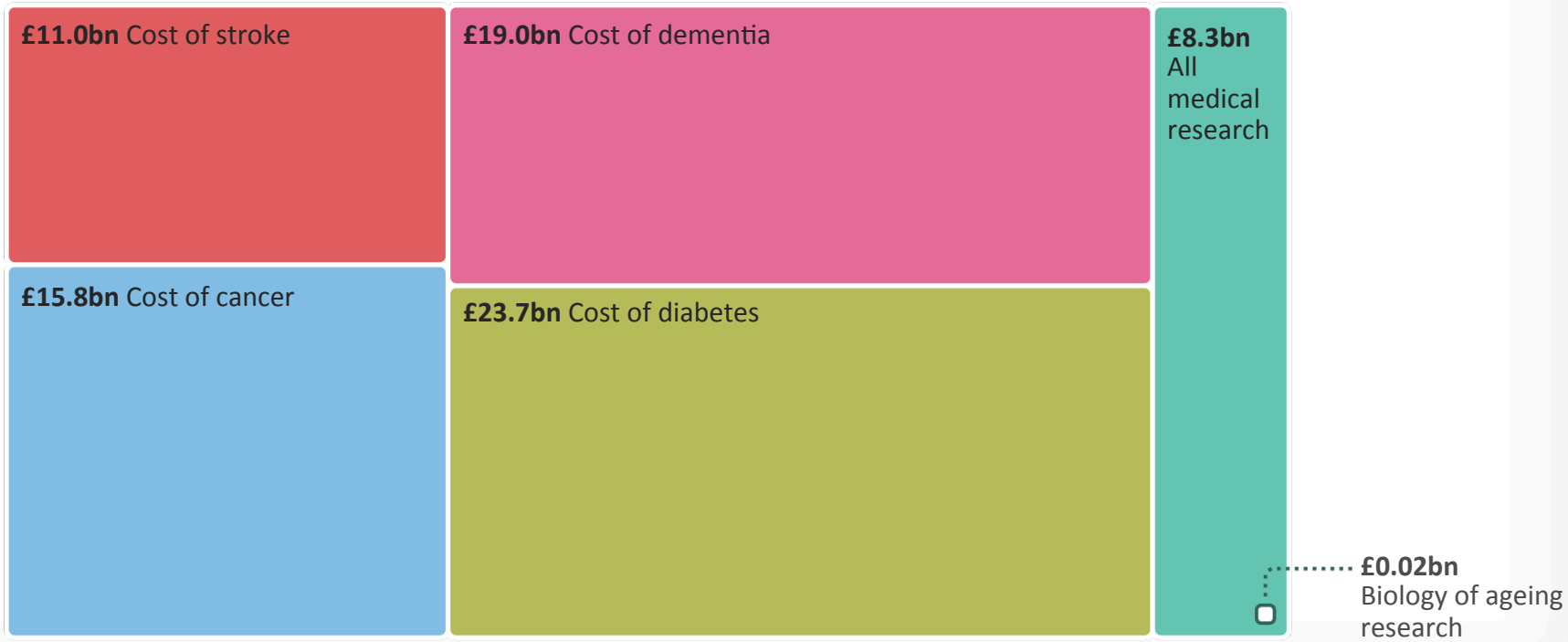


TAME

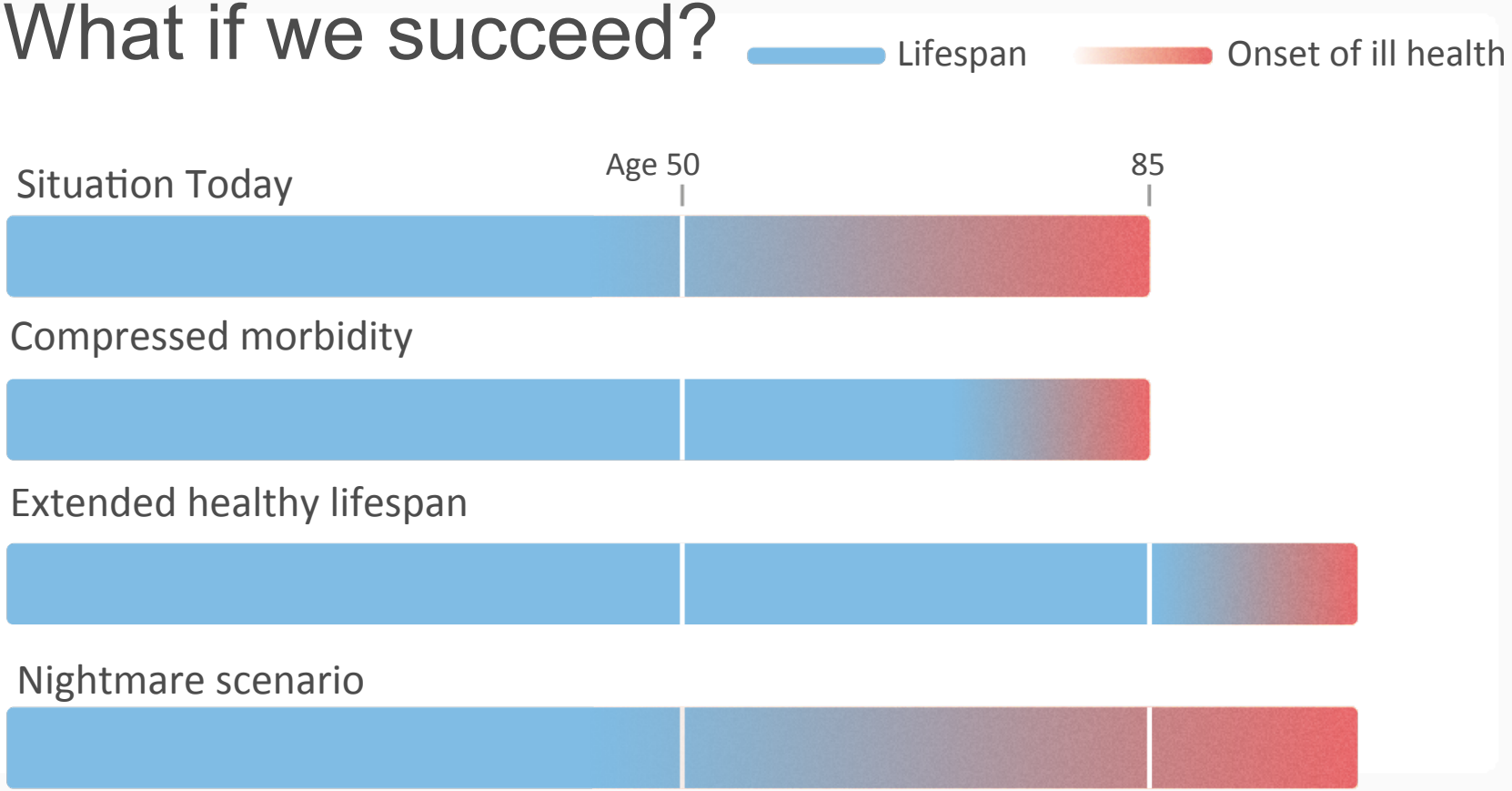
- Will show whether human ageing can be targeted and healthspan extended
- Will allow for FDA indications related to preventing ageing
- Will provided a template for biotech and pharma to move forward with next generation geroscience therapies

TAME requires $10,000,000/year for 5-6 years (for FDA approval). No problem right?

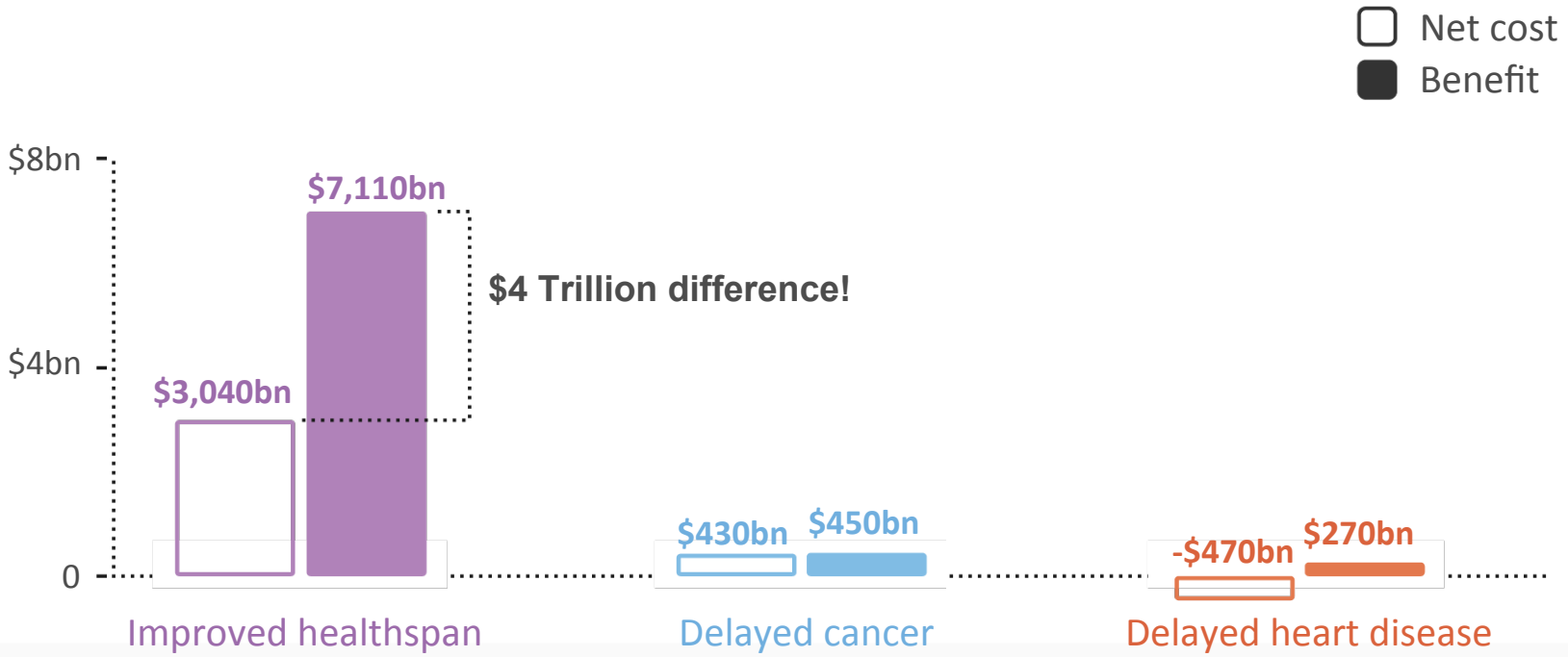
UK disease costs vs. research spend



What if we succeed?

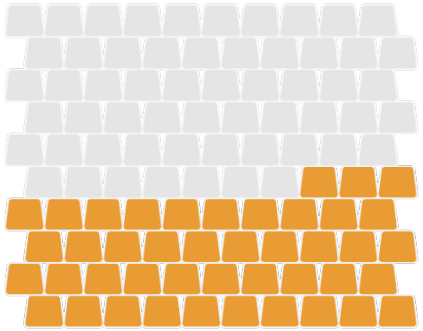


Society benefits from healthy old people

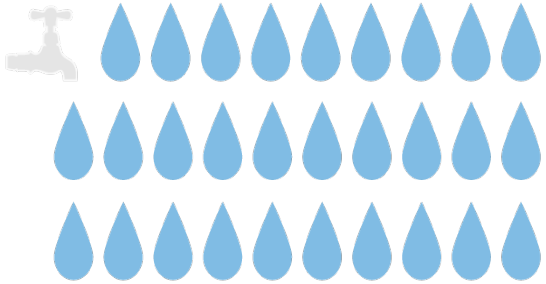


How much is $4 trillion?

The US alone could save $4 trillion if findings from ageing research were translated to the clinic. That is the same as:



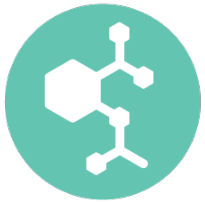
43% of all the gold ever mined



29 years of clean drinking water globally

1.7% of total global wealth

What's needed next?



A concerted effort to deal with the major logjams between the lab, the company and the clinic. The TAME trial is key to this.

An enabling environment for philanthropists, entrepreneurs Ad researchers alike. That's why we're here today.

Global action on a global issue. AFAR is leading on this and we w elcome other partners. Stick around to find out more.

afar american federation for aging research

GEROFUTURES THINK TANKS

Insights and Inspirations | 2021

THINK TANK I
Supporting Basic Science and Geroscience

THINK TANK II
Inviting Investment in Gerotherapeutics

THINK TANK III
Preparing the Translational Research Pipeline