The dam has broken: What does the new science of ageing mean for the pension risk transfer market?

Richard Faragher
Professor of Biogerontology

University of Brighton

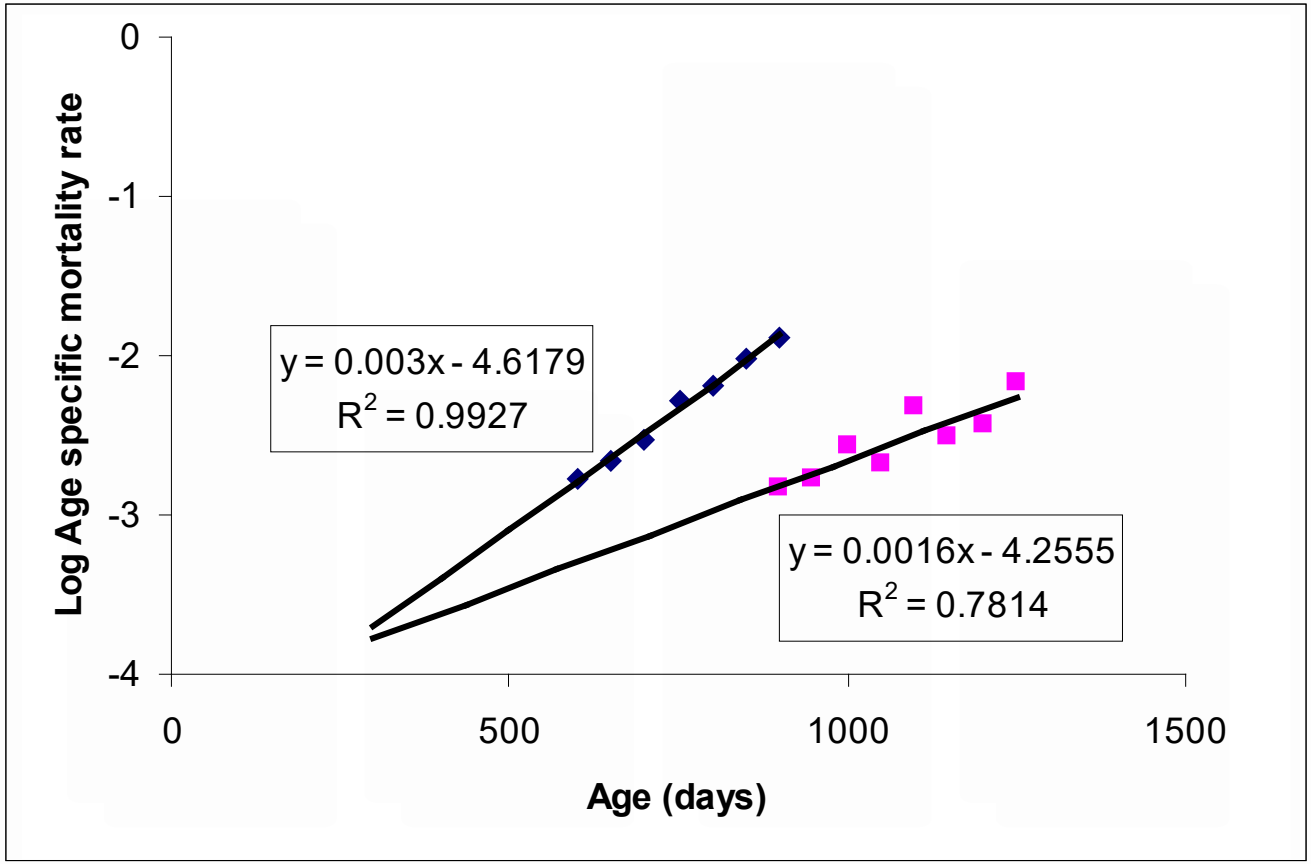
Ageing is similar between species

In geriatric (⩾30 years old) horses:

- **10%** were overweight
- **16%** were underweight
- **77%** of the horses were lame on at least one limb
- **97%** had a reduced range of motion in at least one joint
- **39%** showed abnormal moulting
- **100%** had at least one ophthalmic lesion
- **100%** had dental abnormalities

Ireland *et al.* (2012) Vet. J. 192: 57–64 A survey of health care and disease in geriatric horses aged 30 years or older

Ageing is captured by the Gompertz relationship



Environmental modifications alter rates of ageing

Ageing is ubiquitous and modulable

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

The companion dog as a unique translational model for aging

Andrea Mazzatenta[a,b,*], Augusto Carluccio[a], Domenico Robbe[a], Camillo Di Giulio[b], Alessandro Cellerino[c]

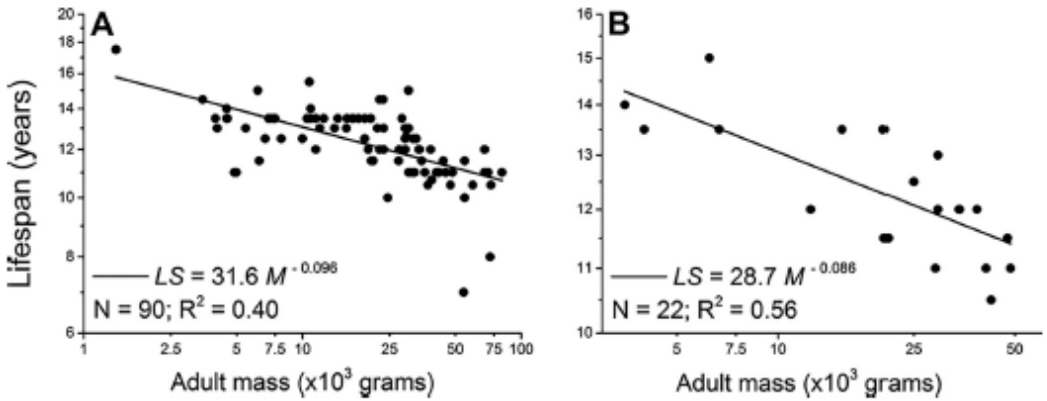


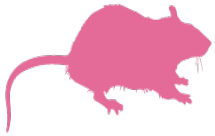
Fig. 3. Lifespan negatively scales, ~0.096 scaling power for the average lifespan across 90 breeds of dogs, with adult body mass in male (A) and female dogs (B). Each point represents one breed. The scaling powers were obtained by regressing the logarithmically transformed data. Reproduced with permission from [172].

Genetic backgrounds alter rates of ageing

Mechanisms and genetic pathways 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.

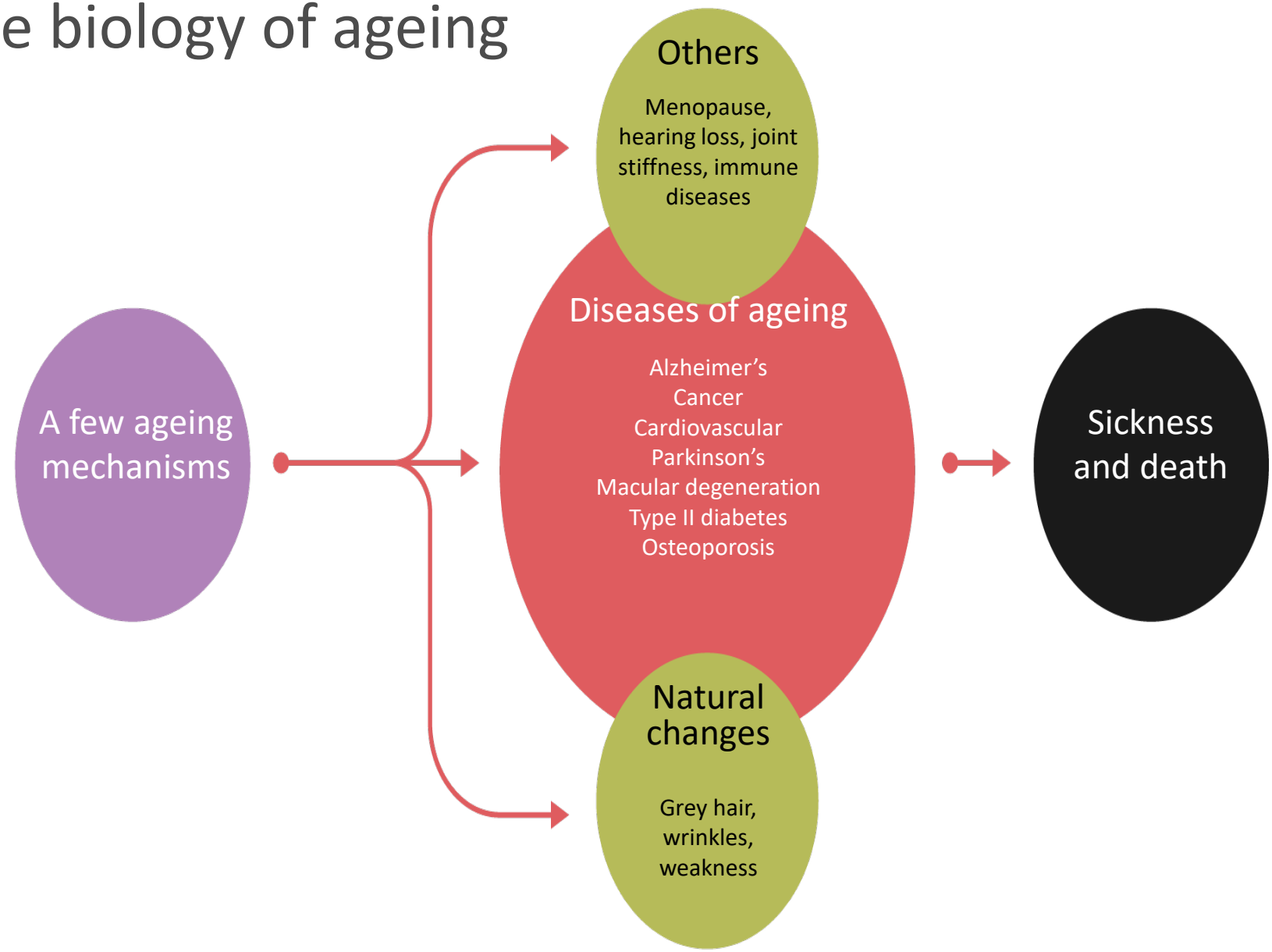
Colin Selman et al.

PNAS

FOXO3A genotype is strongly associated with human longevity.

Bradley J. Willcox et al.

The biology of ageing



What mechanisms maintain health?

- Occur in multiple species
- Nutrient Sensing mechanisms
- Tumour Suppression Mechanisms

Important take home: Targeting one hallmark also positively affects the others..

Lopez-Otın *et al*., Cell 2013

But how important are differences between species?

- Evolution of ageing is shaped by two mechanisms:
  - Antagonistic pleiotropy
  - Mutation accumulation
- The latter is a function of population size
- Humans have teetered on the verge of extinction for the last 60,000 years

Evolution: Human Bottlenecks

Am. J. Hum. Genet. 72:1171–1186, 2003

Features of Evolution and Expansion of Modern Humans, Inferred from Genomewide Microsatellite Markers

Lev A. Zhivotovsky,[1] Noah A. Rosenberg,[2] and Marcus W. Feldman[3]

[1]Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow; [2]Program in Molecular and Computational Biology, University of Southern California, Los Angeles; and [3]Department of Biological Sciences, Stanford University, Stanford, CA

We study data on variation in 52 worldwide populations at 377 autosomal short tandem repeat loci, to infer a demographic history of human populations. Variation at di-, tri-, and tetranucleotide repeat loci is distributed differently, although each class of markers exhibits a decrease of within-population genetic variation in the following order: sub-Saharan Africa, Eurasia, East Asia, Oceania, and America. There is a similar decrease in the frequency of private alleles. With multidimensional scaling, populations belonging to the same major geographic region cluster together, and some regions permit a finer resolution of populations. When a stepwise mutation model is used, a population tree based on T_D estimates of divergence time suggests that the branches leading to the present sub-Saharan African populations of hunter-gatherers were the first to diverge from a common ancestral population (~71–142 thousand years ago). The branches corresponding to sub-Saharan African farming populations and those that left Africa diverge next, with subsequent splits of branches for Eurasia, Oceania, East Asia, and America. African hunter-gatherer populations and populations of Oceania and America exhibit no statistically significant signature of growth. The features of population subdivision and growth are discussed in the context of the ancient expansion of modern humans.

PROCEEDINGS OF THE ROYAL SOCIETY B

FirstCite® e-publishing

Proc. R. Soc. B
doi:10.1098/rspb.2009.1473
Published online

Evidence that two main bottleneck events shaped modern human genetic diversity

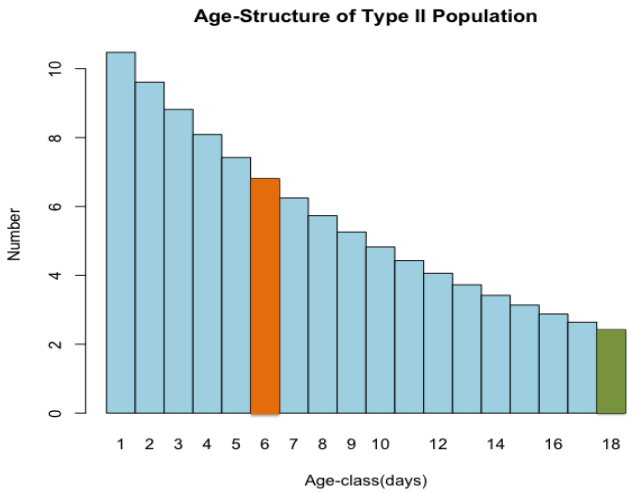
W. Amos* and J. I. Hoffman

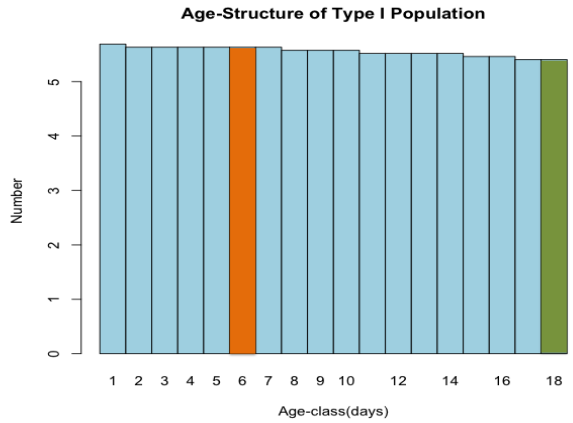
Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, UK

There is a strong consensus that modern humans originated in Africa and moved out to colonize the world approximately 50 000 years ago. During the process of expansion, variability was lost, creating a linear gradient of decreasing diversity with increasing distance from Africa. However, the exact way in which this loss occurred remains somewhat unclear: did it involve one, a few or a continuous series of population bottlenecks? We addressed this by analysing a large published dataset of 783 microsatellite loci genotyped in 53 worldwide populations, using the program 'BOTTLENECK'. Immediately following a sharp population decline, rare alleles are lost faster than heterozygosity, creating a transient excess of heterozygosity relative to allele number, a feature that is used by BOTTLENECK to infer historical events. We find evidence of two primary events, one 'out of Africa' and one placed around the Bering Strait, where an ancient land bridge allowed passage into the Americas. These findings agree well with the regions of the world where the largest founder events might have been expected, but contrast with the apparently smooth gradient of variability that is revealed when current heterozygosity is plotted against distance from Africa.

- Humanity has been through at least TWO major evolutionary bottlenecks.
- This is not the case for most species- including the ones we use to study ageing mechanisms.
- Why does this matter?

Humans may be an outlier…





- The fundamental genetic processes regulating ageing are probably altered by both bottlenecks and shifts in population type.
- For any given species this may alter the relative contribution to ageing from Mutation Accumulation and Antagonistic Pleiotropy.

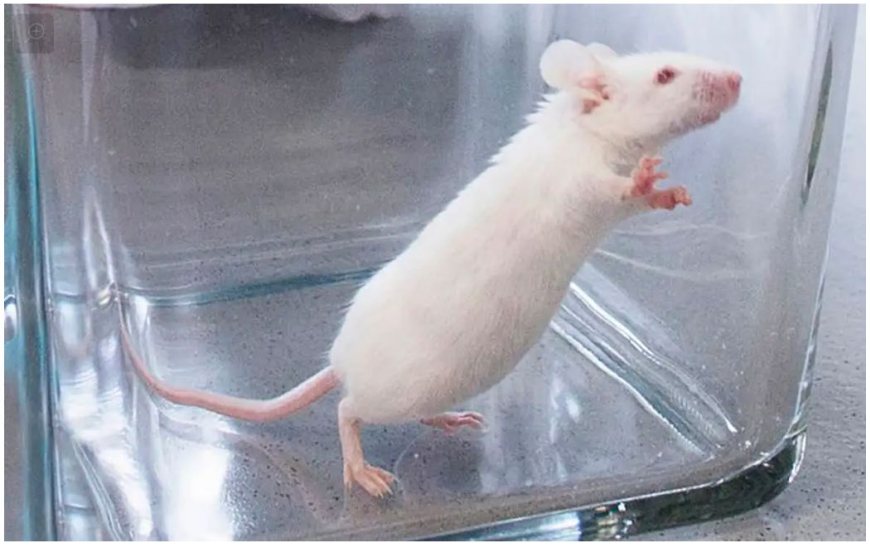
Overall & Faragher (2019) *Population type alters the rate of ageing.* Heredity 123:273.

Or put more simply..

- Most mice die of cancer.
- Most humans don't.
- So anything that reduces cancer incidence or severity in mice will have a bigger impact on their lifespan than it will on people.
- But that doesn't mean the effect on humans will be zero.

Lab Mouse Nervous For First Day Of New Job Getting Cancer

Published January 27, 2017



Ageing mechanisms associate with and predict human pathologies

Received: 4 May 2021 | Revised: 7 October 2021 | Accepted: 12 November 2021

DOI: 10.1111/acel.13524

Aging Cell WILEY

ORIGINAL PAPER

Biological mechanisms of aging predict age-related disease co-occurrence in patients

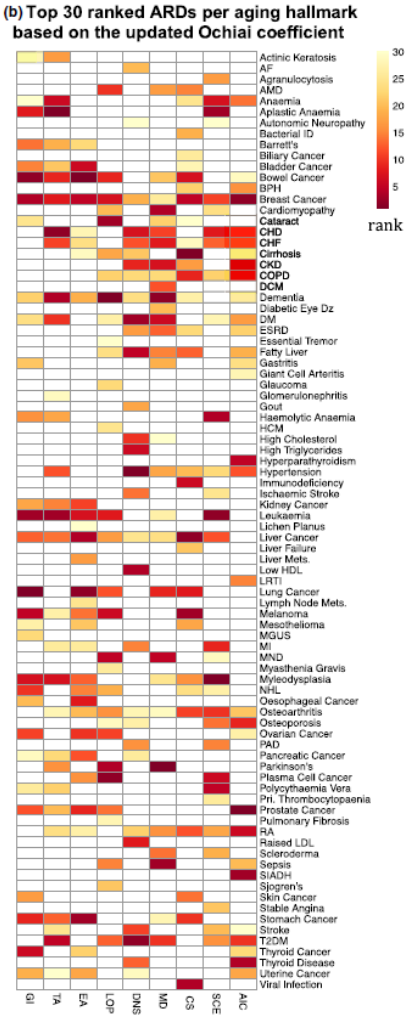
Helen C. Fraser[1] | Valerie Kuan[2,3,4] | Ronja Johnen[5] | Magdalena Zwierzyna[6] | Aroon D. Hingorani[3,4,6] | Andreas Beyer[5,7] | Linda Partridge[1,8]

Abstract

Genetic, environmental, and pharmacological interventions into the aging process can confer resistance to multiple age-related diseases in laboratory animals, including rhesus monkeys. These findings imply that individual mechanisms of aging might contribute to the co-occurrence of age-related diseases in humans and could be targeted to prevent these conditions simultaneously. To address this question, we text mined 917,645 literature abstracts followed by manual curation and found strong, non-random associations between age-related diseases and aging mechanisms in humans, confirmed by gene set enrichment analysis of GWAS data. Integration of these associations with clinical data from 3.01 million patients showed that age-related diseases associated with each of five aging mechanisms were more likely than chance to be present together in patients. Genetic evidence revealed that innate and adaptive immunity, the intrinsic apoptotic signaling pathway and activity of the ERK1/2 pathway were associated with multiple aging mechanisms and diverse age-related diseases. Mechanisms of aging hence contribute both together and individually to age-related disease co-occurrence in humans and could potentially be targeted accordingly to prevent multimorbidity.

KEYWORDS

age-related disease, aging, aging hallmarks, genetics, multimorbidity



And remember modulating one hallmark positively modulates the others…

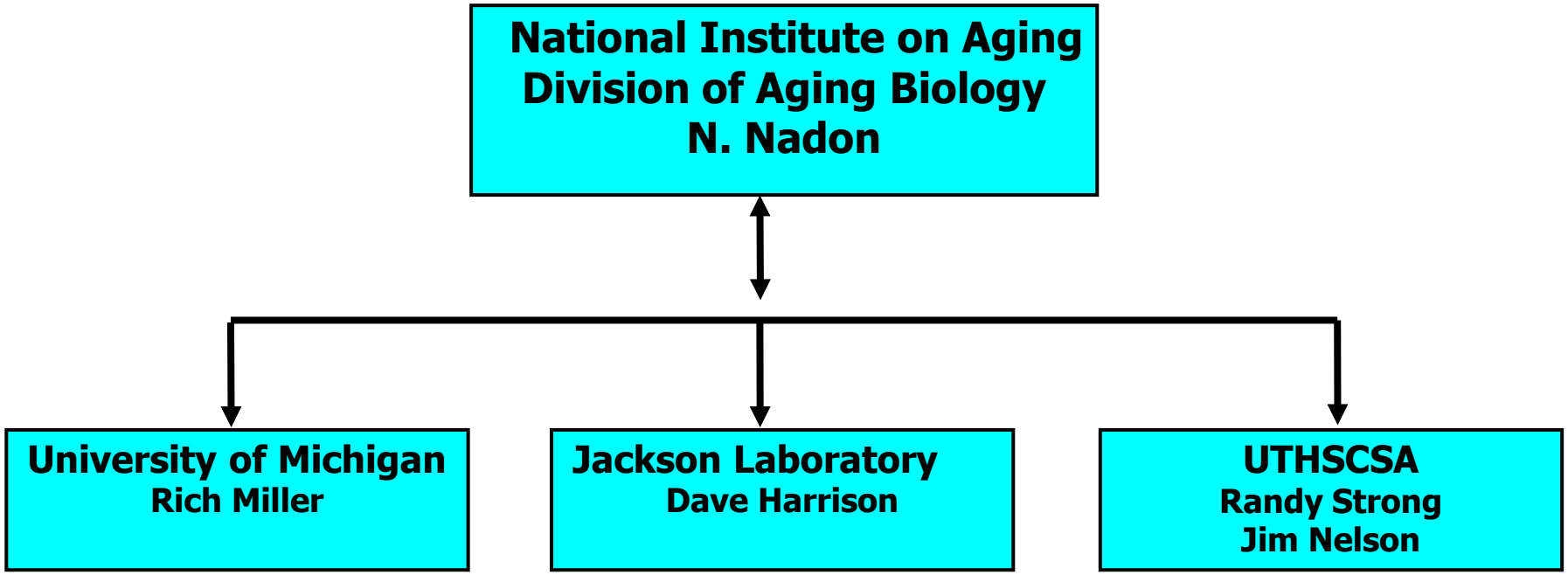
Potential Scenarios

Joseph Lu

Uli Stengele

- 10% increase in life expectancy *business as usual*
- 25-30% increase in life expectancy ***business as unusual***
- 45% increase in life expectancy ***business as extraordinary***
- Modelling currently confidential
- What biological rationales have we used?

Key Features of ITP



Key Features of ITP

- Testing at three sites gives a 80% power to detect 10% change (two-sided), for each sex, pooling across sites.
- Genetically heterogeneous mice (UM-HET3)
  - Grandparents: BALB, B6, C3H, DBA/2
- Anyone can suggest an intervention

  -- Evaluation by Access Committee

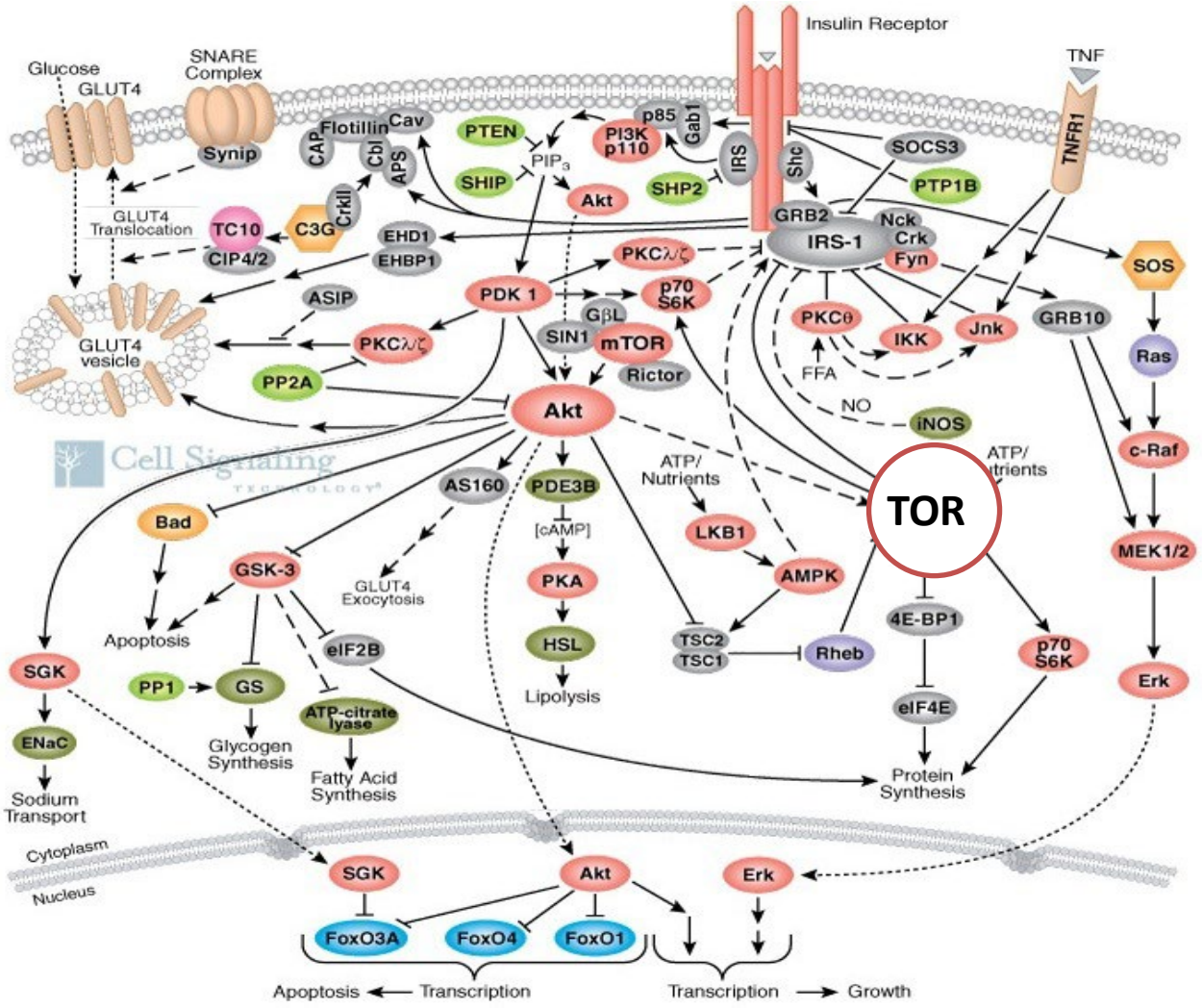
Interventions that Extend Longevity

- *Glycine (4-6% males and females)*
- *Nordihydroguaiaretic Acid (males, 10%)**
- *α-Estradiol – non-feminizing (males, 10%)*
- *Aspirin (males, 10%)*
- *Protandim®- Nrf2 activator (males 7%)*
- **Canagliflozin (14% males)****
- **Acarbose – glucosidase inhibitor (males, 22%)**
- **Rapamycin (males & females, 10-25%)**

*increases tumour incidence

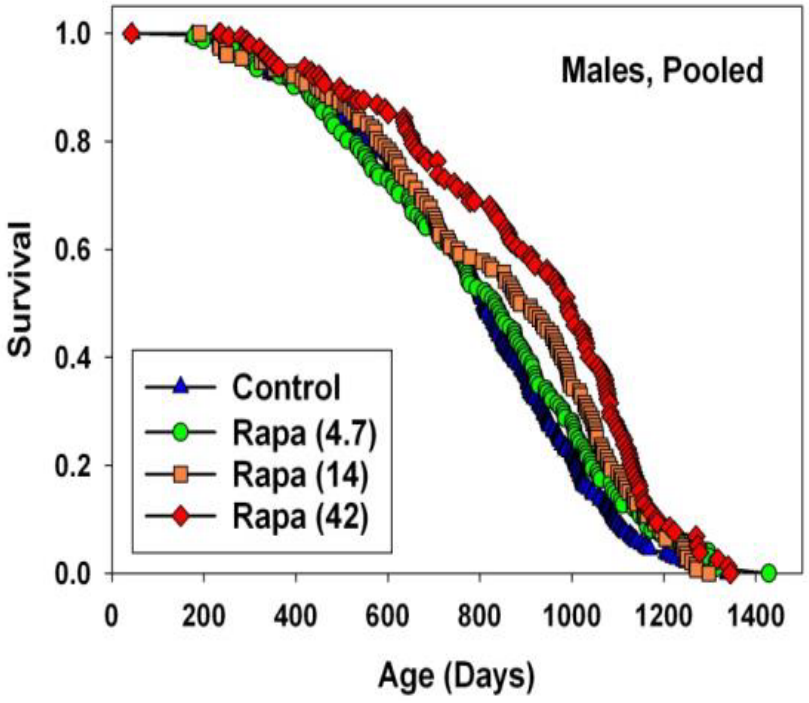
**increased lifespan 9% at 90th percentile survival

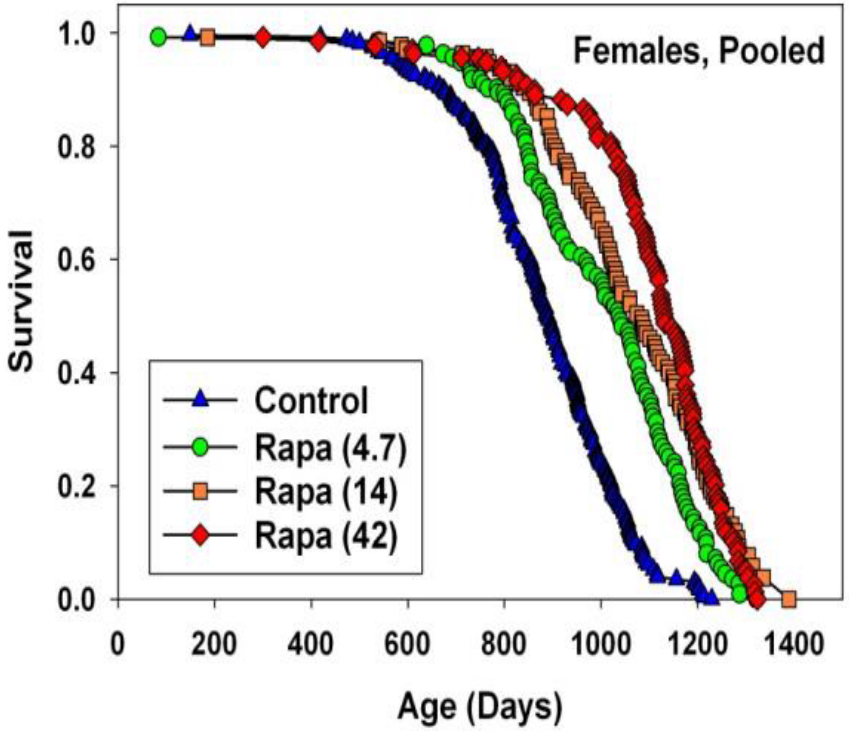
Core Nutrient Signalling Pathway



Most of the long lived mutants in lower organisms are in this pathway

Rapamycin: ***business as unusual***





Miller et al. Aging Cell 2013

Rapamycin improves health and may be useful in early AD

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.

And giving it early isn't a bad idea…

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

INFECTIOUS DISEASE

TORC1 inhibition enhances immune function and reduces infections in the elderly

Joan B. Mannick[1*†], Melody Morris[1], Hans-Ulrich P. Hockey[2], Guglielmo Roma[3], Martin Beibel[3], Kenneth Kulmatycki[1], Mollie Watkins[1], Tea Shavlakadze[1], Weihua Zhou[1], Dean Quinn[4], David J. Glass[1], Lloyd B. Klickstein[1*]

Inhibition of the mechanistic target of rapamycin (mTOR) protein kinase extends life span and ameliorates aging-related pathologies including declining immune function in model organisms. The objective of this phase 2a randomized, placebo-controlled clinical trial was to determine whether low-dose mTOR inhibitor therapy enhanced immune function and decreased infection rates in 264 elderly subjects given the study drugs for 6 weeks. A low-dose combination of a catalytic (BEZ235) plus an allosteric (RAD001) mTOR inhibitor that selectively inhibits target of rapamycin complex 1 (TORC1) downstream of mTOR was safe and was associated with a significant ($P = 0.001$) decrease in the rate of infections reported by elderly subjects for a year after study drug initiation. In addition, we observed an up-regulation of antiviral gene expression and an improvement in the response to influenza vaccination in this treatment group. Thus, selective TORC1 inhibition has the potential to improve immune function and reduce infections in the elderly.

Ineffective flu vaccine resulted in 50,000 excess deaths in the UK in 2018.

Post diagnosis life expectancy for patients with AD is 3 -10 years.

Rapamycin rescues vascular, metabolic and learning deficits in apolipoprotein E4 transgenic mice with pre-symptomatic Alzheimer's disease

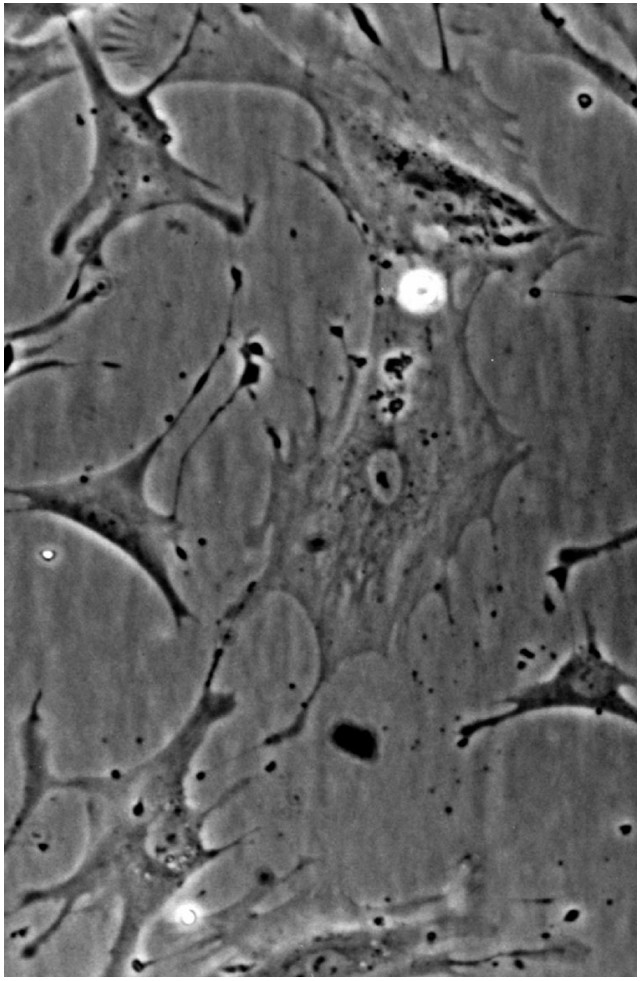
Ai-Ling Lin[1,2,3], Jordan B Jahrling[4,6], Wei Zhang[5], Nicholas DeRosa[4,6], Vikas Bakshi[1], Peter Romero[4], Veronica Galvan[4,6] and Arlan Richardson[7]

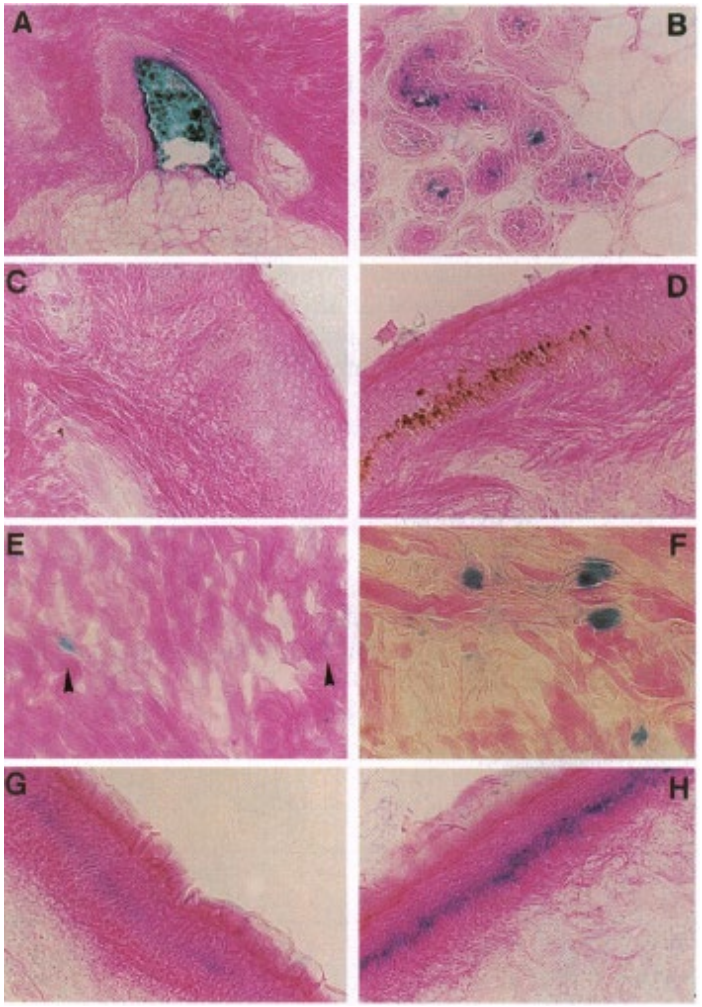
JCBFM

Journal of Cerebral Blood Flow & Metabolism
2017, Vol. 37(1) 217–226

DOI: 10.1177/0271678X15621575
jcbfm.sagepub.com
SAGE

Tumour suppression mechanisms





What is ‘cell senescence’?

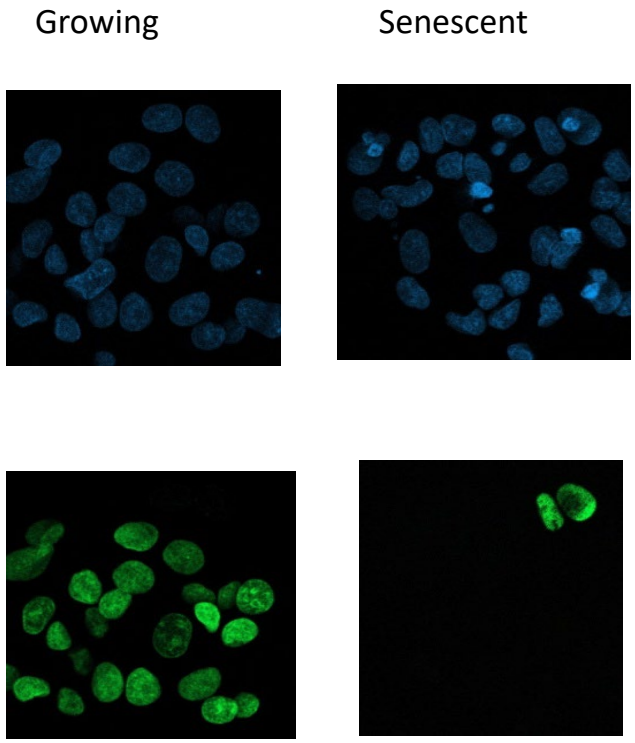
- Viable, stable state of cell cycle (G_1) arrest in cells which are normally proliferation competent.
- Senescent cells have a different phenotype to their growth competent precursors.
- **NOT** cell death.
- **NOT** terminal differentiation.
- “Senescent cells” are **NOT** “cells I got from some old people/old mice/my geriatric dog etc”*

*They’re NOT, really, trust me on this...

How can senescent cells be simply detected?

- Label exclusion: Radiolabelled nucleotides (^{3}H-thymidine) or artificial analogues (e.g. bromodeoxyuridine) are incorporated into cells at DNA replication and excluded from senescent ones

- Detection of endogenous proliferation markers (e.g. PCNA or Ki67)



Why does senescence exist?

VARIATION IN THE LIFE-SPAN OF CLONES DERIVED FROM HUMAN DIPLOID CELL STRAINS

J. R. SMITH and L. HAYFLICK

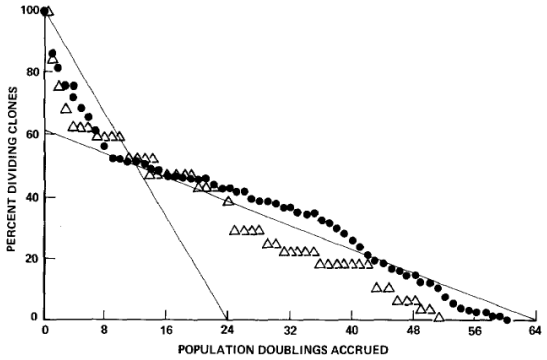


FIGURE 1 The percentage of isolated cells undergoing a specific number of population doublings. The two sets of clones were from different WI-38 subcultivation series. In one set, 216 clones were isolated at the ninth PDL and grown in CMIII (the mass culture stopped growing at PDL 53) ●; 50 clones isolated at the eighth PDL and grown in CMI (the mass culture reached phase III at the 45th PDL) △.

THE JOURNAL OF CELL BIOLOGY · VOLUME 62, 1974 · pages 48–53

- Good evidence that senescence functions as a tumour suppression mechanism. For a single cell with a mutation to expand to a clone of $1x10^6$ cells (e.g. Enough for **one** cell in the clone to acquire a second mutation) takes about 20 population doublings. **This is Antagonistic Pleiotropy in action**.

- Culture of primary cells are typically composed of multiple clones with different reproductive potentials. Most stop growing relatively early.

Senescent cells show altered gene expression

Experimental Eye Research 88 (2009) 277–285

Contents lists available at ScienceDirect

Experimental Eye Research

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

A transcriptomic analysis of the EK1.Br strain of human fibroblastoid keratocytes: The effects of growth, quiescence and senescence

David Kipling [b], Dawn L. Jones [a], S. Kaye Smith [b], Peter J. Giles [b], Katrin Jennert-Burston [a], Badr Ibrahim [a], Angela N.P. Sheerin [a], Amy J.C. Evans [b], William Rhys-Williams [c], Richard G.A. Faragher [a,*]

Experimental Gerontology 44 (2009) 659–665

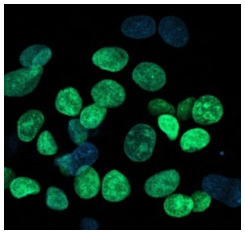
Contents lists available at ScienceDirect

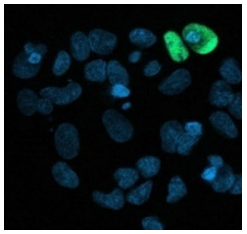
Experimental Gerontology

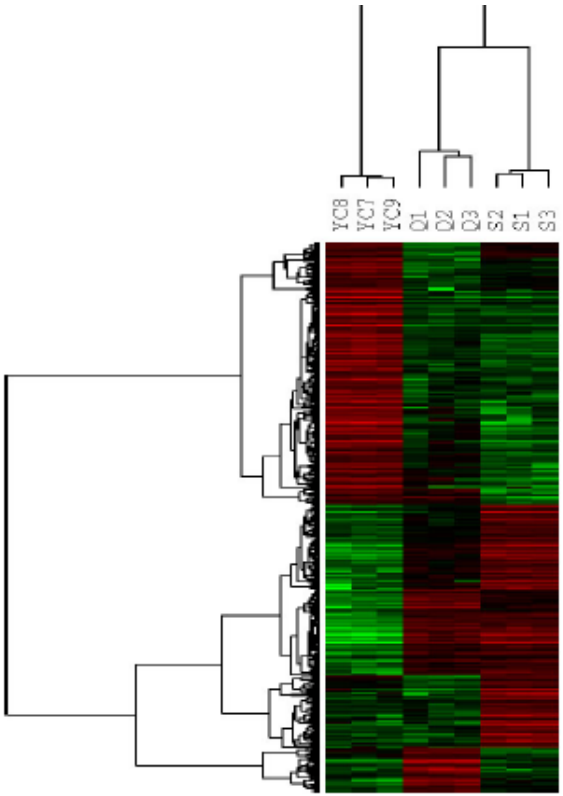
journal homepage: www.elsevier.com/locate/expgero

Microarray analysis of senescent vascular smooth muscle cells: A link to atherosclerosis and vascular calcification

Dominick G.A. Burton [a], Peter J. Giles [b], Angela N.P. Sheerin [a], S. Kaye Smith [b], Jessica J. Lawton [a], Elizabeth L. Ostler [a], William Rhys-Williams [c], David Kipling [b], Richard G.A. Faragher [a,*]







Genes upregulated during proliferation

Genes upregulated in senescence

A lot of potential for degenerative effects

OPINION — BRAIN AGEING SERIES

Insights into CNS ageing from animal models of senescence

Mark Yeoman, Greg Scutt and Richard Faragher

Abstract | In recent years, novel model systems have made significant contributions to our understanding of the processes that control the ageing of whole organisms. However, there are limited data to show that the mechanisms that gerontologists have identified as having a role in organismal ageing contribute significantly to the ageing of the central nervous system. Two recent discoveries illustrate this particularly well. The first is the consistent failure of researchers to demonstrate a simple relationship between organismal ageing and oxidative stress — a mechanism often assumed to have a primary role in brain ageing. The second is the demonstration that senescent cells play a causal part in organismal ageing but remain essentially unstudied in a CNS context. We argue that the animal models now available (including rodents, flies, molluscs and worms), if properly applied, will allow a paradigm shift in our current understanding of the normal processes of brain ageing.

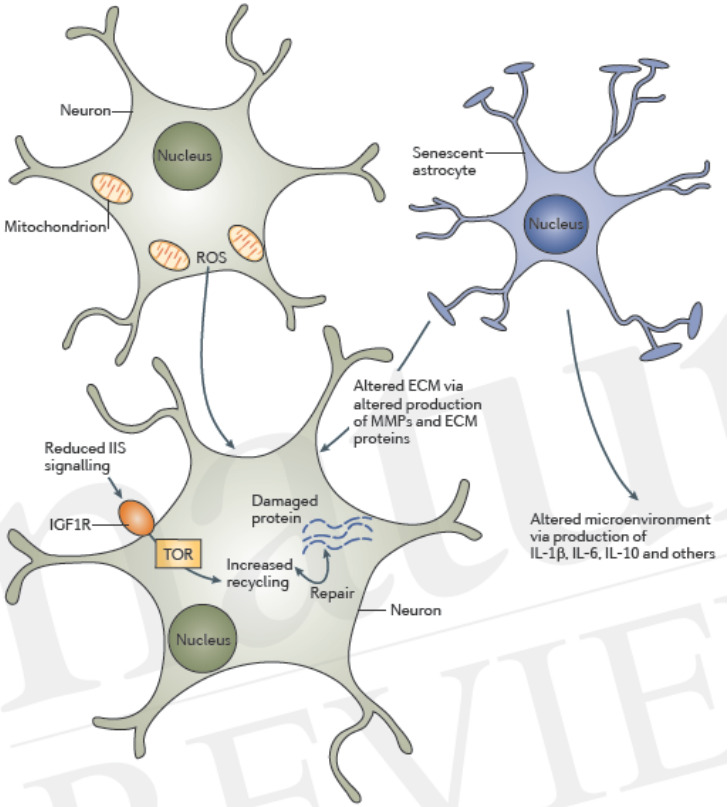


Figure 1 | **Schematic representation of the putative effects of the major ageing mechanisms on the CNS.** Reactive oxygen species (ROS) are produced as a by-product of oxidative metabolism and potentially add to the load of damaged macromolecules accumulated by a cell over time. Reduced signalling through the insulin/insulin-like growth factor signalling (IIS) pathway via mammlian target of rapamycin (mTOR) leads to the increased activity of recycling pathways dealing with oxidized or glycated proteins. Senescent cells in the vicinity produce a mixture of matrix-degrading enzymes and alter their production of matrix proteins. They also typically overproduce some pro-inflammatory cytokines and may cease to produce survival factors. However, many aspects of this signature are strongly cell-type-specific. ECM, extracellular matrix; IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; MMPs, matrix metalloproteinases.

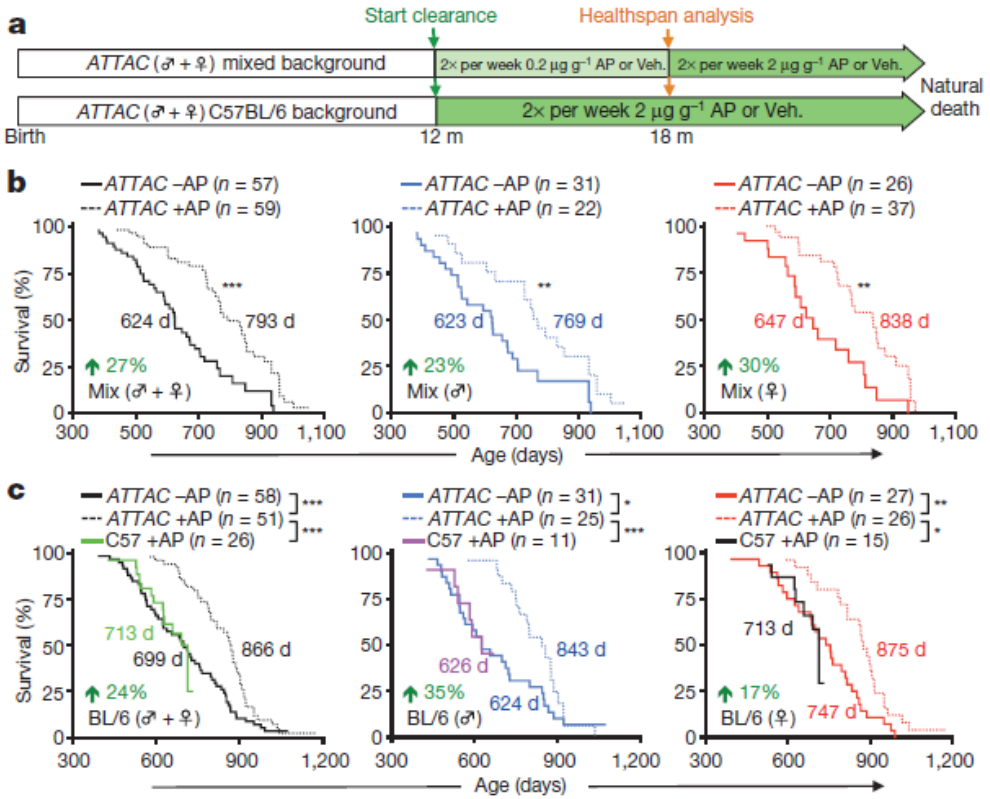
Senolysis: *Business as unusual*

Naturally occurring p16^{Ink4a}–positive cells shorten healthy lifespan

Darren J. Baker[1], Bennett G. Childs[2], Matej Durik[1], Melinde E. Wijers[1], Cynthia J. Sieben[2], Jian Zhong[1], Rachel A. Saltness[1], Karthik B. Jeganathan[1], Grace Casaclang Verzosa[3], Abdulmohammad Pezeshki[4], Khashayarsha Khazaie[4], Jordan D. Miller[3] & Jan M. van Deursen[1,2]

24-27% increase in lifespan by mouse strain.

17-35% increase by sex.



Removing senescent cells in mice increases exercise capacity

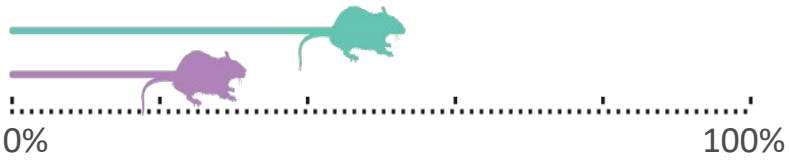
Old mouse with senescent cells removed

Old mouse

Distance travelled at time of exhaustion

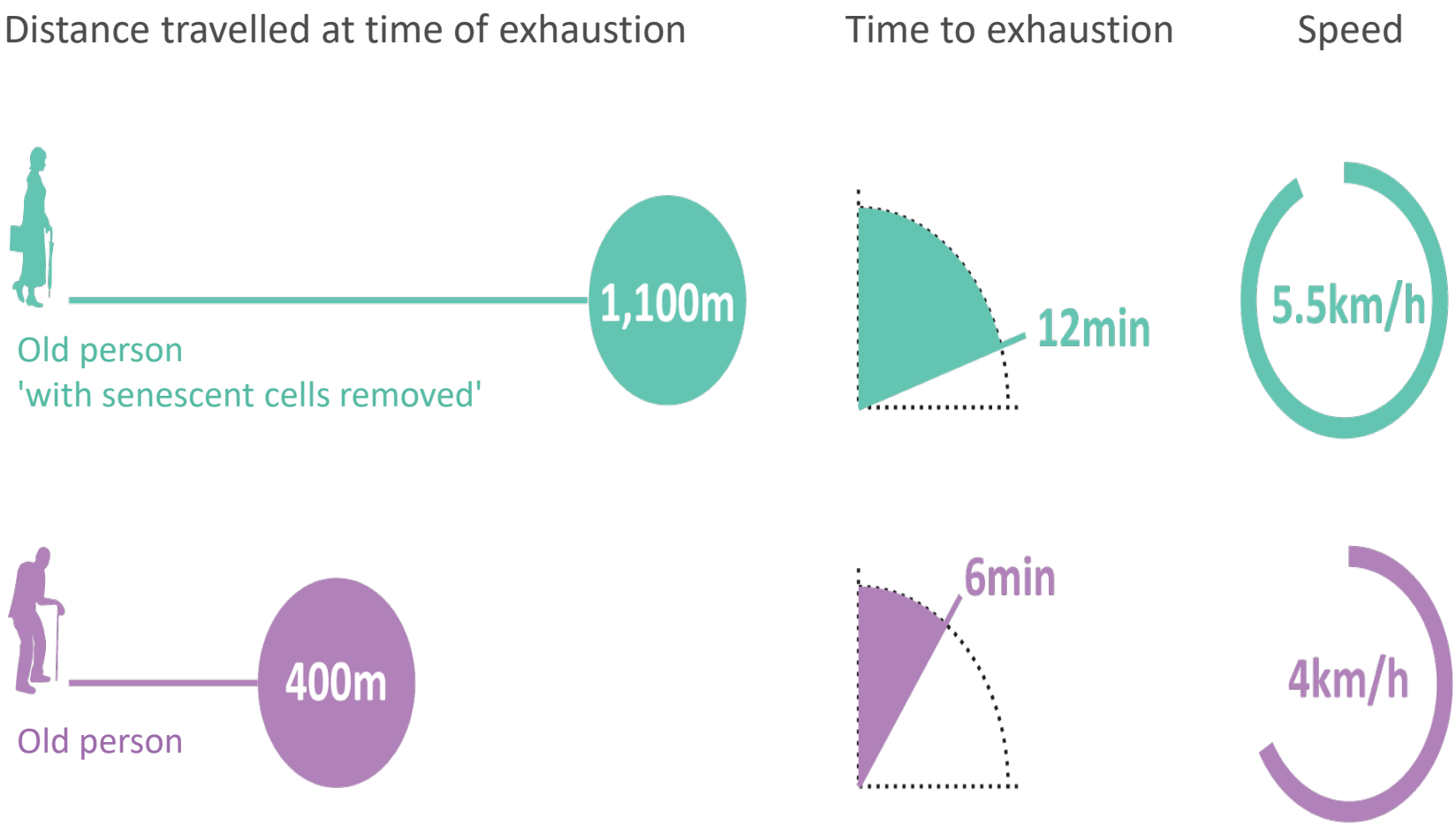
+175%

Running time to exhaustion



+100%

Mice today, independent elders tomorrow?



Rapid progress is 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]

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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

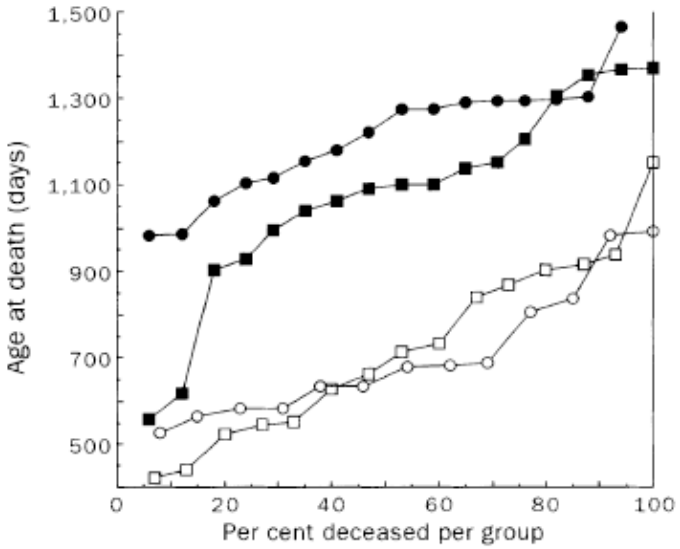
DKD may shorten life expectancy by 16 years…

More than 60 ongoing senolytic trials

ClinicalTrials.gov Search Results 07/07/2022

	Title	Status	Study Results	Conditions	Interventions
1	Senolytic Agents &Osteoarthritis	Not yet recruiting	No Results Available	•Osteoarthritis	•Drug: Quercetin Cap/Tab ,Fisetin Cap/Tab •Drug: Quercetin Cap/Tab,Fisetin Cap/ tab,Glycyrrhizin capsules •Other: Placebo
2	Senolytic Agent Improve the Benefit of Platelet-Rich Plasma and Losartan	Recruiting	No Results Available	•Femoroacetabular Impingement	•Drug: Fisetin •Drug: Placebo
3	Use of Senolytic and Anti-Fibrotic Agents to Improve the Beneficial Effect of Bone Marrow Stem Cells for Osteoarthritis	Recruiting	No Results Available	•Osteoarthritis, Knee	•Drug: Fisetin •Drug: Losartan •Drug: Placebo - Losartan •Drug: Placebo Fisetin
4	Senolytic Therapy to Modulate Progression of Alzheimer's Disease	Active, not recruiting	No Results Available	•Alzheimer Disease	•Drug: Dasatinib + Quercetin
5	Senolytic Drugs Attenuate Osteoarthritis-Related Articular Cartilage Degeneration: A Clinical Trial	Active, not recruiting	No Results Available	•Osteoarthritis, Knee	•Dietary Supplement: Fisetin •Drug: Placebo oral capsule
6	Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD) Study	Recruiting	No Results Available	•Alzheimer Disease, Early Onset •Mild Cognitive Impairment	•Drug: Dasatinib + Quercetin •Other: Placebo Capsules
7	An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer	Recruiting	No Results Available	•Frailty •Childhood Cancer	•Drug: Dasatinib plus Quercetin •Drug: Fisetin
8	Senescence in Chronic Kidney Disease	Enrolling by invitation	No Results Available	•Chronic Kidney Disease	•Drug: Group 2: Dasatinib •Drug: Group 2: Quercetin
9	Cellular Senescence and COVID-19 Long-Hauler Syndrome	Recruiting	No Results Available	•SARS-CoV2 Infection	
10	Targeting Senescence to Reduce Osteoarthritis Pain and cartilagE Breakdown (ROPE)	Not yet recruiting	No Results Available	•Osteoarthritis, Knee	•Drug: High-dose/short-duration Fisetin •Drug: Low-dose/sustained-duration Fisetin •Other: Oral placebo capsule
11	Targeting Cellular Senescence With Senolytics to Improve Skeletal Health in Older Humans	Recruiting	No Results Available	•Healthy	•Drug: Dasatinib •Drug: Quercetin •Drug: Fisetin
12	COVFIS-HOME: COVID-19 Pilot Study of Fisetin to Alleviate Dysfunction and Decrease Complications	Enrolling by invitation	No Results Available	•Covid19 •Coronavirus Infection	•Drug: Fisetin
13	COVID-FIS: Pilot in COVID-19 (SARS-CoV-2) of Fisetin in Older Adults in Nursing Homes	Enrolling by invitation	No Results Available	•Covid19 •SARS-CoV Infection	•Drug: Fisetin •Drug: Placebo
14	COVID-FISETIN: Pilot in SARS-CoV-2 of Fisetin to Alleviate Dysfunction and Inflammation	Enrolling by invitation	No Results Available	•Covid19	•Drug: Placebo •Drug: Fisetin

Business as extraordinary?



Longevity in male and female normal and Ames dwarf mice. Each point on the graph represents an individual animal surviving to the specific age indicated versus the percentage of animals deceased per group. Dwarfs live longer than normal mice regardless of gender ($P < 0.0001$). Mean age at death (days) ± s.e.m: normal male (open squares), 723 ± 54; normal female (open circles), 718 ± 45; dwarf male (closed squares), 1,076 ± 56; dwarf female (closed circles), 1,206 ± 32. One dwarf female is still alive.

48%-67% lifespan increase depending on sex in *Ames* dwarf mice.

Multiple long lived strains exist

Table 1
Survival characteristics for mouse models with increased life span

Mouse models		Life span (days)[a]				Body weight[b] (% of WT)
Mutant mice	Genetic background	Wild-type mice	Mutant mice	Percent increase	n^c	
Ames dwarf mice (Brown-Borg et al., 1996)	Ames stock					33
Females		718 ± 45	1206 ± 32	68	15/17	
Males		723 ± 54	1076 ± 56	49	13/17	
Snell dwarf mice (Flurkey et al., 2002)	DW/J *Pit1*^{dw} × C3H/HeJ *Pit1*$^{dw\text{-}J}$					33
Females		811 ± 20	1148 ± 39	42	48/23	
Males		822 ± 34	1037 ± 53	26	23/20	
Ghrhr$^{lit/lit}$ mice (Flurkey et al., 2001)	C57BL/6					67
Females		857 ± 169	1070 ± 127	25	Not indicated	
Males		886 ± 148	1093 ± 186	23	Not indicated	
GHR/BP$^{-/-}$ mice (Coschigano et al., 2000)	129Ola × BalbC					40
Females		749 ± 41	1031 ± 41	38	13/11	
Males		629 ± 72	975 ± 106	55	7/7	
GHR/BP$^{-/-}$ mice (Coschigano et al., 2003)	C57BL/6					41
Females		821 ± 49	956 ± 80	16	17/19	
Males		756 ± 68	951 ± 50	26	22/14	
p66$^{shc-/-}$ mice (Migliaccio et al., 1999)	129/Sv					100
Sex not indicated		761 ± 191	973 ± 37	30	14/15	
*Igf*1$r^{+/-}$ mice (Holzenberger et al., 2003)	129/Sv					92–94
Females		568 ± 49	756 ± 46	33	17/20	
FIRKO mice (Blüher et al., 2003)	129/Sv × C57Bl/6					75–85
Mixed sex		753	887	18	67/60	

[a] Mean ± SEM.
[b] Weight at 10 months of age.
[c] Number of wild-type mice/number of mutant mice.

ACTUARIAL SPECIALTIES | HEALTH | LIFE INSURANCE

Breaking the Dam

What the revolution in our understanding of the mechanisms of aging may mean for human life expectancy

RICHARD FARAGHER, JOSEPH LU, ULI STENGELE AND FRED SLATER

JUNE 2023

Figure 1

Scenario	Assumed Increase in Life Expectancy of Women Aged 65 by 2040[9]	Increase in Value of Immediate Annuities
A. Compounds in clinical trials made available immediately (Dasatinib & Quercetin)[10]	2 years	8%
B. Increased understanding of the biology of ultra-long-lived mice[11] Interventions that reduce mortality rates by 55% in 10 years	6 years	16%
C. Scenario B would happen twice—now and from 2050	10 years	25%

Note: Life expectancies are calculated based on U.S. Social Security life tables and mortality improvements, for illustration.

Other routes to progress

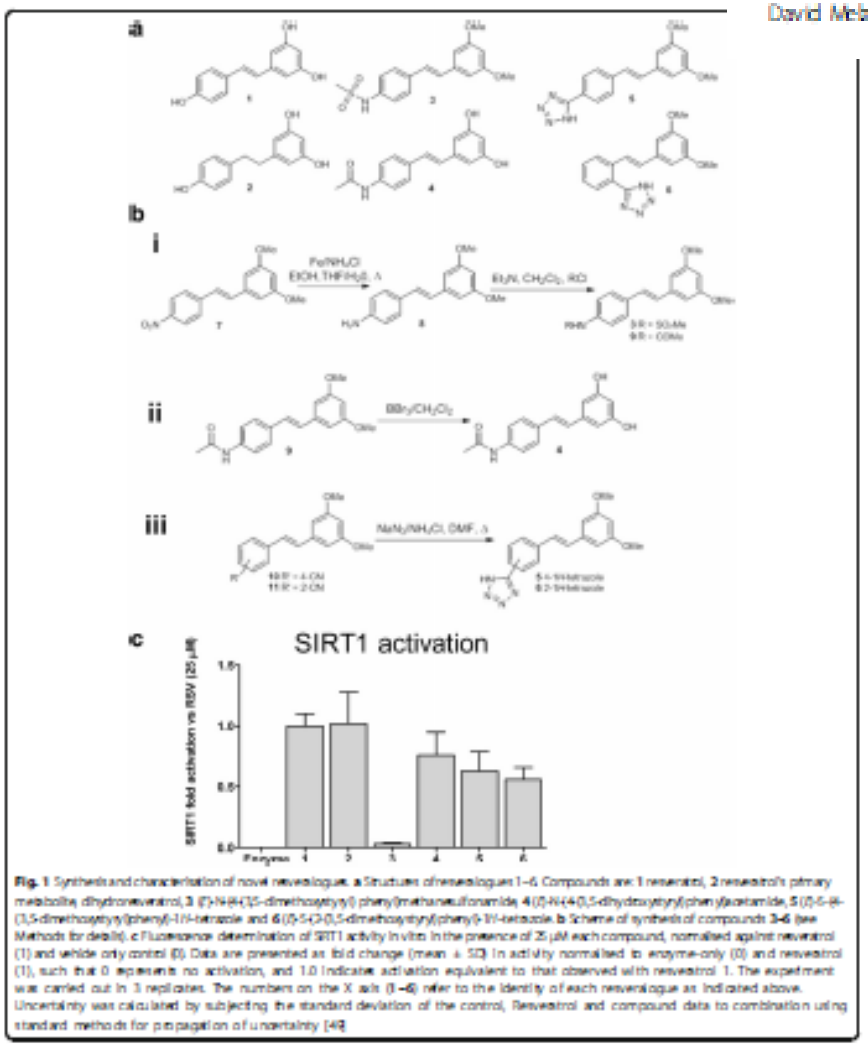
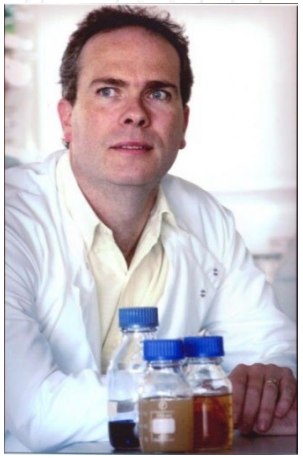


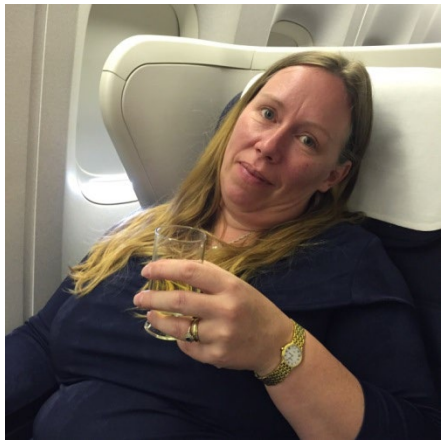
Fig. 1 Synthesis and characterisation of novel resveratrogues. **a** Structures of resveratrogues 1–6. Compounds are: **1** resveratrol, **2** resveratrol's primary metabolite, dihydroresveratrol, **3** (*E*)-*N*-[4-(3,5-dimethoxystyryl) phenyl]methanesulfonamide, **4** (*E*)-*N*-[4-(3,5-dihydroxystyryl)phenyl]acetamide, **5** (*E*)-5-[4-(3,5-dimethoxystyryl)phenyl]-1*H*-tetrazole and **6** (*E*)-5-[3-(3,5-dimethoxystyryl)phenyl]-1*H*-tetrazole. **b** Scheme of synthesis of compounds **3–6** (see Methods for details). **c** Fluorescence determination of SIRT1 activity in vitro in the presence of 25 μM each compound, normalised against resveratrol (1) and vehicle only control (0). Data are presented as fold change (mean ± SD) in activity normalised to enzyme-only (0) and resveratrol (1), such that 0 represents no activation, and 1.0 indicates activation equivalent to that observed with resveratrol 1. The experiment was carried out in 3 replicates. The numbers on the X axis (**1–6**) refer to the identity of each resveratrogue as indicated above. Uncertainty was calculated by subjecting the standard deviation of the control, Resveratrol and compound data to combination using standard methods for propagation of uncertainty [49]

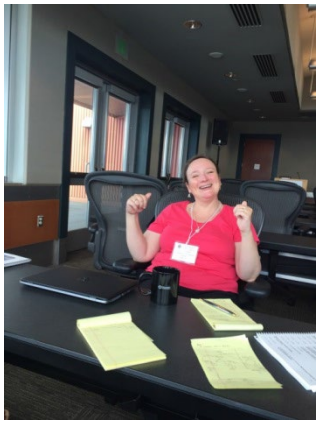
RESEARCH ARTICLE Open Access

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*]







Resveralogues reverse senescence

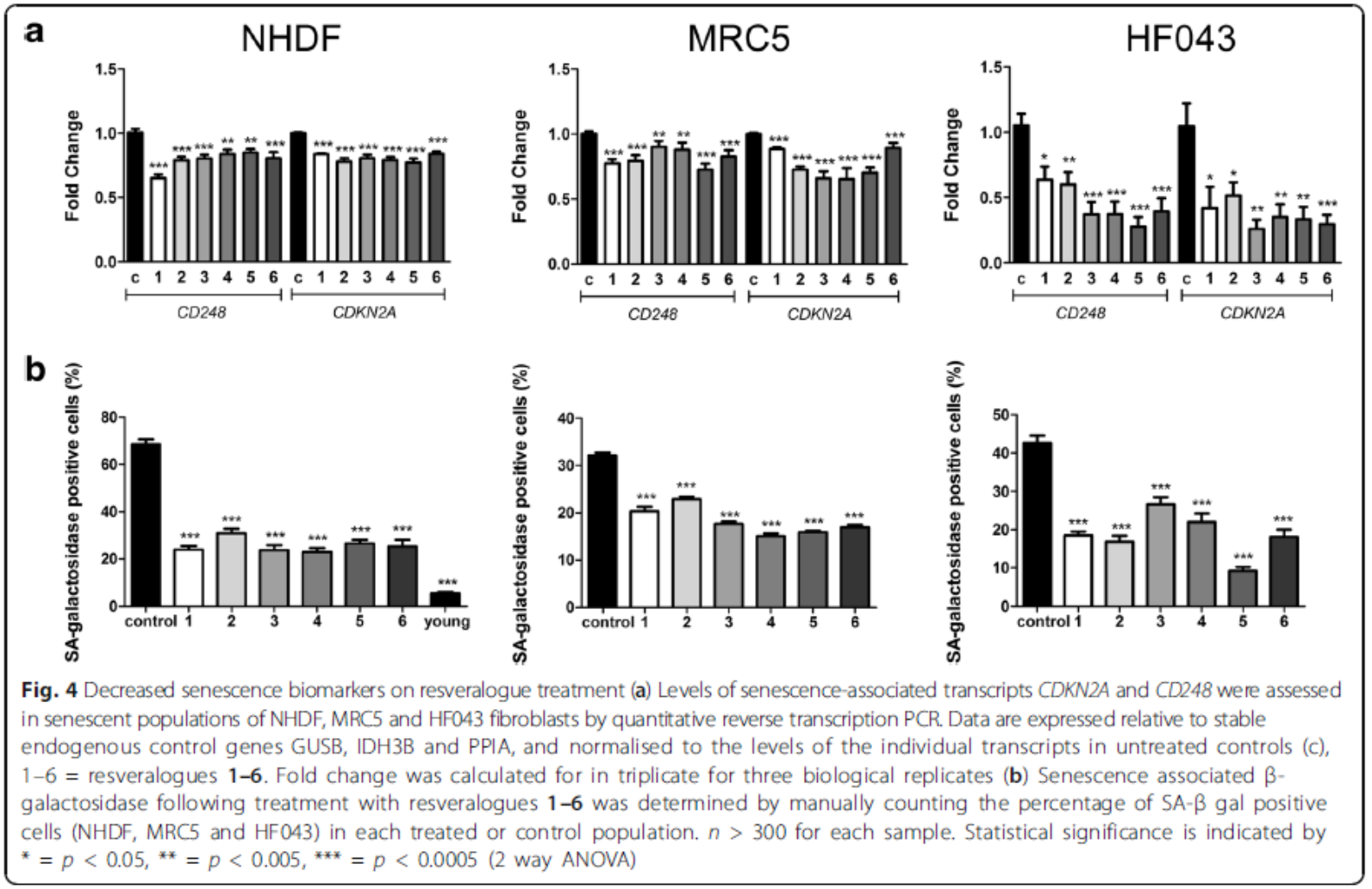
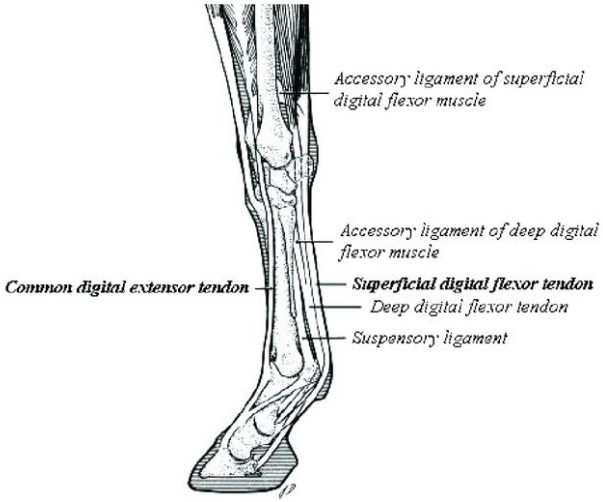
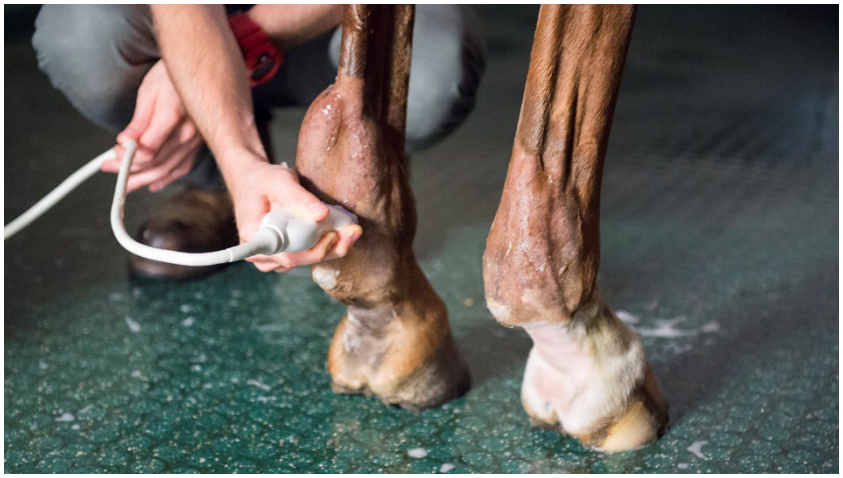


Fig. 4 Decreased senescence biomarkers on resveralogue treatment (**a**) Levels of senescence-associated transcripts *CDKN2A* and *CD248* were assessed in senescent populations of NHDF, MRC5 and HF043 fibroblasts by quantitative reverse transcription PCR. Data are expressed relative to stable endogenous control genes GUSB, IDH3B and PPIA, and normalised to the levels of the individual transcripts in untreated controls (c), 1–6 = resveralogues **1–6**. Fold change was calculated for in triplicate for three biological replicates (**b**) Senescence associated β-galactosidase following treatment with resveralogues **1–6** was determined by manually counting the percentage of SA-β gal positive cells (NHDF, MRC5 and HF043) in each treated or control population. $n > 300$ for each sample. Statistical significance is indicated by * = $p < 0.05$, ** = $p < 0.005$, *** = $p < 0.0005$ (2 way ANOVA)

Broad clinical applications for this compound series

- Tendinopathy is common with ageing and causes severe morbidity in human athletes and performance horses.
- The equine superficial digital flexor tendon (SDFT) is a functional homologue of the Achilles tendon.





Lens

Resveratrol Inhibits Wound Healing and Lens Fibrosis: A Putative Candidate for Posterior Capsule Opacification Prevention

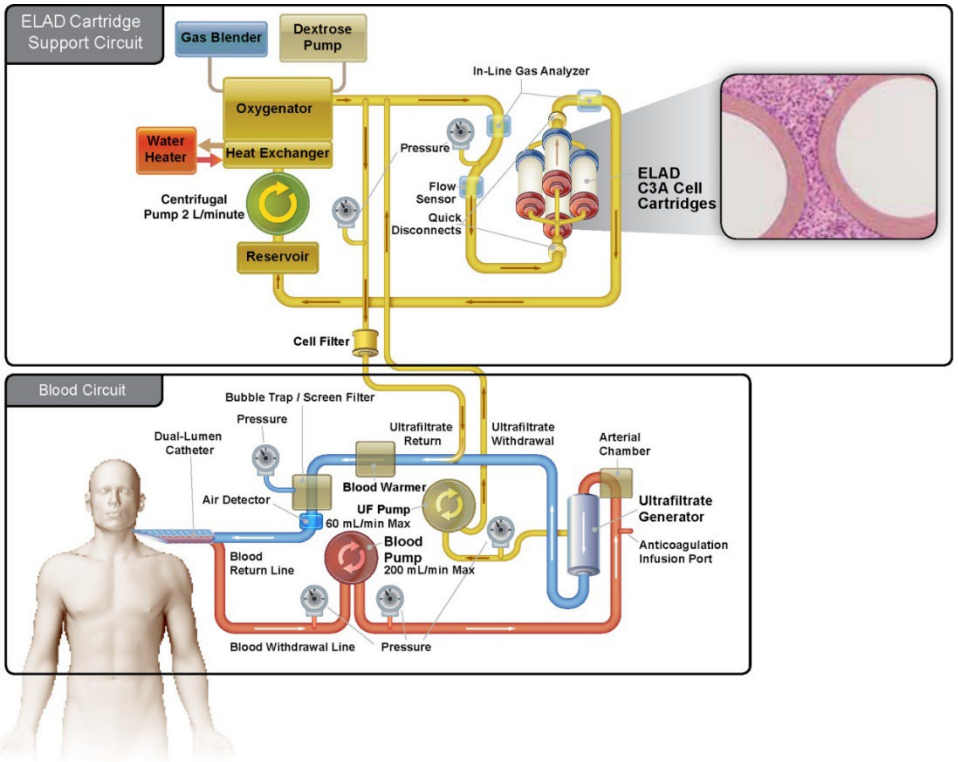
Andrew J. O. Smith, Julie A. Eldred, and I. Michael Wormstone

School of Biological Sciences, University of East Anglia, Norwich Research Park, Norwich, United Kingdom

Purpose. Posterior capsule opacification (PCO) is a common complication of cataract surgery. In addition to improved surgical methods and IOL designs, it is likely additional agents will be needed to improve patient outcomes. Presently no pharmacological agent is in clinical use to prevent PCO. Here we investigate the putative ability of resveratrol (RESV), a naturally occurring polyphenol, as a therapeutic agent.

Conclusions. RESV can counter PCO-related physiological events in two human lens model systems. RESV therefore has the potential to be used as a candidate agent for the prevention of PCO, which in turn could benefit millions of cataract patients.

Where might this be *essential*?

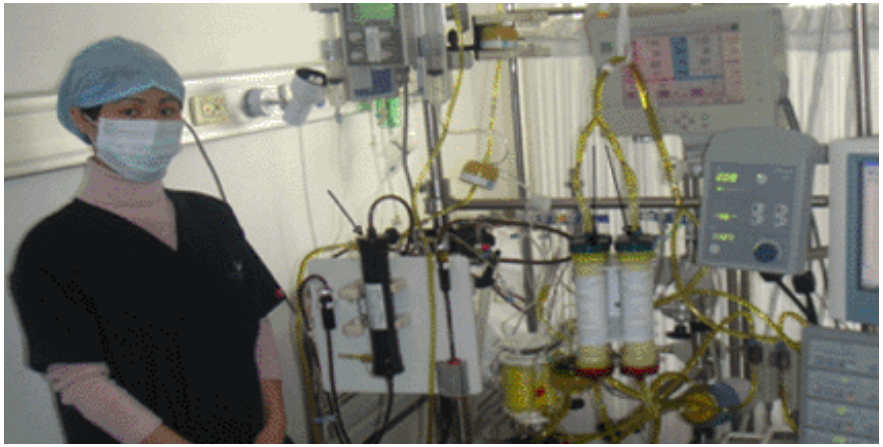


Probably within bioartificial organs especially BALS

Core of these systems are a series of hollow fibre cartridges containing ~800g of immortalised liver cells.

These should:
[1] Produce albumin.
[2] Turn ammonia into urea
[3] Detoxify xenobiotics

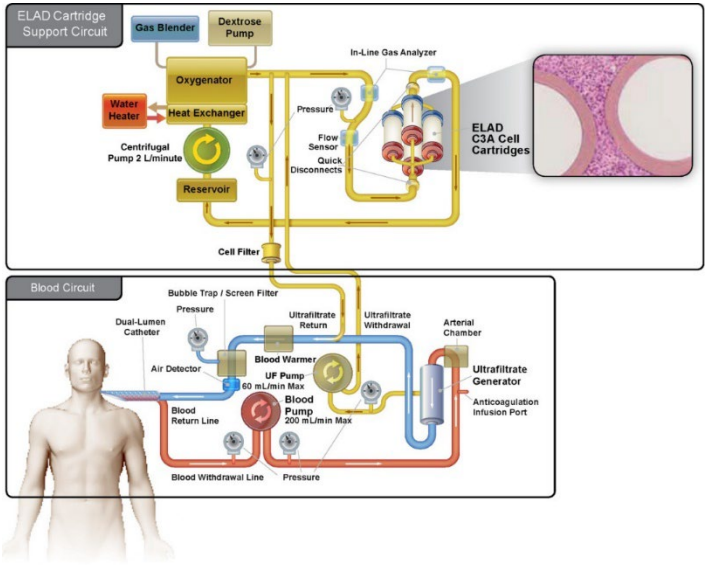
Hepatocyte functional failure is a critical barrier to working BALS but why?



Shareholders gut stock after Vital Therapies bails on Elad after failed trial

SEPTEMBER 13, 2018 BY FINK DENSFORD

Vital Therapies (NSDQ:VTL) saw share price drop 91.3% this week after the company announced that the leading clinical trial of its ELAD cell-based therapy for treating liver failure failed to meet its primary and secondary endpoints and that it was "ceasing any further development" of the product.

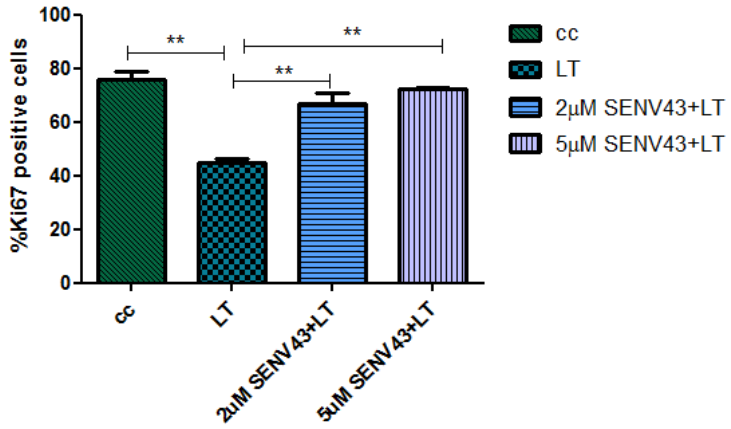


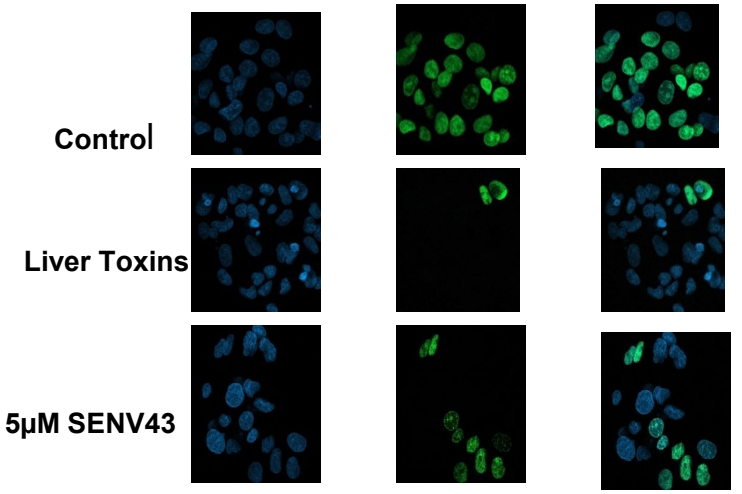
A cocktail of molecules accumulate in plasma when liver function is acutely or chronically compromised (e.g. ammonia, bilirubin, bile acids etc).

Collectively known as 'liver toxins'.

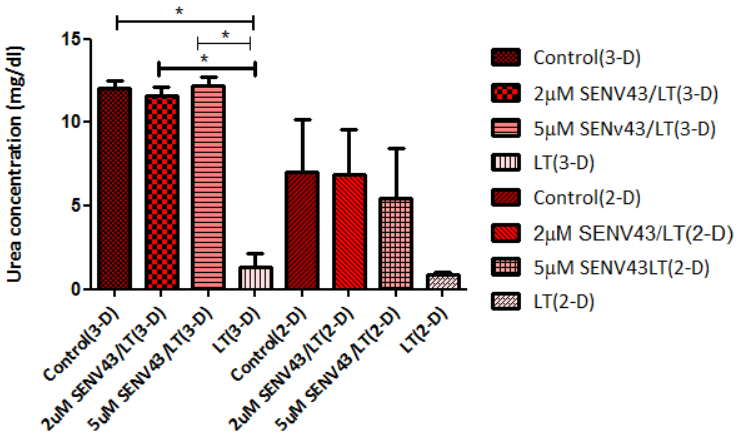
Liver toxins cause hepatocyte senescence which we can block with our compounds

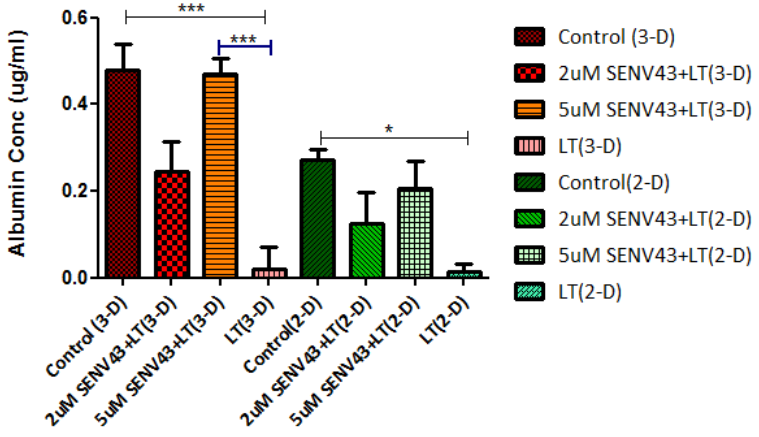
The percentage of Ki67 positive cells in 3-D surfaces after treatment with liver toxins





CC = control; LT= Liver toxins





Are BALS now a reality?

- Exposure to liver toxins for <2 hours causes healthy hepatocytes to enter cellular senescence. This is what has prevented BALS from functioning.
- Preventable and reversable using resveralogues
- A variety of options and clinical trial designs that could take an early stage company quickly into Phase 2. Move to Phase 3 is only limited by money.
- It could rejuvenate the BAL market (conservatively estimated to be worth £200 million annually)
- Heterogenous potential to increase life expectancy depending on disease subtype.

Conclusions

- There is significant potential for developments in geroscience to impact life expectancy over the time frame considered by the industry.
- There is a real need for collaboration between basic scientists, actuaries and economists to better model future scenarios.
- We are happy to answer your questions – if only we can understand them!

THE LANCET
Healthy Longevity

COMMENT | VOLUME 3, ISSUE 5, E318-E320, MAY 01, 2022

Linking interdisciplinary and multiscale approaches to improve healthspan—a new UK model for collaborative research networks in ageing biology and clinical translation

Lynne S Cox • Richard G A Faragher

Open Access • Published: May, 2022 • DOI: https://doi.org/10.1016/S2666-7568(22)00095-2 • Check for updates

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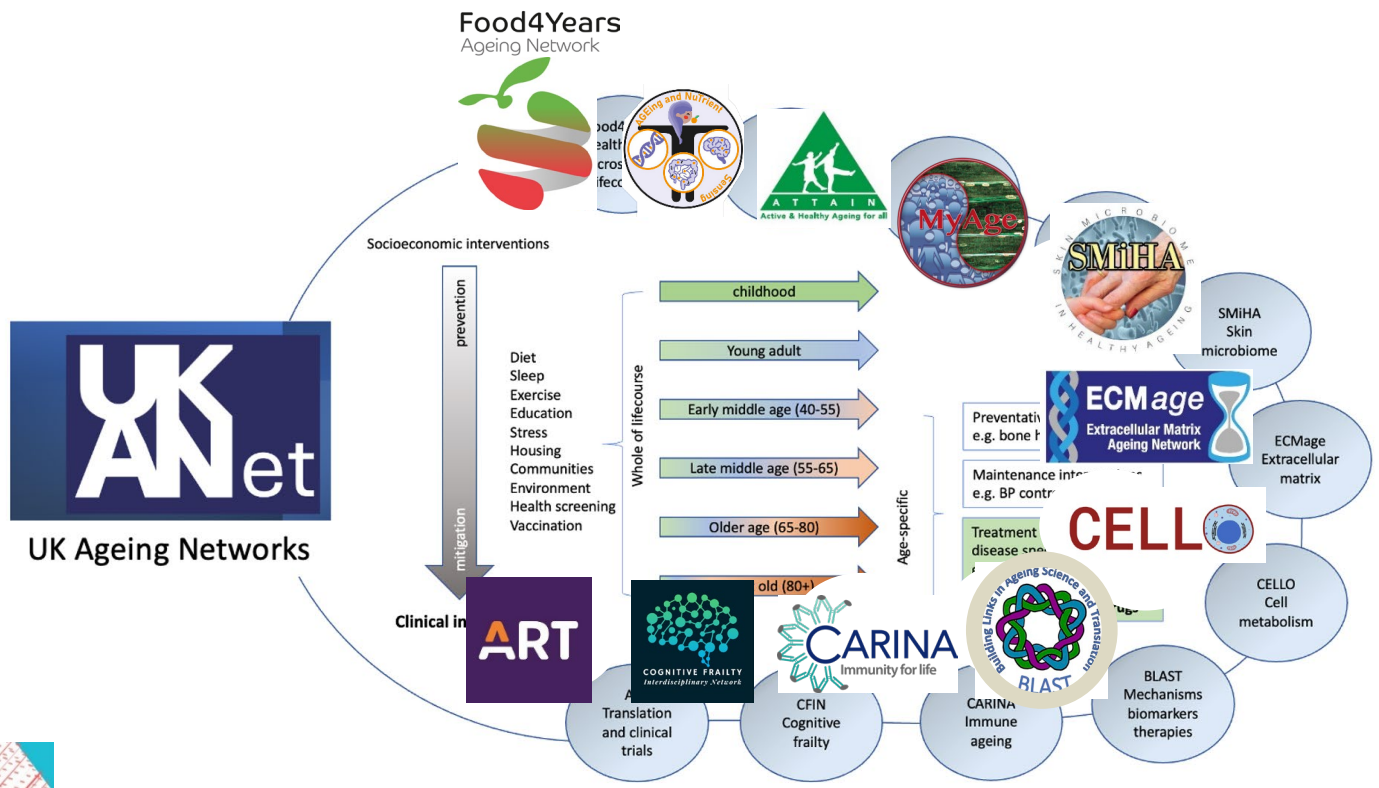

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