St Annes and the Sciences: The New Science of Ageing

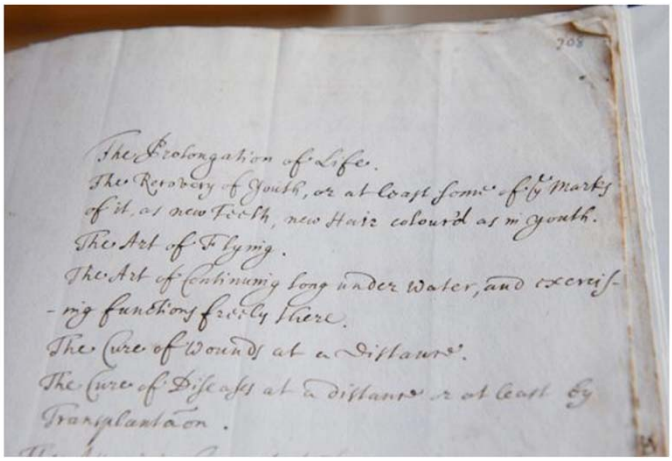
St Annes Royal Charter Celebration May 2012

Linda Partridge

Max Planck Institute for Biology of Ageing, Cologne, Germany
Institute of Healthy Ageing, UCL, UK

"The Prolongation of Life" & "The Recovery of Youth"

Robert Boyle (1627-1691)
Scientist & natural philosopher

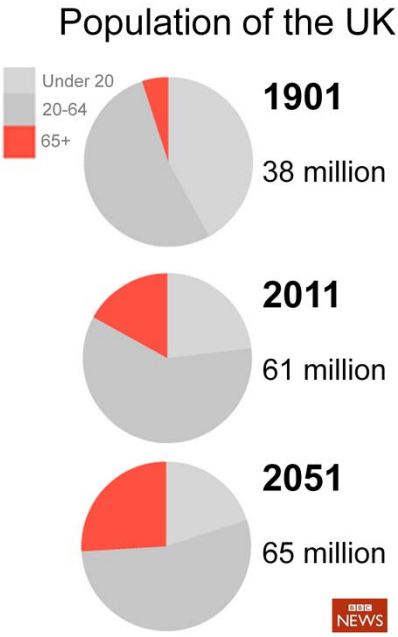


His scientific wish-list from the 1660s

Robert Boyle, 17th century scientist famous for XXX composed a scientific wish list , for the projects that he regarded as the most important but the most challenging. At the very top was the prolongation of life and the recovery of youth

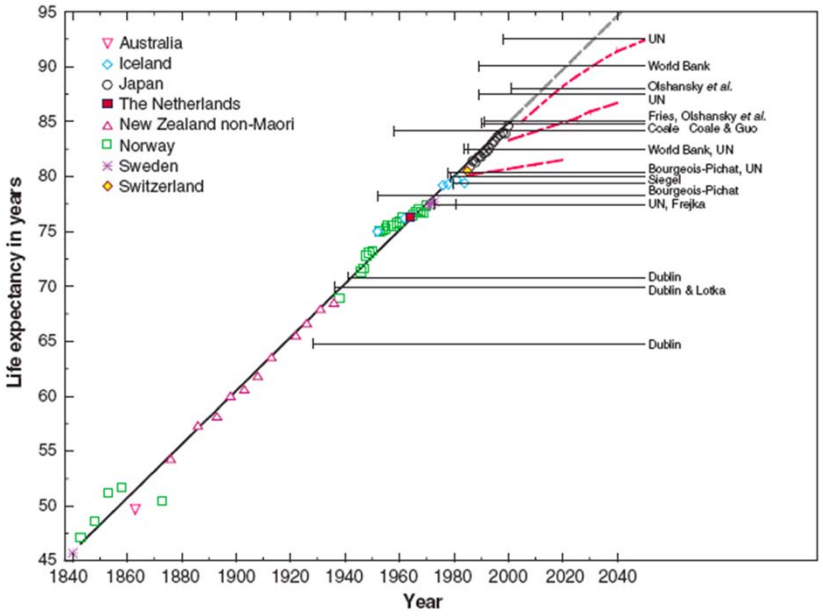
Boyle did not live to see it, but the main reasons that ageing is so much in the news and high on the political agenda now, is that this prolongation of life has been happening in developed countries since the middle of the 19th century

Ever more people are ageing successfully



Thanks to successful improvements in public health, nutrition and medicine people are living longer and enjoying later life… and this is something to celebrate. Partly as the result of this, the number of older people is increasing (this is also the result of falling birth rates)

Rising life expectancy



Oeppen & Vaupel (2002) *Science*

Maximum human longevity

Jeanne Calment (1875-1997), died age 122

Sunflowers (1888), Van Gogh

The downside to longer life

1.7m 'will have dementia by 2051'

More than 1.7 million people in the UK will have dementia by 2051, costing billions of pounds each year, experts have forecast.

The grim project
on the most up-
evaluation of de

Currently 700,0
person in every
cost of £17bn.

BBC NEWS

Dementia cost 'to top 1% of GDP'

By Michelle Roberts
Health reporter, BBC News

The costs associated with dementia will amount to more than 1% of the world's gross domestic product this year at $604bn (£388bn), a report says.

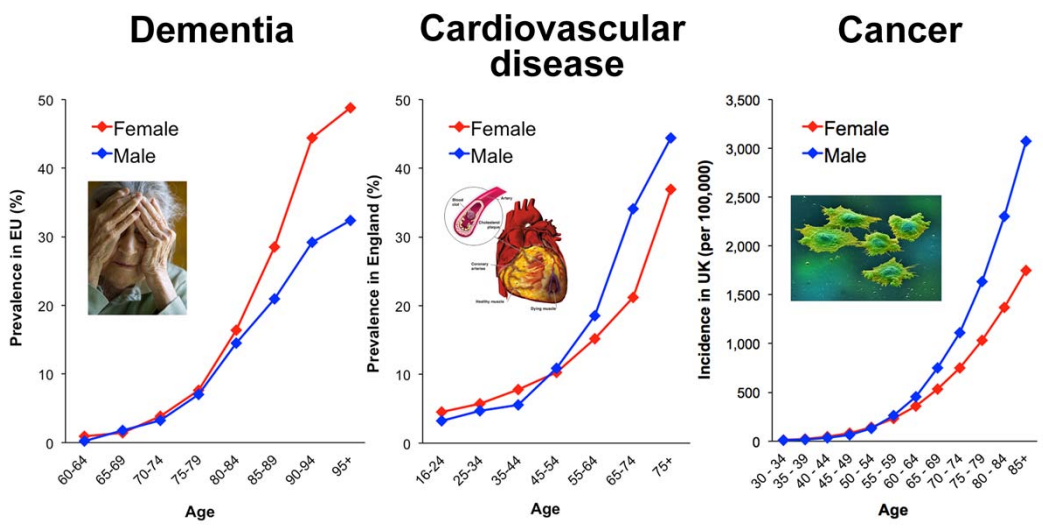
The World Alzheimer Report says this is more than the revenue of retail giant Wal-Mart or oil firm Exxon Mobil.

The authors say dementia poses the most significant health and social crisis of the century as its global financial burden continues to escalate.

Dementia care costs are rising fast, says the report

September 2010

Ageing is THE major risk factor for predominant killer diseases



…and the ageing population is unaffordable

theguardian

Britain rated 'extreme' fiscal risk because of ageing population and debt

Britain is now one of 12 nations rated 'extreme risk' in the Fiscal Risk Index compiled by global analysts Maplecroft

Home help at a housing association home in Scotland. Britain is seen to be at high fiscal risk because of an increase in the ageing population Photograph: Murdo Macleod

The UK's ageing population and huge debt have propelled it into the top 10 of countries threatened by unsustainable public finances, new research has found.

Britain is now one of 12 nations rated "extreme risk" in the Fiscal Risk Index compiled by global analysts Maplecroft.

February 2011

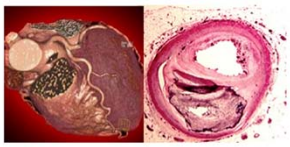
In the context of the global financial crisis, the the increase in the number of dependent, older people runs the risk of driving the UK ever further into debt.

Ageing: the scientific challenge

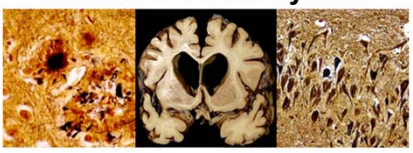
- Understand the biological mechanisms of ageing
- Use the knowledge to intervene in ageing to improve late life health

Age-related pathology suggests ageing is intractable

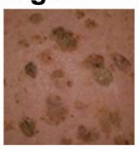
Cardiovascular



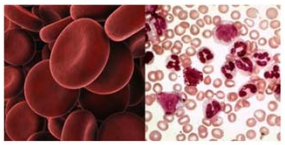
Central nervous system



Integumental

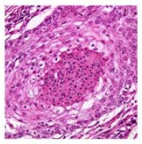


Haematopoetic

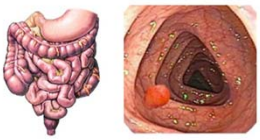


Musculoskeletal

Epithelia



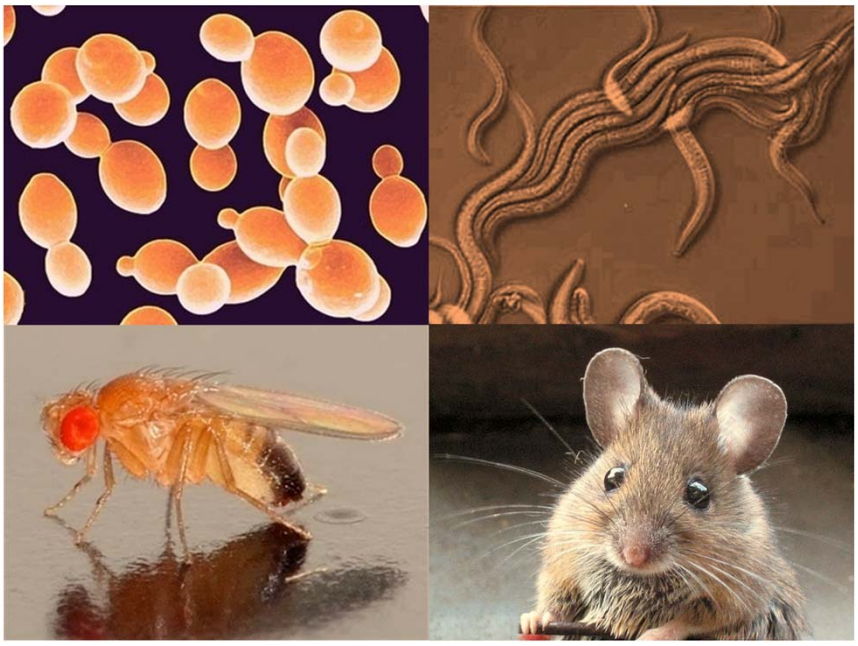
Gastrointestinal



Special senses

Endocrine

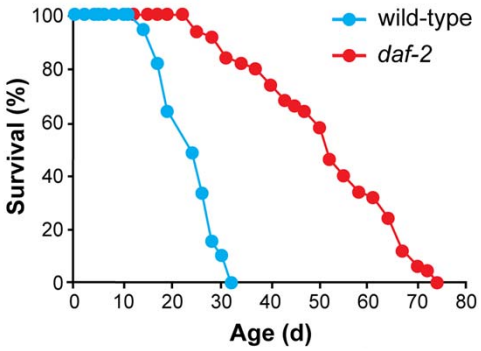
Laboratory model organisms



These are the lab model organisms. These creatures – the single celled yeast, the nematode worm, the fruit fly and the mouse – are the workhorses of modern biology - the things that we know about genetics, cell biology, development, metabolism, behaviour have come largely through the study of this cast of characters. We have all evolved from the same common ancestor, and the resulting evolutionary conservation of biological mechanisms is strong. Indeed, we can often take a human gene and insert it into the genome of yeast, and find that it performs its cellular function quite normally. This means that we can make initial discoveries in simpler organisms- single celled - then inverts that are also cheaper to work with, and then progress to the more complex and less tractable mammalian situation.
These organisms have very different lifestyles - use of oxygen, food, warm blooded.
Different types of biochemical damage? If they all age differently - the only way to understand ageing in humans would be to study human ageing, which is extremely difficult because on the whole we cannot do experiments and humans live too long.
Collective mental block But eventually Michael Klass **hero** broke the hex and did a standard chemical mutagenesis with the nematode worm

Ageing is malleable: lifespan extension in nematode worms

- A mutation in a single gene can substantially increase longevity
- Initial mutants were in genes encoding an insulin/IGF signalling pathway



Data from David Gems

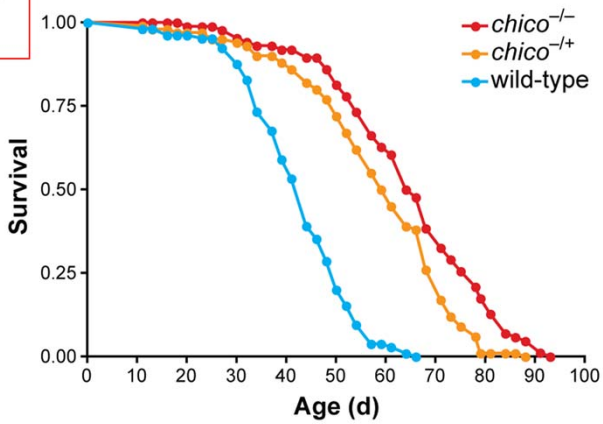
Evolutionary conservation to *Drosophila*

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

David J. Clancy,[1] David Gems,[1]* Lawrence G. Harshman,[2] Sean Oldham,[3] Hugo Stocker,[3] Ernst Hafen,[3] Sally J. Leevers,[4,5] Linda Partridge[1]

6 APRIL 2001 VOL 292 SCIENCE

wild-type *chico*$^{-/-}$

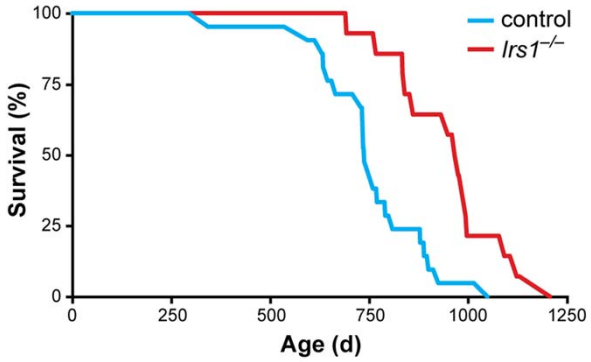


And to mice:
Irs1-null mutants are long-lived

The FASEB Journal • Research Communication Vol. 22 March 2008

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

Colin Selman,* Steven Lingard,* Agharul I. Choudhury,* Rachel L. Batterham,* Marc Claret,* Melanie Clements,* Faruk Ramadani,† Klaus Okkenhaug,† Eugene Schuster,§ Eric Blanc,§ Matthew D. Piper,† Hind Al-Qassab,* John R. Speakman,‖ Danielle Carmignac,¶ Iain C. A. Robinson,¶ Janet M. Thornton,§ David Gems,† Linda Partridge,† and Dominic J. Withers*,1



Irs1-null mice are healthier

Preservation of:

- Glucose homeostasis
- Immunity (T cells)
- Motor function

Delayed onset of:

- Osteoporosis
- Cataracts
- Ulcerative dermatitis

Selman *et al.* (2008) *FASEB J.*

Human longevity is associated with genetic variation in the IIS pathway

FOXO3A genotype is strongly associated with human longevity

Bradley J. Willcox*†§, Timothy A. Donlon*¶, Qimei He*, Randi Chen*†, John S. Grove*¶, Katsuhiko Yano*†, Kamal H. Masaki*†‡, D. Craig Willcox*,**, Beatriz Rodriguez*†‡, and J. David Curb*†‡

Mini review

The insulin/IGF-1 signaling in mammals and its relevance to human longevity

Marielisa Rincon, Eric Rudin, Nir Barzilai*

Haplotypes in the human *Foxo1a* and *Foxo3a* genes; impact on disease and mortality at old age

Maris Kuningas*,[1,2], Reedik Mägi[3], Rudi GJ Westendorp[1], P Eline Slagboom[4], Maido Remm[3] and Diana van Heemst[1]

Impaired IGF1R signaling in cells expressing longevity-associated human *IGF1R* alleles

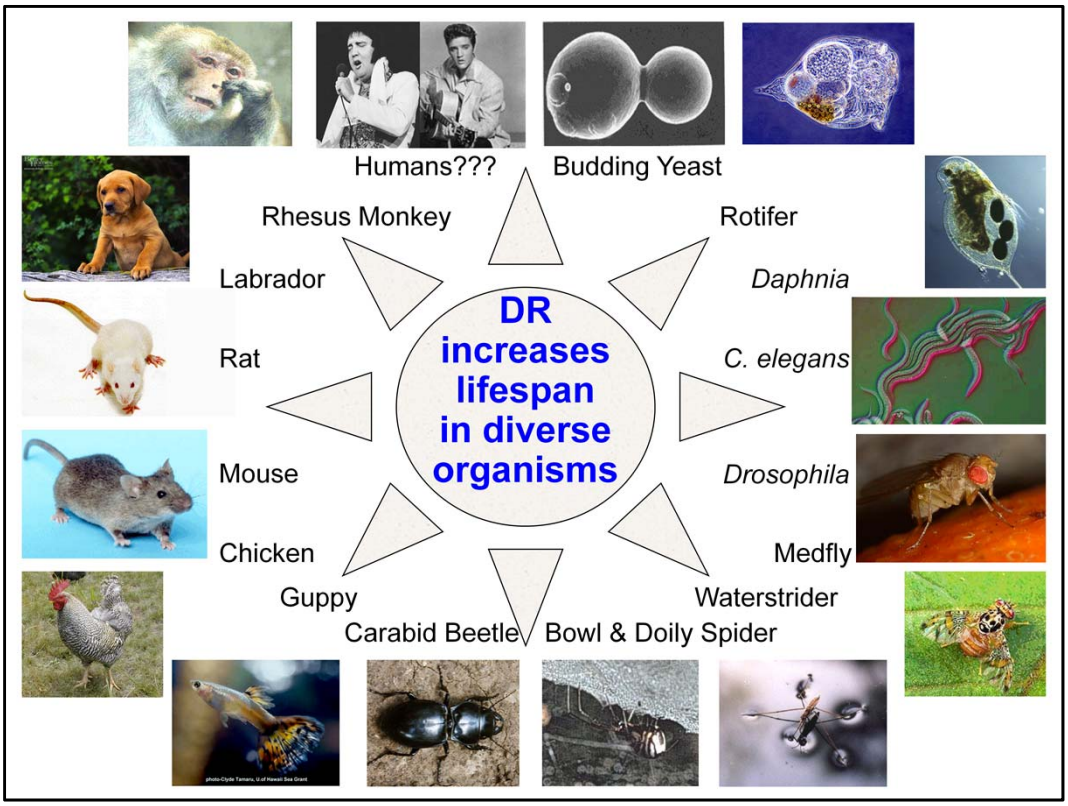
Cagdas Tazearslan,[1,*] Jing Huang, [1,*,†] Nir Barzilai[1,2] and Yousin Suh[1,2]

Association of *FOXO3A* variation with human longevity confirmed in German centenarians

Friederike Flachsbart[a], Amke Caliebe[b], Rabea Kleindorp[a], Hélène Blanché[c], Huberta von Eller-Eberstein[d], Susanna Nikolaus[d], Stefan Schreiber[a,1,2], and Almut Nebel[a,1]

Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity

Ludmila Pawlikowska,[1,2,*] Donglei Hu,[3,*] Scott Huntsman,[3] Andrew Sung,[4] Catherine Chu,[4] Justin Chen,[4] Alexander H. Joyner,[5] Nicholas J. Schork,[5] Wen-Chi Hsueh,[2,3] Alexander P. Reiner,[6] Bruce M. Psaty,[6,7] Gil Atzmon,[8] Nir Barzilai,[8] Steven R. Cummings,[9] Warren S. Browner,[9] Pui-Yan Kwok[2,4] and Elad Ziv[2,3] for the Study of Osteoporotic Fractures



Invertebrates, fish, mammals – and there are some long term studies going on with rhesus monkeys in the US.

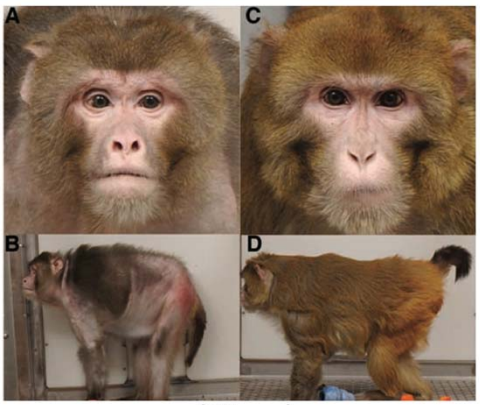
DR in primates…including humans?

Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys

Ricki J. Colman,[1]* Rozalyn M. Anderson,[1] Sterling C. Johnson,[1,2,3] Erik K. Kastman,[2,3] Kristopher J. Kosmatka,[2,3] T. Mark Beasley,[4] David B. Allison,[4] Christina Cruzen,[1] Heather A. Simmons,[1] Joseph W. Kemnitz,[1,2,5] Richard Weindruch[1,2,3]*

SCIENCE VOL 325 10 JULY 2009

control DR



(28 yrs)

Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans

Luigi Fontana*†, Timothy E. Meyer*, Samuel Klein*, and John O. Holloszy*‡

PNAS | April 27, 2004 | vol. 101 | no. 17 | 6659–6663

7 yrs of DR

81.6 kg 60.8 kg

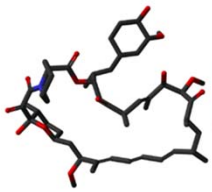
Rapamycin treatment from middle-age extends lifespan in mice

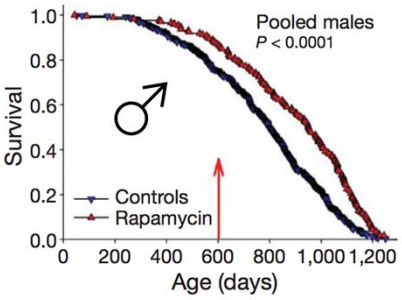
nature NATURE|Vol 460|16 July 2009

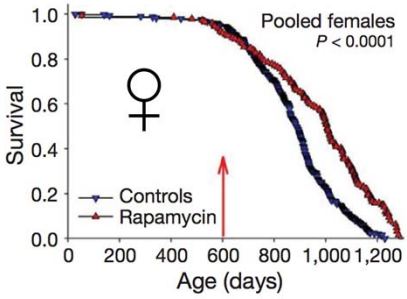
LETTERS

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison[1]*, Randy Strong[2]*, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8]†, Marco Pahor[8]†, Martin A. Javors[9], Elizabeth Fernandez[2] & Richard A. Miller[10]*





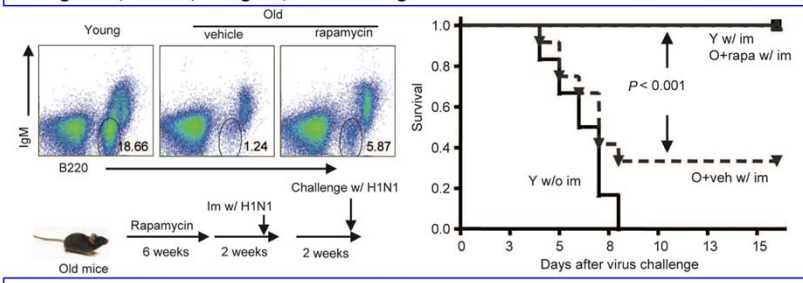


Wide therapeutic potential

mTOR Regulation and Therapeutic Rejuvenation of Aging Hematopoietic Stem Cells

Chong Chen,[1] Yu Liu,[1] Yang Liu,[1,2]* Pan Zheng[1,3]*

Science Signaling (2009)



Inhibition of mTOR by Rapamycin Abolishes Cognitive Deficits and Reduces Amyloid-β Levels in a Mouse Model of Alzheimer's Disease

Patricia Spilman[8], Natalia Podlutskaya[1,2], Matthew J. Hart[5], Jayanta Debnath[7], Olivia Gorostiza[8], Dale Bredesen[8], Arlan Richardson[2,4,6], Randy Strong[2,3,6], Veronica Galvan[1,2]*

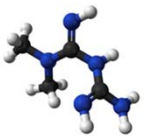
PLoS ONE (2010)

Broadening the therapeutic scope for rapamycin treatment

Fiona M. Menzies and David C. Rubinsztein*

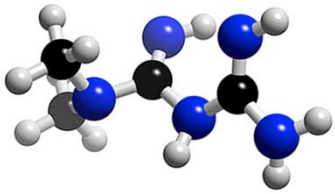
Autophagy (2010)

Towards a preventative medicine for age-related disease


- Metformin – originates from French lilac
- Extends lifespan in laboratory animals
- Mimics many effects of dietary restriction
- Widely prescribed for type II diabetes

Metformin and cancer in humans



RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients

Josie M M Evans, Louise A Donnelly, Alistair M Emslie-Smith, Dario R Alessi, Andrew D Morris

BMJ (2005)

New Users of Metformin Are at Low Risk of Incident Cancer

A cohort study among people with type 2 diabetes

GILLIAN LIBBY, MSC[1]
LOUISE A. DONNELLY[1]
PETER T. DONNAN, PHD[1]
DARIO R. ALESSI, PHD[2]
ANDREW D. MORRIS, FRCP[3]
JOSIE M.M. EVANS, PHD[1]

Diabetes Care (2009)

Protecting against diseases of ageing

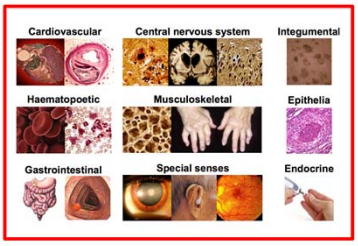
Protect against the ageing process itself.

So… to conclude… believe that the key to really protecting against diseases of ageing - such as Alzheimers - is to understand its root cause: the ageing process.

Treatment for age-related diseases: current strategy

Cancer	Cancer research	Treatment for cancer
Cardiovascular disease	CV research	Treatment for CV disease
Alzheimer disease	AD research	Treatment for AD
Parkinson disease	PD research	Treatment for PD
Macular degeneration	AMD research	Treatment for AMD
Type II diabetes	Diabetes research	Treatment for diabetes
Osteoporosis	Bone research	Treatment for OP

Proof of principle: targeting ageing protects against diseases of ageing

AGEING → 

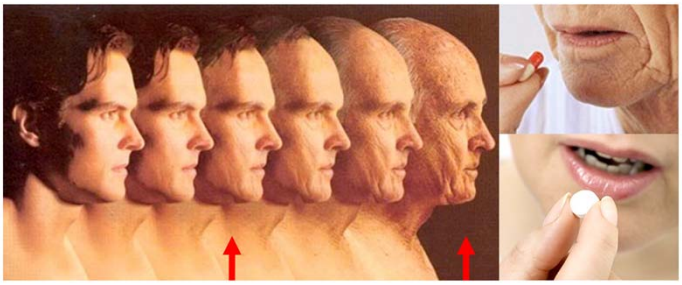
→ Protect against age-related diseases

Diseases of ageing

Treatment

The challenges of translating findings into drugs

Goal: increased healthspan



Long-term drug treatment

Broad-spectrum polypill

Safety?

Clinical trials

Pharmaceutical industry

Regulators

Funding

Summary

- Ageing is malleable
- Nutrition and nutrient-sensing pathways are important in ageing and present drugable targets
- These findings point to a broad-spectrum, preventative medicine for the diseases of ageing.