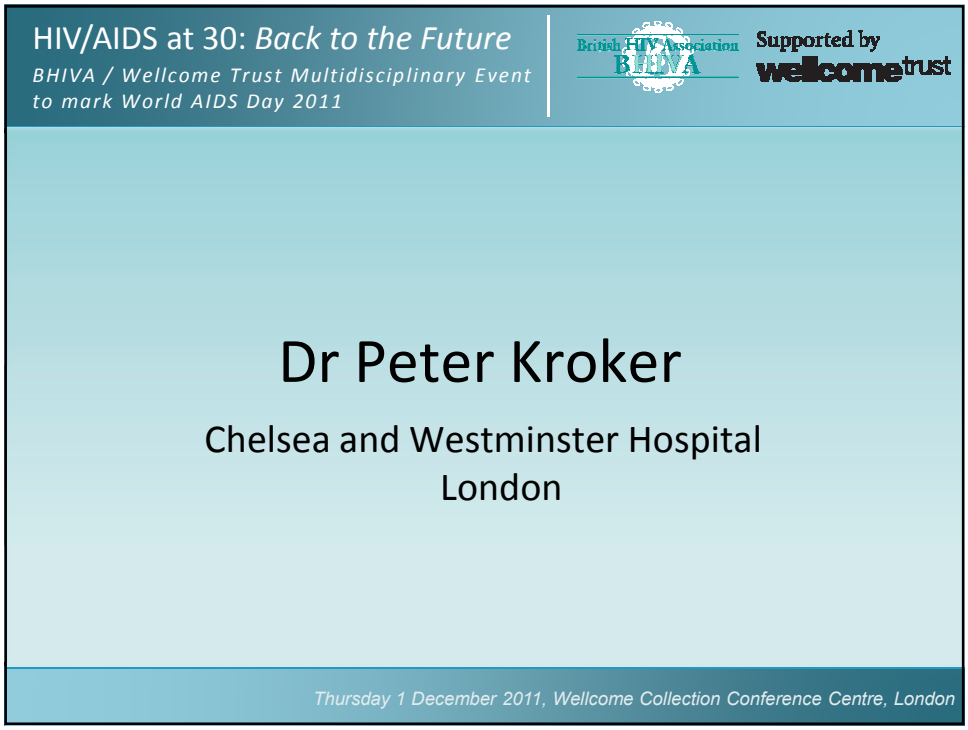

HIV/AIDS at 30: Back to the Future
BHIVA / Wellcome Trust Multidisciplinary Event to mark World AIDS Day 2011
British HIV Association BHIVA
Supported by wellcome trust
HIV/AIDS at 30:
Back to the Future
Multidisciplinary Event
to mark World AIDS Day
1500–2045
Thursday 1 December 2011
Wellcome Collection Conference Centre
London
In support of World AIDS Day
British HIV Association (BHIVA) 2011


HIV/AIDS at 30: Back to the Future
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British HIV Association BHIVA
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Dr Peter Kroker
Chelsea and Westminster Hospital
London
Thursday 1 December 2011, Wellcome Collection Conference Centre, London

Current challenges in HIV: The ageing population

Lucas Cranach: The Fountain of Youth (1546)

Dr Peter Kroker MD FRCP

Chelsea and Westminster Hospital (London)

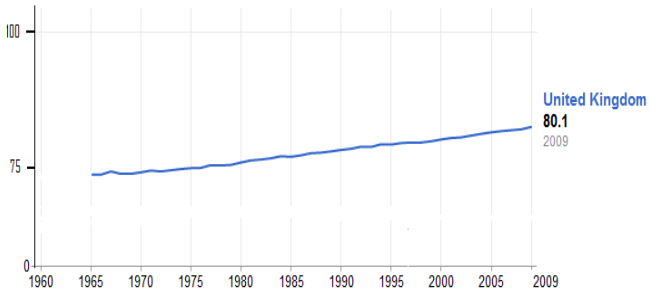
The NHS: The untold success story

- In 1900: 50% of deaths before 45th birthday
- In 2010: 4% of deaths before 45th Birthday

- In 1900: 12% of deaths after 75th birthday
- In 1951: 39% of deaths after 75th birthday
- In 2010: 66% of deaths after 75th birthday

Source: Office for National Statistics

Life Expectancy in United Kingdom increases by approx. 2 years every decade

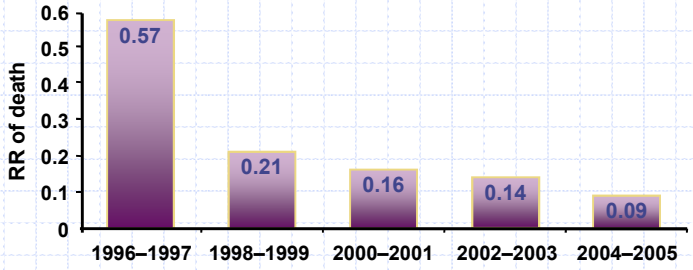


Life Expectancy 2006 -> 2008: The best and the worst

	Males	Females
United Kingdom (all regions)	77.3 -> 77.4	81.5 -> 81.6
Kensington & Chelsea	83.7 -> 84.3	87.8 -> 88.9
Glasgow City	70.8 -> 70.7	77.1 -> 77.2

Source: Office for National Statistics: Interim Life Tables 2005-07

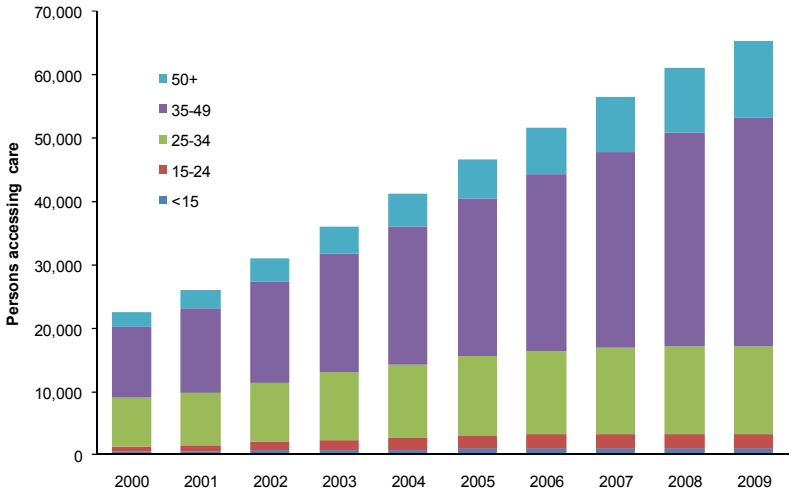
Relative risk of death among patients with HIV by year compared to pre-1996



	% of patients expected to survive		
	5 years	10 years	15 years
Age <45	99%	96%	91%
Age >45	95%	87%	72%

Porter K. Bhaskaran K. AS 2007

Diagnosed HIV-infected individuals seen for care by age, UK 2000–2009



•Excludes individuals with age not reported, 5 in 2000 and 0 in 2009.

HIV in Older Age Groups

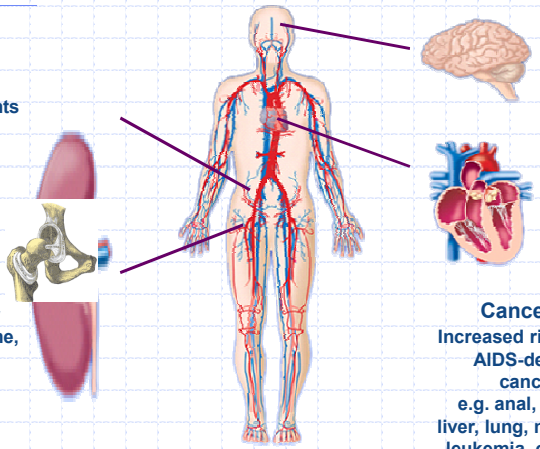
- Old age at seroconversion is associated with increased risk of disease progression and death
- Older age at any given CD4 count is associated with increased risk of disease progression and death
- AIDS diagnoses occur at higher CD4 counts
- There are worse outcomes after AIDS-defining illnesses (PCP)

CASCADE, Lancet 355(9210):1131–7. 2000.
Phillips AN et al. JAIDS 4(10):970–5. 1991.
Gebo KA. Drugs Aging 23(11):897–913. 2006
Keitz J et al. Gen Intern Med 11(10):591–6. 1996.
Grabar S et al. AIDS 18(15):2029–38. 2004.

Emerging co-morbidities in HIV

Renal dysfunction
30% of HIV+ patients have abnormal kidney function[1]

Reduced bone mineral density
Increased prevalence of osteoporosis or osteopenia in spine, hip or forearm: 63% of HIV+ patients[2]



Neurocognitive dysfunction
Neurological impairment present in ≥50% HIV+ patients[3]

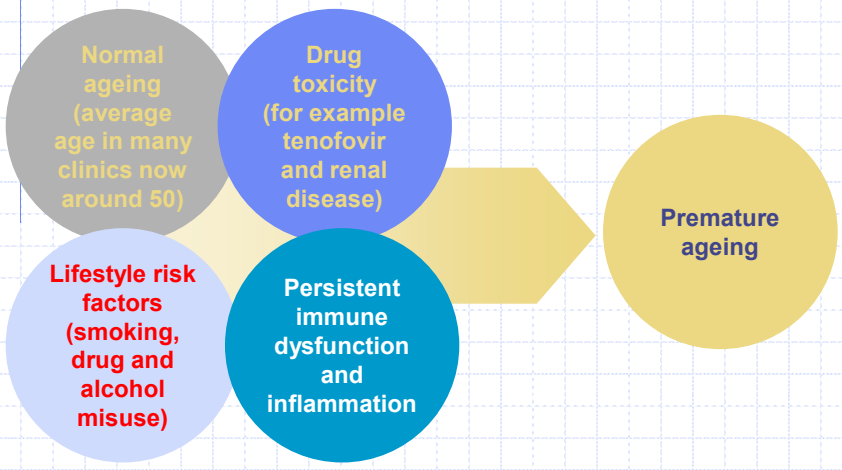
Cardiovascular disease
75% increase in risk of acute MI[4]

Cancer
Increased risk of non-AIDS-defining cancers
e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal[5]

Frailty
Increased frailty phenotype if HIV infected
3-14x; Associated with CD4 count

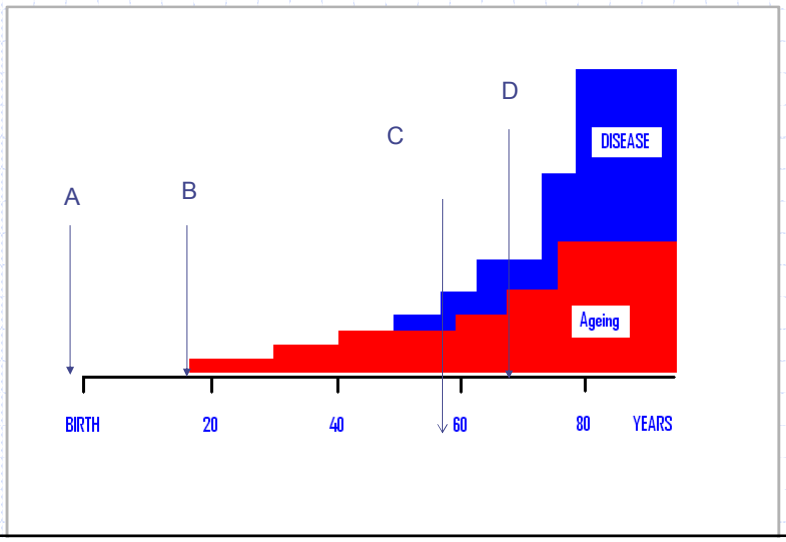
Gupta SK *et al. Clin Infect Dis* 2005;40:1559–85.
Brown TT *et al. J Clin Endocrinol Metab* 2004;89(3):1200–06.
Clifford DB. *Top HIV Med* 2008;16(2):94–98.
Triant VA *et al. J Clin Endocrinol Metab* 2007;92:2506–12.
Patel P *et al. Ann Intern Med* 2008;148:728–36.

HIV and ageing

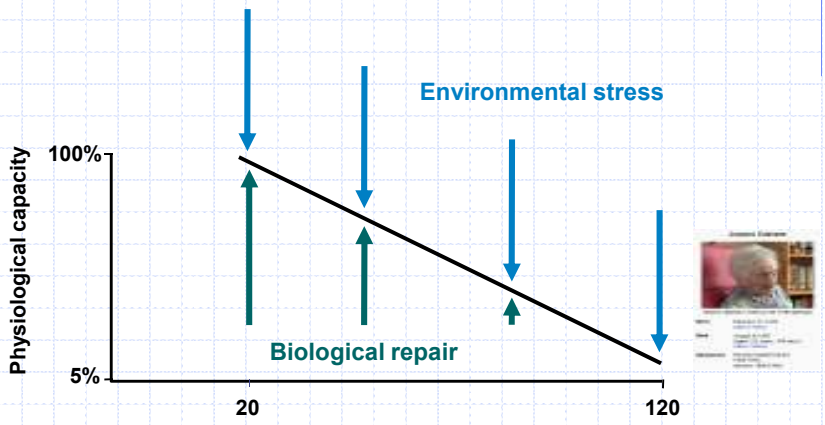


Adapted from Deeks SG, Phillips AN. *Br Med J* 2009;338:a3172

Human Ageing and Disease



Metabolic Stress: Repair theory of ageing



Adapted from Kirkwood, TBL The origins of human ageing
Phil. Trans. R. Soc. Lond (1997), 352, 1765-1772

Molecular Changes with Ageing

- **Cell loss/dysfunction/atrophy**
  (Thymic atrophy, sarcopenia, osteoporosis)
- **Immune system decline**
- **Cancer and DNA replication defects**
  (Telomeres and Hayflick's limit)
- **Mitochondrial dysfunction/mutation**
- **Extracellular molecular debris**
  (Advanced Glycation Endproducts, Amadori products e.g. HbA1c)
- **Intercellular cross linking/"Protein Misfolding"**
  (Amyloid deposition e.g. Alzheimer's disease)
- **Intracellular storage defects/debris**
  (e.g. Lipofuscin)
- **Cell communication defects**
  (e.g. p16INK4a, p53 activation)

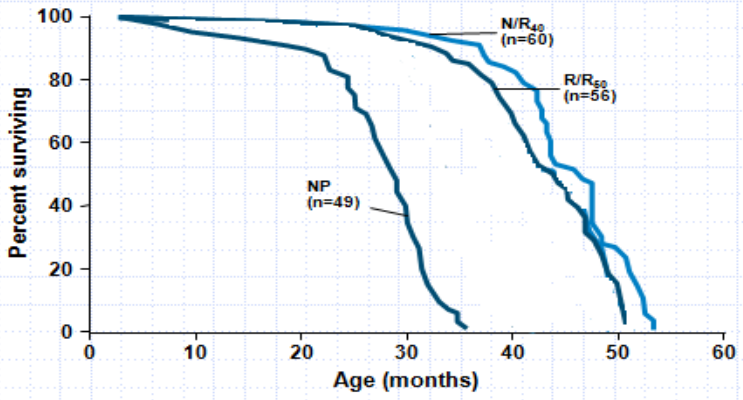
Medical interventions extend life span

Proof of Concept Studies

1. Calorie/dietary restrictions (up to Humans)
2. Anti-proliferative treatment (mice)
3. Genome and epigenetic alteration (C. elegans)
4. Removal of intracellular debris (C. elegans)
5. Telomerase activation reverses ageing (mice)
6. Removal of senescent cell populations (mice)
7. Epigenetic modifications (C. elegans)
8. Stem cell therapy (up to Humans)

How to extend life span

Dietary restrictions in animals



Weindruch R *et al.* J Nutr 1986;116:641-654
Ageing and AIDS, Dr Peter Kroker 2011

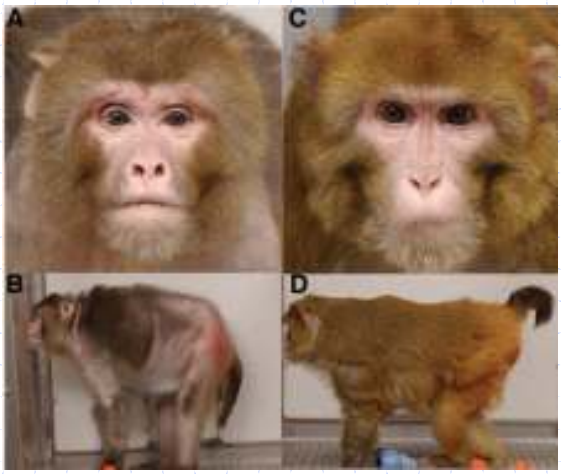
Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys

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*]

Caloric restriction (CR), without malnutrition, delays aging and extends life span in diverse species; however, its effect on resistance to illness and mortality in primates has not been clearly established. We report findings of a 20-year longitudinal adult-onset CR study in rhesus monkeys aimed at filling this critical gap in aging research. In a population of rhesus macaques maintained at the Wisconsin National Primate Research Center, moderate CR lowered the incidence of aging-related deaths. At the time point reported, 50% of control fed animals survived as compared with 80% of the CR animals. Furthermore, CR delayed the onset of age-associated pathologies. Specifically, CR reduced the incidence of diabetes, cancer, cardiovascular disease, and brain atrophy. These data demonstrate that CR slows aging in a primate species.

Science **325**, 201 (2009)

Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys



Science **325**, 201 (2009)

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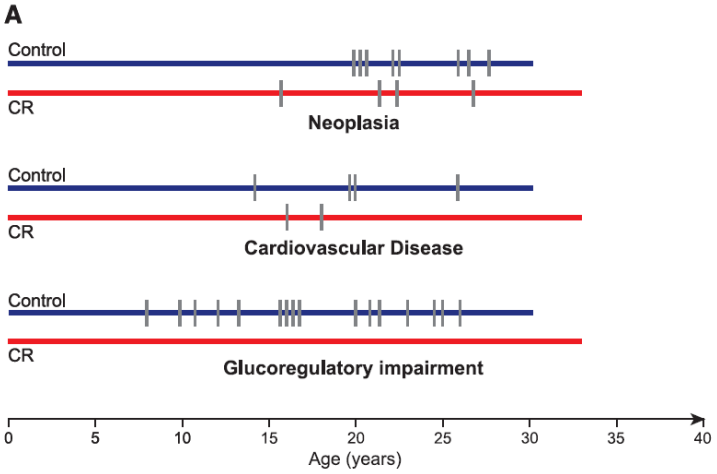
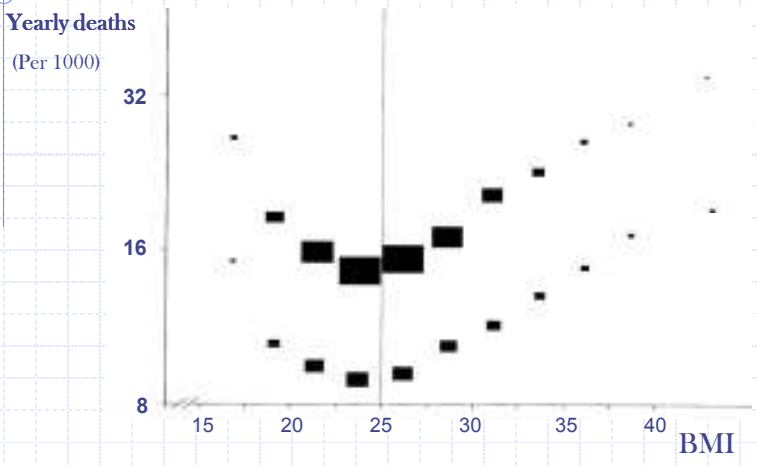


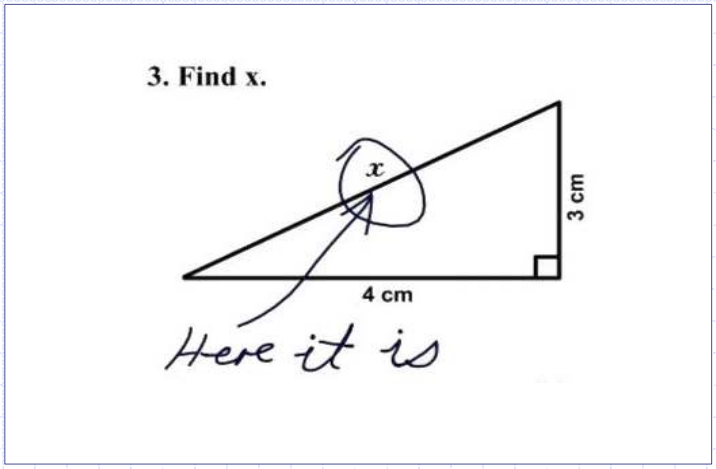
NATURE Vol 460 July 2009, 339-346

Lighter is not always better – The "optimal" BMI is 24

Lancet 2009; 373,9669,1083-1096



CR Effects without Starvation ?



How does calorie restriction work?

1. **Glucoregulation** (**"Glycation theory of ageing"**)
   Strongest link with low Insulin/IGF-1
1. Oxidative stress ("ROS"=reactive oxygen species, mitochondrial proton leaks)
2. Response to infection/stress (e.g. heat shock proteins, immune parameters)
3. Lipid metabolism (mitochondrial membrane stability and ROS escape)
4. Multiple pathways: Sirtuins, TOR, Redox-Signalling

Low carbohydrate diet reduces cancer in rodents

The researchers investigated mice predisposed to breast cancer. Half of the mice were fed a typical Western diet developed breast cancer in the first year of life, and 70 percent of them died. But, half of the mice given a low carbohydrate, high protein diet reached normal lifespan even though they were predisposed to develop cancer and only 30 percent developed the disease.

Cancer Res. 71, 4484–4493 (2011) 10.1158/0008-5472.CAN-10-3973

Low carbohydrate diet reduces cancer in rodents

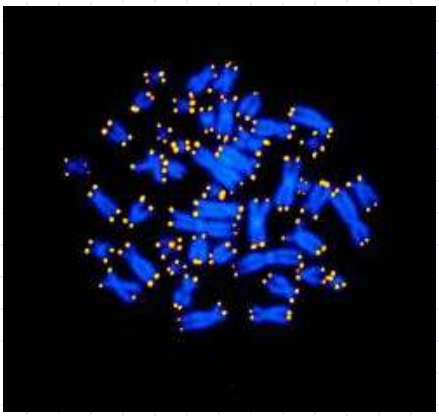
Cancer: Low carb, low tumour growth

A low-carbohydrate, high-protein diet slowed tumour growth in mice compared with a typical high-carbohydrate Western-style diet.

Gerald Krystal at the BC Cancer Research Centre in Vancouver, Canada, and his colleagues compared the growth of both human and mouse tumours in mice fed diets comprising 8%, 10%, 15% or 55% carbohydrate. All four diets had the same calorie content. At the 10% and 15% levels, mice showed slower tumour growth than animals eating the high-carbohydrate diet, and did not lose weight.

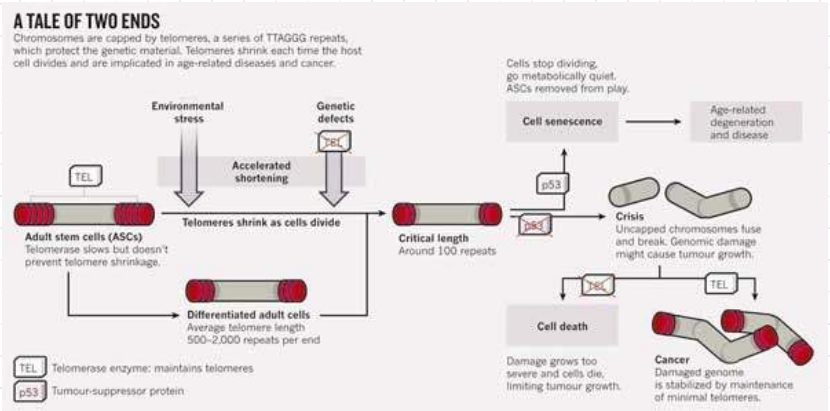
Cancer Res. 71, 4484–4493 (2011) 10.1158/0008-5472.CAN-10-3973

Proof of Concept – Telomerase activation



From: Nature 2011

Proof of Concept – Telomerase activation



Proof of Concept – Telomerase activation

Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice

Mariela Jaskelioff, Florian L. Muller, Ji-Hye Paik, Emily Thomas, Shan Jiang, Andrew C. Adams, Ergun Sahin, Maria Kost-Alimova, Alexei Protopopov, Juan Cadiñanos, James W. Horner, Eleftheria Maratos-Flier & Ronald A. DePinho

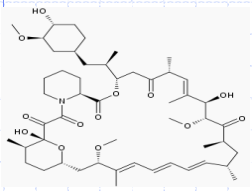
Affiliations | Contributions | Corresponding author

Nature **469**, 102–106 (06 January 2011) | doi:10.1038/nature09603
Received 08 May 2010 | Accepted 26 October 2010 | Published online 28 November 2010

Mice with inactivated telomerase aged rapidly similar to the clinical picture observed in human Progeria or Down's Syndrome. Reactivation of telomerase reversed most age-related changes and rejuvenated the mice on all cellular levels.

mTOR pathway inhibition extends lifespan in animals

RAPAMYCIN
(Sirolimus)

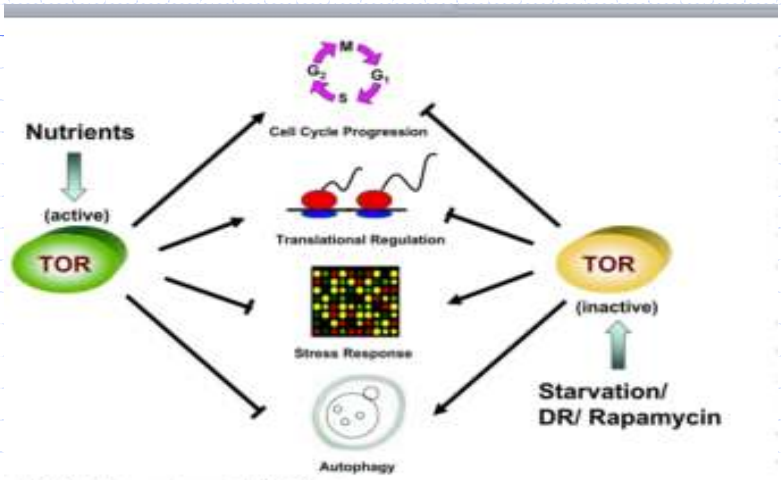


Found in Streptomyces hygroscopicus isolated from soil samples on the Easter Islands (Rapa Nui, hence Rapamycin)

mTOR: **m**ammialian **T**arget **O**f **R**apamycin

Serine/Threonine Protein Kinase with effects on cell growth, survival and proliferation, DNA transcription and a major player in signalling pathways of protein synthesis

mTOR pathway inhibition extends lifespan in animals

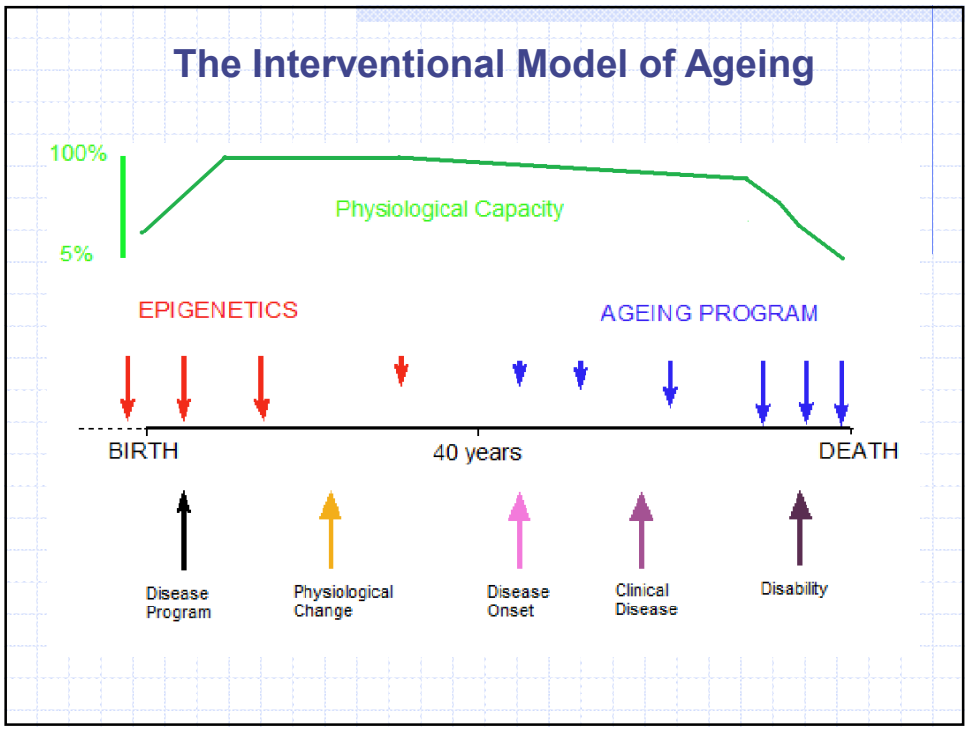


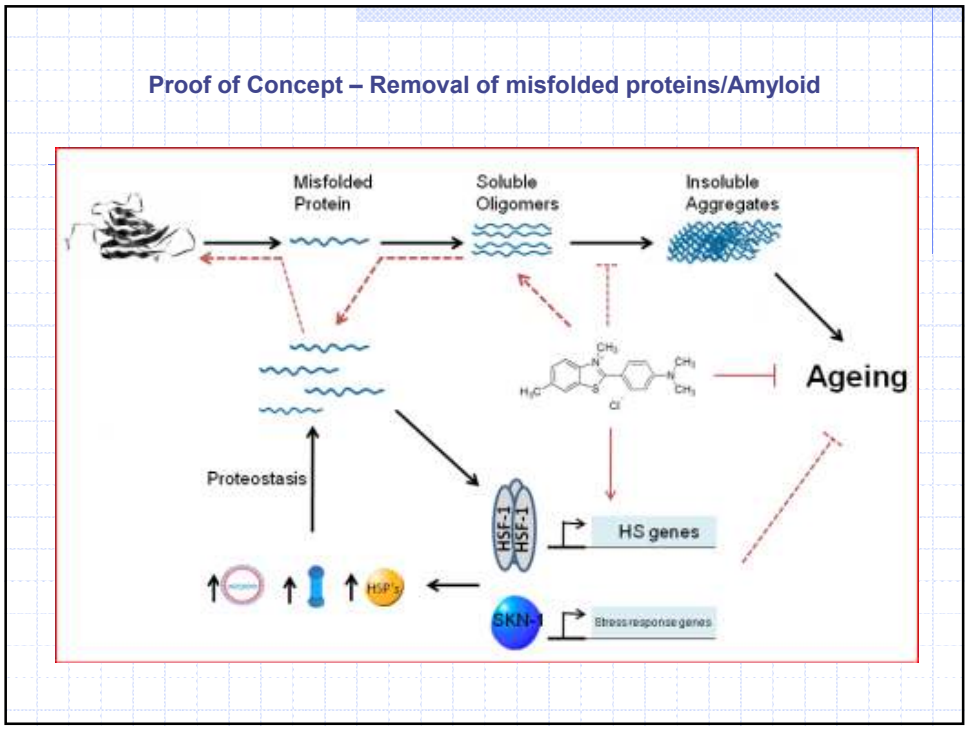
doi:10.1371/journal.pgen.0030084.g002

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

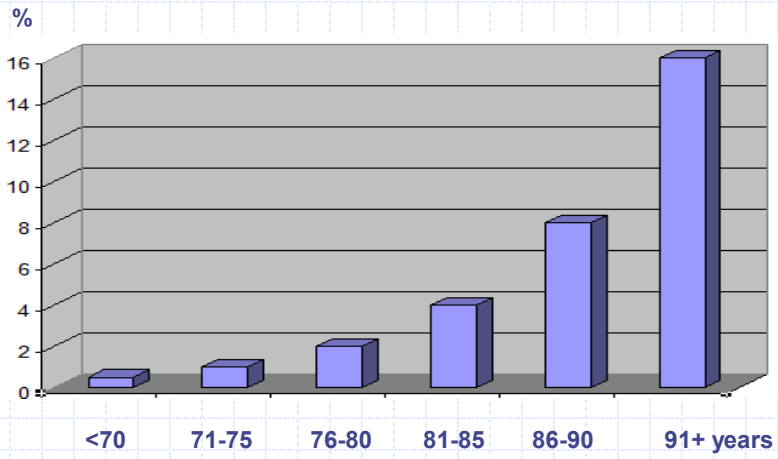
David E. Harrison[1]*, Randy Strong[2]*, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8]†, Marco Pahor[8]†, Martin A. Javors[9], Elizabeth Fernandez[2] & Richard A. Miller[10]*

NATURE Vol 460 July 2009, 339-346


The Interventional Model of Ageing
100%
5%
Physiological Capacity
EPIGENETICS
AGEING PROGRAM
BIRTH
40 years
DEATH
Disease Program
Physiological Change
Disease Onset
Clinical Disease
Disability


Proof of Concept – Removal of misfolded proteins/Amyloid
Misfolded Protein
Soluble Oligomers
Insoluble Aggregates
Ageing
Proteostasis
HSF-1
HSF-1
HS genes
HSP's
SKN-1
Stress response genes

Prevalence of Alzheimer's Disease in U.K.



Proof of Concept – Removal of misfolded proteins/Amyloid

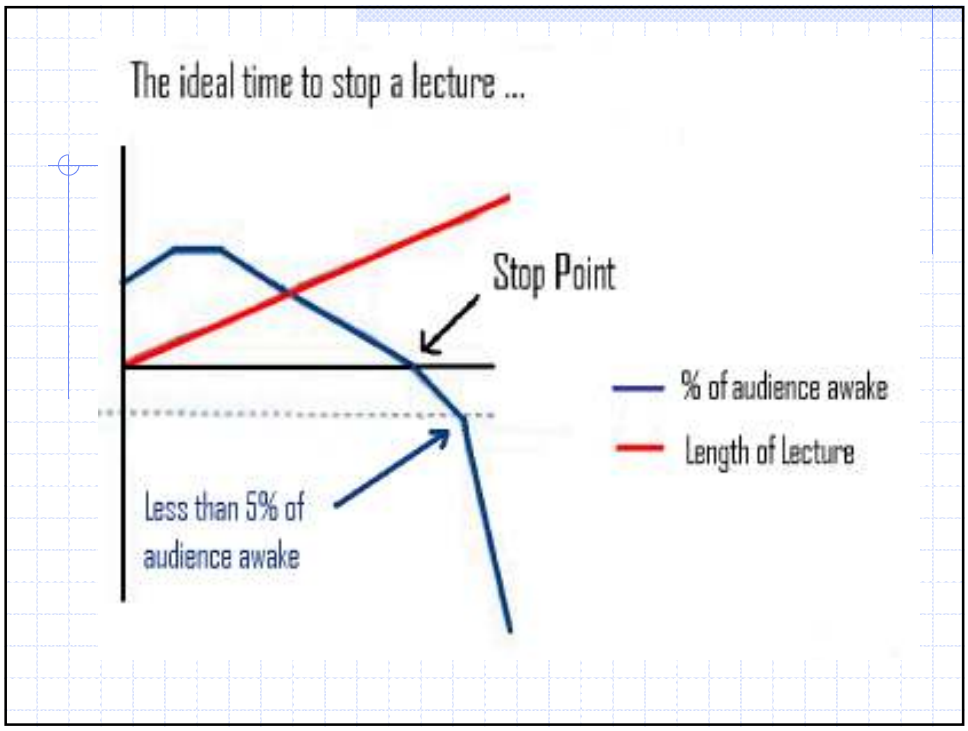
Amyloid-binding compounds maintain protein homeostasis during ageing and extend lifespan

Silvestre Alavez, Maithili C. Vantipalli, David J. S. Zucker, Ida M. Klang & Gordon J. Lithgow

Affiliations | Contributions | Corresponding authors

Nature **472**, 226–229 (14 April 2011) | doi:10.1038/nature09873
Received 19 October 2009 | Accepted 26 January 2011 | Published online 30 March 2011 | Corrected online **14 April 2011**

The lifespan-boosting effects of a chemical compound — called **Thioflavin T or Basic Yellow 1** – which is used for histological stains — support the idea that the build-up of denatured ("misfolded") proteins underlies ageing. Drugs that recognize such toxic detritus and alert the cell's natural repair and protein-recycling systems can be used to treat diseases of old age. **Curcumine and Rifampicin** showed similar effects. **The median life expectancy gain was 60% in C. elegans.**



Summary and Service Models

There are (and there will be) no controlled clinical trials showing evidence of general anti-ageing effects of drugs or other interventions in humans (with the likely exception of CR)

There are no biomarkers to measure the speed and course of our ageing process. Ageing in HIV patients – as in the general population - is multi-factorial. We do not know the contribution magnitude of single components (e.g. drug toxicity) in individuals.

However, there is an increasing number of organ- or disease-specific markers which justify treatment, e.g. BMI, BP, HbA1c, cholesterol. Targeting known risks, e.g. smoking and diet is probably the best step forward to delay ageing in all patient groups.

The current service model for HIV patients is exemplary and has proved successful; cooperative models for older patients with other specialities and adapting the existing HIV Clinic are in my opinion the best way forward.

Dr Peter Kroker 2011

One day we will know …

“Truth emerges more readily from error than from confusion”

Francis Bacon (1620)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