WHY DO WE AGE?

UNSW AUSTRALIA

Never Stand Still | Medicine | Psychiatry

Perminder Sachdev

Co-Director, Centre for Healthy Brain Ageing

Director, Neuropsychiatric Institute, POWH

p.sachdev@unsw.edu.au

CHeBA Healthy Brains Positive Ageing

TWO CERTAINTIES OF LIFE

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

A THIRD CERTAINTY

Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death.

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

ARE AGEING AND DEATH INEVITABLE?

CHeBA
Healthy Brains Positive Ageing

UNSW
AUSTRALIA

HOW OLD CAN ONE GET?

A Great Basin Bristlecone Pine forest
Pinus longaeva

Long-lived aquatic animals

White sturgeon

>100 years

Black coral colony

around 4,000 years old

Turritopsis dohrnii

the immortal jellyfish

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

Highest recorded life span of 255 years

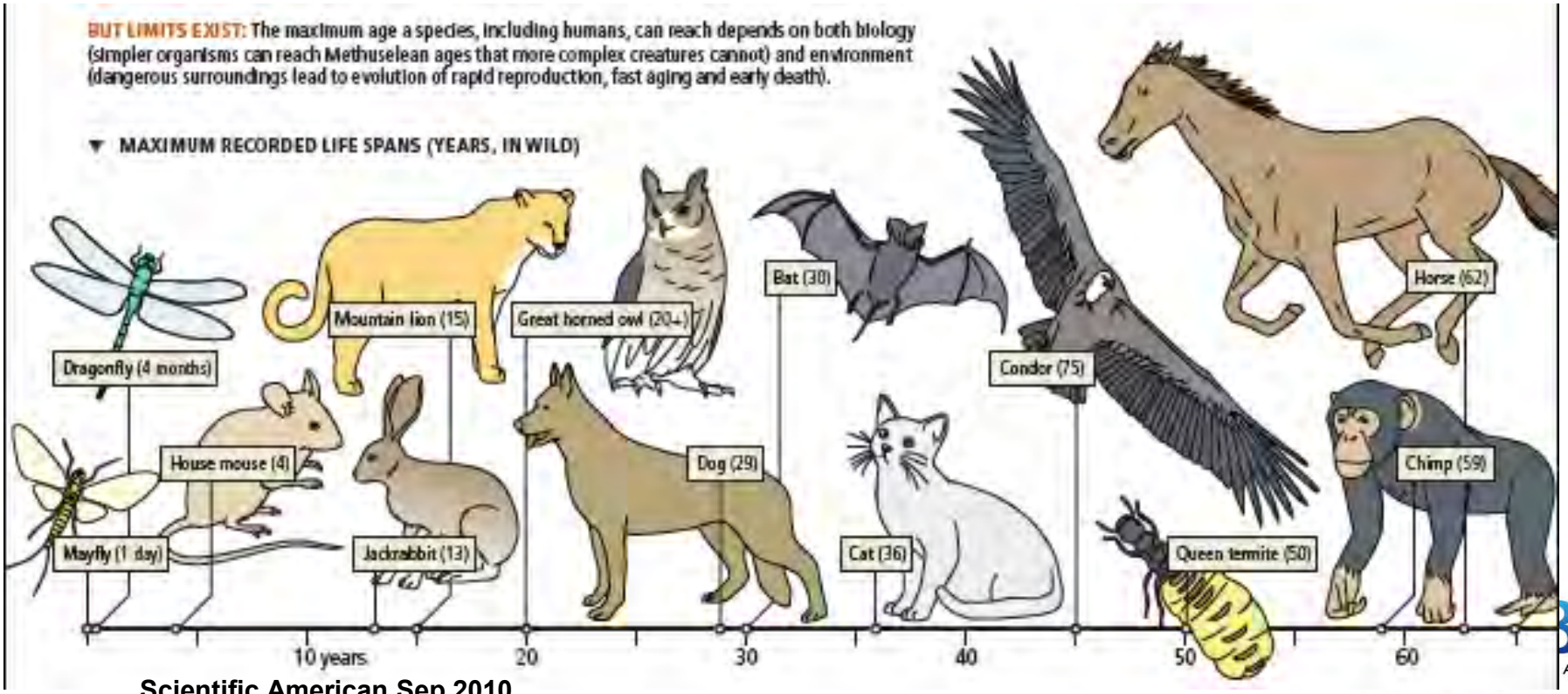
Aldabra Giant Tortoise

Geochelone gigantea

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

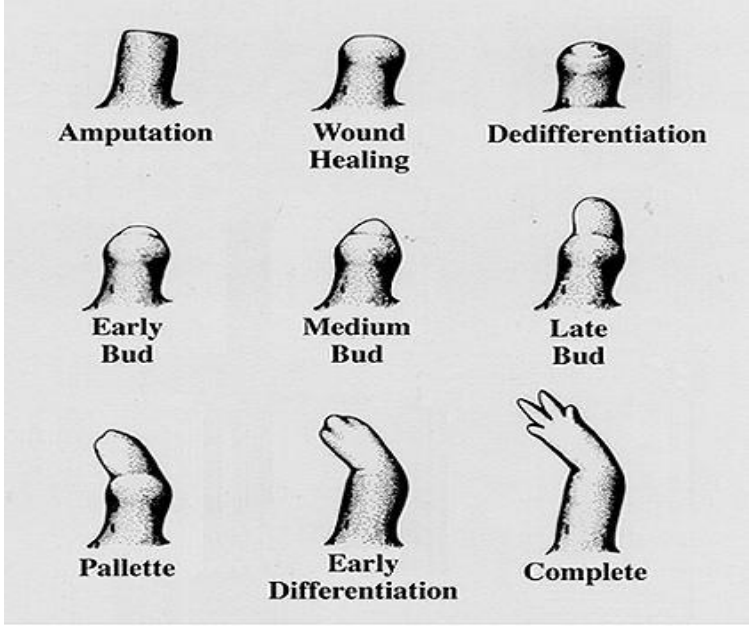
Terrestrial animals

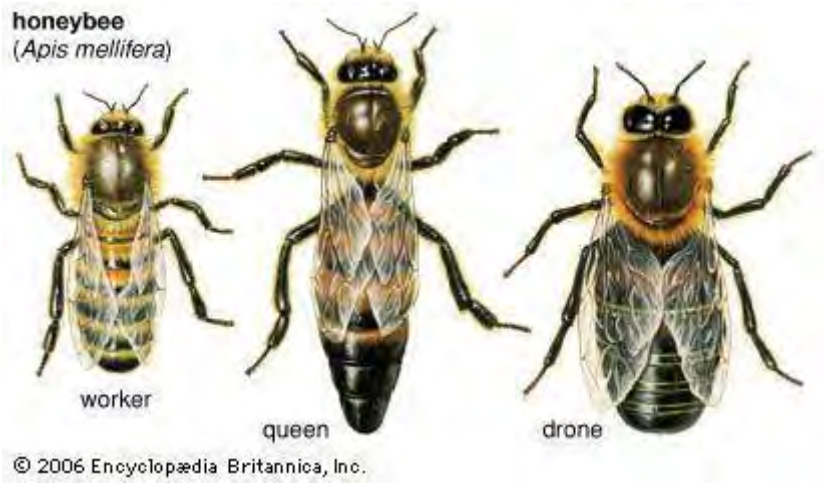


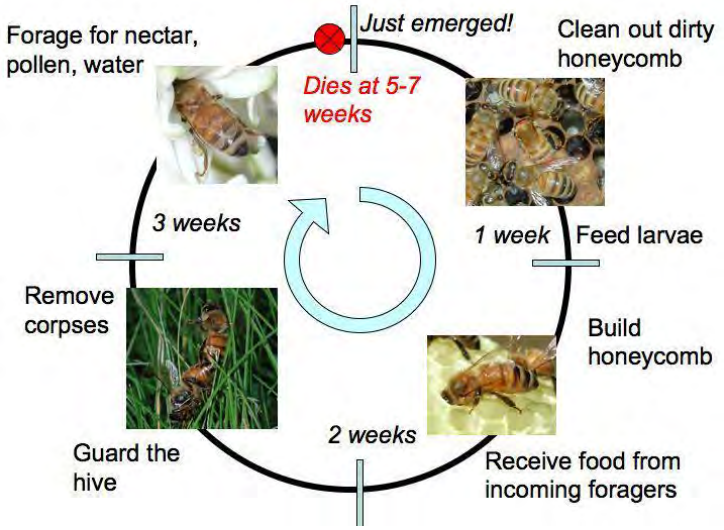
Scientific American Sep 2010

An adult salamander

Msx1 to the Rescue







Honey bee castes have different lifespans even though a queen or a worker can be formed from the same egg

CHeBA
Healthy Brains Positive Ageing

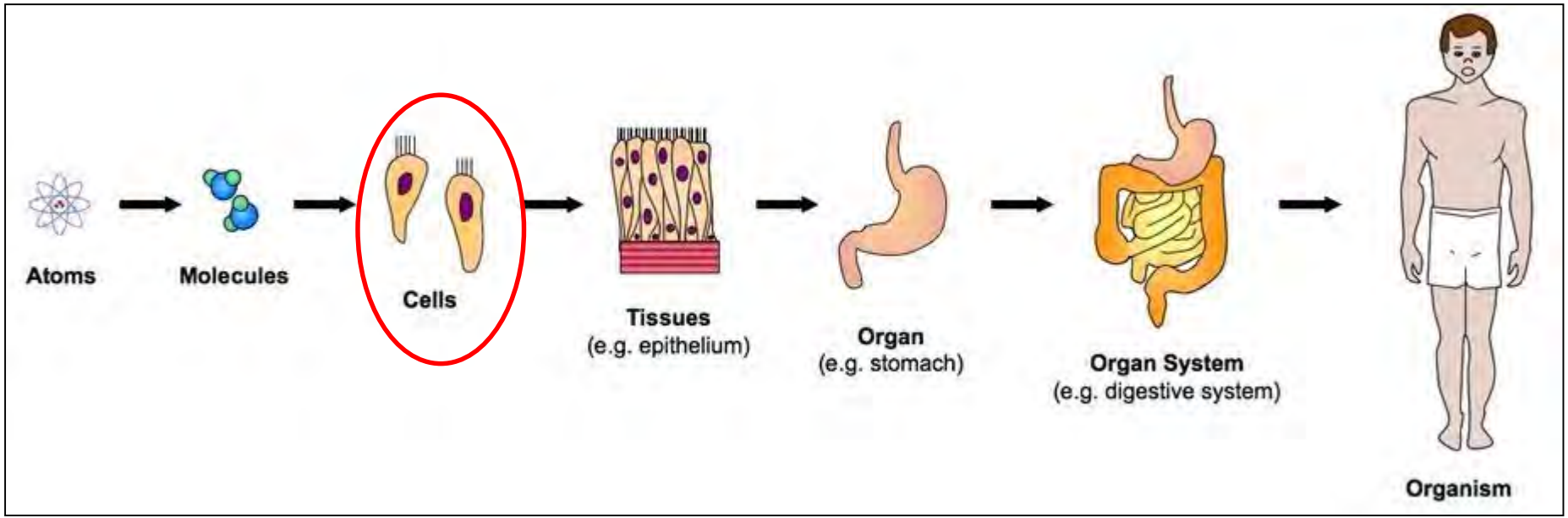
UNSW AUSTRALIA

Madame Jeanne Calment of Arles, France, photographed in 1994 at the age of 119. She died in 1997, aged 122, of 'natural causes'.

"Living independently until the age of 110….. Despite visual and hearing loss, she maintained autonomy in the face of the dependence imposed by the regulations of a nursing home - refusing care and visitors she did not want, smoking in a public place, and insisting on her daily glass of port.."

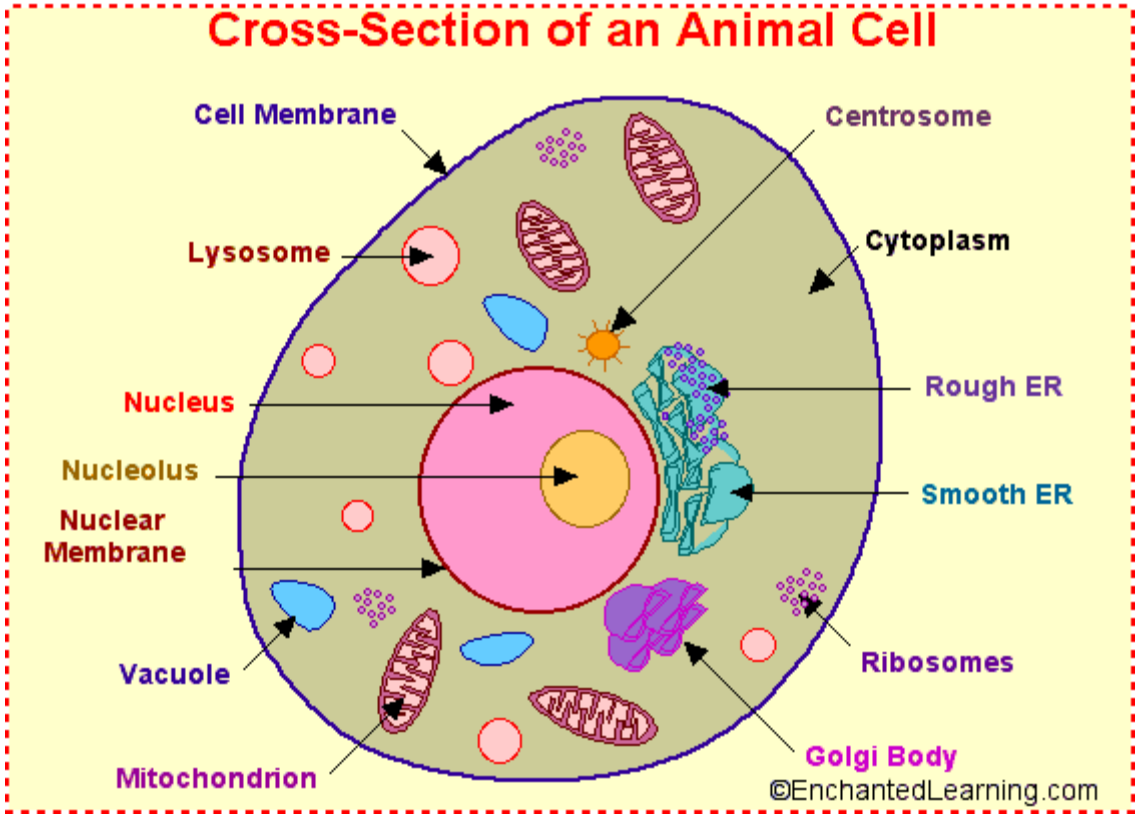
Ritchie, 1997

Levels of organisation



CHeBA
Healthy Brains Positive Ageing

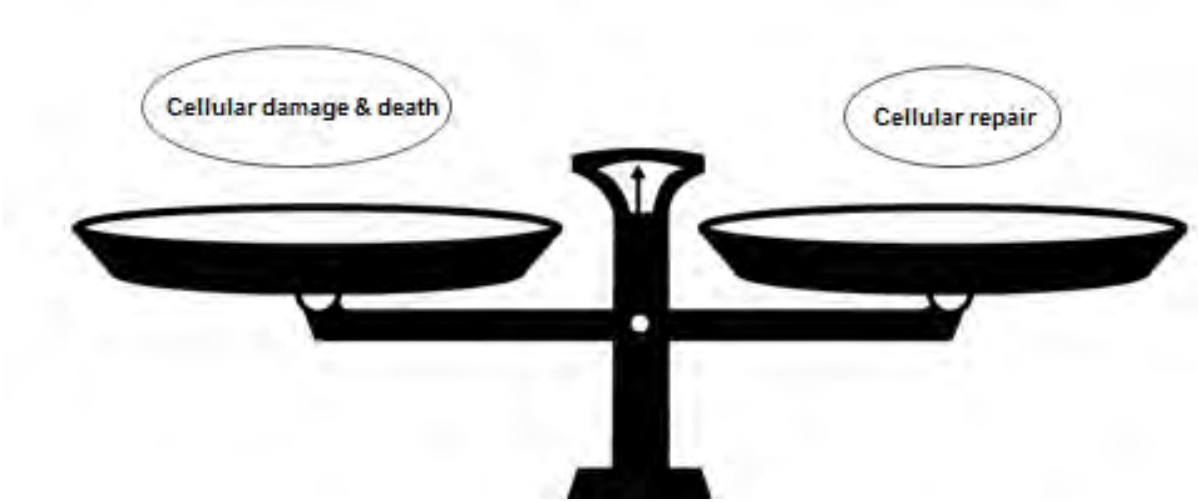
UNSW
AUSTRALIA



CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

THE CELLULAR BALANCE



CHeBA
Healthy Brains Positive Ageing

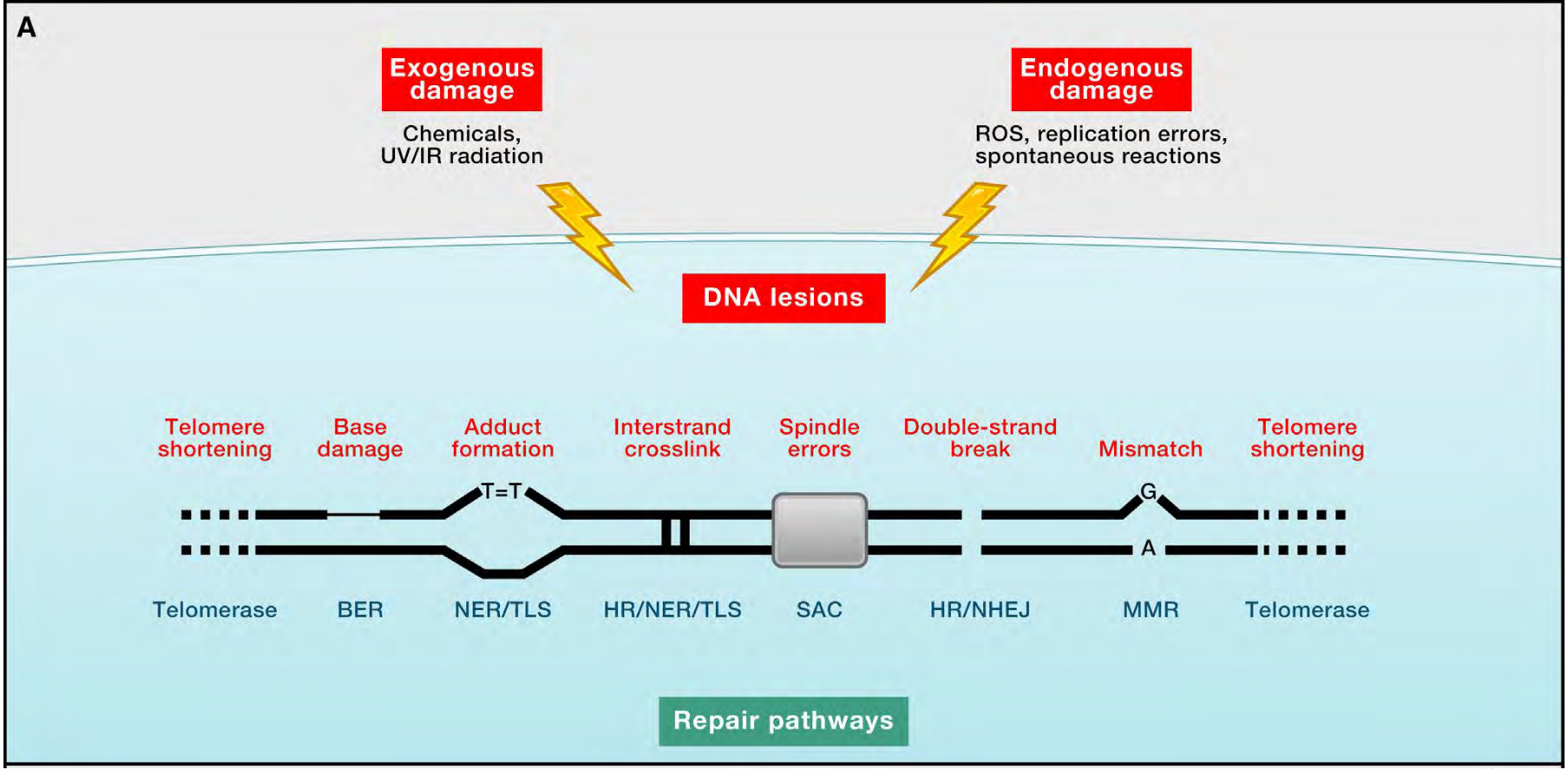
UNSW AUSTRALIA

Hallmarks of Ageing

Cell 153, June 6, 2013

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

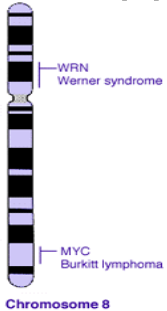


1. Genomic Instability

CHeBA Healthy Brains Positive Ageing

UNSW AUSTRALIA

14 48

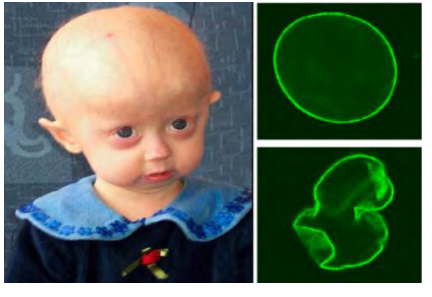


Progeria

Hutchinson-Gilford Syndrome ⇨

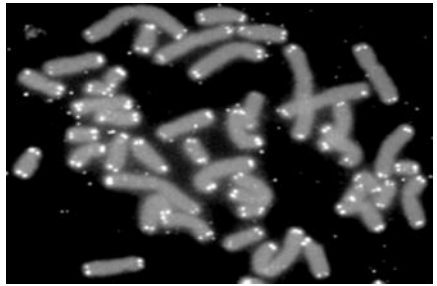
Accelerated ageing diseases

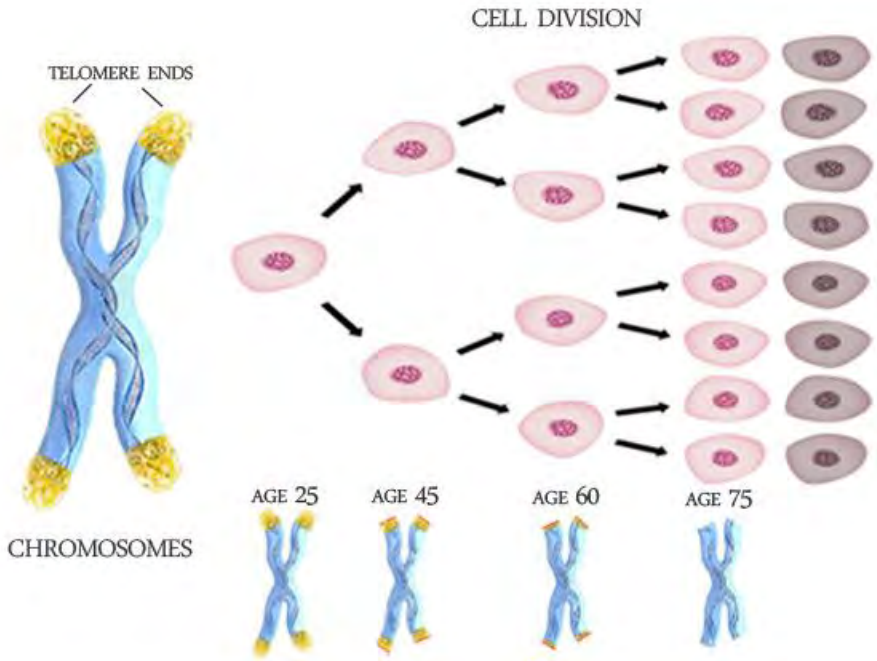
⇦ Werner Syndrome
Cockayne's syndrome
Xeroderma pigmentosa



In HGPS patients, the cell nucleus has dramatically aberrant morphology (bottom, right) rather than the uniform shape typically found in healthy individuals (top, right)

2. Telomere attrition





CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

Replicative Senescence

- Cellular senescence – Hayflick Limit 52 (40-60)

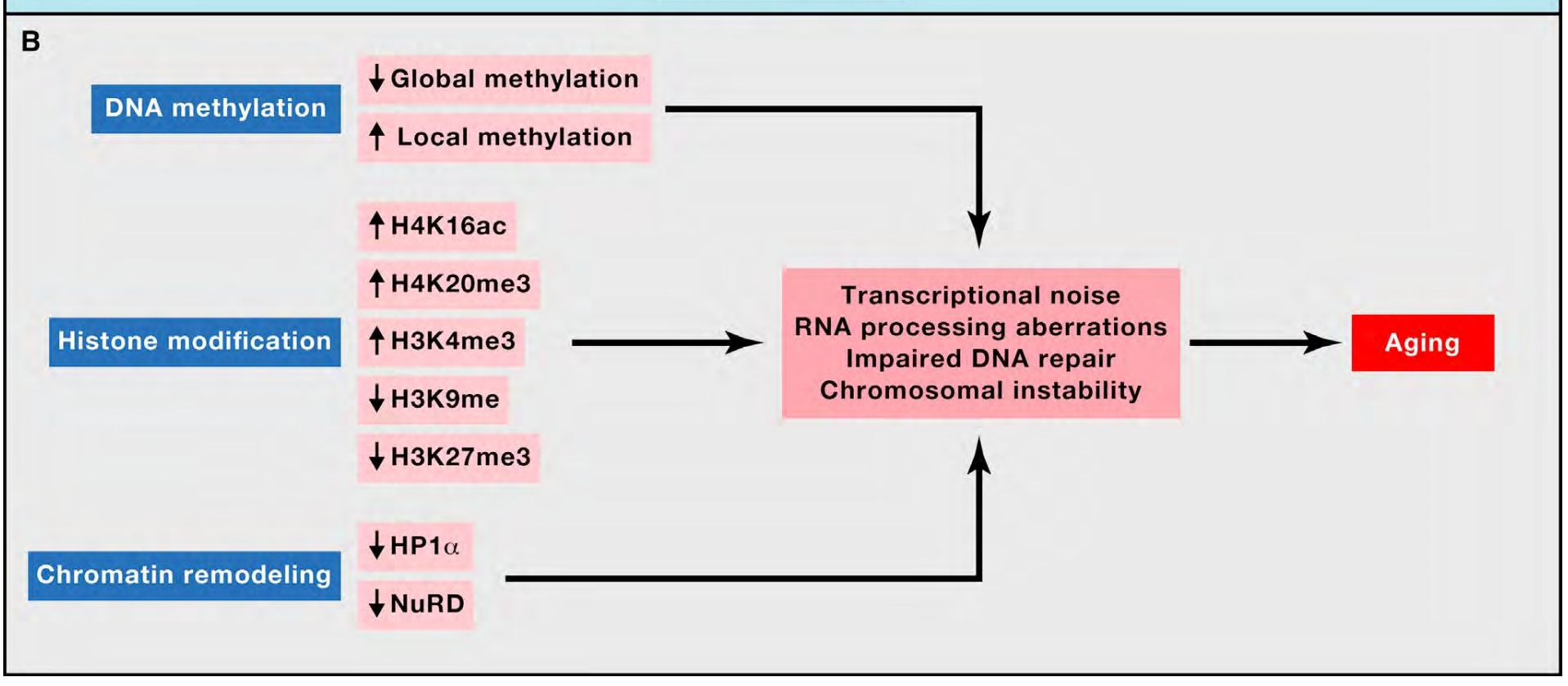
Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res* 1965;37:614-36.

- Mouse 14-28

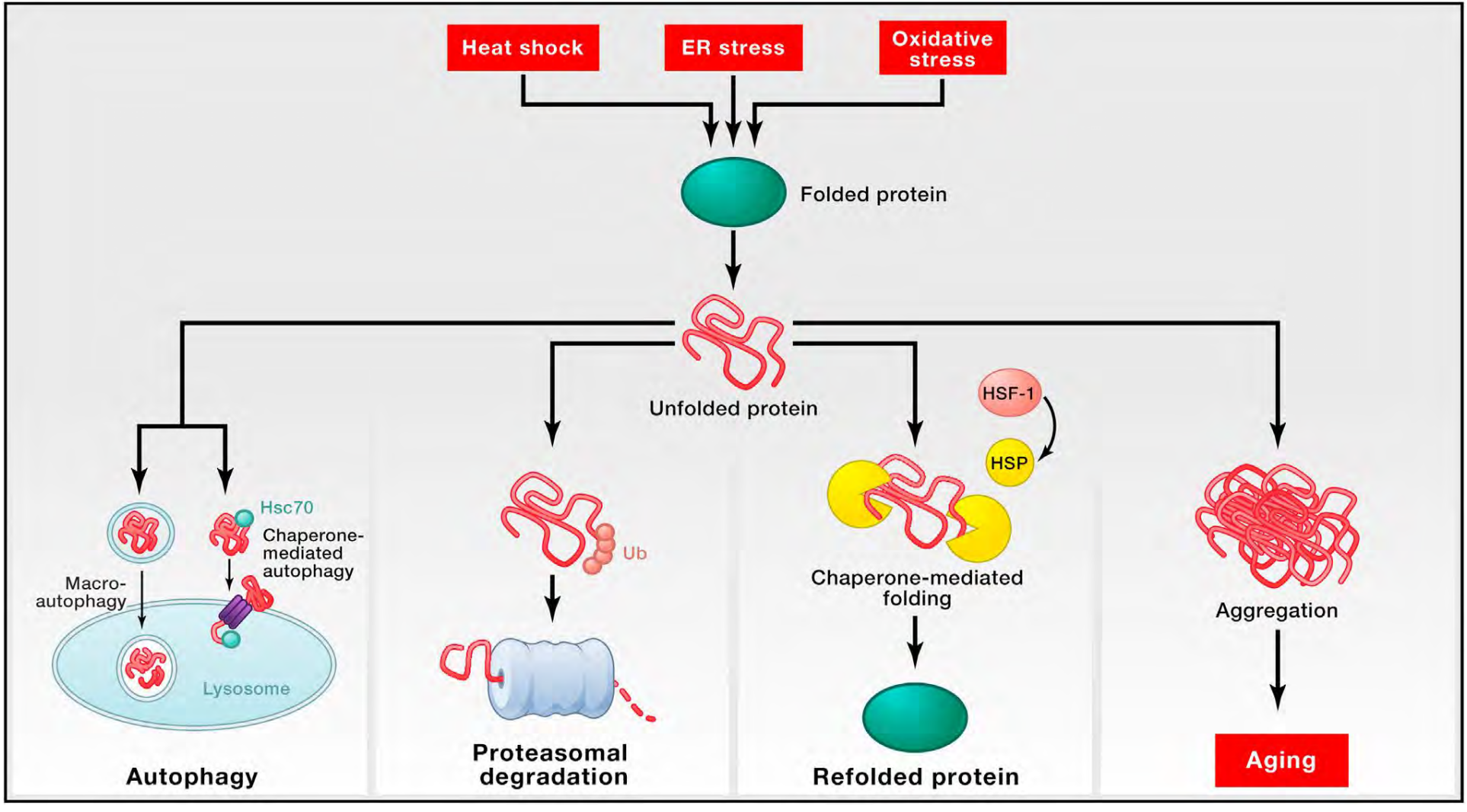
- Tortoise 100

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

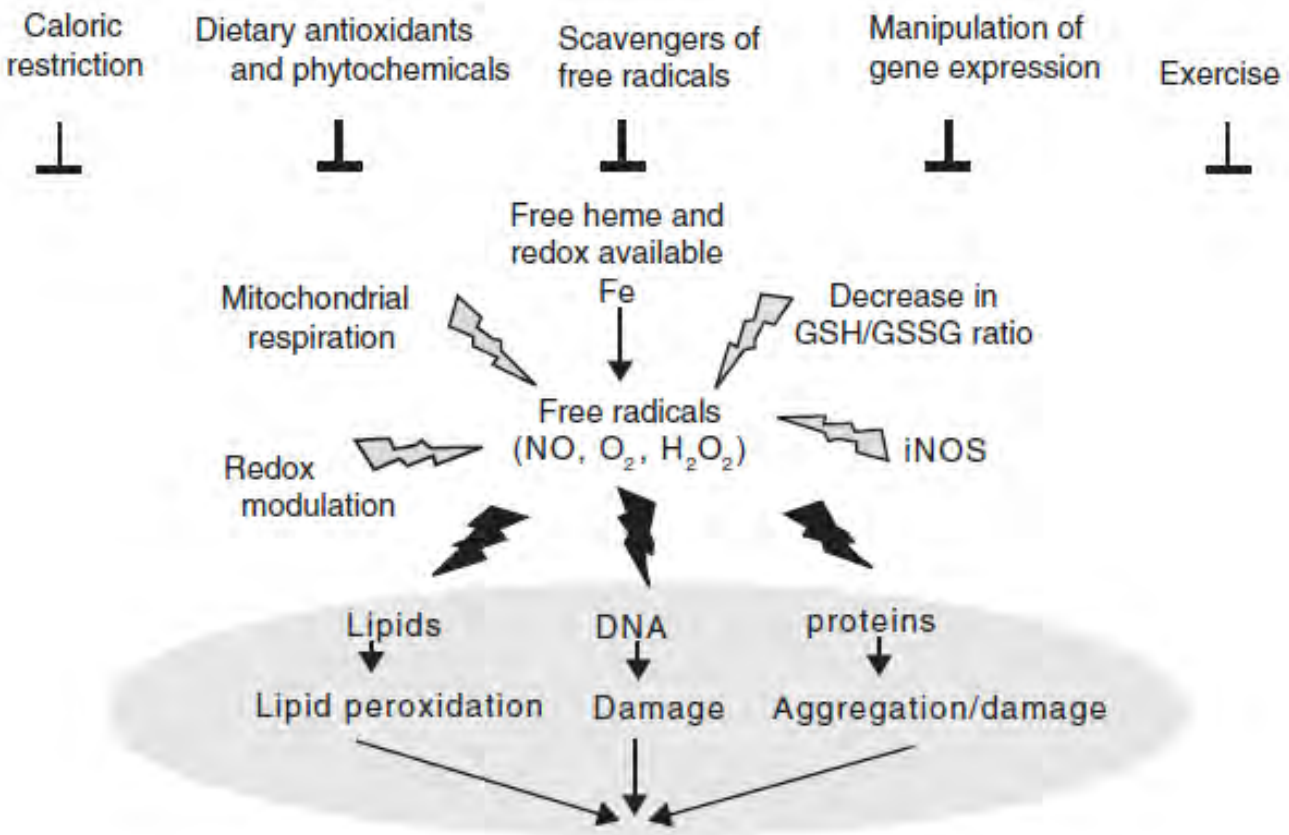


3. Epigenetic alterations. Alterations in the methylation of DNA or acetylation and methylation of histones, as well as of other chromatin-associated proteins, can induce epigenetic changes that contribute to the aging process.



4. Loss of Proteostasis

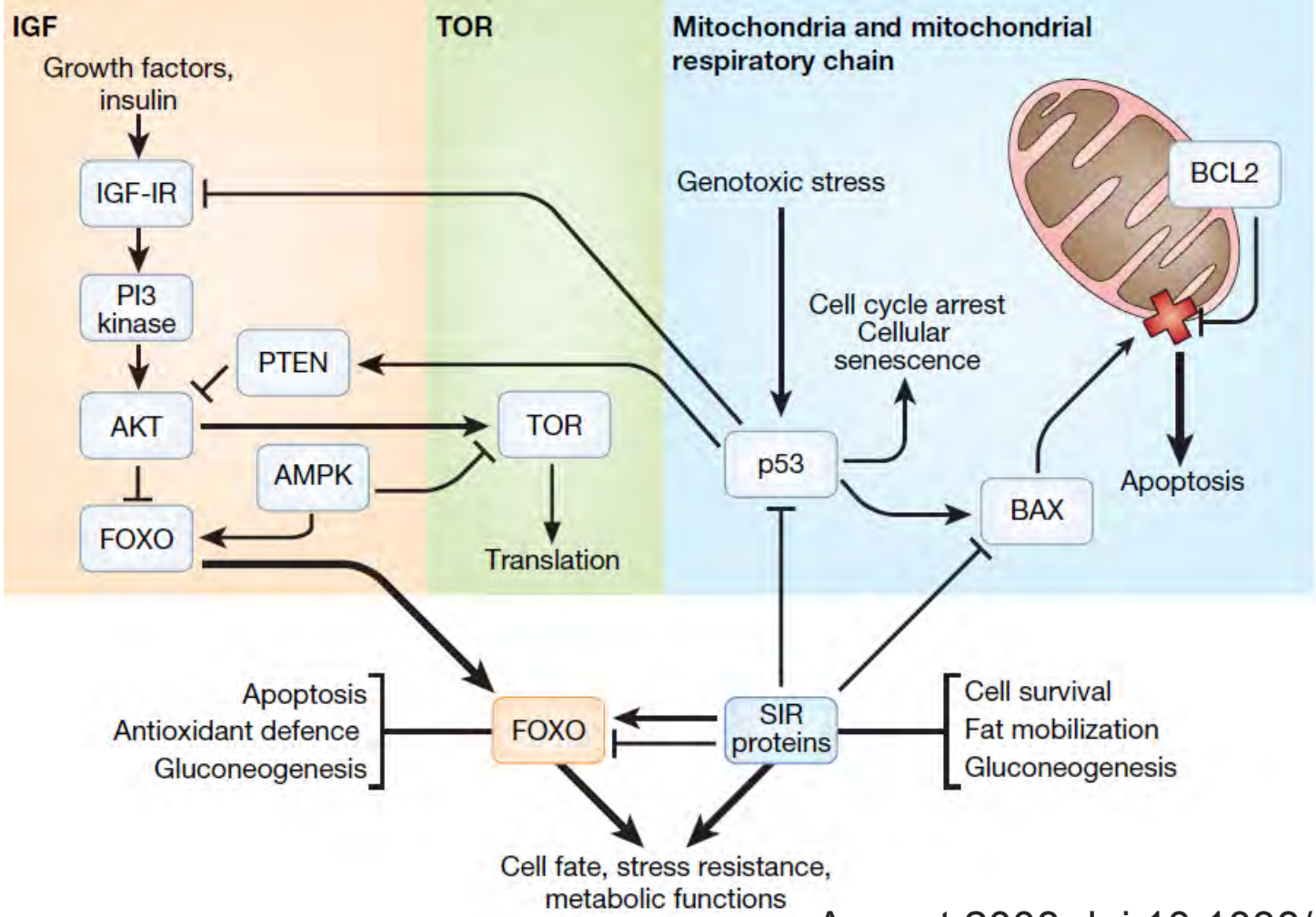
Oxidative stress (free radical) theory of ageing



CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

5. Nutrient Sensing

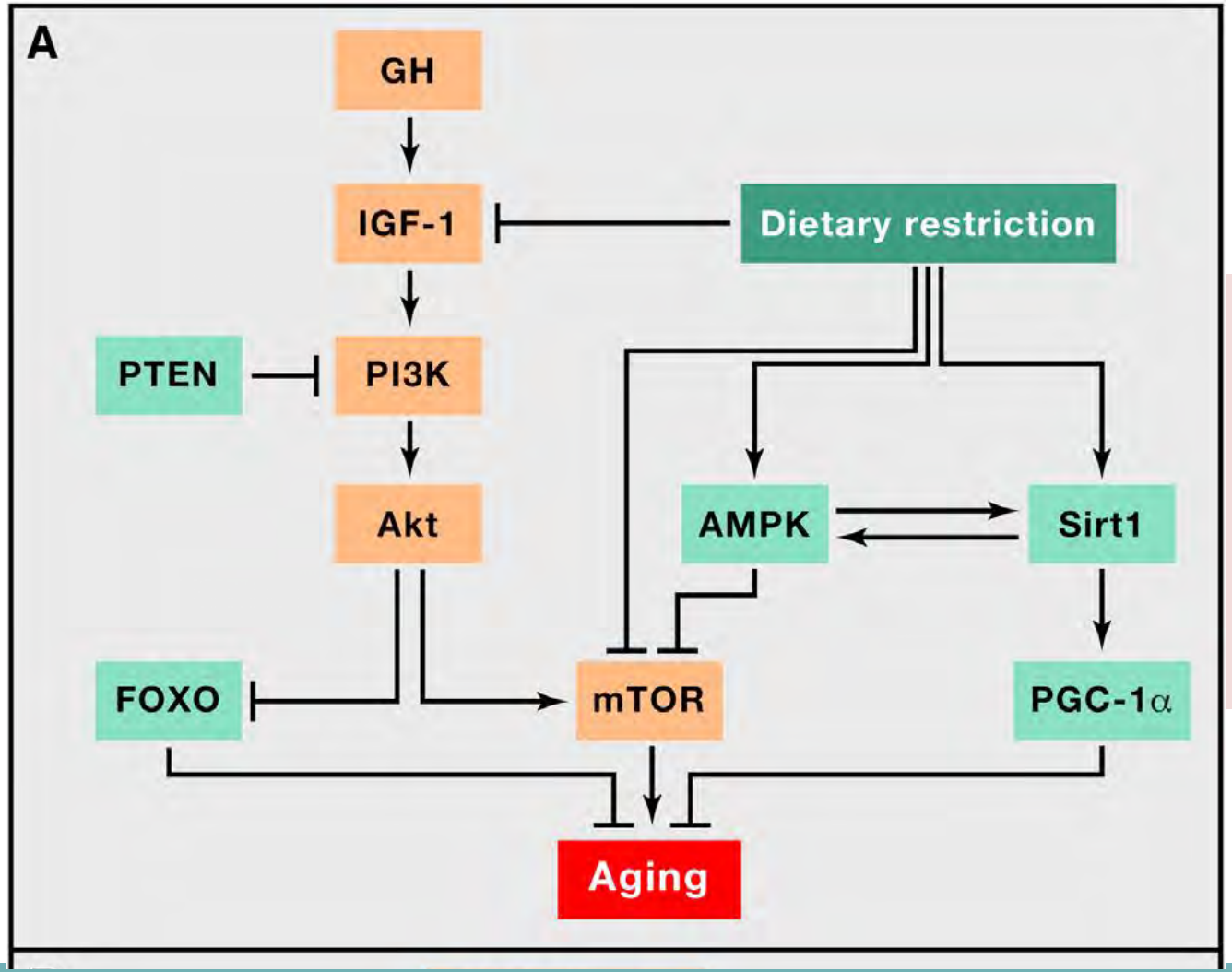


Potentially conserved pro-ageing pathways

CHeBA Healthy Brains Positive Ageing

August 2008 doi:10.1038/nature07216

UNSW AUSTRALIA

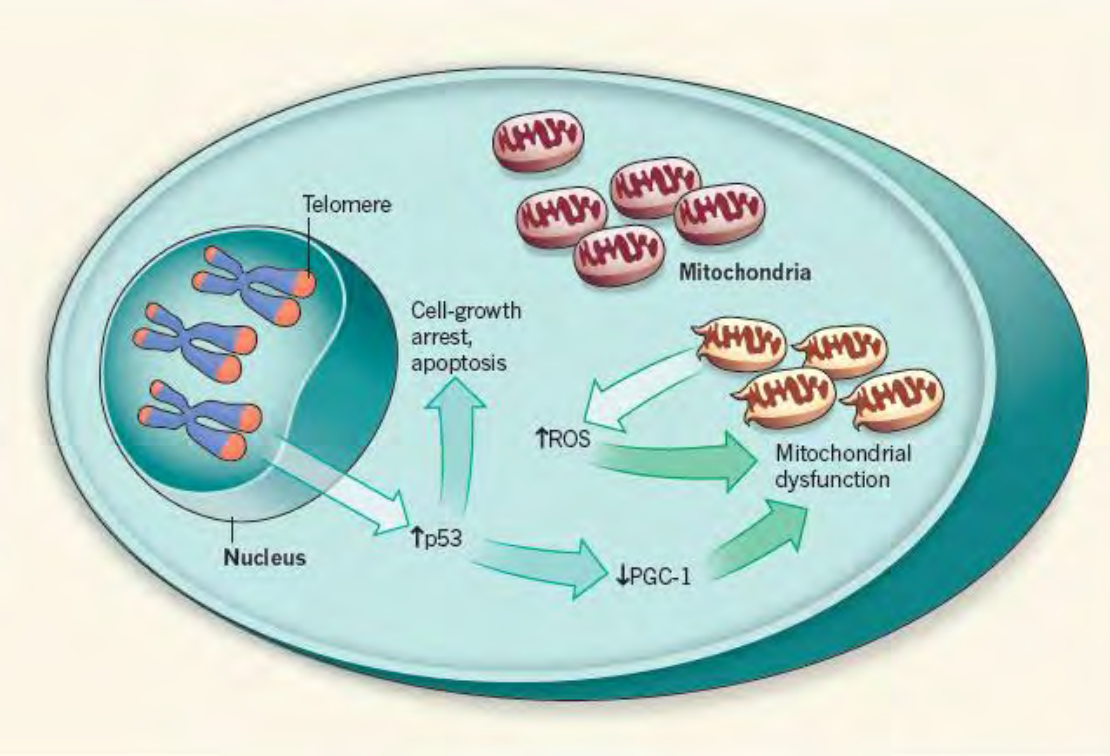


Caloric restriction

Available evidence strongly supports the idea that anabolic signalling accelerates ageing and decreased nutrient signalling extends longevity. Further, a pharmacological manipulation that mimics a state of limited nutrient availability, such as rapamycin, can extend longevity in mice

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

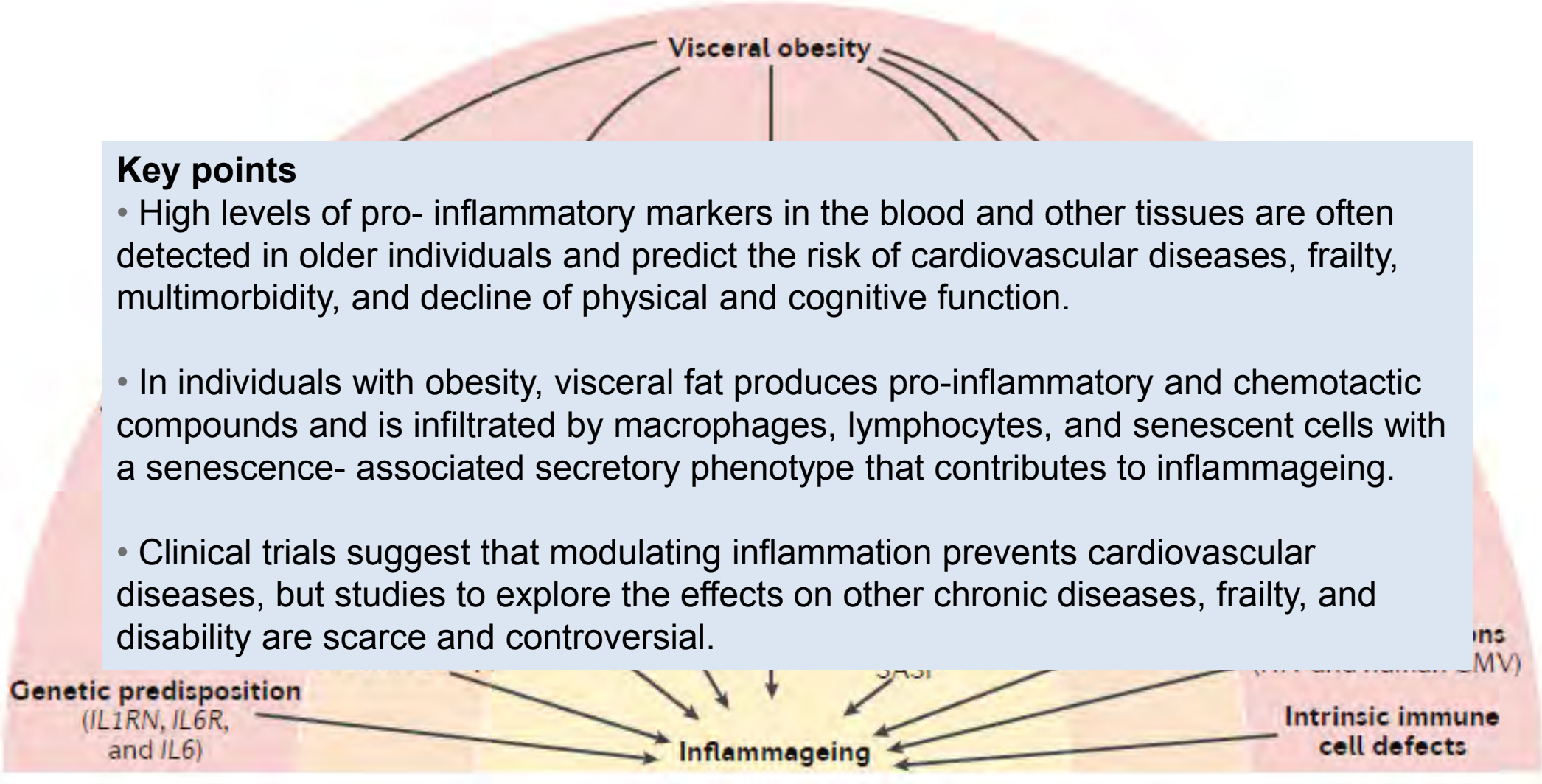


The nucleus, mitochondria and ageing.

Mitochondrial function has a profound impact on the aging process. Mitochondrial dysfunction can accelerate aging in mammals, but it is less clear whether improving mitochondrial function, for example through mitohormesis, can extend lifespan in mammals, though suggestive evidence in this sense already exists.

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA



Key points

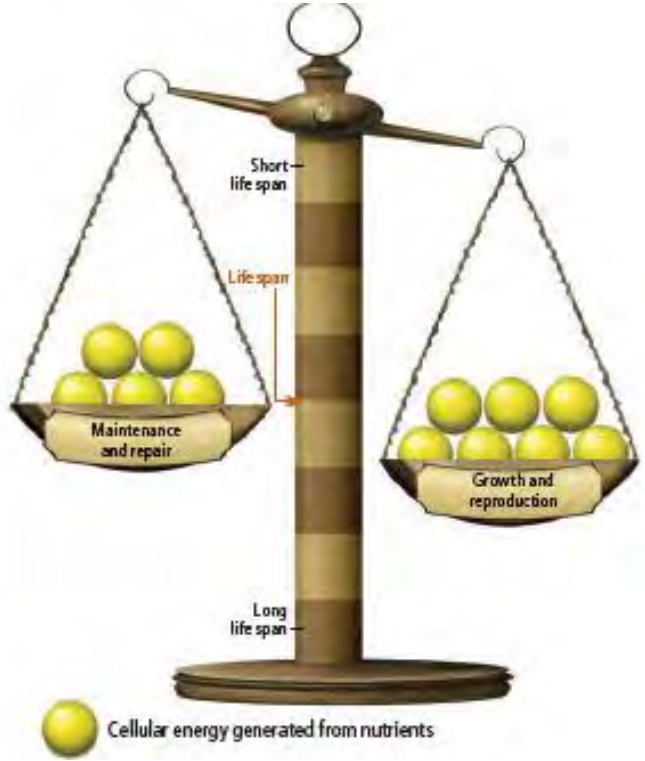
- High levels of pro- inflammatory markers in the blood and other tissues are often detected in older individuals and predict the risk of cardiovascular diseases, frailty, multimorbidity, and decline of physical and cognitive function.

- In individuals with obesity, visceral fat produces pro-inflammatory and chemotactic compounds and is infiltrated by macrophages, lymphocytes, and senescent cells with a senescence- associated secretory phenotype that contributes to inflammageing.

- Clinical trials suggest that modulating inflammation prevents cardiovascular diseases, but studies to explore the effects on other chronic diseases, frailty, and disability are scarce and controversial.

Potential causes of inflammageing.

HOW ENERGY IS ALLOCATED IN THE BODY



Ageing has to be understood in the context of evolution

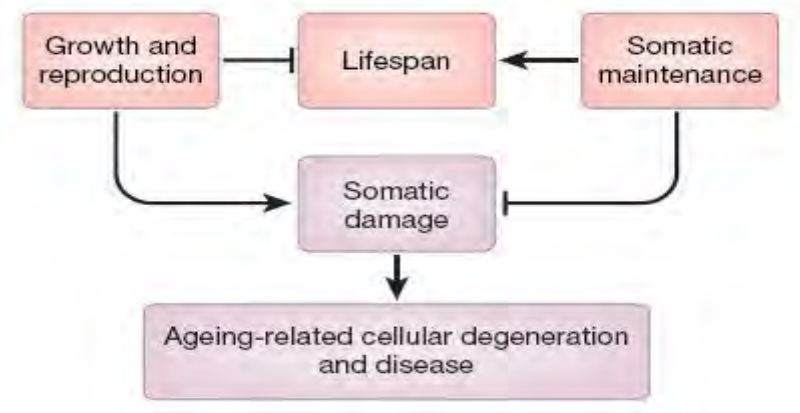
Scientific American Sep 2010

CHeBA
Healthy Brains Positive Ageing

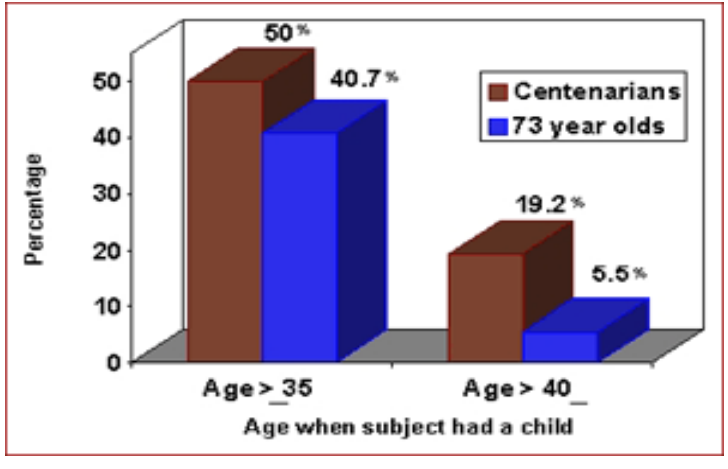
UNSW AUSTRALIA

Evolutionary theory of ageing

Disposable Soma



According to the 'disposable soma theory', organisms must compromise between energy allocation to growth and reproduction or somatic maintenance and repair.



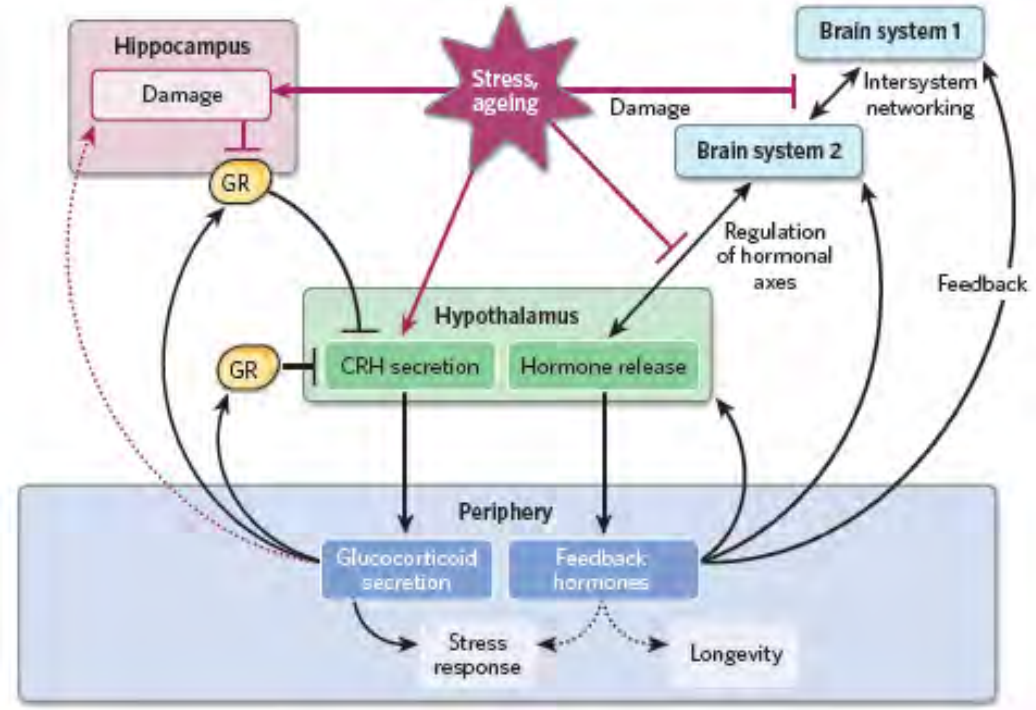
Centenarian women's reproductive systems age slowly

Experiments on dietary restriction and genetic or chemical alteration of nutrient-sensing pathways

	Life-span increase		Beneficial health effects	
	Dietary restriction	Mutations/ drugs	Dietary restriction	Mutations/ drugs
 Yeast	3-fold	10-fold (with starvation/ DR)	Extended reproductive period	Extended reproductive period, decreased DNA damage/mutations
 Worms	2- to 3-fold	10-fold	Resistance to misexpressed toxic proteins	Extended motility Resistance to mis-expressed toxic proteins and germ-line cancer
 Flies	2-fold	60–70%	None reported	Resistance to bacterial infection, extended ability to fly
 Mice	30–50%	30–50% (~100% in combination with DR)	Protection against cancer, diabetes, atherosclerosis,cardio-myopathy, autoimmune, kidney, and respiratory diseases; reduced neurodegeneration	Reduced tumor incidence; protection against age-dependent cognitive decline, cardio-myopathy, fatty liver and renal lesions. Extended insulin sensitivity
 Monkeys	Trend noted	Not tested	Prevention of obesity; protection against diabetes, cancer, and cardiovascular disease	Not tested
 Humans	Not determined	Not determined (GHR-deficient subjects reach old age)	Prevention of obesity, diabetes, hypertension Reduced risk factors for cancer and cardiovascular disease	Possible reduction in cancer and diabetes

Fontana et al, 2010. Science

The brain as a potential regulator of organismal ageing

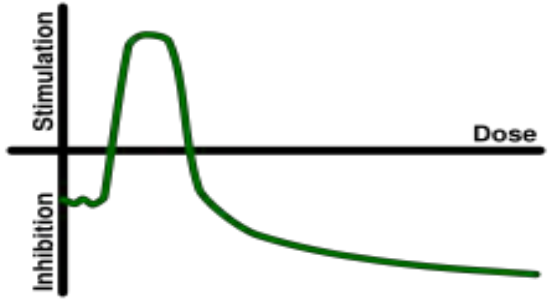


NATURE|Vol 464|25 March 2010

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA

Hormesis (from Greek *hormæin*, meaning "to excite") is the term for generally-favourable biological responses to low exposures to toxins and other stressors.



A non-monotonic curve
A very low dose of a chemical agent may trigger from an organism the opposite response to a very high dose

Repetitive mild stress exposure has anti-aging effects

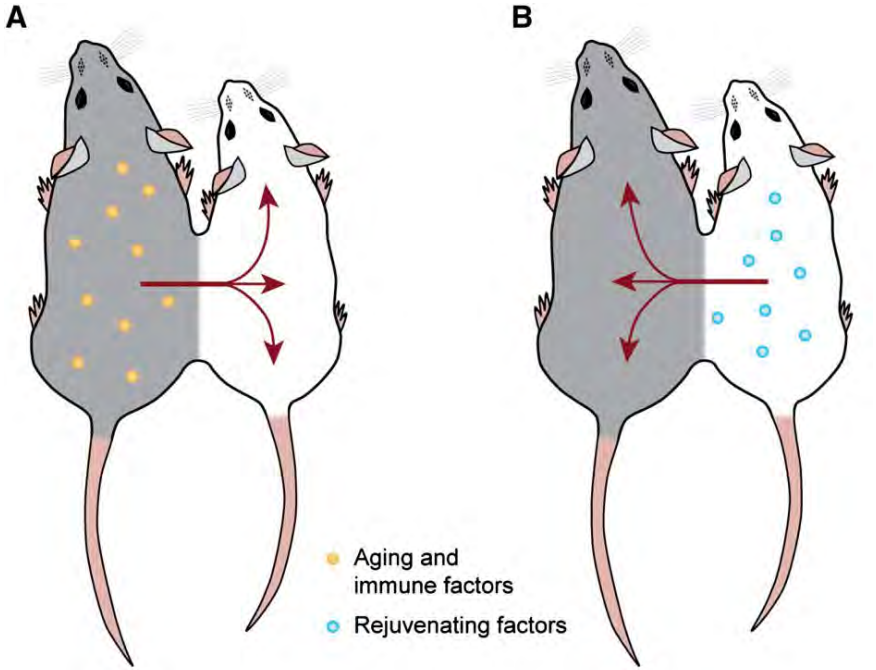
- Exercise is a paradigm for hormesis in this respect
- Others are heat shock, irradiation, pro-oxidants, hypergravity and food restriction
- Some natural and synthetic molecules, such as celasterols from medicinal herbs and curcumin from a spice turmeric have also shown to have hormetic beneficial effects - "hormetins"
- Psychological Stress as a hormetin

Genetics

- **Demographic selection**
  - **Evidence in medflies, nematode and humans**
  - **Apo E4 ↓ and E2 ↑ (Rebeck et al, 1994)**
  - **Apo B locus (Italian Centenarian Study)**
  - **HLA – DRw9 ↓ and DR1 ↑ (Okinawa Study)**
  - **Chr 4 D4S1654**
  - **Chr 11 11.p15.5**


The Blue Zones
Loma Linda, California
Nicoya, Costa Rica
Ogliastra Region, Sardinia
Ikaria, Greece
Okinawa, Japan
HUFF POST LIVE

Parabiosis



Aging

- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

Rejuvenation

- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?

Oxytocin
Blood borne chemokines – including CCL2/ MCP-1 and CCL11/Eotaxin

S.A. Villeda, T. Wyss-Coray / Autoimmunity Reviews 12 (2013) 674–677

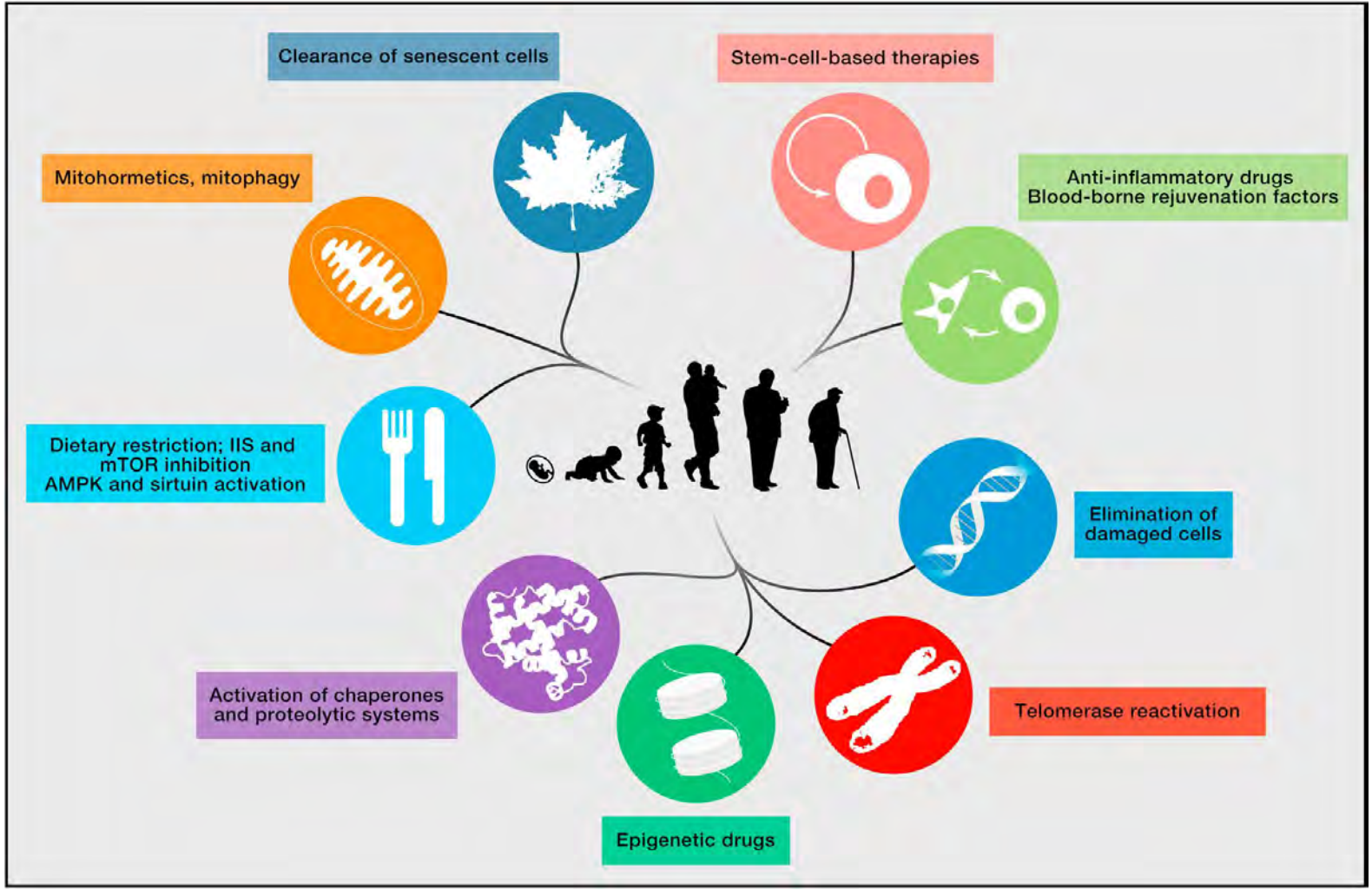
Wagers, A. et al. *Science* 297, 2256–2259 (2002).

Why Do Women Live Longer?

Not only is she likely to live longer than he does, but she will help him live longer, too

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA



Interventions that might extend human healthspan

CHeBA
Healthy Brains Positive Ageing

UNSW AUSTRALIA