The Actuarial Profession: Mortality and Longevity 15th April 2008

What might the future hold?

The ageing process and the prospects for prolonging life expectancy

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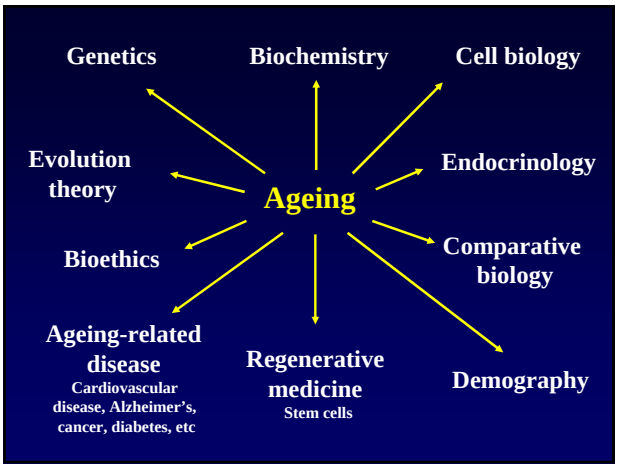
Institute of
Healthy Ageing

Today's talk

- Introduction to biogerontology
- Goals of research on ageing
- The new genetics of ageing
- Prospects for treatments for ageing

What is Biogerontology?



10 questions about ageing

1) Comparative biology: How does ageing and longevity vary between species? Are there non-ageing organisms?

Maximum lifespans in mammals

3 years | 59 years | 110 years

Pinus longaeva (Bristlecone pine) ~5000 years

Urticina felina (Dahlia anemone) Non ageing

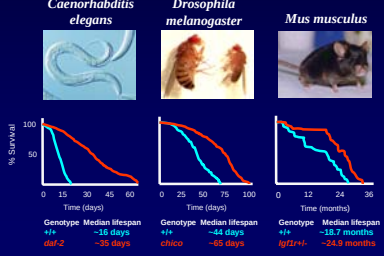
2) Evolutionary biology: How/why does ageing evolve? How does it contribute to fitness?

3) Genetics: Are ageing and longevity controlled by the genome, and if so how?

4) Model organisms: Can aging be suppressed and lifespan increased?

- Reduced insulin/ IGF-1 signalling
- Dietary restriction

Caenorhabditis elegans | *Drosophila melanogaster* | *Mus musculus*



5) **Molecular biology/ biochemistry:** What is the basis of ageing and longevity?
6) **Cell biology:** How does cellular senescence contribute to ageing and cancer? How are telomeres important?
7) **Gerontology:** How does ageing give rise to ageing-related disease?
8) **Immunology:** Why does the immune system fail in ageing? How does this impact health in later life?

Future prospect and bioethics

9) What are the prospects for treatments for ageing?
10) What should the aims of ageing research be? Is ageing a disease?

What is biogerontology for?

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We are living longer

Mme. Jeanne Calment
Born February 1875
Died August 1997, aged 122 years

Living longer has a downside

Alzheimer's disease

Iris Murdoch

Ageing-related pathologies are very diverse

Cardiovascular, eg. atherosclerosis, arteriosclerosis, hypertension, valvular fibrosis and calcification
Central nervous, eg. ß-amyloid depositions, neuritic plaques, neurofibrillary tangles and others leading to Parkinson's and Alzheimer's diseases
Gastrointestinal, eg. colonic polyps, diverticulosis of colon
Haematopoietic, eg. anaemias, chronic lymphocytic leukaemia
Integumentary, eg. senile keratoses, epidermal atrophy
Musculoskeletal, eg. skeletal muscle atrophy, osteoporosis, osteoarthritis
Special senses, eg. cataracts, macular degeneration, loss of high frequency auditory and olfactory acuity
Endocrine, eg. non-insulin-dependent diabetes mellitus.
Epithelia. eg. carcinomas
Peripheral nervous, e.g. segmental demyelination

George Martin, *Senescence and health in old age*

The Biology of Ageing

Ageing → Disease

Treatments 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

Treatments for age-related diseases
Future strategy?

AGEING → Cancer, Cardiovascular disease, Alzheimer disease, Parkinson disease, Macular degeneration, Type II diabetes, Osteoporosis → Treat/protect against all symptoms of ageing/age-related diseases

Treatment → Symptoms of ageing

Protection against age-related disease in rodents by dietary restriction

- Autoimmune disorders
- Cancer (breast, prostate, immune system and GI tract)
- Cataracts
- Type II diabetes
- Hypertension
- Kidney failure

Treating Diseases of Ageing

Understand the Biology of Ageing

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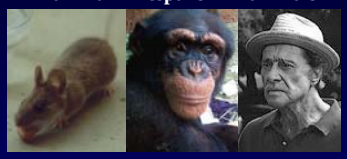
The New Genetics of Ageing

What *is* ageing?

Maximum lifespans in mammals



3 years | 73 years | 122 years

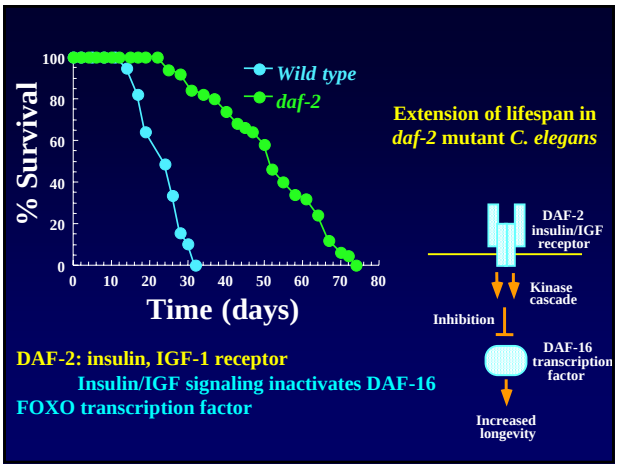
Genes control ageing

Understanding Lifespan: The Classical Genetic Approach

- Isolate mutants with altered rates of ageing
- Map, clone and sequence genes concerned
- Identify lifespan-determining proteins, biochemistry, etc
- Understand ageing?

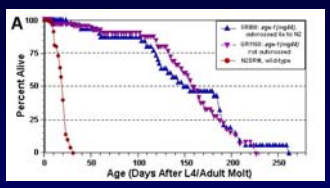
C. elegans

Lifespan 2-3 weeks



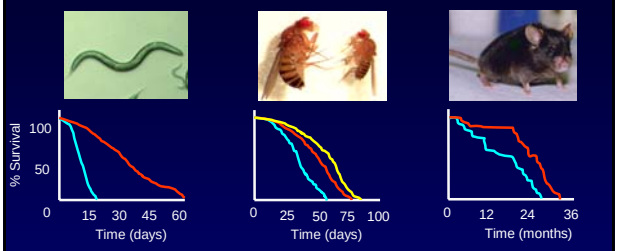
Null mutation of *age-1* phosphatidylinositol 3-kinase

Ayyadevara *et al. Aging Cell* 2008



~10-fold extension of medium, maximum adult lifespan in *C. elegans*!

Insulin/IGF-1 signaling controls ageing: Is this peculiar to nematodes?



Genotype	Median lifespan
+	16 days
daf-2	35 days

Klass 1983
Kenyon 1993
Kimura, Ruvkun 1998

Genotype	Median lifespan
+/+	44 days
chico/+	60 days
chico/chico	65 days

Partridge, Gems, Tatar 2001

Genotype	Median lifespan
+/+	18.7 months
Igf1r$^{+/-}$	24.9 months

Holzenburger 2003
Blüher, Kahn 2003

Irs1 mutant mice have delayed ageing. Selman, Gems, Partridge, Withers, *FASEB J.* 2008

Understanding Lifespan: The Classical Genetic Approach

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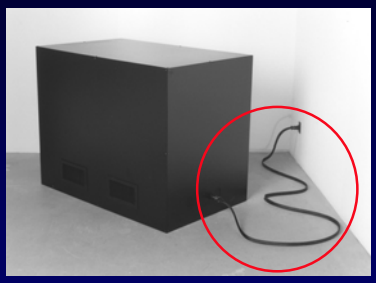
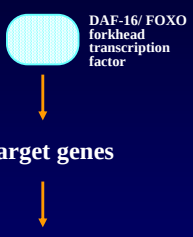
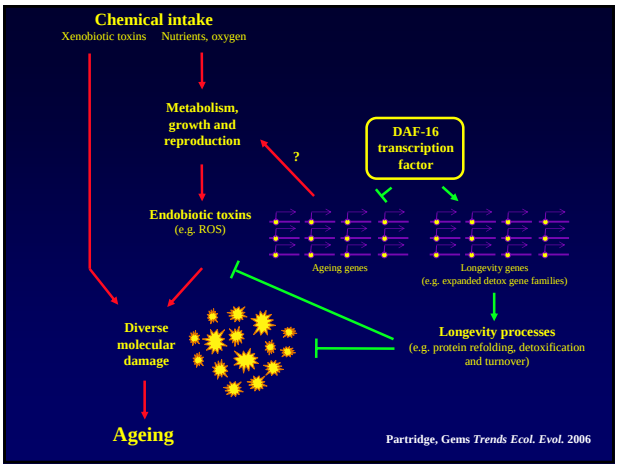


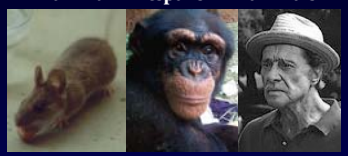
Understanding Ageing



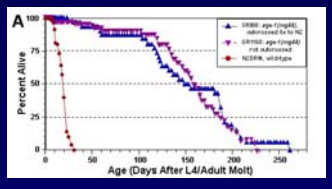


The Prospects for Treatments for Ageing

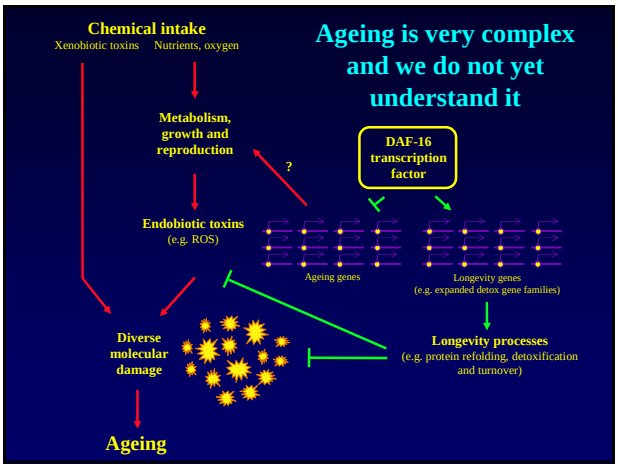
Maximum lifespans in mammals



3 years | 73 years | 122 years



The ageing process can show great plasticity



Developments within Biogerontology

1983: First long lived *C. elegans* mutant described
1996: First long-lived mouse mutant, first longevity genes sequenced in *C. elegans*
2001: Long-lived insulin/IGF-1 mutant fruitflies
2003: Long-lived insulin/IGF-1 mutant mice
2005: Drugs extending lifespan in *C. elegans*
2008: 10-fold increase of lifespan in *C. elegans*

Rapid progress in biogerontology

Proven treatments for human ageing derived from biogerontology

Average life expectancy likely to decrease due to epidemic of obesity

The Future

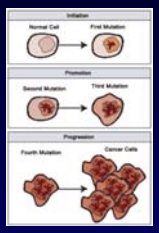
- Effective treatments for ageing are not imminent
- The genetics of ageing is rapidly identifying potential drug targets
- The fundamental biology of ageing is likely to be solved at some point
- Treatments for ageing are very likely to be devised at some point
- When, what level of efficacy?

A magic bullet for ageing?

Bacterial pathogens

Antibiotics = broad spectrum treatment

Magic bullet



Cancer

Chemotherapy
Radiotherapy
Surgery

No magic bullet

Ageing

Mechanism unknown (accumulation of molecular damage)

Magic bullet unlikely?

Looking into the future

2008-2020: Drugs targeting longevity control pathways identified and proven effective in nematodes, fruitflies and mice
2013-2030: First successful human trials, show reduction in age-related pathology at advanced ages
However: effects are small (+1-3 yrs) relative to benefits e.g. of exercise, controlled diet, social engagement
2008-2025: Underlying biology of ageing is understood
2015-2040: More powerful treatments from full understanding of ageing, effective in nematodes, fruitflies and mice
2020-2050: First successful human trials, substantial effects, initially +2-5 years, but increasing decade by decade

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