Biological Basis of Aging - Theories of Aging
Johns Hopkins Bloomberg School of Public Health
Feb 12, 2019

Srijita Dhar and Robert Brosh
National Institute on Aging, NIH
Born in Arles, France

Her father lived to the age of 94 and her mother to the age of 86.

At 85, she took up fencing. She rode a bicycle to the age of 100.

Long Life?
Garlic, vegetables, red wine, and avoiding brawls.
Olive oil, poured on all her food and rubbed on her skin, and nearly 2 pounds of chocolate eaten every week.
Aging is leading risk factor for many chronic diseases, disabilities, and frailty.

Genetic Control Theory

We are each born with a distinctive genetic code, i.e., our DNA blue print.

Genetic Control Theory proposes that each individual harbors a predetermined tendency to certain types of physical and mental functioning.

Genetic inheritance plays a major role in determining how quickly we age and how long we live.
The Central Dogma

DNA contains the original codes for making the proteins that living cells need. mRNA is a copy of a gene located on the DNA molecule. mRNA will leave the nucleus of the cell and the ribosome will read its coding sequences and put the appropriate amino acids together.
## DNA Damage

### Type of Damage:
- **Double-strand break**
- **Chemical bond between neighboring nucleotides** (Ultraviolet (UV) light)
- **Chemical modification of a nucleotide**
- **Chemical Linkage of Two Strands**
- Reactive oxygen species (ROS)
- Chemotherapeutic drugs
- Other cellular and environmental chemicals
- Normal modifications that regulate what genes are active

### Common Causes:
- Normal cellular activity
- Ionizing radiation (including X-rays)
- Chemotherapeutic drugs
- DNA repair of other types of damage
- Cellular and environmental chemicals
- Normal modifications that regulate what genes are active

### Endogenous DNA Damage

<table>
<thead>
<tr>
<th>DNA Lesions</th>
<th>No. Lesions/Cell/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depurination</td>
<td>AP site 10,000</td>
</tr>
<tr>
<td>Oxidation</td>
<td>8oxoG 400-1,500</td>
</tr>
</tbody>
</table>

### Exogenous DNA Damage

<table>
<thead>
<tr>
<th>Peak hr sunlight</th>
<th>DNA Lesions</th>
<th>No. Lesions/Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>sunlight</td>
<td>Pyr dimers, 6-4 photo pr. aromatic DNA adducts</td>
<td>100,000</td>
</tr>
<tr>
<td>Cigarette smoke (1 pack/day-40 yr)</td>
<td>DSBs</td>
<td>0.0002</td>
</tr>
<tr>
<td>Dental x-rays</td>
<td>DSBs</td>
<td>0.016</td>
</tr>
<tr>
<td>Mammography</td>
<td>DSBs</td>
<td>12</td>
</tr>
<tr>
<td>Chernobyl accident (neighbors)</td>
<td>DSBs</td>
<td>0.2-160</td>
</tr>
<tr>
<td>Hiroshima /Nagasaki atomic bombs</td>
<td>DSBs</td>
<td></td>
</tr>
</tbody>
</table>

### Additional Information:
- **DSBs**: Double-strand breaks
- **AP site**: Apurinic/apyrimidinic site
- **8oxoG**: 8-oxoguanine
- **Pyr dimers, 6-4 photo pr. aromatic DNA adducts**: Pyrimidine DNA dimers, 6-4 photoproduction aromatic DNA adducts
- **Cigarette smoke (1 pack/day-40 yr)**: Aromatic DNA adducts
- **Chest x-rays**: DSBs 0.0008
- **Dental x-rays**: DSBs 0.0002
- **Mammography**: DSBs 0.016
- **Chernobyl accident (neighbors)**: DSBs 12
- **Hiroshima /Nagasaki atomic bombs**: DSBs 0.2-160
Mutations increase at the same rate as DNA repair decreases with aging

DNA repair decreases with age

Mutation frequency increases with age

0.06% per year

0.06% per year


DNA lesions implicated in aging

Mechanisms by which DNA damage drives aging

- Driving cells to senescence: Alter metabolism, secrete proinflammatory factors, and alter local tissue environment
- Exhausting regenerative capacity: Cause autonomous and nonautonomous stem cell dysfunction
- Impacting mitochondrial function: Change metabolism, mitochondrial functions, and autophagy
- Introducing protein aggregation: Interplay with DNA damage, DNA damage response, and autophagy

Do DNA double-strand breaks drive aging?

Persistent γ-H2AX foci

Can DNA damage be suppressed by lifestyle choices?

Dietary Restriction increases health and lifespan in diverse organisms. Limiting food consumption to 5-7 hrs/day, Intermittent fasting, Selective amino acid restrictions, and Fiber lead to increased Insulin sensitivity, reduced Sex hormone, improved Stem cell function, decreased Cell senescence, increased Mitochondrial function, increased Autophagy, increased DNA repair, reduced Inflammation, and increased Tissue repair. These changes improve organ function and reduce resistance to stress, leading to improved health and longevity.

Caloric Restriction and Aging—It May Not Be That Simple


**Study**
- **Wis (2009)**
- **NIA (2012)**

**Life Extended?**
- Increase lifespan
- No increase lifespan

**Age**
- young
- young/old

**Diet**
- 29% sucrose ad libitum
- 3% sucrose portioned

*Both studies show that CR delays onset and incidence of chronic disease in monkeys*

*Note—NIA monkeys lived much longer than Wisconsin monkeys!*

*Although a senior citizen — the average tissue monkey lifespan in captivity is 27 — Canto, above, is aging fairly well. Outwardly, he has a nice coat, elastic skin, a smooth gait, upright posture and an energetic demeanor. His bloodwork shows he is as healthy as he looks.*

Human equivalent
- Meals prepared by Mike Linksvayer, 36

<table>
<thead>
<tr>
<th>Monkey Menu</th>
<th>Human Menu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily calories</td>
<td>480</td>
</tr>
<tr>
<td>Monkeys also receive an apple each day</td>
<td>Beverages, snacks and desserts not shown. Diet varies according to food type, sex and activity level.</td>
</tr>
</tbody>
</table>

*Both studies show that CR delays onset and incidence of chronic disease in monkeys*

*Note—NIA monkeys lived much longer than Wisconsin monkeys!*

*Owen, 26*

He gets more food, but Owen, above, isn’t aging as well. His posture has been affected by arthritis. His skin is wrinkled and his hair is falling out. Owen is frail and moves slowly. His bloodwork shows unhealthy levels of glucose and triglycerides.*
1990’s: Decade of Discovery for Helicases Linked to Accelerated Aging

The Bloom Syndrome Gene Product Is Homologous to RecQ Helicases

Nathan A. Elia,*† Jennifer Gunter,† Jia-Tao Zhang,*† Joel Striggow,* David J. Lannon,† Susan Chivers,† Maria Prodehous,* and James Berman*†

Laboratory of Human Genetics
New York Blood Center
New York, New York 10019

*Department of Molecular Genetics
Bachman and Microbiology
University of Cincinnati College of Medicine
Cincinnati, Ohio 45267

Summary

The Bloom’s syndrome (BS) gene, BLM, plays an important role in the maintenance of genome stability in somatic cells. A condition for BS is identified by direct selection of a BS cell from a BS segment of the genome to which BLM has been eliminated by semaphage cDNA vector. In this novel method, cells were used from a patient with BS that had undergone anheiotic bone marrow transplantation. Within 50 days, the specific cell clone was identified by detecting the expression of the BS cell product (BLM) in the cell clone. The presence of the cell was determined by detection of the distribution of DNA in the clone. The BLM gene is expressed in bone marrow and skin cells, and may be a candidate gene for bone marrow transplantation.
DNA Helicase

- Molecular motor
- Uses fuel of ATP hydrolysis to disrupt hydrogen bonds between complementary strands of the DNA double helix
- Facilitates replication, DNA repair, and recombination
Human DNA Helicases of the RecQ and Fe-S Families

# Chromosomal Instability of Human Cells Deficient in RecQ and Fe-S Helicases

<table>
<thead>
<tr>
<th>Family</th>
<th>Helicase</th>
<th>Associated Disease / Cancer</th>
<th>Chromosomal Instability</th>
</tr>
</thead>
<tbody>
<tr>
<td>RecQ</td>
<td>WRN</td>
<td>Werner syndrome</td>
<td>Chromosomal deletions and rearrangements; telomere loss</td>
</tr>
<tr>
<td></td>
<td>BLM</td>
<td>Bloom syndrome</td>
<td>Elevated sister chromatid exchange</td>
</tr>
<tr>
<td></td>
<td>RECQL1</td>
<td>Breast cancer</td>
<td>Elevated sister chromatid exchange</td>
</tr>
<tr>
<td></td>
<td>RECQL4</td>
<td>Rothmund-Thomson syndrome, RAPADILINO, Baller-Gerold syndrome</td>
<td>Chromosomal rearrangements; aneuploidy</td>
</tr>
<tr>
<td></td>
<td>RECQL5</td>
<td>Breast cancer</td>
<td>Chromosomal rearrangements; CPT(^a)-induced elevated sister chromatid exchange; microsatellite instability</td>
</tr>
<tr>
<td>Fe-S</td>
<td>FANCJ</td>
<td>Fanconi anemia</td>
<td>Elevated sister chromatid exchange; MMC(^b)-induced chromosomal breakage; microsatellite instability</td>
</tr>
<tr>
<td></td>
<td>RTELI1</td>
<td>Dyskeratosis congenita, Hoyeraal-Hreidarsson syndrome</td>
<td>Telomere shortening and instability; anaphase bridges; trinucleotide repeat expansions</td>
</tr>
<tr>
<td></td>
<td>DDX11</td>
<td>Warsaw Breakage syndrome</td>
<td>Sister chromatid cohesion defects; MMC(^a)-induced chromosomal breakage</td>
</tr>
<tr>
<td></td>
<td>XPD</td>
<td>Xeroderma pigmentosum, Cockayne syndrome, Trichothiodystrophy</td>
<td>UV(^b)-induced chromosome aberrations; abnormal chromosome segregation in XP-D and XP-D/CS cells</td>
</tr>
</tbody>
</table>
Werner Syndrome
Rare autosomal recessive disorder

Mutations in WRN helicase gene is solely responsible for this Premature Aging Disorder

Clinical Features
• gray hair
• wrinkled skin
• cataracts
• osteoporosis
• heart disease
• diabetes
• cancer

www.pathology.washington.edu
### Major Phenotypes of Werner Syndrome

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Occurrence frequency (%)</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth retardation</td>
<td>100</td>
<td>18.9</td>
</tr>
<tr>
<td>Gray hair, alopecia</td>
<td>100</td>
<td>20.1</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>100</td>
<td>22.8</td>
</tr>
<tr>
<td>Skin sclerosis</td>
<td>100</td>
<td>26.4</td>
</tr>
<tr>
<td>Cataract</td>
<td>100</td>
<td>31.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70</td>
<td>31.5</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td>40</td>
<td>34.7</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>80</td>
<td>35.6</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>60</td>
<td>39.5</td>
</tr>
<tr>
<td>Immune abnormalities</td>
<td>80</td>
<td>40.0</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>20</td>
<td>40.6</td>
</tr>
<tr>
<td>Brain atrophy</td>
<td>40</td>
<td>40.7</td>
</tr>
<tr>
<td>Malignancy</td>
<td>20</td>
<td>41.3</td>
</tr>
</tbody>
</table>

Patients with WS appear to age rapidly following puberty, and are at increased risk of developing cancer and cardiovascular disease.
Pathogenesis of Werner Syndrome

- WRN loss
- Genomic Instability
- Mutation
- Cellular Dysfunction
- Senescence
- Cell Loss

Accelerated Aging
Cancer

Pathogenesis of Werner Syndrome

- WRN gene mutation
- Telomere dysfunction & Chromosomal aberration
  - Mitochondrial compromise
  - Oxidative stress
  - Modified lipid metabolism & inflammation
  - Multi-phenotypes of premature aging
- p53
- Abnormal tumor profile
- Cell growth
- Abnormal tumorigenesis

Genomic Processes Facilitated by DNA Helicases

DNA Helicases at replication forks

Estep and Brosh, 
*Biochem Soc Trans* (2017) 46: 77-95
DNA Helicases in homologous recombination and telomere maintenance

DNA Repair & Genomic Stability promotes Healthy Aging !!
The Hallmarks of Aging

- Altered intercellular communication
- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of proteostasis
- Deregulated nutrient sensing
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
Premature aging observed in DNA repair deficient ERCC1-/- mice

Dietary restriction extends health and lifespan of \textit{Ercc1}^{Δ/−} and \textit{Xpg}^{−/−} mouse mutants

2.3 g food/day ↓ 30% ↓ 1.6 g food/day

- 50% more neurons
- Full motor function
- Reduced DNA damage

W Vermeij \textit{et al}.
\textit{Nature} (2016) 537:427-31
Cellular Senescence

Hayflick Limit
Stop cell division

Nature Reviews | Molecular Cell Biology

Telomeres

Cells with shortened Telomeres hit a Crisis Point
Cells age as telomeres shorten

Shelterin proteins bind to chromosome end and protect it.

Telomerase: Reverse transcriptase that elongates telomeres. Active in the germline and during early development.
Unified model of senescence


**Persistent damage, pathology and ageing**

1. Senescence accumulation
2. Chronic inflammation
3. Fibrosis

**Tissue dysfunction**

1. Functional cell
2. Senescent cell
3. Cytokines, chemokines and matrix remodelling factors (SASP)
4. Macrophage
5. CD4+ T lymphocyte
6. Fibroblast
Stem cells – the elixir of life?


Stem cell usage over a person’s life span

Change in stem cell diversity with aging – Cause or result?

Adapted from Goodell and Rando, Science (2015) 350:1199-204
Extrinsic factors affecting stem cells in aging


Conboy and *Rando*, *Cell Cycle* (2012) 11:2260-7
Stem Cells and Aging

• Stem cell composition – Pluripotent and adult (multipotent and unipotent)

• Age dependent change in SC composition

• Stem cell activity declines after reproductive years – natural selection

• Stem cell diversity drops sharply with aging

• Stem cell differentiation are affected by their environmental niche

• Aging reduces the proliferation and differentiation capacity and induces fibrosis
Composition of human gut microbiome

- **Proteobacteria** – < 10% of gut microbiome, facultative anaerobes, acid resistant, fast growing
- **Firmicutes** - Facultative anaerobes, acid resistant, fast growing, 90% of gut bacteria along with bacteroidetes
- **Bacteroidetes** – not acid resistant, adherent to mucus, fermentative polysaccharide-degrading microbe
- **Actinobacteria** – < 10% of gut microbiome, anaerobes, maintenance of gut homeostasis and barrier, bifidobacteria (probiotic), non-attached, outer-mucus in colon
- **Verrucomicrobia** – methanotrophic, healthy < 10% of gut microbiome, increases up to 80% after antibiotics
Progression of gut microbiome in humans

Adapted from Kundu et al. Cell (2017) 171:1481-93
How will I age? – Listen to your gut!

Adapted from Arboleya et al. Front Microbiol (2016) 7:1204

B. breve, B. bifidum, B. longum
Breast fed - B. longum ssp. Infantis
Infants - C-section - B. longum ssp. Longum

Early life

- C-section
- Allergies, NEC, IBS – Increase B. adolescentis, decrease B. longum

Adulthood

- Obesity/Diabetes – decrease B. animalis

Old age

- Centenaries – Increases B. Longum, B. Adolescentis, B. bifidum

Impacts

- Breast fed – B. longum ssp. Infantis
- C-section – B. longum ssp. Longum
- Allergies, NEC, IBS – Increase B. adolescentis, decrease B. longum
- Obesity/Diabetes – decrease B. animalis
- Centenaries – Increases B. Longum, B. Adolescentis, B. bifidum

Bifidobacteria

- ~ 60 - 70%
- ~ 30 - 40%
- ~ 10%
- ~ 0 - 5%
How will I age? – Listen to your gut! Again..

Striatum (ST) – Forebrain, role in motor and action planning, decision-making, motivation,
Substansia Niagra (SN) - Midbrain, role in reward and movement

Phyla – Proteobacteria
Family - Enterobacteriaceae

Adapted from JG Choi et al. Sci Rep (2018) 8:1275
Gut-Nervous System Axis in Aging & Neurodegenerative Diseases

Activating Inflammation and Immune Response

Gut Microbiome and Aging

• The composition of gut microbiome changes dramatically with aging

• Influencing Factors:
  ✓ Vaginal delivery/ C-section
  ✓ Breast milk fed/ Formula fed
  ✓ Antibiotics
  ✓ Obesity/Diabetes
  ✓ Adult community dwelling/ Long term care facilities

• During aging and/or obesity – reduction in the microbial number and variety

• Increased fiber, decreased fat, calorie restriction, FMT – reduced dysbiosis, increased lifespan.
Are there unique mechanisms contributing to longevity of long-lived mammalian species?

Vera Gorbunova
University of Rochester

Anti-cancer mechanisms play a significant role.
Comparative genomics of ageing

Gorbunova et al., Nat Rev Genetics (2014) 15:531-40
Hypothesis: Anti-cancer mechanisms to achieve longevity

Down-regulation of Growth hormone signaling pathways has both anti-cancer and anti-aging effects in long-lived dwarf mice.

Inhibition of somatic telomerase activity
- Replicative senescence due to shortened telomeres prevents infinite cell division that occurs during cancer progression

Slower rate of telomere shortening
- Preserve telomere stability by greater DNA repair or increased expression of telomere-binding proteins

# DNA Damage Response

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Genes</th>
<th>Alterations</th>
<th>Species</th>
<th>Control species</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA damage response</td>
<td>TP53</td>
<td>Upregulation</td>
<td>Human and naked mole-rat</td>
<td>Mouse</td>
</tr>
<tr>
<td></td>
<td>Chek1, Rif1</td>
<td>Upregulation</td>
<td>Long-lived bats and rodents</td>
<td>Short-lived counterparts</td>
</tr>
<tr>
<td>Base excision repair</td>
<td>MBD4, MUTYH, NEIL1, NEIL2,</td>
<td>Upregulation</td>
<td>Human and naked mole-rat</td>
<td>Mouse</td>
</tr>
<tr>
<td></td>
<td>TDG, POLL</td>
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<td></td>
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<tr>
<td>Nucleotide excision repair</td>
<td>Ercc1</td>
<td>Upregulation</td>
<td>Long-lived bats and rodents</td>
<td>Short-lived counterparts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bowhead whale</td>
<td>Nine mammals</td>
</tr>
<tr>
<td></td>
<td>Ercc3</td>
<td>Positive selection</td>
<td>Bowhead whale</td>
<td>Minke whale, cow, and dolphin</td>
</tr>
<tr>
<td>DNA mismatch repair</td>
<td>MSH3, Msh6, Pms2</td>
<td>Upregulation</td>
<td>Human and naked mole-rat</td>
<td>Mouse</td>
</tr>
<tr>
<td>DNA double-strand break</td>
<td>NHEJ1, XRCC6, POLL</td>
<td>Upregulation</td>
<td>Long-lived bats and rodents</td>
<td>Short-lived counterparts</td>
</tr>
<tr>
<td>repair</td>
<td>Pnkp, Rad51b, Prpf19, Slx4</td>
<td>Upregulation</td>
<td>Long-lived bats and rodents</td>
<td>Short-lived counterparts</td>
</tr>
<tr>
<td></td>
<td>ATM, PRKDC, RAD50, KU80</td>
<td>Positive selection</td>
<td>Myotis davidii, Pteropus alecto</td>
<td>Eight non-bat mammals</td>
</tr>
<tr>
<td>Fanconi anemia DNA repair</td>
<td>Faap100, Fancg</td>
<td>Upregulation</td>
<td>Long-lived bats and rodents</td>
<td>Short-lived counterparts</td>
</tr>
</tbody>
</table>

Perturbation of Insulin/Insulin Growth Factor-1 (IGF-1) Signaling Pathway in Long-Lived Strains or Species

Multiple mechanisms that perturb Insulin/IGF-1 signaling pathway identified in long-lived species

Unique mutations down-regulate insulin/IGF-1 signaling

IGF-1 in cancer

• The anabolic signals by insulin or IGF-1 can promote tumour development by inhibiting apoptosis, and by stimulating cell proliferation.

• Epidemiological evidence is accumulating and suggests that the risk of cancers of the colon, pancreas, endometrium, breast and prostate are related to circulating levels of insulin, IGF-1, or both.

• Nutritional energy balance, macronutrient composition of the diet and physical activity levels appear to be major determinants of IGF-1 bioactivity.


King B et al., Experimental Biology and Medicine 238(5):502-8
Maintenance of a Functional Proteome
Proteostasis Network

Protein homeostasis (proteostasis) maintained by protein synthesis, chaperone-assisted protein folding, and proteolytic systems.

Proteostasis declines with age due largely to impaired chaperone response to stress and decreased function of protein degradation or elimination pathways.

Interventions that enhance proteostasis improve health and increase lifespan.

- Improved translational fidelity
- Higher level of chaperone expression
- Stronger proteasome activity

Molecular Mechanisms Determining Lifespan in Mammals

Anti-cancer mechanisms
- Telomerase inhibition - large animals
- Concerted cell death - blind mole rats
- Hyaluronan - naked mole rats via contact cell inhibition
- p53 gene expression - elephants

Longer lifespan

- Telomerase inhibition
- Gene upregulation
- Reduced IGF-1 levels
- Enhanced oxidative protection
- Telomere maintenance
- More active sirtuins?
- Reduced cellular senescence?
- Repressed mTOR signaling?
- AMPK signaling?
- Suppressed neuropeptide signaling?

Understand molecular mechanisms responsible for longevity of naturally long-lived species to develop safe and effective anti-aging treatments and improve human health.

Novel anticancer mechanisms identified in several long-lived species including elephants, naked mole rats, and blind mole rats.

Long-lived species evolved more efficient DNA repair machinery by upregulating expression or altering sequences of DNA repair genes.

Long-lived species alter telomere-binding proteins to protect telomeres.

Perturbation of insulin/IGF-1 signaling pathway may contribute to longevity of long-lived mouse strains, small dog breeds, long-lived rodents, and Brandt’s bats.

Naked mole rats improve translational fidelity, increase expression of chaperones, and augment proteasome activity and autophagy to maintain proteostasis.
Outstanding Questions

What are the anti-cancer mechanisms in other long-lived and/or large-sized species? Which of these species-specific anti-cancer mechanisms, when transferred to other species including humans, can decrease cancer incidence or promote longevity?

How to safely and efficiently strengthen the DNA repair machineries? Which of the identified DNA repair genes with either increased expression levels or altered sequences are responsible for increased genomic stability in long-lived species?

Multiple regulatory mechanisms are known to modulate lifespan in model organisms, such as the insulin/IGF-1 signaling pathway. To what extent do these mechanisms account for the huge variation of mammalian lifespans in natural species? How do long-lived species fine-tune these pathways? Can these mechanisms be further intervened in long-lived species without deleterious effects?

Outstanding Questions Cont’d

Considering that the large long-lived species have short telomeres and repressed telomerase activity, how they maintain telomere length is not fully understood. Do they eliminate senescent cells more efficiently? Do their stem cells renew aged cells more efficiently? How do their stem cells themselves maintain self-renew capacity to support longer lifespans?

How do other long-lived species maintain proteostasis? How can proteostasis be further improved in long-lived species?

How do humans regulate all the aforementioned mechanisms? Given the fact that human is already a relatively long-lived species, is human lifespan or health span able to be extended? In other words, can we slow down the aging rate in humans?

Reported Age at Death of Supercentenarians

Max reported age at death

Duration of life is limited.

Jeanne Calment
122 yr

$y = 0.1531x - 191.07$

$R^2 = 0.45855$

X Dong et al.  
Nature 1–3 (2016)
Goal of Aging Research: Extend Healthspan