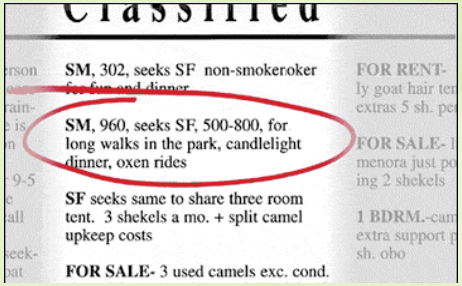
Prospects for lifespan extension


Classified

SM, 302, seeks SF non-smokeroker

SM, 960, seeks SF, 500-800, for long walks in the park, candlelight dinner, oxen rides

SF seeks same to share three room tent. 3 shekels a mo. + split camel upkeep costs

FOR SALE- 3 used camels exc. cond.

FOR RENT- ly goat hair ten extras 5 sh. per

FOR SALE- menora just po ing 2 shekels

1 BDRM.-can extra support p sh. obo

Assigned reading: Position Statement on Human Aging

A&S300-002 Jim Lund

Current status

"Advocates of what has become known as antiaging medicine claim that it is now possible to slow, stop or reverse aging through existing medical and scientific interventions. Claims of this kind have been made for thousands of years, and they are as false today as they were in the past."

Position Statement on Human Aging, S. Jay Olshansky, Ph.D., Leonard Hayflick, Ph.D., Bruce A. Carnes, Ph.D., +48 other leading aging researchers.

Do not go gentle into that good night,
Old age should burn and rave at close of day;
Rage, rage against the dying of the light.
-Dylan Thomas

Prospects for lifespan extension over the next 50 years

- What's required?
- Segmental lifespan extension: staying ahead of the curve.
- Aging does not need to be completely treatable or reversible immediately--treatments to extend lifespan give you more time, and in that time additional treatments can be developed.

How do you tell if an aging treatment really works?

- Bad: indicators of junk science.
- Good: ??

Non-biological lifespan extension: Cryonics

- Many fish and frogs can be frozen and revived, long established.
- Many small animals (nematodes), single celled animals (*E. coli*, yeast).
  - Exceptions, fruit fly.
- Human sperm, eggs, and embryos can be frozen and thawed now.

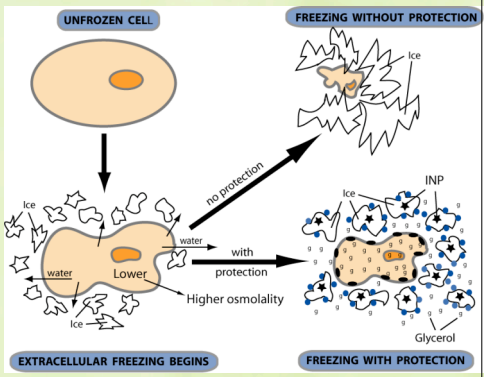
Freeze Tolerant Animals

- Terrestrial insects
- Intertidal molluscs & barnacles
- Amphibians & reptiles:
  - frogs (6 species)
  - hatchling painted turtles
  - garter snakes
  - lizards (some)

From Dr. Ken Storey, Carleton University, Ottawa, Canada

Surviving Freezing

- **Extracellular freezing only**
- **Up to 70% of body water frozen**
- **High 'polyols'**
- **Acclimation required**
- **Glucose**
- **Glycerol**
- **Sorbitol**



From Dr. Ken Storey, Carleton University, Ottawa, Canada

WOOD FROG, *Rana sylvatica*

Garter snake, *Thamnophis sirtalis*

SPRING PEEPER, *Hyla crucifer*

Vertebrate Freeze Tolerance

Painted turtle hatchlings
Chrysemys picta marginata

Box turtle, *Terrapene carolina*

From Dr. Ken Storey, Carleton University, Ottawa, Canada

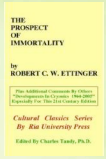
Cryopreserved Tissues

- Sperm
- Embryos
- Skin
- Cornea
- Veins
- Blood cells
- Heart valves
- Teeth, bone
- Bone marrow
- Pancreatic tissue
- Thyroid tissue
- Parathyroid tissue
- Fetal tissues (some)
- **Rat liver**

From Dr. Ken Storey, Carleton University, Ottawa, Canada

Cryonics

- Popular interest sparked by “The Prospect of Immortality” by Robert C. W. Ettinger, 1964.
  - Founded the Cryonics Institute and the related Immortalist Society.



Human cryopreservation started in 1976:

- Cryonics Institute, $25-35K for preservation, $100/yr in liquid nitrogen.
- Alcor Life Extension Foundation
  - Freezing human now, heads only!
- **Can’t be thawed! Near term propects poor.**

Prosthetics

- Currently:
  - Joints
  - Corneas
  - Pacemakers
- Future propects?
- Will have a role in extending lifespan/heathspan, but will not affect the underlying aging.

Regeneration and related technologies

- Liver has the natural ability to regenerate.
- Infants have some regeneration capability, but it is lost during childhood.
- Some vertebrates can regenerate organs and limbs.
  - Example: Salamander (tail, limbs).
- Organ culture is being explored.
- Organ engineering, cell printing.
  - Bladder recently created in culture from patient cell samples! (Atala et al., 2006)
- Rejuvenation of aging tissues using stem cells.

What's required for biological lifespan extension?

1. Understanding of the aging process.
   - Gerontologists are closing in on aging mechanisms.
2. Developing manipulations of organisms that retard or reverse the aging process.
   - Starting to develop as an offshoot of research into aging.
3. Technologies to implement aging treatments: drugs, gene therapy, cell therapy, etc.
   - Barely begun.

How can anti-aging treatments be assessed?

- Proof of efficacy in animal models.
- Human trials would take many decades!
- Can other measures of efficacy be developed?
- **Biomarkers of aging**

Biomarkers of aging

- Measure a set of parameters that gauge a person's biological age.
  - Functional tests.
  - Physiological tests.
  - Gene expression.
- In animal studies treatments that extend lifespan show a delay or reversal of aging gene expression changes.

National Institute on Aging's Biomarkers Program

Last reading assignment

Time to Talk SENS: Critiquing the Immutability of Human Aging

Aubrey D. N. J. de Grey, Bruce N. Ames, Julie K. Andersen, Andrzej Bartke, Judith Campisi, Christopher B. Heward, Roger J. M. McCarter and Gregory Stock

Ann NY Acad Sci. 2002

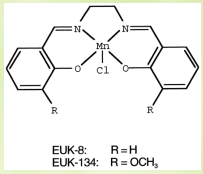
Near term anti-aging treatments

Drugs that act on known aging pathways.

Mimic genetic or dietary manipulations.

Near term anti-aging treatments

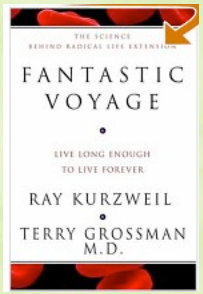
- Antioxidants
  - EUK-8, EUK-134 (Have superoxide dismutase (SOD) and catalase activities), Melov et al., 2000.
- Caloric restriction
  - 2-deoxyglucose
  - Phenformin
  - Metformin
- Sirt (sirtuin) activators
  - Resveratrol
  - Resveratrol 2.
  - STACs (14 small molecule sirtuin activators).
  - Quercetin (protein kinase inhibitor).
  - Piceatannol
- Activators of the insulin-like signaling pathway?



EUK-8: R = H
EUK-134: R = OCH_3

Interest in the prospects for lifespan extension

- Fantastic Voyage : Live Long Enough to Live Forever by Ray Kurzweil and Terry Grossman, M.D.

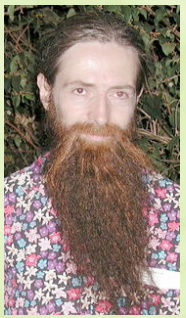


Fantastic Voyage: Live Long Enough to Live Forever

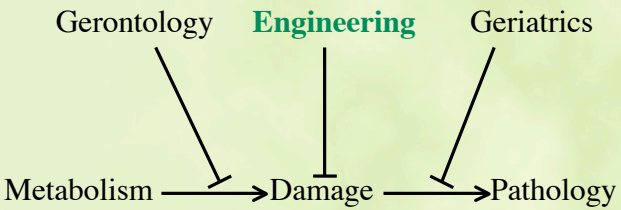
- Bridge I: what you can and should do today to extend your life expectancy.
  - Optimal diet and supplements.
- Bridge II: drugs and devices that extend lifespan.
  - Drugs, somatic gene therapy, recombinant technology, therapeutic cloning, etc.
- Bridge III: nanotech antiaging measures and post-human biology.

Aubrey de Grey and SENS

- Strategies for Engineered Negligible Senescence (SENS).
- Seven causes of aging and their potential methods of treatments.
- A "goal-directed rather than curiosity-driven" approach to the science of aging.
- Believes the next great social debate starts when aging research progresses to the point that public funds could be used to accelerate the arrival of effective treatment for aging.



Three paradigms for intervention



Claim: **only the "engineering" approach can achieve substantial extension of human healthspan any time soon**

Metabolism → *Damage* → Pathology:

The seven deadly things

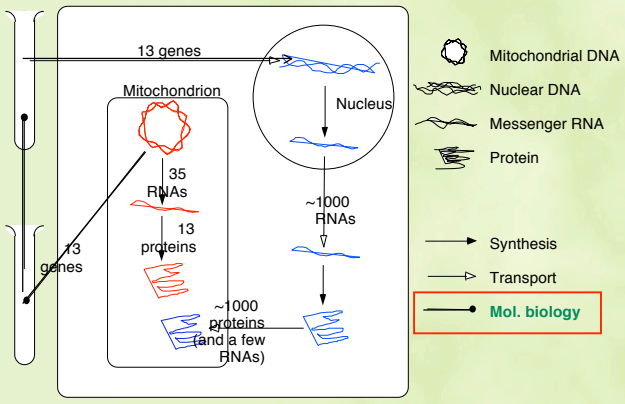
Respiration (oxidation)	***Cell loss/atrophy***	Neurodegeneration
Carbohydrate metabolism (glycosylation)	***Nuclear mutations and epimutations***	Atherosclerosis
Cell turnover (mutations, telomere shortening, dysregulation, stem cell depletion)	***mtDNA mutations***	Cancer
	Senescent cells	Diabetes
	AGE crosslinks	Hormone decline
	Extracellular junk	Blindness
	Lysosomal junk	Immune decline
Etc, etc, etc	**Er.... that's it!**	*Etc, etc, etc*

20 years is an instructively long time to find nothing out

Damage rising w/ age	*Proposed as contributing to aging by*
Cell loss, cell atrophy	Brody (1955) or earlier
Extracellular junk	Alzheimer (1907)
Extracellular crosslinks	Monnier and Cerami (1981)
Senescent cells	Hayflick (1965)
Mitochondrial mutations	Harman (1972)
Lysosomal junk	Strehler (1959) or earlier
Nuclear [epi]mutations (only cancer matters)	Szilard (1959) and Cutler (1982)

Mitochondrial biogenesis: ripe for tweaking

de Grey 2000, *Trends in Biotechnology* 18:394-399



Is it really that easy? No, but....

Gearing **1986**: one small protein relocated in yeast

Nagley **1988**: shown to be functional

Galanis **1991**: a second small protein relocated in yeast

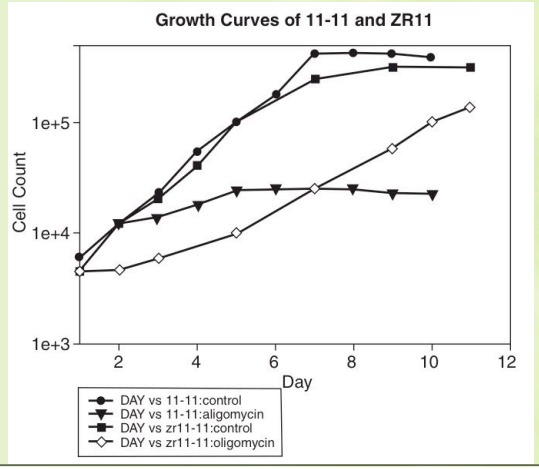
Lander/Lodish **1990**: suggestion of therapeutic potential

Zullo **2000** (after 9 years): one big protein in rodent cells

Manfredi **2001** (after 6 years): same one in human cells

Guy **2002** (after 1 year): a different one in human cells

Demonstration of transferal of mitchondrial ATPase6 to the nucleus



Clues from very unexpected quarters

1990: *Chlamydomonas reinhardtii* mito. genome sequenced

SIX of the "dirty baker's dozen" missing!

Feb 1998: **NONE** cloned; AdG starts complaining about this

July 1998: King/Gonzalez-Halphen collaboration begins

~2001: *C. reinhardtii* COX2, COX3, ATP6, ND4L cloned

2002: *C.r.* ATP6 found to work unaltered in human cells

1991: *Vigna radiata* COX2 cloned

2002: importability found to depend on ***TWO*** a.a. changes

Steps to biomedical application

1) Derive 13 cell lines, each mutant for just one protein
2) Develop constructs that rescue respiration in these cells
3) Combine all 13, seek respiration without ***any*** mtDNA
4) Assay competence in mice using germline transformation
5) Assay competence in mice using somatic gene therapy

--- to get to here should take 6-8 years ---

6) Test in humans as for mitochondriopathies

Strategies for Engineered Negligible Senescence

1. Some tissues lose cells with advancing age, like the heart and areas of the brain. Stem cell research and regenerative medicine are already providing very promising answers to degeneration through cell loss.
2. We must eliminate the telomere-related mechanisms that lead to cancer. de Grey suggests selectively modifying our telomere elongation genes by tissue type using targeted gene therapies.
3. Mitochondrial DNA: Add nuclear copies of mitochondrial genes to protect them. Other strategies for manipulating and repairing damaged mitochondrial DNA in situ have been demonstrated for the first time in 2005.
4. Some of the proteins outside our cells, such as those vital to artery walls and skin elasticity, are created early in our life and never recycled or recycled very slowly. These long-lived proteins are susceptible to chemical reactions that degrade their effectiveness. Scientists can search for suitable enzymes or compounds to break down problem chemical cross-links that they body cannot handle.

Strategies for Engineered Negligible Senescence

5. Certain classes of senescent cell accumulate where they are not wanted, such as in the joints. We could in principle use immune therapies to tailor our immune systems to destroy cells as they become senescent and thus prevent any related problems.
6. As we age, junk material known as amyloid accumulates outside cells. Immune therapies (vaccines) are currently under development for Alzheimer's, a condition featuring prominent amyloid plaques, and similar efforts could be applied to other classes of extracellular junk material.
7. Junk material builds up within non-dividing, long-life span cells, impairing functions and causing damage. The biochemistry of this junk is fairly well understood; the problem lies in developing a therapy to break down the unwanted material. de Grey suggests searching for suitable non-toxic microbial enzymes in soil bacteria that could be safely introduced into human cells.

The Methuselah Mouse Prize

Mprize™

- Mprize fund: $3.4 million (4/06)
- "Longevity Prize" for the oldest-ever *Mus musculus*.
  - World record lifespan for a mouse.
  - Current: Growth Hormone Receptor Gene Knockout, live 5.0 yrs., Andrzej Bartke.
- "Rejuvenation Prize" for the best-ever late-onset intervention.
  - Improvement in five different markers that change significantly with age.
  - Caloric restriction starting at 1.6 yrs, live 3.7 yrs., Steve Spindler.

"I wish it were possible, from this instance, to invent a method of embalming drowned persons, in such a manner that they might be recalled to life at any period, however distant; for having very ardent desire to see and observe the state of America a hundred years hence, I should prefer to an ordinary death, being immersed with a few friends in a cask of Madeira, until that time, then to be recalled to life by the solar warmth of my dear country."

- Benjamin Franklin, 1773 letter to Jacques Barbeu Dubourg