“The Eureka Moment.”

“To intervene in aging... didn’t require a complete understanding of all the myriad interacting processes that contribute to aging damage. To design therapies you have to understand aging damage itself.”

“Aubrey de Grey, Cambridge University

“Ending Aging”
St. Martin’s Press, Sept. 2007
Aubrey de Grey, Cambridge University
“Aging is not a single inexorable process.”

“All the core knowledge needed to develop “Strategies for Engineered Negligible Senescence” (SENS) is already in our possession; it mainly just needs to be pieced together.”

Strategies for Engineered Negligible Senescence: Why Genuine Control of Aging May Be Foreseeable
Aubrey de Grey, Cambridge University

Edmonton Aging Symposium
March 30-31, 2007
www.edmontonagingsymposium.com

Presentation archive
http://www.edmontonagingsymposium.com/
index.php?pagename=eas_archive

The seven horsemen of aging:

Too few cells
Too many cells
Chromosomal DNA mutations
Mitochondrial DNA mutations
Junk inside the cells
Junk outside the cells
Protein X-links

Aubrey de Grey
Ending Aging
Too Few Cells:
Stem Cells and Regeneration

Adult Stem Cells replace aging and worn out cells. Repair is directed by a singular molecular switch. Using tissue from a young adult resets the switch in the damaged tissue of an older patient.

Irina Conboy PhD
Bioengineering, University of California, Berkeley
http://bioeng.berkeley.edu/cv.php?facultyid=3021

Too Few Cells:
Stem Cells and Regeneration

Amit Patel has for the past several years pioneered the effort to use adult stem cells, directly planted on injured myocardium, for repair of heart muscle.

University of Pittsburg Medical center
http://www.mirm.pitt.edu/people/bios/Patel1.asp

Too Many Cells:

Cellular senescence occurs when cells lose their ability to divide. Senescent cells produce products damaging to surrounding cells. Research is ongoing to rescue these lost functions or have these cells self-destruct.

Judith Campisi PhD, Buck Institute
http://www.buckinstitute.org/site/index.php?option=com_content&task=view&id=113&Itemid=100
Chromosomal DNA Mutations:
Cancer:
Cancer, with out-of-control cell division, is often the result of damaged DNA. Usually the p53 gene sensor shuts these cells down. New approaches to cancer are aimed at these DNA mutations.

Karl Riabowol PhD, University of Calgary
http://www.ucalgary.ca/riabowol_lab/home.html

Mitochondrial DNA Mutations
Mitochondria are the power plants of the cell. Its DNA directs oxidation to create energy. When Mitochondrial DNA regulation is damaged, many diseases can emerge. Particularly affected are neural tissues, i.e. Parkinson’s disease.

Konstantin Khrapko PhD
Harvard Medical School, Beth Israel Hospital
http://research.bidmc.harvard.edu/research/ResearchPlinfo.ASP?Submit=Display&PersonID=1451

Junk Inside the Cells
i.e. artherosclerosis and macular degeneration
Within cells liposomes, acting like a stomach, degrade and digest unwanted cellular debris. Ultimately some debris is not degraded and a residue results.

Jay Jerome PhD, Vanderbilt University Medical Center
http://www.vicc.org/dd/display.php?id=4150
Junk Inside the Cells
i.e. arthrosclerosis and macular degeneration

The efficacy of the liposomes can be augmented with microbial enzymes.

Bruce Rittmann PhD, The Biodesign Institute
http://www.biodesign.asu.edu/people/bios/bruce-rittmann/

Junk Outside the Cells
i.e. Alzheimer’s disease

PBT2:
Improves memory performance within 5 days of oral dosing
Reduces brain plaques
Restores normal neural synapses

Ashley Bush, Harvard
Mental Health Research Institute of Victoria
http://www.pranabio.com/company_profile/scientific_advisory_board/ashley_bush.asp

Junk Outside the Cells
i.e. Alzheimer’s disease

Vaccines and immune therapy enable the body to prevent or recognize and remove Amyloid plaques of Alzheimer’s disease.

Cynthia Lemere PhD
Brigham and Woman’s Hospital, Harvard Medical School
http://lemerelab.net/index.html
Protein X-Links

Long-lived proteins are modified by cross-links causing inflammation and scarring. It is accelerated in diabetes by a process of "glycation". Molecular reversibility of glycation appears possible.

Howard Haines PhD
Synvista Therapeutics
http://www.alteon.com/

AGEMAP

Analyzing thousands of genes in 16 tissues at 4 ages across diverse species show that organs age at different rates in different hosts. Two major factors in aging:
- Slowing of the metabolism
- inflammation

Stuart Kim
Stanford University and the National Institute on Aging (NIA)
http://genetics.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pgen.0030201

US Life Expectancy by Years

Source: National Vital Statistics
What can we do today to extend our life’s expectancy?

– Diet
– Exercise
– Medications

Diet

Caloric reduction (30%), in primates, markedly extended life and decreased disease.

Richard Weindruch
University of Wisconsin

Canto, left, a rhesus monkey, is aging fairly well at 25 on a calorie restriction diet. Owen, though only a year older than Canto, is frail and moves slowly. He eats a normal diet.

Courtesy of the National Institute on Aging
Dietary Restriction Project
Diet

- Restriction of calories to between 1200 and 2000 depending upon BMI
- Large quantities of fruit and vegetables
- Seafood as the preferred protein
- Beef, lamb, pork in 3 – 4 oz portions maximum
- Wine 6 – 8 oz per day, preferably red

Men and women who consume high glycemic index foods have an increased incidence of age-related macular degeneration."

Chung-Jung Chiu DDS PhD, Allen Taylor PhD, Tufts University
American Journal of Clinical Nutrition
http://www.ajcn.org/cgi/content/abstract/86/1/180

Exercise

25 sedentary adults over 65 underwent skeletal muscle biopsies. 596 genes were surveyed.

Program: 26 week whole body resistance exercise training, 1 hour twice a week.
Exercise
Repeat biopsies:
• dramatic enrichment of genes associated with mitochondrial function
• The “transcriptional signature of aging was markedly reversed.”
  
  Dr Simon Melov, McMaster University Medical Center, Hamilton, Ontario
  May 23, 2007 online in Public Library of Science peer-reviewed journal “PLoS One”
  http://www.plosone.org/article/fetchArticle.action?articleURI
  =info:doi/10.1371/journal.pone.0000465

Exercise
“Resistance exercise decreases oxidative damage to DNA”

“Endurance exercise reverses age associated alterations in mRNA”

Exercise
People who exercise regularly:
• In middle age, decrease their incidence of Alzheimer’s disease 67%
• Starting in their 60’s reduce their risk by half.

  Dr Sandra Aamodt,
  Editor in chief Nature Neuroscience
  Co author: Sam Wang, Princeton molecular biologist of “Welcome to your brain”
Fitness

Aerobic exercise results in remarkable increase in brain volume, particularly in the frontal lobes dealing with high-order thinking such as attention and memory.

*Journal of Gerontology*
Dr. Arthur F. Kramer
Beckman Institute,
University of Illinois

Exercise

The Mayo Clinic’s “Office Treadmill”

A vertical work station: a treadmill, computer, keyboard and work space. At just 1 mph, subjects expended an additional 100 calories per hour. One radiologist introduced it for reading film with dramatic weight loss.
Health Behaviors Study
20,000 people, age 45-79 over 10 years

• Measures:
  – Non-smoker
  – Moderate alcohol use (1-7 glass/wine/week)
  – 5 or more servings fruit & vegetables/day
  – Exercise

• Results: all + factors with all – factors:
  – 74 year olds = the life expectancy of a 60 y.o.

Professor K. T. Khaw, University of Cambridge
Published online "Public Library of Science Medicine", January 14, 2008
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050012

Cumulative survival %

SOURCE: Public Library of Science Medicine

"What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?"
“Sirtris” manufactures a SIRT1 enzyme which increases metabolic rate, decreases body fat and improves mitochondrial function. This "protects from metabolic diseases," notably with increased insulin sensitivity. These therapies mimic the attributes of significant dietary caloric reduction.

Dr. David Sinclair, Harvard University Medical School

Sirtris announced completion of phase one trials of SIRT1 (SRT 501) therapeutics to modulate glucose metabolism. The object of the trial was adult onset diabetes (type 2). The trial showed a marked reduction in the blood sugar in 67 patients compared with a similar number of controls (Placebo).

Chistoph Westphal CEO, Sirtris
JPMorgan Health Care Conference: January 8, 2008
San Francisco, CA

Sirtris announced Completion of Phase One human trials of SIRT1 (SRT 501) therapeutics to modulate glucose metabolism.

The phase 2 study in combination with metformin will be completed Q3 2008.

Chistoph Westphal
JPMorgan Health Care Conference: January 8, 2008
San Francisco, CA
Sirtris announced the isolation of SIRT3 and SIRT4 which direct protein in the mitochondria. They play a significant role in the production of energy and the "youth" of the cell. Additionally, they identified a protein NAD involved in the relief of age-related processes.

David Sinclair, Harvard Medical School
the journal Cell, September 20, 2007

Medications: Sirtris

Resveratrol

The active ingredient in red wine. It is felt that Resveratrol (50 milligrams a day) mimics calorie restriction by activating the SIRT-2 family of enzymes. A purified and reconstituted compound is the core of Sirtris' anti-aging claims.

Alzheimer's Drug Trials
A new "Era of Hope"

- Anti-Amyloid: Alzhemed
- Dimebon
- Immunotherapy AN1792
- Avandia

**Anti-Amyloid: Alzhemed**

- 1052 double-blind patients, US and Canada
- Taking drug or placebo twice a day, 18 months.
- Await results of phase 3 studies, but “significant differences” have been identified.

Dr. Paul Aisen  
Professor of Neurology and Medicine  
Georgetown University Medical Center

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**Dimebon**

- 183 Russian patients
- Taking drug or placebo three times a day, 6 months
- “Significant improvement” against all baseline measures without side effects

Dr. Rachel Doody  
Effie Marie Cain Chair of Alzheimer's Disease  
Professor of Neurology, Baylor College of Medicine

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**Alzheimer's Vaccine: AN1792**

- 159 Irish patients treated with this immunotherapy
- 6% suffered encephalitis, several died
- Of the remaining, at 4.5 years, those who have an antibody response (20%) show significant long term benefits
- No further encephalitis was observed

Dr. Rachel Doody  
Effie Marie Cain Chair of Alzheimer's Disease  
Professor of Neurology, Baylor College of Medicine
Avandia
(Better known as a “problematic” diabetes medication)
• 337 patients treated with this study
• 82% completed the course
• 48% minor, 9% serious side effects
• No cardiac sequela
• Patients with genetic marker:
  • APOE e4 (-) responded
  • APOE e4 (+) no response.
Dr. Michael Gold
GalaxoSmithKline

Etanercept (Enbrel)
(FDA approved for immune-mediated disorders: ie Rheumatoid Arthritis)
• peri-spinal injection
• reduces tumor necrosis factor-alpha, TNF
• rapid cognitive improvement
• one detailed patient
• all patients showed sustained and marked improvement
  E. L. Tobinick, Hyman Gross
  Journal of Neuroinflammation January 9, 2008
  http://www.jneuroinflammation.com/content/5/1/2

Can we wait for all of the answers before taking selective measures to extend healthy life?
Where next?

J. Rothberg, founder of 454 Life Science, is footing the bill to sequence the genomes of 100 people over 100 years of age!

The question: Do centenarians have unique genetic characteristics?