“Extreme Longevity: Secrets on the Oldest Old”

by

L. Stephen Coles, M.D., Ph.D., Director
Supercentenarian Research Foundation
UCLA Molecular Biology Institute
817 Levering Avenue, Suite 8
Los Angeles, CA 90024-2767; USA
E-mails: scoles@ucla.edu; scoles@grg.org;
URLs: www.grg.org; www.supercentenarian-research-foundation.org;

Wednesday, June 8, 2011; [2:00 – 2:30] PM CDT
OECD Conference
Melia Reforma Hotel; Mexico City, DF; MEXICO
Blind Men Touching the Elephant

Aging/Senescence – Energy (photons from the sun) → Sexual Reproduction vs. Damage Repair (Reboot OS: “No babies are born old”) Nature’s Objective Function: Minimize Species Extinction within an ecosystem s.t. Environmental Constraints (Entropy) (Antagonistic Pleiotropy) (Recessive/Dominant Genes)
Blind Men Theories of Aging

- Evolutionary Theory -- Disposable Soma [Tom Kirkwood]/Immortality of the Germ Line -- Sponges/Sea Anemones
- Genomic Drift {DNA Mutations: Deletions, Insertions, Substitutions, Double-Strand Breaks} Epigenomic Drift {CH$_3$, C$_2$H$_5$}
- Protein Misfolding - Chaperone Failure in Rough ER; Recycling
- ROS; Oxidative Stress (Collagen Crosslinking; Glycation)
  SOD Zn/Mn; Glutathione; Catalase {2H$_2$O$_2$ $\rightarrow$ 2H$_2$O + O$_2$} CR
- Mitochondrial Theory [sarcopenia; frailty]
- Neurological (hypothalamic clocks {circadian [diurnal]; lunar [menstruation]; puberty/-menopause/andropause})
- Endocrinological [ACTH, TSH, hGH, LH, FSH,…]
- Immunological {thymic involution; autoimmunity; IL-x; inflammation; interstitial pneumonia; aspiration pneumonia}
- Stem-Cell Depletion [telomere erosion; deafness/blindness]
  Extra Cellular Matrix (ECM); Trophic Factors; Cytokines
- Lipofuscin Accumulation and other undigestable garbage
Metaphor with Aging:
Alchemy $\rightarrow$ Chemistry

(Periodic Table of the Elements)

Goal: Transmutation of Base Metals into Gold or Silver $\rightarrow$ Science
Queen Bee/Queen Ant

Bowhead Whale

**Heterochronic Parabiosis** -- Young and Old Mouse with a common blood supply
Old Mouse ➔ Young/
Young Mouse ➔ Old

Grandparenting Effect

Age-1 in *C. elegans*
True Longevity Right Shift
Not just Rectangularization
The total number of humans that have ever lived has been estimated at 110 Billion. Approximately six percent of all those people are still alive today (6.88 B).
World Life Expectancy Throughout History
Rectangularization of US Longevity over One Century

Average Life Expectancy in [1900-1902] = 49.24 years or 47.3 years for 1900 alone; in 2004 = ~78 years
Demographics of Centenarians

Supercentenarians
Who is a Supercentenarian?

- As of today (Thursday, May 19th), there are 88 Validated Living Supercentenarians World Wide (USA : nonUS = 21 : 67) (Female : Male = 83 : 5)!
- Once you were to make it to becoming a Supercentenarian, the chances of living even one more year is like flipping a coin (H:T or 50 percent mortality rate)!
- Therefore, these individuals are a very precious resource for humanity, and we need to act quickly; otherwise, whatever they have to teach us about how they managed to live so long will be lost forever.

June 8, 2011
Supercentenarians
The Oldest Documented Supercentenarian in History

According to the *Guinness Book of World Records*, the oldest documented Supercentenarian in history was French woman Madame Jeanne-Louise Calment, who died in 1997 at 122 years, 164 days.
Rectangularization of Longevity

While Prof. James Fries’s “Compression of Morbidity" hypothesis may not be entirely correct, there is a definite “Rectangularization” of the human longevity curve, and it is becoming stronger with the passage of time.

If we take Japanese centenarians as one example...

- In 1992, there were 3,000 centenarians; oldest person = 114 yo
- In 1998, there were 10,000 centenarians; oldest person = 114 yo
- In 2009, there were 40,000 centenarians; oldest person = 114 yo

Rather than seeing an increase in the maximum ages, as expected, we are seeing an increase in the mortality rates instead, especially at ages 112, 113, 114, and 115, with very few persons anywhere reaching age 116 (last occurrence was 2006) and age 117 or more turns out to be an extreme outlier (last occurrence was in 1997).
Mortality and $P$(Survival)
by Don Gennnery, Biostatistician at JPL (Jan. 19, 2010)

Figure 3. Results from Social Security and manual fit spliced together at age 90 (with approximate ±1σ limits).

Figure 4. Probability of surviving to each age, derived from the curve in Figure 3.
“It ain’t over ‘til it’s over.” – Yogi Berra

Jack LaLane (L), died at 96 yo; David Murdock (R), 87 yo
California billionaire plans his birthday party at 125 yo.
$500 million was spent on a state-of-the-art science center
dedicated to the hypothesis that food plants hold the key to
a longevity.
## Oldest by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>122</td>
</tr>
<tr>
<td>(While Jeanne Calment reached age 122, she definitely was not walking around at age 120.)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>115</td>
</tr>
<tr>
<td>(The oldest British person since modern birth registration began in 1837.)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>114</td>
</tr>
<tr>
<td>Italy</td>
<td>114</td>
</tr>
<tr>
<td>Sweden</td>
<td>113</td>
</tr>
</tbody>
</table>
Mortality Plateau for Fruit Flies


Figure 1. Mortality data for 1381 Drosophila melanogaster (Canton S strain). The continuous line shows a moving three point average. The crucial test concerns the slope of the line after 90% of the population have died, in this case after week 16. The lines added indicate fitted lines for the first 90% and the last 10%.
Human Mortality [85 -125] yo
by Don Gennery, Biostatistician at JPL (Jan. 19, 2010)

Figure 1. Estimates of mortality rate as a function of age, derived from various data.

Figure 2. Enlarged portion of Figure 1.
# Supercentenarian Mortality Rates 2007 and 2010 [*]

**August 7, 2007**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Surviving</th>
<th>Deaths</th>
<th>Yearly Survival</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>122</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>121</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.00%</td>
<td>99.90%</td>
</tr>
<tr>
<td>120</td>
<td>2</td>
<td>-1</td>
<td>1</td>
<td>50.00%</td>
<td>99.90%</td>
</tr>
<tr>
<td>119</td>
<td>3</td>
<td>-1</td>
<td>2</td>
<td>33.33%</td>
<td>99.80%</td>
</tr>
<tr>
<td>118</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0.00%</td>
<td>99.70%</td>
</tr>
<tr>
<td>117</td>
<td>5</td>
<td>-2</td>
<td>4</td>
<td>40.00%</td>
<td>99.70%</td>
</tr>
<tr>
<td>116</td>
<td>10</td>
<td>-5</td>
<td>7</td>
<td>50.00%</td>
<td>99.50%</td>
</tr>
<tr>
<td>115</td>
<td>23</td>
<td>-13</td>
<td>22</td>
<td>56.52%</td>
<td>99.00%</td>
</tr>
<tr>
<td>114</td>
<td>62</td>
<td>-39</td>
<td>68</td>
<td>62.90%</td>
<td>97.70%</td>
</tr>
<tr>
<td>113</td>
<td>126</td>
<td>-64</td>
<td>150</td>
<td>50.79%</td>
<td>93.79%</td>
</tr>
<tr>
<td>112</td>
<td>266</td>
<td>-140</td>
<td>321</td>
<td>52.63%</td>
<td>87.39%</td>
</tr>
<tr>
<td>111</td>
<td>511</td>
<td>-245</td>
<td>618</td>
<td>47.95%</td>
<td>73.37%</td>
</tr>
<tr>
<td>110</td>
<td>999</td>
<td>-488</td>
<td>1234</td>
<td>48.85%</td>
<td>48.85%</td>
</tr>
</tbody>
</table>

**April 1, 2010**

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>Surviving</th>
<th>Deaths</th>
<th>Yearly Survival</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>122</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>100.00%</td>
<td>100.00%</td>
</tr>
<tr>
<td>121</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.00%</td>
<td>99.92%</td>
</tr>
<tr>
<td>120</td>
<td>2</td>
<td>-1</td>
<td>1</td>
<td>50.00%</td>
<td>99.92%</td>
</tr>
<tr>
<td>119</td>
<td>3</td>
<td>-1</td>
<td>2</td>
<td>33.33%</td>
<td>99.92%</td>
</tr>
<tr>
<td>118</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0.00%</td>
<td>99.84%</td>
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<td>117</td>
<td>5</td>
<td>-2</td>
<td>4</td>
<td>40.00%</td>
<td>99.84%</td>
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<tr>
<td>116</td>
<td>10</td>
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<td>7</td>
<td>50.00%</td>
<td>99.68%</td>
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<tr>
<td>115</td>
<td>23</td>
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<td>22</td>
<td>56.52%</td>
<td>99.43%</td>
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<tr>
<td>114</td>
<td>62</td>
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<td>68</td>
<td>62.90%</td>
<td>98.22%</td>
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<tr>
<td>113</td>
<td>126</td>
<td>-64</td>
<td>150</td>
<td>50.79%</td>
<td>94.49%</td>
</tr>
<tr>
<td>112</td>
<td>266</td>
<td>-140</td>
<td>321</td>
<td>52.63%</td>
<td>87.84%</td>
</tr>
<tr>
<td>111</td>
<td>511</td>
<td>-245</td>
<td>618</td>
<td>47.95%</td>
<td>73.99%</td>
</tr>
<tr>
<td>110</td>
<td>999</td>
<td>-488</td>
<td>1234</td>
<td>49.92%</td>
<td>49.92%</td>
</tr>
</tbody>
</table>

* The data above, supplied by Miguel Quesada and Robert Young, does not include living cases.
Hypothesis: *Nature, Not Nurture* Causes Aging and Senescence

- Potential Longevity (Both Average Life Expectancy and Maximum Lifespan) Lies in the expression of our genes
- Longevity-Determining Genes (a few hundred genes out of 21,000+) and not our environment or life-style dictate how long we may be able to live
- Our greatest system vulnerability is *vascular fragility* (we have ~60,000 miles of blood vessels)
## Maximum Lifespan of Selected Mammals

<table>
<thead>
<tr>
<th>Mammal</th>
<th>Lambda Max (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Tree Shrew</td>
<td>1</td>
</tr>
<tr>
<td>Mouse</td>
<td>5</td>
</tr>
<tr>
<td>Rat</td>
<td>6</td>
</tr>
<tr>
<td>Bat</td>
<td>32</td>
</tr>
<tr>
<td>Sheep</td>
<td>20</td>
</tr>
<tr>
<td>Dog (large breed)</td>
<td>20</td>
</tr>
<tr>
<td>Domestic House Cat</td>
<td>25</td>
</tr>
<tr>
<td>Lion (Zoo, not in the Wild)(King of Beasts)</td>
<td>26</td>
</tr>
<tr>
<td>Horse</td>
<td>45</td>
</tr>
<tr>
<td>Hippo</td>
<td>45</td>
</tr>
<tr>
<td>Rhino</td>
<td>50</td>
</tr>
<tr>
<td>Elephant (Asian) $(Sunita$ female from the San Diego Zoo)</td>
<td>60</td>
</tr>
<tr>
<td>Elephant (African)</td>
<td>70</td>
</tr>
<tr>
<td>Monkey (Rhesus)</td>
<td>35</td>
</tr>
<tr>
<td>Chimp (Cheetah; b. 1932; Palm Springs, CA) (actually b. ~1960)</td>
<td>&gt;76</td>
</tr>
<tr>
<td>Human (Jeanne-Louise Calment, France)</td>
<td>122</td>
</tr>
<tr>
<td>Methuselah (amongst the Antedeluvian Patriarchs)</td>
<td>969</td>
</tr>
<tr>
<td>Bowhead Whale (Wild, not in a Zoo)</td>
<td>&gt;225</td>
</tr>
</tbody>
</table>

**Ratio:** 225:1

Survival (Logistic Function)
There is an Exponential Rise in Mortality with Age

All Causes of Mortality
(Death Rate Per 100,000)

With advancing age, mortality from all causes rises exponentially.
Instantaneous Mortality Rate
(Moore’s Law for Actuaries)
Female Advantage

Female:Male Overall Ratio ~10:1. And by age

- 110 Years  90 percent are women
- 112 Years  92 percent are women
- 115 Years  95 percent are women

Why is that?

1. Women Deliver Babies (C-Sections)
2. Men Fight for Species Survival (T, Cortisol)
3. Estrogen? (Post Menopausal > ½ Life)
4. “XX” (Mosaic) and not “XY” (Y = tiny)
Mortality Rates for Each Sex
Derived from Social Security Period Life Table for 2006

Instantaneous mortality rate (per year)

Age

Males
Females

Donald B. Gennery
April 11, 2011

June 8, 2011

Supercentenarians
## Progressive World Record Holders

*(Table D on www.grg.org)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Years</th>
<th>Days</th>
<th>Born</th>
<th>Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Peters</td>
<td>111</td>
<td>354</td>
<td>April 6, 1745</td>
<td>March 26, 1857</td>
</tr>
<tr>
<td>Delina (Ecker) Filkins</td>
<td>113</td>
<td>214</td>
<td>May 4, 1815</td>
<td>December 4, 1928</td>
</tr>
<tr>
<td>Martha Graham</td>
<td>114</td>
<td>c. 180</td>
<td>December 1844</td>
<td>June 25, 1959</td>
</tr>
<tr>
<td>Shigechiyo Izumi [?]</td>
<td>120 [105]</td>
<td>237</td>
<td>June 29, 1865</td>
<td>February 21, 1986</td>
</tr>
<tr>
<td>Jeanne Calment</td>
<td>122</td>
<td>164</td>
<td>February 21, 1875</td>
<td>August 4, 1997</td>
</tr>
</tbody>
</table>
Numbers of Supercentenarians
Average Age of Top 100 Validated Oldest Living Persons by Gender
Numbers of Supercentenarians (Smoothed)

Data from Afrim Alimeti and Louis Epstein, September 9, 2009
SRF Has Performed Nine Autopsies  
(UCLA Department of Pathology and Laboratory Medicine)

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Age</th>
<th>R</th>
<th>S</th>
<th>City</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Elma Corning</td>
<td>112</td>
<td>W</td>
<td>F</td>
<td>Los Angeles</td>
<td>TTR</td>
</tr>
<tr>
<td>2.</td>
<td>Henry Hartman</td>
<td>111</td>
<td>W</td>
<td>M</td>
<td>San Diego</td>
<td>TTR</td>
</tr>
<tr>
<td>3.</td>
<td>Marion Higgins</td>
<td>112</td>
<td>W</td>
<td>F</td>
<td>Seal Beach</td>
<td>TTR</td>
</tr>
<tr>
<td>4.</td>
<td>George Johnson</td>
<td>112</td>
<td>B</td>
<td>M</td>
<td>Richmond</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>5.</td>
<td>William Seegers</td>
<td>106</td>
<td>W</td>
<td>M</td>
<td>Richmond</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>6.</td>
<td>Daniel Guzman-Garcia</td>
<td>111</td>
<td>W</td>
<td>M</td>
<td>Cali, Colombia</td>
<td>TTR</td>
</tr>
<tr>
<td>7.</td>
<td>Sally Gappell</td>
<td>109</td>
<td>W</td>
<td>F</td>
<td>Los Angeles</td>
<td>TTR</td>
</tr>
<tr>
<td>8.</td>
<td>Gertrude Baines</td>
<td>115</td>
<td>B</td>
<td>F</td>
<td>Los Angeles</td>
<td>TTR</td>
</tr>
<tr>
<td>9.</td>
<td>Milan Herzog</td>
<td>101</td>
<td>W</td>
<td>M</td>
<td>Los Angeles</td>
<td>TTR</td>
</tr>
</tbody>
</table>
Supercentenarian Genome Project
(IRB approval July 2010)

The SRF in collaboration with…

• UCLA (Dept. of Chemistry and Biochemistry Molecular Biology Institute)
• Stanford University (Depts. of Developmental Biology and Human Genetics)
• Institute for Systems Biology of Seattle, WA
• Complete Genomics of Mountain View, CA
Two Subjects from San Diego, CA
Soledad Mexia, 111 and Frederica Maas, 110

June 8, 2011
Supercentenarians
Sample QC Report

Project Code: P031
Source DNA Plate BC: CS00330-DNA
Number of Samples: 4
Sample Receipt Date: July 21st, 2010
Quantification QC Date: July 22nd, 2010
Gel QC Date: July 22nd, 2010

Quantification Results
Quantification performed using Quant-iT™ PicoGreen® ds DNA kit from Invitrogen.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Source Vol. (µl)</th>
<th>Source Conc. reported (ng/µl)</th>
<th>Source Conc. measured (ng/µl)</th>
<th>Available DNA (µg)</th>
<th>QC Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS00330-DNA_A01</td>
<td>200</td>
<td>125</td>
<td>125.4</td>
<td>25.1</td>
<td>PASS</td>
</tr>
<tr>
<td>GS00330-DNA_B01</td>
<td>200</td>
<td>125</td>
<td>177.1</td>
<td>35.4</td>
<td>PASS</td>
</tr>
<tr>
<td>GS00330-DNA_C01</td>
<td>200</td>
<td>125</td>
<td>138.3</td>
<td>27.7</td>
<td>PASS</td>
</tr>
<tr>
<td>GS00330-DNA_D01</td>
<td>200</td>
<td>125</td>
<td>106.4</td>
<td>21.3</td>
<td>PASS</td>
</tr>
</tbody>
</table>

Summary:
All 4 samples pass QC with sufficient quantity of DNA for sequencing.
Marion Higgins of California, 112 and Maria Capovilla of Ecuador, 116
Liquid Nitrogen Dewar
Delma Kollar of Creswell, OR, 113 with Syd Bergeson, Granddaughter
Lila Denmark, M.D. of Athens, GA, 112 yo

June 8, 2011

Supercentenarians
Mary Hutcherson, Daughter
Besse Cooper of Monroe, GA, 114, Former World’s Oldest and Son, Sidney Cooper
Mississippi (Sweetie) Winn, 113 yo and Great Niece, Mary Hollins of Shreveport, LA (Passed Away)
Eunice Sanborn of Jacksonville, TX, 114 (former World’s Oldest; passed away)
Germaine Degueldre of BELGIUM, 110
Marie-Therese Bardet of FRANCE, 112
Walter Breuning of Great Fall, MT, Was World’s Oldest Man, 114 (passed)
2011 Guinness Book of World Records

Supercentenarians

June 8, 2011
Mansoor Pazargad of IRAN, 113 (Passed Away)

June 8, 2011
Elsie Thompson, 112 yo
Clearwater, FL
Beulah Christie, 109 3/4 yo; Melbourne, FL
Charlotte Flowers, 111 yo
West Palm Beach, FL
Antonia Gerena-Rivera, 110 yo
Miami, FL (born in Puerto Rico)
Maria Gomes Valentim, 114, Carangola, Minas Gerais, Brazil, Now Oldest in the World Today!

June 8, 2011

Supercentenarians
Sra. Leandra Becerra Lurasmbre, 123 of Zapopan, Guadalajara, MEXICO
Centenarian Identical Twins

Female Centenarian Identical Twins (and two of their children)

June 8, 2011
## Argument: Here’s Why We Should Not Give Up Hope

<table>
<thead>
<tr>
<th>Era</th>
<th>Life Expectancy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 100 Kya (Hunter/Gatherers)</td>
<td>18</td>
</tr>
<tr>
<td>2. 5 Kya (Ancient Egypt)</td>
<td>25</td>
</tr>
<tr>
<td>3. 1400 AD (Middle Ages)</td>
<td>30</td>
</tr>
<tr>
<td>4. 1800 (USA)</td>
<td>37</td>
</tr>
<tr>
<td>5. 1900 (USA)</td>
<td>49</td>
</tr>
<tr>
<td>6. 2000 (USA)</td>
<td>78</td>
</tr>
<tr>
<td>7. 2045 (Singularity)</td>
<td>Escape Velocity</td>
</tr>
</tbody>
</table>

June 8, 2011
Argument: Here’s Why We Should Not Give Up Hope

DNA Robots Are Being Worked on at NYU, UC Berkeley, and all around the world
Augument: Here’s Why We Should Not Give Up Hope

- The best is yet to come
- Real Life Extension is still 25 years away; but in order for us to benefit from it, we’ll need to be here when it comes. (And I will surely be among the first to know as we get closer.)
- And for that, we will need to have a “Bridge Plan” to make sure we’re still around.

Thomas Kinkade  “The Bridge of Hope”
singularity

n: The moment when technological change becomes so rapid and profound, it represents a rupture in the fabric of human history.
Time Magazine (February 21, 2011)

June 8, 2011

Supercentenarians
The Accelerating Pace of Change

1. The accelerating pace of change...

   - Agricultural Revolution: 8,000 years
   - Industrial Revolution: 120 years
   - Light-bulb: 90 years
   - Moon landing

2. ...and exponential growth in computing power...

   Computer technology, shown here climbing dramatically by powers of 10, is now progressing more each hour than it did in its entire first 90 years.

   - UNIVAC I: The first commercially marketed computer, used to tabulate the U.S. Census, occupied 943 cu. ft.
   - Colossus: The electronic computer, with 1,500 vacuum tubes, helped the British crack German codes during WW II

3. ...will lead to the Singularity

   - Apple II: At a price of $1,298, the compact machine was one of the first massively popular personal computers
   - Power Mac G4: The first personal computer to deliver more than 1 billion floating-point operations per second

   - Human genome sequenced

   - World Wide Web

   - Surpasses brainpower equivalence to that of all human brains combined in 2023

   - Surpasses brainpower of mouse in 2015

   - 2045: Surpassates all human brains combined
What Can You Do about It?

The Supercentenarian Research Foundation invites you to partner with us in fighting the debilitating effects of aging.

An estimated 100,000 people die every day due to age-related diseases.

A study of Supercentenarians can help inform us of the root causes of aging.

Please join us in raising $1 million for this study.

June 8, 2011
Thank you