Biomarkers and Human Longevity: Genetics and Beyond

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(JCVI, UCSD, La Jolla, CA; TGen, Phoenix AZ)

1. Facts Concerning Aging and the Aging Population
2. US-Based Academic Aging Research Initiatives
3. Factors Associated with Healthy Aging
   • Telomeres
   • Blood Biomarkers
   • Epigenetics
   • Genetic Factors
4. Anti-Aging or Healthy Aging-Promoting Interventions
5. A Potential Unique Study Design for Aging Research
Disclosures

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Facts Concerning the Aging Population
Fun Facts About the Global Aging Population

- In 10 years > 1 billion over age 60
- By 2050 > 2 billion people over age 60
- 80% will be living in developing economies
- In China, by 2020 average worker > 50
- 50,000+ in Japan > 100 years currently
- Heritability of human lifespan >25%
- Associated variants in FOXO3 & APOE
- Lack of Negatives or Surplus of Positives?

http://unfpa.org/ageingreport/
Issues in the Identification of Factors Contributing to Aging

• Can one distinguish disease processes vs. senescence?

• How does one differentiate cause from effect?

• Myriad genetic, epigenetic, environmental factors

• Overt gene x environment interactions are at play

• Study designs involving humans are problematic:
  ✓ May need very large cohorts
  ✓ Need surrogate endpoints for survival
  ✓ Older individuals may have problematic phenotypes
  ✓ Secular changes complicate birth cohort studies
  ✓ Study trajectories/changes, but this takes time
  ✓ Integrated studies are needed but are costly

• Aging syndromes (e.g., Werner’s) are not good models
US-Based Academic Initiatives
The NIA Contracted “Longevity Consortium (LC)”

- Initiated more than a decade ago
- Focus on the genetic basis of human lifespan/healthspan
- Dozens of cohort studies are part of the LC
- Model organism component
- Cores and opportunity funds for external investigators
- Current off-shoot focusing on genetic drug targets (www.longevitygenomics.org)

[Image of longevity consortium website]
The NIA Sponsored “Long Life Family Study (LLFS)”

http://dsgweb.wustl.edu/llfs
Cross-Disciplinary Geroscience Interest Group (GSIG)

- Trans-National Institutes of Health initiative
- The **process** of aging is related to age-related disease
- Bring together aging and chronic disease researchers
- Factors increasing healthspan & “compress morbidity”
- The GSIG is taking a broader “systems-level” approach
Factors Associated with Healthy Aging
Telomeres

**Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection**

Elizabeth H. Blackburn,1,2 Elissa S. Epel,3 Jue Lin1

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- Issues: cause or effect?
- Telomerase manipulations
- Tissue specificity?
- Genetic influences

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**Genome-wide meta-analysis points to CTC1 and ZNF676 as genes regulating telomere homeostasis in humans**

Maximos Margani1,2, Shih-Jen Herang3, Timothy D. Spector4, Steven C. Hunt5, Mosayyi Kimer4, Annette L. Fitzpatrick5, Lone Christiansen6, Inge Petersen7, Clara C. Elbers8, Tamara Harris9,10, Wei Chen11, Sotanur R. Srinivasan11, Jeremy D. Kerl12, Athanaios Benetos13, Salih El Shamsi14, Sophie Vavrik-Sned15, Kaare Christiansen6, Gerald S. Berenson8,16, Ana M. Valdes10, Ana Viluena, Melissa Garcia17, Donna K. Arnett17, Ulrich Broeckel18, Michael A. Province9, James S. Pankow11, Candace Kammerer11, Yongmei Liu19, Michael Nalls20, Sarah Tishkoff21, Fridjol Thomas20, Eliaz Dvir20, Bruce M. Psaty18,20,32, Joshua C. Bia3, Jerene I. Rotten20, Kent D. Taylor20, Eric Smith20, Nicholas J. Schork32, Daniel Levy2 and Abraham Aviram18

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**Table 1. Cohort characteristics for the telomere length GWAS analysis**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Mean, age (year range)</th>
<th>Women (%)</th>
<th>Body mass index (mean ± SD)</th>
<th>Telomere length (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Heart Study</td>
<td>3146</td>
<td>59 (31–86)</td>
<td>51</td>
<td>28.1 ± 5.0</td>
<td>6.96 ± 0.58 (Kb)</td>
</tr>
<tr>
<td>Family Heart Study</td>
<td>2506</td>
<td>57 (30–87)</td>
<td>54</td>
<td>28.9 ± 5.7</td>
<td>6.76 ± 0.67 (Kb)</td>
</tr>
<tr>
<td>Cardiovascular Health Study</td>
<td>1061</td>
<td>75 (05–90)</td>
<td>62</td>
<td>26.6 ± 4.4</td>
<td>6.31 ± 0.63 (Kb)</td>
</tr>
<tr>
<td>Bogalusa Heart Study</td>
<td>333</td>
<td>35 (20–45)</td>
<td>42</td>
<td>29.0 ± 6.9</td>
<td>7.22 ± 0.70 (Kb)</td>
</tr>
<tr>
<td>REasons and Evaluation of Carotid Endarterectomy (REACH)</td>
<td>920</td>
<td>60 (38–87)</td>
<td>50</td>
<td>29.5 ± 6.3</td>
<td>6.78 ± 0.63 (Kb)</td>
</tr>
<tr>
<td>Framingham Offspring Study (FOS)</td>
<td>3122</td>
<td>48 (25–82)</td>
<td>52</td>
<td>28.1 ± 4.9</td>
<td>6.97 ± 0.64 (Kb)</td>
</tr>
<tr>
<td>Replication</td>
<td>337</td>
<td>73.6 (60–80)</td>
<td>50</td>
<td>27.7 ± 4.8</td>
<td>6.53 ± 0.53 (Kb)</td>
</tr>
<tr>
<td>Amsterdam ECB</td>
<td>620</td>
<td>43.2 (21–86)</td>
<td>33</td>
<td>27.2 ± 4.5</td>
<td>7.29 ± 0.63 (Kb)</td>
</tr>
<tr>
<td>AIRE-MDRC-Nancy ERAS-Ponce</td>
<td>316</td>
<td>63.7 (25–84)</td>
<td>51</td>
<td>27.4 ± 4.6</td>
<td>6.25 ± 0.54 (Kb)</td>
</tr>
<tr>
<td>Danish collection</td>
<td>964</td>
<td>80.7 (20–101)</td>
<td>77</td>
<td>28.3 ± 4.0</td>
<td>5.74 ± 0.87 (Kb)</td>
</tr>
</tbody>
</table>
Blood and Other Tissue Biomarkers

Loss of diversity in blood and other tissues

Parabiosis: finding circulating factors

Fig. 2. Stem cell diversity and dynamics with age. Top: Peripheral blood from young individuals is generated from around 1000 active HSCs. By the age of 70, the clonal diversity collapses, resulting in dominance of one HSC clone, such that about 20% of individuals have one clone that dominates 20–80% of blood cell production. Bottom: Repopulation of the surface of skin young skin is continuously replenished from stem cells, each with a highly restricted domain (represented by circle). Random mutations generate small variations across the surface in terms of even cells and their progeny (colored circles). With time, some clones expand markedly, resulting in clonally derived patches with a common set of genetic variants (38).
Epigenetics
Genetic Association Studies

GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy

Genetic Signatures of Exceptional Longevity in Humans

A: Overall Survival in NECS Set

B: Overall Survival in ELIX/NECS2 Set
Lack of Disease-Associated Variants in Healthy Elderly?

Genome-wide association study (GWAS)-identified disease risk alleles do not compromise human longevity


PNAS | October 19, 2010 | vol. 107 | no. 42

Abstract

We developed a new statistical framework to find genetic variants associated with extreme longevity. The method, informed GWAS (iGWAS), takes advantage of knowledge from large studies of age-related disease in order to narrow the search for SNPs associated with longevity. To gain support for our approach, we first show there is an overlap between loci involved in disease and loci associated with extreme longevity. These results indicate that several disease variants may be depleted in centenarians versus the general population. Next, we used iGWAS to harness information from 14 meta-analyses of disease and that GWAS to identify longevity loci in two studies of long-lived humans. In a standard GWAS analysis, only one locus in these studies is significant (APOE/TOMM40) when controlling the false discovery rate (FDR) at 10%. With iGWAS, we identify eight genetic loci to associate significantly with exceptional human longevity at FDR < 10%. We followed up the eight lead SNPs in independent cohorts, and found replication evidence of four loci and suggestive evidence for one more with exceptional longevity. The loci that replicated (FDR < 5%) included APOE/TOMM40 (associated with Alzheimer’s disease), CDKN2B/ANRIL (implicated in the regulation of cellular senescence), ABO (tags the O blood group), and SH2B3/ATXN2 (a signaling gene that extends lifespan in Drosophila and a gene involved in neurological disease). Our results implicate new loci in longevity and reveal a genetic overlap between longevity and age-related diseases and traits, including coronary artery disease and Alzheimer’s disease. IGWAS provides a new analytical strategy for uncovering SNPs that influence extreme longevity, and can be applied more broadly to boost power in other studies of complex phenotypes.
DNA Sequences of Two Supercentenarians (>114 yrs)

Whole genome sequences of a male and female supercentenarian, ages greater than 114 years

- Treat longevity like a rare disease
- Identify novel variants
- Count up all disease-causing variants

Some novel DNA sequence variants, but their biological significance is unknown at this time...
Sequencing Multiple Supercentenarians

Whole-Genome Sequencing of the World’s Oldest People

Hisco J. Glerman¹, Kristen Fortney¹, Jared C. Roach², Natalie S. Coles³, Hong Li², Gustavo Glusman¹, Glenn J. Markov¹, Justin D. Smith¹, Leroy Hood², L. Stephen Coles³, ⁵, Stuart K. Kim¹⁺

Table 1. Characteristics of supercentenarians.

<table>
<thead>
<tr>
<th>Age</th>
<th>Age at Draw</th>
<th>Sex</th>
<th>Race</th>
<th>Major Age-related Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>114</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>110</td>
<td>F</td>
<td>HS</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>112</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>112</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>114</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>110</td>
<td>F</td>
<td>HS</td>
<td>None</td>
</tr>
<tr>
<td>114</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>113</td>
<td>111</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>113</td>
<td>112</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>113</td>
<td>113</td>
<td>F</td>
<td>AA</td>
<td>None</td>
</tr>
<tr>
<td>111</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>110</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>111</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>111</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>111</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>111</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
<tr>
<td>110</td>
<td>110</td>
<td>F</td>
<td>CAU</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 3. Protein-altering variants in TSHZ3 in Georgia Centenarian cohort.

<table>
<thead>
<tr>
<th>Position on Chr19</th>
<th>Ref/Var</th>
<th>AA Pos</th>
<th>AA1/AA2</th>
<th>Supercent</th>
<th>Cent</th>
<th>Nona</th>
<th>1000G EUR MAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>31769738</td>
<td>G/A</td>
<td>321</td>
<td>R/W</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31769366</td>
<td>C/T</td>
<td>445</td>
<td>V/M</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.0013</td>
</tr>
<tr>
<td>31769293</td>
<td>T/C</td>
<td>469</td>
<td>E/G</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>31769021</td>
<td>T/C</td>
<td>560</td>
<td>M/V</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31768639</td>
<td>G/A</td>
<td>687</td>
<td>P/A</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31768594</td>
<td>A/C</td>
<td>702</td>
<td>L/W</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31768267</td>
<td>G/A</td>
<td>811</td>
<td>T/M</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31768178</td>
<td>C/T</td>
<td>841</td>
<td>E/K</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>novel</td>
</tr>
<tr>
<td>31767599</td>
<td>C/T</td>
<td>1034</td>
<td>E/K</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>novel</td>
</tr>
</tbody>
</table>

Position (bp) on chromosome 19 (Chr19) of variant, reference (Ref) and variant (Var) allele, Amino Acid (AA) position, AA1 (ref), AA2 (var), Supercentenarian carriers (shown for reference), Centenarians carriers, Nonagenarians carriers, Minor allele frequency (MAF) in 1000G EUR.

doi:10.1371/journal.pone.0112430.0003
Digital Aging Atlas Website and Database

Welcome to the Digital Ageing Atlas, the portal of ageing-related changes

The Digital Ageing Atlas (DAA) is a portal of age-related changes, covering different biological levels. It integrates molecular, physiological, and pathological age-related data to create an interactive portal that serves as the first centralized collection of human ageing changes and pathologies.

To facilitate integration, systems/local studies of ageing, the DAA provides a standardized source for ageing-related data, as well as tools to query and visualize the data, including anatomical models. Data in the DAA is manually curated from the literature and retrieved from public databases. Further detailed analyses users are able to download the entire database. More information on how to use the DAA is available on our website.

The DAA primarily focuses on human ageing, but also includes supplementary mouse data. In particular, our expression data, in accordance with the information on human ageing.

Database Statistics

<table>
<thead>
<tr>
<th>Human</th>
<th></th>
<th>Molecular changes</th>
<th>Pathological changes</th>
<th>Physiological changes</th>
<th>Physiological changes</th>
<th>Genes DysReg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (Supplementary gene expression)</td>
<td></td>
<td>Molecular changes</td>
<td>Qims</td>
<td>Physiological changes</td>
<td>Physiological changes</td>
<td>Genes DysReg</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td>Tissues</td>
<td>References</td>
<td>364</td>
<td>331</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Molecular changes</td>
<td>Qims</td>
<td>Physiological changes</td>
<td>Physiological changes</td>
<td>Genes DysReg</td>
</tr>
</tbody>
</table>

Search results for mitochondria

Sections

- Mitochondria
- Mitochondria

Changes

- Physiological changes
- Molecular changes
Human Aging Genomic Resources

The Human Aging Genomic Resources (HAGR) is a collection of databases and tools designed to help researchers study the genetics of human aging using modern approaches such as functional genomics, network analysis, systems biology and evolutionary analyses.

Search our resources:

Quick Search

Search all of the databases in HAGR at once.

If you have a list of genes you would like to search you can use the quick search input:

GenAge

A tabo resource in HAGR is GenAge, which includes a central database of genes related to human aging and a database of aging-related genes associated with specific organisms.

- Search human genes
- Search model organism genes

Age

An Age reference in HAGR is Age, which provides a correlation of data on aging, longevity, and life history that is ideal for comparative biology of aging.

GenDr

GenDr is a database of genes associated with dietary restriction and genetic manipulation experiments and gene expression profiling.

- Search gene manipulations
- Search gene expressions

LongevityMap

The LongevityMap is a database of human genetic variants associated with longevity. Over 1,000 genes and variants are currently included in context of longevity and health.

- Search gene and variants

Other Datasets, Tools and Projects

Other projects we are involved in include: evolutionary studies, genome sequencing, metagenomics, and gene expression analysis. The latter allowed us to identify a set of genes commonly altered during mammalian aging which resembles a novel molecular signature of aging.

In addition to developing databases and performing numerous analyses, we develop computational tools and software, including a Perl toolkit called the Aging Research Computational Tools (ARCT) and a method to calculate the rate of aging in a given population based on demographic parameters.

If you are interested in the genetics of aging, please subscribe to our newsletter or visit our website for additional tools and resources. For more on our tools and software, please visit our documentation and downloads. Images of HAGR are © 2008, unless otherwise noted, and are licensed for non-commercial use, or under a Creative Commons Attribution-NonCommercial-ShareAlike license.

http://genomics.senescence.info/
Mortality Calculators Based on Epidemiology Literature
(Largely based on non-genetic, self-reported factors)

https://www.myabaris.com/tools/life-expectancy-calculator-how-long-will-i-live/

I would live to 91 if I did not get divorced...

Focus on health behaviors (e.g., flossing)
Anti-Aging or Healthy Aging-Promoting Interventions
Healthy aging: The ultimate preventative medicine

Matt Kaeberlein,1* Peter S. Rabinovitch,1 George M. Martin1,2

Box 1. Geroscience interventions with translational potential.

Dietary restriction: Dietary restriction (DR) is the most studied intervention for delaying aging (15). Although not universally effective, a majority of studies have documented significant increases in both life span and health span when DR is applied in laboratory models, including nonhuman primates (17). Limited studies also indicate important health benefits, including reversal of disease risk factors (15), in people who practice DR. Although DR is not a viable translational approach at the population level, research in this area has inspired the search for alternative dietary modifications (e.g., low-protein diets) or small-molecule DR mimetics (e.g., mTOR inhibitors, see below) that can provide the health benefits of DR without requiring reduced food consumption.

Exercise: A large body of literature provides evidence that the health benefits of exercise are consistent with the enhancement of health span (18, 19). However, poor compliance, especially in the elderly population, makes this intervention challenging to apply. Thus, there is high interest in developing pharmacologic interventions that would synergize with lower levels of exercise.

mTOR inhibitors: Rapamycin extends life span and promotes health span in mice, as well as in simpler organisms. Treatment beginning late in life is sufficient to extend life span, reverse cardiac decline, and improve immune function in mice (20). A recent study also reported that a rapamycin derivative significantly boosts immune function in elderly people (10).

Metformin and acarbose: Metformin and acarbose are widely used diabetes drugs. Metformin improves health span in mice and may slightly extend life span (21), whereas acarbose markedly extends life span in male mice and modestly extends life span in female mice (22). In a nonrandomized retrospective analysis, diabetic patients taking metformin have reduced mortality compared with diabetic patients not receiving metformin, and they may live longer than nondiabetics not receiving metformin (23).

NAD precursors and sirtuin activators: As discussed by Verdin in a companion Review (24), nicotinamide adenine dinucleotide (NAD) precursors such as nicotinamide riboside and nicotinamide mononucleotide have been reported to improve health span in mouse models of muscle aging and cognitive decline. The mechanism of action is not clear, but it may involve activation of sirtuin NAD-dependent protein deacetylases, along with enhanced mitochondrial function (25). Other, possibly more specific, sirtuin activators also improve health span and slightly extend life span in mice (26).

Modifiers of senescence and telomere dysfunction: Senescent cells accumulate during aging and secrete factors that promote inflammation and cancer (27). As discussed in the companion Review by Blackburn et al. (28), telomere dysfunction is a major cause of cell senescence, and strategies to enhance telomerase function offer promise for improving health span (29), although the possibility of increased cancer risk must be addressed. Likewise, genetic and pharmacological strategies to target and kill senescent cells enhance both life span and markers of health in short-lived mice with high levels of senescent cells (30, 31).

Hormonal and circulating factors: Age-related changes in important hormones (including sex-steroids, growth hormone, and insulin-like growth factor 1) are well documented; however, the risks and benefits of hormone supplementation in aging remain largely controversial (32). As discussed in the companion Review by Goodall and Rando (33), heterochronic paradigms experiments in which the circulatory system of an aged mouse is shared with that of a young mouse suggest that additional, more subtle humoral factors affect age-associated declines in several tissues, including the brain, muscle, liver, and heart (34). Some progress has been made toward defining these factors (35), and an effort is under way to determine whether transfusion of young plasma can delay Alzheimer’s disease (36).

Mitochondrial-targeted therapeutics: As discussed in the companion Review by Wang and Hekimi (37), mitochondrial dysfunction is a major contributor to aging and age-related diseases, although the mechanisms are more complex than initially suggested by the Harman-free radical theory of aging (38). Attention is now being directed to interventions that augment mitochondrial function, energetics, and biogenesis, including mitochondrial-targeted antioxidants and NAD precursors (39).

“It is clear that directly targeting aging is theoretically superior to treating individual chronic diseases, but until recently, translational approaches to achieve this goal have been just that—purely theoretical.”
The NAD, SIRT1/2, PARP Pathway

- Pathway affected by Caloric Restriction (CR)
- CR Mimetics have been pursued and tested
- Pathway also involved in DNA repair

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**NAD⁺ in aging, metabolism, and neurodegeneration**

Eric Verdin

Blood NAD levels tracked over time (www.tannerproject.org)
Key Findings in Mice:

- Giving NAD precursor nicotinamide riboside (NR) increased NAD levels
- Increased NAD = Rejuvenated MuSC
- Increased NAD prevented MuSC and delayed NSC senescence
- Increased NAD prevented MuSC senescence in Mdx (DMD) mice

Fig. 2. Improved muscle stem cell numbers and muscle function in NR-treated aged mice.

Fig. 5. Increased stem cell number and function in NR-treated Mdx mice. Mdx mice received a dietary
Blood to blood

By splicing animals together, scientists have shown that young blood rejuvenates old tissues. Now, they are testing whether it works for humans.

BY MEGAN SCIDELLARI

Two mice perch side by side, nibbling aboard pellets. As one turns to the left, the other turns to the right. In this experiment, each mouse is treated with young blood from a genetically identical sibling. The treatment is performed by removing blood from the donors and injecting it into the recipients.

Researchers hope to find drugs that extend a person’s healthy years.

Ageing pushed as treatable condition

Regulators asked to consider innovative trial design.

BY FRANK AND HAYDEN

Doctors and scientists want drug regulators and research funding agencies to consider medicines that delay aging-related disease as legitimate drugs. Such treatments have a physiological basis, researchers say, and could extend a person’s healthy years by slowing down the processes that underlie common diseases of aging — making them worthy of government approval.

On 24 June, researchers will meet with regulators from the US Food and Drug Administration (FDA) to make the case for a clinical trial designed to show the validity of the approach.

Current treatments for diseases related to aging “just exchange one disease for another,” says psychiatrist Mir Barzilai of the Albert Einstein College of Medicine in New York. That is because people treated for one aging-related disease often go on to die from another relatively soon thereafter. “What we want to show is that if we delay aging, that’s the best way to delay disease.”

Barzilai and other researchers plan to test that notion in a clinical trial called Targeting Aging with Metformin, or TAME. They will give the drug metformin to thousands of people who already have one or two of three conditions — cancer, heart disease or cognitive impairment — or are at risk of them.

People with type 2 diabetes cannot be enrolled because metformin is already used to treat that disease. The participants will then be monitored to see whether the medication forestalls the illnesses they do not already have, as well as diabetes and death.

On 24 June, researchers will try to convince FDA officials that if the trial succeeds, they will have proved that a drug can delay aging. That would set a precedent that aging is a disorder that can be treated with medicines, and perhaps spur progress and funding for aging research.

During a meeting on 27 May at the US National Institute on Aging (NIA) in Bethesda, Maryland, Robert Temple, deputy director for clinical science at the FDA’s Center for Drug Evaluation and Research, indicated that the agency is open to the idea.

Barzilai and his colleagues echo claims of a quest for immortality, because they think that such assertions have led to a perception that the field is frivolous and irresponsible. “The perception is that we are all looking for a fountain of youth,” says Stephanie Sedrakman, executive director of the American Federation for Aging Research in New York. “We want to avoid that.”
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The Team

We are scientists from the fields of medicine, drug development, molecular biology, and genetics.

Through our research we're aiming to devise interventions that slow aging and counteract age-related diseases.

Arthur Levinson, Ph.D.
Founder & CEO

Hal V. Barron, M.D.
President of Research & Development

David Botstein, Ph.D.
Chief Scientific Officer

Cynthia Kenyon, Ph.D.
Vice President, Aging Research

Robert L. Cohen, M.D.
Calico Fellow

Jonathan W. Lewis, Ph.D.
Vice President, Business Development

http://www.calicolabs.com
A Potential Unique Study Design for Aging Research
Cilento Initiative on Aging Outcomes (CIAO!)

- Aging in complex, with many genetic and non-genetic influences
- Characterize local food stuffs (locally raised plants and animals)
- Sample households with family members and unrelateds
- Leverage multiple contrasts:
  - Within family heterogeneity (i.e., genetic studies)
  - Across family heterogeneity
  - Unrelateds within and across households
  - Environmental exposure differences
  - Another community (if not enough heterogeneity)

Recent Press:

http://www.sandiegouniontribune.com/news/2016/apr/01/ucsd-study-centenarians/
Questions?

“The world revolves around numbers, but DNA makes the world go round”