How to Die Young at a Very Old Age

Demystifying aging-NIH 2016
Demystifying Biology of aging
Aging itself is the strongest risk factor for all age related diseases

Genetics and environment of the individual determine which disease occurs first
What is the evidence for success in the goal of delaying aging?

- Healthy life-span has been extended in numerous models.
- Relevant drugs have been used in humans (Metformin, Acarbose, Rapalogs....).
Do we, humans, age at different rates?
Genetics of human longevity
Can a study design depict the challenges of genetics of aging?

• Only ~1/10,000 individuals is 100 years old
  (n~600; 95-112; LGP, LonGenity n~3,000)

• A homogenous population of Ashkenazi Jews (AJs)

• There is a remarkable family history of exceptional longevity in parents, siblings and offspring of “centenarians”

• Hypothesis:
  1) Perfect genome/environment
  2) Protective genes to assure human’s longevity
Appearance of all diseases in relationship to age

Diseases include:
- Cancer
- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Dementia
- Osteoporosis

Medical cost ($) during the last 2 years of life

In press JAGS
90 years before

Cover of PLoS Biology April 2006
Centenarians interaction with the environment
(n=477, 75% females)

<table>
<thead>
<tr>
<th>‘Environmental’ risk</th>
<th>Centenarians Men</th>
<th>Centenarians Women</th>
<th>NHANES1 Men</th>
<th>NHANES1 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over weight/obese:</td>
<td>48%</td>
<td>44%</td>
<td>•55%</td>
<td>41%</td>
</tr>
<tr>
<td>Smoking:</td>
<td>60%</td>
<td>30%</td>
<td>•75%</td>
<td>26%</td>
</tr>
<tr>
<td>Alcohol (daily):</td>
<td>24%</td>
<td>12%</td>
<td>•22%</td>
<td>11%</td>
</tr>
<tr>
<td>Physical activity:</td>
<td>43%</td>
<td>47%</td>
<td>•57%</td>
<td>44%</td>
</tr>
<tr>
<td>(Moderate: regular walking, bicycling, housework)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetarians:</td>
<td>2.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Swapnil Rajpathak and Jill Crandall

Demystifying - Genetics of aging

- Rapid aging (Progeria) vs. exceptional longevity
Lessons from human genetics studies

1) >90% variants occur in non-coding regions
2) Small effects

Genome-Wide Association Studies (GWAS)
Lessons from human genetics studies

Sequencing

1) Coding variants: Strong effects

2) Targets for drug development

Rare Variants/Extreme Phenotypes
Do centenarians simply have perfect genome?

WGS of 44 Ajs centenarians:
ClinVar database ~15,000 pathogenic variants
A total of 227 autosomal and seven X-chromosomal coding SNVs.

- **Parkinson**- 2 mutations in L444P (GAB)
- **AD**-APOE, UBQLN2 (also ALS)
- **Other degenerative**- SEMA4A, RP1, FZD4, MYO1A, CYP1B1, VSX1, and WDR36
- **Neoplastic**-APC, BRCA1, RET, RNASEL, and STK11
- **Cardiac (dominant)**-ABCC9, ACTN2, ANK2, CACNA1C, JPH2, KCNE2, MYL2, and TMEM43
- **Other dominant**- 18 variants for autosomal-dominant diseases and 6 mutations for X-Chromosomal diseases
- **Other recessive**- 72 variants for recessive traits include four variants that have least one homozygous
- Similar prevalence of common SNPs for age-related disease

Do centenarians simply have perfect genome?

WGS of 44 Ajs centenarians:
ClinVar database ~15,000 pathogenic variants
A total of 227 autosomal and seven X-chromosomal coding SNVs.

- Parkinson- 2 mutations in L444P (GAB)
- AD-APOE, UBQLN2 (also ALS)
- Other degenerative- SEMA4A, RP1, FZD4, MYO1A, CYP1B1, VSX1, and WDR36
- Neoplastic-APC, BRCA1, RET, RNASEL, and STK11
- Cardiac (dominant)-ABCC9, ACTN2, ANK2, CACNA1C, JPH2, KCNE2, MYL2, and TMEM43
- Other dominant- 18 variants for autosomal-dominant diseases and 6 mutations for X-Chromosomal diseases
- Other recessive- 72 variants for recessive traits include four variants that have least one homozygous
- Similar prevalence of common SNPs for age-related disease
Modeling changes in the frequency of a genotype as a function of age

Genotypic Frequency

Longevity genes

Age
Trends of favorable longevity Genotypes/Allele
(All validated or have phenotype/function)
Diminished GH/IGF-1 action improves longevity across nature

Small dogs live longer than large dogs

Longer lifespan in daf-2 mutants

Ponies live longer than thoroughbreds

IGF-1R+/- females, but not males, live longer
IGF-I and risk of age-associated diseases
prospective population-based case-control studies

Chan et al, 2002
Harman et al, 2000
Stattin et al, 2000
Stattin et al, 2000 (<59 yrs)
Hankinson et al, 1998
Hankinson et al, 1998 (<50 yrs)
Toniolo et al, 2000
Toniolo et al, 2000 (premenopausal)
Zhao et al, 2003
Giovannucci et al, 2000
Kaaks et al, 2001
Ma et al, 1999
Probst-Hensch et al, 2001
Lukanova et al, 2000
London et al, 2002

Garnero et al, 2000
Sandhu et al, 2002
Juul et al, 2002

Prostate cancer
Breast cancer
Bladder cancer
Colorectal cancer
Lung cancer

Osteoporotic fractures
IGT/T2DM
Ischemic Heart disease
IGF1R domain structure and coding variants

SNPs in centenarians
SNPs related to IR and growth retardation

Yousin Suh, PhD

Genotyping IGF1R Mutations in the full groups (n=700) revealed 9 centenarians vs. 1 control (~2%) harbor nonsynonymous mutations (p<0.02) and carriers have higher IGF-I ((p<0.04) and tend to be shorter

Prevalence of $d3$-GHR homozygotes with age groups

A. AJ (female and male of control and centenarian),

B. Older Order Amish males.

C. French Caucasian males,

D. white male of the CHS study
Evidence for GH/IGF-1 role in exceptional longevity in humans

- IGF-1R 2%
- D3GHR 12%
- MicroRNA clusters ~30%
Role of IGF-1 in survival in individuals with exceptional longevity

Groups defined based on the median IGF-1 level of 96 ng/mL

Milman et al. Aging Cell 2014
**TAME: Targeting/taming Aging with Metformin**

- **Biology of Aging:** Metformin has age-delaying effects on nematodes and mice. Multi mechanisms possible.
- **Intervention in non-type 2 diabetes mellitus (T2DM):** Metformin delays T2DM (DPP)
- **Intervention in T2DM:** Metformin delays CVD (UKPDS)
- **Association:** Metformin is associated with less cancer in patients with T2DM
- Early support that metformin may delay cognitive decline and AD.
- And:
Metformin targets multiple pathways of aging

- Oxidative stress Scenolytic
Metformin decreases mortality in T2DM and in non-diabetics

Bannister et al Diabetes, Obesity and Metabolism 2014.
TAME (Targeting Aging with MEtformin)

• To show that multiple morbidities of aging can be targeted by metformin
  • (FDA) To obtain a new indication for the delay of age-related morbidities.
  • To provide a paradigm for studying other drugs targeting multiple morbidities of aging
  • To apply the discoveries of geroscience as a powerful new tool for achieving primary prevention of multiple diseases.
TAME: Targeting Aging with METformin

**Primary Prevention**

- Slow gait speed OR obesity plus hypertension and/or dyslipidemia (not CVD, Cancer, or Dementia).

**Secondary Intervention**

- 1 or 2 of CVD, Cancer, MCI present at baseline

**Inclusion Criteria**

- 3000 subjects
- 65-79 yo

**Double blind placebo control study**

**Time to clinical occurrence of composite outcome:**
- MI, Stroke, CHF, revascularization, PAD, cancer, MCI or dementia, Death.

**Time to occurrence of composite outcome:**
- Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, development of ADL limitation, MCI, or dementia transition

**Time to onset of 14 age-related chronic health conditions (e.g. depression, osteoporosis, osteoarthritis), rate of acute events (e.g. falls, pneumonia), change in measures of function (gait speed, etc.), and quality of life measures (pain, sleep quality, fatigue)**

- Primary Prevention
- Secondary Intervention
- Tertiary outcomes

**Primary Prevention**

- TAME: Targeting Aging with METformin
Multi-morbidity Incidence: Rochester Epidemiology Project

Figure 2  Incidence rates (per 1000 person-years) of two chronic conditions (second condition in a dyad) and of three chronic conditions (third condition in a triad) in men and women separately (A and C), and stratified by ethnicity (B and D).

St Sauver JL et al. Risk of developing multimorbidity across all ages in a historical cohort study. BMJ Open 2015; 5:e006413
What did I try to demystify (and why)?

- Age = age-related disease
- Do you study your animals models for diseases at the relevant old age?
- Did we fall in a trap of silos in the NIH(s)?
- There is a biology to aging (the target is well defined).
- Intervention has delayed aging in many species (genetics of exceptional longevity if a subject for drug development in humans).
- Targeting aging in humans is a practical horizon for the next decade. (TAME-Ron Howard NGO)
TAME consortium:

- Steve Austad
- Nir Barzilai
- Morgan Canon
- Harvey Cohen
- Mark Collins
- Jill Crandall
- Mark Espeland
- Richard Faragher
- Jon Gelfond
- Tamara Harris
- Steve Kritchevsky
- George Kuchel
- Jamie Justice
- Brian Kennedy
- Jim Kirkland
- Anne Newman
- John Newman
- Michael Pollak
- Walter Rocca
- Felipe Sierra
- Stephanie Studenski
- Ella Temprosa
- Joe Verghese
- Jeannie Wei

Contributed to development:
- Luigi Ferucci
- Eileen Crimmins
- Marcel Salive
- Jay Olshansky
- Caroline Blaum
- David Sinclair
- Rafa deCabo
- Sofiya Milman
- Stephanie Lederman

Efforts so far are sponsored by AFAR.
Thanks you!

**Glucose homeostasis with aging**
Derek Huffman Ph.D
Gil Atzmon Ph.D
Yousin Suh Ph.d (lab)
Sofiya Milman MD
Hassy Cohen MD (USC)
Hongqian Liang Ph.D
Kai Mao Ph.D
Pasha Aponets Ph.D
Marielisa Rincon MD

**Support:** AFAR, NIH: E-NSC, R01, P01 (genes), P01 (metabolic), K08, Ellison Medical Foundation, LWPES, DRTC, Glenn Foundation, Aviva and Sammy Ofer

**LGP/LonGenity:**
Gil Atzmon Ph.D.
Yousin Suh Phd (lab)
Sofiya Milman MD
Bill Greiner R.N.
Jill Crandall MD
Hassy Cohen MD (USC)
Richard Lipton M.D (EAS)
Joe Verghese MD
Roee Holtzer PhD
Carol Stamm
Janet Schein
Wanda Guzman (Res. Coord.)
Erica Weiss
Leah Sutton
Khadija Isamil MS
Jenny Deluty MS
Vafa Tabatabaie MD
Kenny Ye PhD

**Other Collaborators**
Jim Kirkalnd (Mayo Clinic)
Dan Promislow (U Wash.)
Anne L.S. Chang (Stanford)
Amir Lerman (Mayo Clinic)
Tom Pearls (BU)
Paola Sebastiani (BU)
Sree Nair (Mayo Clinic)
John Greally MD PhD (Einstein)
Alan Shuldiner M.D. (UMD)
Francis Collins MD (NIH)
Gad Rennert (Technion)
Sigal Fishman MD (Tel Aviv)
Norman Fleischer M.D (Einstein)
Harry Shamoon M.D. (Einstein)
Alan Permutt MD (WashU)
Karl skorecki MD (Technion)
Diddahally Govindaraju (BU)
Ben Glazer MD (Hadassah)
Zohar Nir PhD (Negev)
Josephe Attardi Ph.D. (Cal Tech)
Cynthia Kenyon PhD
Ann Brunett PhD
A major barrier to conducting a study of centenarians

Is there an appropriate control group?

The cohort assembled to date ("LonGenity") is unique:

• Offspring of centenarians are enriched with longevity phenotypes and genotypes
• Study of offspring permits comparisons with age- and gender-matched controls.
• All Ashkenazi Jews
Offspring are less likely to have age-related diseases than controls.

**p<0.01**

JAGS 2004; 52:274
"Fountain of Youth"
Lucas Cranach the Elder, (1546)

How do we: 1) Use a simple/current tool 2) Get to the fountain of youth 3) No one get hurt
Use current technology, focus on ‘fountain of youth’ and no body gets hurt!
Diabetes risk related to parental age at death
The Diabetes Prevention Program

Offspring of longer-lived parents had lower diabetes risk, independent of parental diabetes and DPP treatment

J Geron 2011; 66A:1211
Parental longevity associated with lower risk of Alzheimer's disease and memory decline.

(Lipton, ... Barzilai et al J Am Geriatr Soc. 2010)
Lipid gene (CETP VV) protects from cognitive and not only from cardiovascular aging.

Role of HDL-C in survival in individuals with exceptional longevity

Median survival is extended by \(~ 1\) year

Groups defined based on the median HDL-C level of 52 mg/dL