Targeting Aging to Delay Multiple Chronic Diseases: A New Frontier

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Mayo Clinic Robert and Arlene Kogod Center on Aging

NIH

March 8, 2012
Aging World Population

% of population
60 years or older

- <5
- 5-12.4
- 12.5-20
- >20
Number of Americans 65 Years of Age and Older (1900-2050)

 Millions

Year

1900 1920 1940 1960 1980 2000 2010 2050

Projected

U.S Census Bureau

65 years old and older
85 years and older
Evolution of Aging Research

To understand the aging process
Evolution of Aging Research

To understand, extend the aging process
Evolution of Aging Research

To understand, extend, and improve the aging process
3 Insights in 3 Years

Healthspan
Translation
Geroscience
3 Insights in 3 Years

Healthspan
Translation
Geroscience
Successful Aging

Compressing Period of Decline
What Do Older People Want?

Want: Autonomy
    Control
    Independence

Are not resigned to an old age of frailty

Int. J. Aging Hum. Devel. 50:361, 2000

Do not appear to want ↑ lifespan at all costs
Limits to Healthspan

Disability
Longevity
Frailty
Chronic Disease
3 Insights in 3 Years

Healthspan
Translation
Geroscience
Intervention/Translation

Are close to the point of translating interventions based on the biology of aging:

- Caloric restriction
- Rapamycin
- Protein aggregation inhibitors
- Remove senescent cells

Others (enumerated 37 existing, developing, and potential strategies at Groningen Conference on 10/27/11)
Rapamycin Increases Maximum Lifespan in Mammals

- Rapamycin orally beginning at 600 days of age
- 2.24 mg rapamycin/kg/day
- 60-70 ng rapamycin/ml blood
- Age at 90% mortality ↑ 14% in females and 9% in males
- Delayed cancer
- Effective if started after 600 days old

Chronic Disease

Aging is becoming a modifiable risk factor
3 Insights in 3 Years

Healthspan
Translation
Geroscience
Aging is the Single Biggest Risk Factor for Stroke, Heart Attacks, Cancers, Dementia, Diabetes, Most Chronic Diseases, and Frailty

The Silver Book: Chronic Disease and Medical Innovation in an Aging Nation
Intersection Between Aging and Chronic Disease

- Delay age-related chronic diseases as a group, rather than one at a time.
- Manipulations that increase healthspan appear to delay chronic disease (caloric restriction, rapamycin, eliminating senescent cells).
- Can the period of morbidity at the end of life be compressed? (supercentenarians).
- Tremendous economic implications: cost of 2 yrs before death 1/3 in those at 100 vs. 70.
Not only survival, but also delay of disability, frailty, and onset of age-related chronic diseases as a group
Levels

Laboratory
Institutional
National
Levels

Laboratory
Institutional
National
Cellular Senescence

Senescence Associated β-Galactosidase

25th passage human subcutaneous preadipocytes
Cellular Senescence

Senescence Associated β-Galactosidase

Young tissue (fully functional) Old tissue (dysfunctional)

Courtesy Jan van Deursen

Normal (healthy) cell Senescent cell Dysfunctional cell Metalloproteinases, Cytokines, etc...

\[ \gamma H2A.X \]
Senescent Cells Accumulate with Aging and Obesity in Rats

- **SA β-Gal**
- **All Nuclei**

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<th>3M</th>
<th>Lean</th>
<th>Obese</th>
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Pathway Analysis - Metacore

Passage 15 vs. 11
Passage 17 vs. 11
Passage 22 vs. 11

1. Cell adhesion ECM remodeling
2. Immune response Alternative complement pathway
3. Cell adhesion Cell-matrix glycoconjugates
4. Cell adhesion Chemokines and adhesion
5. Immune response Classical complement pathway
6. Immune response Lectin induced complement pathway
7. Immune response Oncostatin M signaling via MAPK in human cells
8. Immune response IL-17 signaling pathways
9. Blood coagulation Blood coagulation
10. Cell adhesion Endothelial cell contacts by non-junctional mechanisms
Co-Culture with Senescent Preadipocytes Inhibits Adipogenesis

**Abdominal subcutaneous preadipocytes from lean, young kidney transplant donors. Radiated vs. non-irradiated. Co-cultured with subcutaneous DiI-stained cells from the same subjects. Exposed to DM for 2wks (representative of experiments from 2 subjects).**
Preadipocytes from elderly or obese subjects or after repeated replication produce MCP-1 and induce macrophage migration.
Inguinal Fat From Wild Type Mice is More Highly SA $\beta$-Gal$^+$ Than From Ames Mice (deficient prophet of pituitary transcription factor-1)

Wild type          Ames

Age 20 months
Representative of 3 experiments
Adipogenesis Is Preserved In Aged Ames Mice

19 M wild type  20 M Ames dwarf

Representative of 5 experiments
p16 and IL-6 Are Lower in Preadipocytes From 18M Snell Dwarf and GHRKO Than Wild Type Mice

Snell Dwarf

GHRKO

Wild Type
Targeting Senescent Cells

Aging $\rightarrow$ fat tissue senescent cells  
4/2005; JLK, TT
Targeting Senescent Cells

Aging → ↑ fat tissue senescent cells

IGF-1 induces senescence *in vitro*
Targeting Senescent Cells

Aging → ↑ fat tissue senescent cells 4/2005; JLK, TT
IGF-1 induces senescence *in vitro* 2007; JX, DT
Cellular senescence is delayed in long-lived GH/IGF1-deficient mice 8/2007; JLK, TT, AB
Targeting Senescent Cells

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- Target senescent cells to → ↑function 9/2007; JLK, TzV
Targeting Senescent Cells

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- Target senescent cells to → ↑ function 9/2007; JLK, TvZ
- Attempts to eliminate using ligand-Diphtheria toxin 2007; JLK, TT, JM
Targeting Senescent Cells *In Vivo*

Senescence-activated promoter

p16 or p53-related promoter

2008; JLK, TT

Nature 479:232, 2011
Targeting Senescent Cells *In Vivo*

Couple senescence-activated promoter to a drug-activated suicide gene

2008; JLK, TT

Nature 479:232, 2011
Targeting Senescent Cells 

In Vivo

Senescence-activated promoter

Suicide gene

Drug

GFP

Add GFP to the construct

6/13/2008; TT

Nature 479:232, 2011
Targeting Senescent Cells

In Vivo

Senescence-activated promoter

ATTAC

FKBP Caspase 8-Flag

ATTAC (apoptosis through targeted activation of caspase)

AP20187

GFP

6/2008; JK

Nature 479:232, 2011
INK-ATTAC

Ink promoter  ATTAC  IRES GFP

FKBP  Caspase 8-  Flag

IRES for transcribing eGFP

AP20187

2008; JvD

Nature 479:232, 2011
INK-ATTAC

p16Ink4a promoter fragment based on active region in replicative senescence

2008; JvD, DB

Nature 479:232, 2011
Rationale: BubR1 → ↑p16 & ↑ fat tissue senescence
• ↓p16 in BubR1 → ↓fat tissue senescence & correction of ↓ lifespan

2008; JvD, DB

Nature 479:232, 2011
INK-ATTAC

Transgenic as opposed to knock-in 2008; JvD
INK-ATTAC

Transgenic as opposed to knock-in 2008; JvD
Accelerate accumulation of senescent cells 2008; JLK
INK-ATTAC

Transgenic as opposed to knock-in 2008; JvD
Accelerate accumulation of 2008; JLK
senescent cells
Thiazolidinediones 2008; TT
Activating INK-ATTAC Eliminates Senescent Cells

Control +TZD  AP20187 +TZD
Activating INK-ATTAC Eliminates Senescent Cells

Untreated Treated with AP20187

GFP in IAT SA-β-galactosidase activity

Treated with AP20187 every 3 days

DB, TW, BC, & JvD
INK-ATTAC

- Transgenic as opposed to knock-in 2008; JvD
- Accelerate accumulation of senescent cells 2008; JLK
- Thiazolidinediones 2008; TT
- High fat feeding 2008; JLK, TT
- Breed with BubR1 2008; JvD
INK-ATTAC

↑ Healthspan:
↓ Sarcopenia with ↑ Activity & Strength
↓ Cataract

Nature 479:232, 2011
INK-ATTAC: Next Steps

Chronological aging

Side effects: wound repair, infection

Age-related conditions
  Cancer
  Diabetes
  Atherosclerosis
  Gliosis/ Alzheimer’s/ Parkinson’s

Transplantation and aging: seed vs. soil

Small molecule: mouse and human screens

Biologicals

SASP inhibitors
Levels

Laboratory

Institutional

National
Strategic Alliances With Other Centers At Mayo

Robert and Arlene Kogod Center on Aging

Cancer Center; Alzheimer’s Center; Minnesota Obesity Center; Cardiology; Ophthalmology

Healthy Aging and Independent living

Cellular senescence

Aging bone, muscle, & joints

Aging, diabetes, & metabolic syndrome

Regenerative medicine and aging

Center for Innovation; Cancer Center; Physical Medicine and Rehabilitation

Center for Translational Science Activities; Orthopedics; Rheumatology

Center for Individualized Medicine; Regenerative Medicine; Cardiology; Dermatology

Center for Translational Science Activities; Minnesota Obesity Center; Department of Medicine
Research Activities

- 213 publications from 01/10 to 08/11
- 89 grants from the National Institutes of Health
  - 44 from the National Institute on Aging
- 160 active IRB protocols
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Healthspan Assessment Lab: Models and outcomes of aging

Chronological Aging

Accelerated Aging

Diseases of Aging

genes

drugs
diet
exercise
devices
cells

Impact on clinically-relevant measures of healthspan

Courtesy of Nathan LeBrasseur
Healthspan Assessment Lab: Models and outcomes of aging

Impact on clinically-relevant measures of healthspan

Note: Disease Models on an Aging Background

Courtesy of Nathan LeBrasseur

Chronological Aging

Accelerated Aging

Diseases of Aging

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Healthspan Assessment Lab

Courtesy of Nathan LeBrasseur
Amelioration of Chronic Diseases by Manipulating Aging Processes

Youthful function ➔ Aging/cellular senescence ➔ Disease-specific mechanisms ➔ Age-related chronic disease ➔ Impaired healthspan

- Frailty
- Sarcopenia
- Cancers
- Infection/Immune/Inflammation
- Metabolic/Diabetes/Atherosclerosis
- Neurodegenerative/Neurovascular
- Impaired vision
- Osteoporosis
Levels

Laboratory
Institutional
National
Basic/Clinical Divide

- 7,600 geriatricians in US
- <10 have Division of Aging Biology, NIH R01’s
- Few basic aging researchers attend clinical geriatrics meetings
- Few geriatricians attend basic aging meetings
Funding

Translational research is expensive

Discovery and mechanism-based research are essential to support continued translation

Geroscience: Intersection between aging and chronic disease
Aging at the Nexus of Chronic Disease

- Infection
- Musculoskeletal
- Cancer
- Osteoporosis
- Diabetes
- Calcific vascular
- Eye
- Atherosclerosis
- Neurovascular
- Parkinson’s/Neurodegenerative
- Dementia
Geroscience at NIH

How can NIH fuel progress at this nexus between fundamental aging mechanisms and genesis of chronic diseases as a group?

NIH organizational structures drive structures within Academic Institutions nationally and world-wide

A Geroscience initiative at NIH will translate into productive collaborations among disciplines at academic institution, departmental, and laboratory levels
Apollo Project
2 Step Process

Remove dead tissue
  - Delay age-related cellular damage
  - Remove senescent cells
  - Ameliorate the SASP
  - Stop chronic inflammation
  - Remove damaged proteins

Replace with good tissue
  - Transplantation
  - Stem cells
  - Restore endogenous progenitor function
Acknowledgements

T Tchkonia        J Campisi
T Pirtskhalava    A Bouloumie
N Giorgadze       C Pothoulakis
M Gagua           M Jensen
T Thomou          A Teferi
Y Zhu             C Conover
M Cartwright      A Bartke
I Karagiannides   M Masternak
A Cartwright      Y Ikeno
E Lubbers         J Kopchick
S Brozovich       D Berryman
J van Deursen     E List
D Baker           M Adamo
N LeBrasseur      M Lenburg
T White           R Miller
S Khosla          M Adamo
T von Zglinicki   C Boney
N Timchenko       R Forse
T Lash            
A Terzic          

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Acknowledgements

Felipe Sierra, Dave Finkelstein, Evan Hadley, Jose Velasquez, and many others at NIA and the NIH

AG P01 41122
AG13925, AG31736, Noaber Foundation, Glenn Foundation, Ted Nash Foundation, Ellison Foundation