Barriers to the Pre-Clinical Development of Therapeutics that Target Aging Mechanisms

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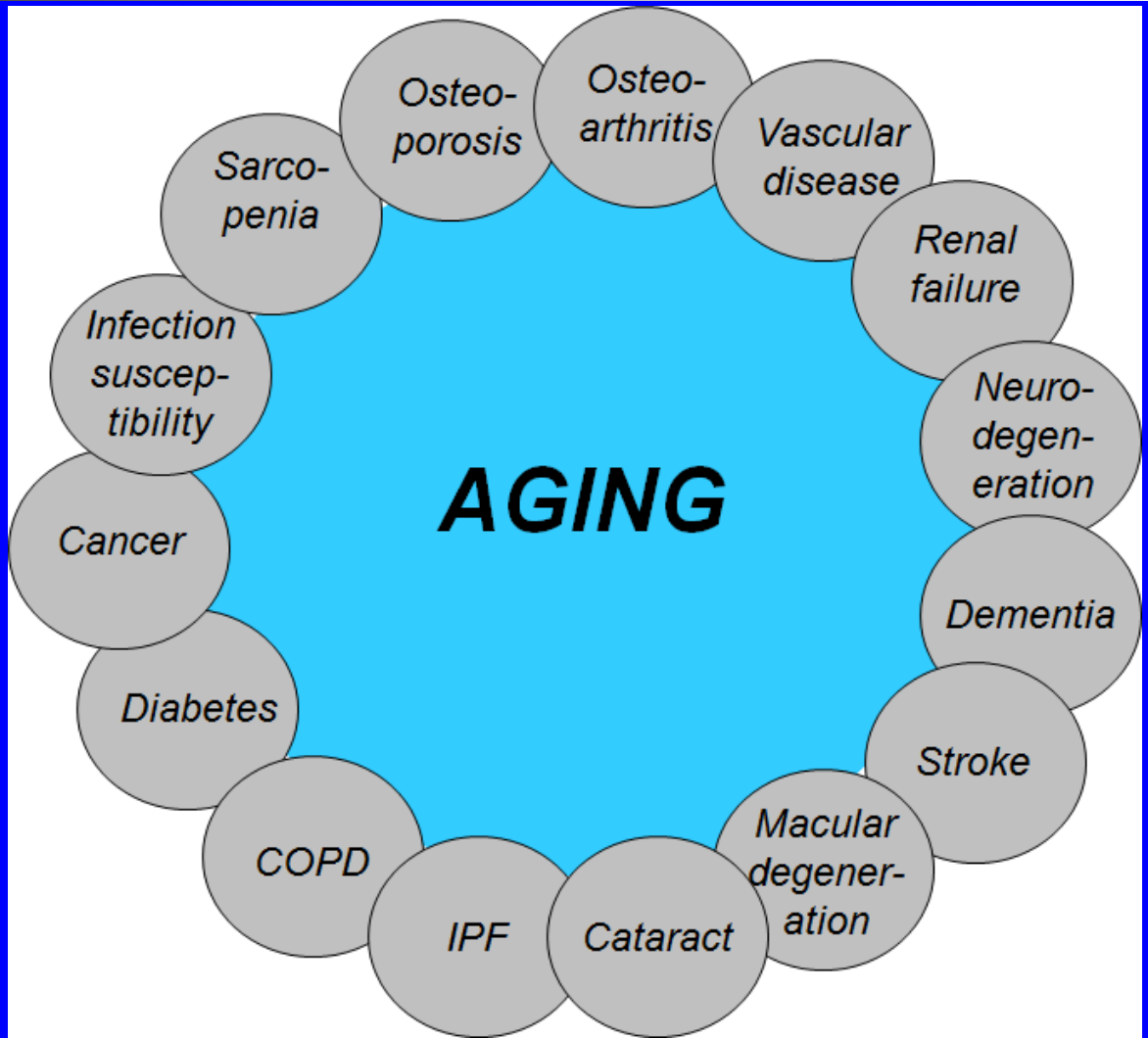
GEMSSTAR Models and Studies of Aging

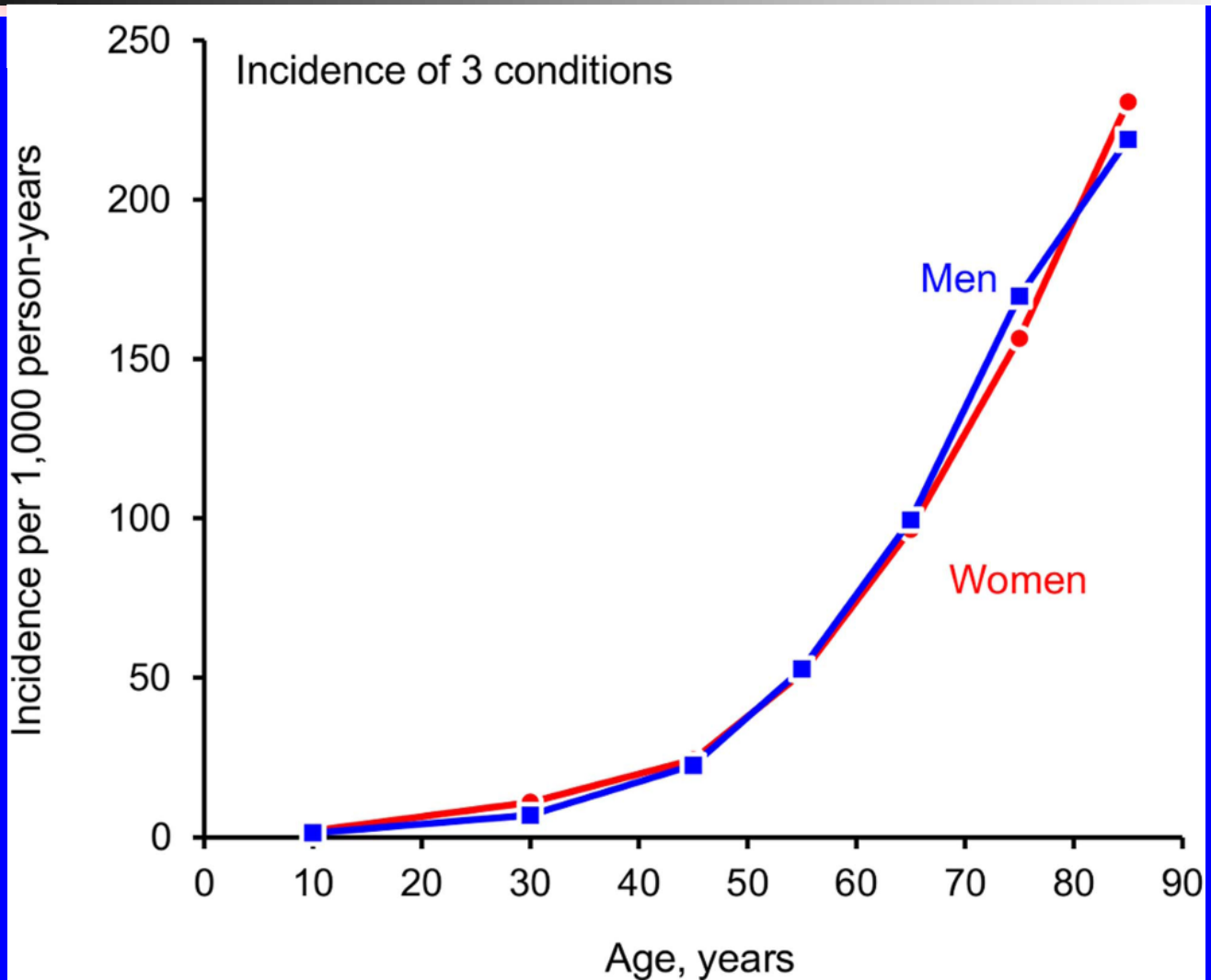
Bethesda

September 23, 2016

Aging is at the Nexus of Chronic Disease



Incidence of Multimorbidity Increases with Age



Rochester Epidemiology Project
St. Sauver, J.L., *et al.*, BMJ Open, 2015

Consequences of Fundamental Aging Processes

Fundamental Aging Mechanisms

Inflammation (chronic, low-grade, sterile)

Cellular Senescence

Macromolecular Dysfunction (DNA, protein aggregation, autophagy, AGE's, lipotoxicity)

Stem Cell and Progenitor Dysfunction

Phenotypes

Geriatric Syndromes:
Sarcopenia
Frailty
Immobility
MCI

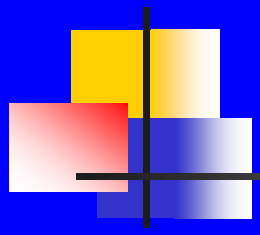
Chronic Diseases:
Dementias
Atherosclerosis
Diabetes
Osteoporosis
Osteoarthritis
Renal dysfunction
Blindness
Chronic lung disease

Deceased Resilience:
Infections
Delirium
Delayed wound healing
Slow rehabilitation

Geroscience Hypothesis

Targeting fundamental aging processes delays, prevents, alleviates, or reverses multiple geriatric syndromes, chronic diseases, and loss of resilience

Progress in Aging Research



Description

↓

Mechanism

↓

→ Intervention

↓

Translation

↓

Application

Geroscience Network

Albert Einstein
Buck Institute
EU/University of Groningen/Newcastle/ MOUSEAGE
Harvard
Hopkins
Mayo
Scripps
Stanford
University of Alabama at Birmingham
University of Arkansas
University of Colorado
University of Connecticut
University of Florida
University of Michigan
University of Minnesota
University of Texas San Antonio
University of Southern California
University of Washington
Wake Forest

Many other groups in retreats and faculty exchanges

Supported by NIA
R24 AG044396
PI: J Kirkland
Co-PI's: N Barzilai, S Austad

EATRIS
AFAR
Albert Einstein
Arizona State University
Barshop Institute, UT Health
Brown University
Buck Institute
Calico
Copenhagen University
Duke University
Ellison Medical Foundation
ERIBA
FDA
George Washington Univ.
Glenn Foundation
Harvard Medical School
Johns Hopkins
Mayo Clinic
McGill University
NIA
Novartis Institute
Ohio State University
Ohio University
Roswell Park Cancer Institute
Sanford Burnham
Scripps Research Institute
Southern Illinois University
Stanford University
University Medical Center Groningen
University of Alabama at Birmingham
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University of Minnesota
University of Oklahoma
University of Pittsburgh
University of Rochester
University of Sheffield
University of Southern CA- Davis
University of Texas Health Science Center – San Antonio
University of Washington
University of Wisconsin Madison
USC Davis School of Gerontology
Wake Forest
Washington University in St. Louis

54 Institutions

115 Individuals

David Allison
Julie Andersen
Jacquie Armstrong
Steven Austad
Gohar Azhar
Anne Bang
Andrzej Bartke
Nir Barzilai
Fred Baumer
Ilaria Bellantuono
David Bermlohr
Christin Burd
Cornelius Calkoven
Morgan Canon
Alanna Chamberlain
Harvey Cohen
Pinchas Cohen
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Jeanne Wei
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Raymund Yung
Ben Ziemer

R24 Retreats

Retreat 1 - Drug Screening Towards Developing Biomarkers for Aging
Retreat 2 - Model Systems of Aging
NIA Workshop on Resilience in Aging Animal Models
Retreat 3 - Drug Interventions in the Elderly
Retreat 4 - TAME Study Protocol Development
Retreat 5 - Continuing a Geroscience Network
Retreat 6 - Developing Investigators with Translational Expertise (October, 2016)

Journals of Gerontology Series A, August 16, 2016

- Moving Geroscience Into Uncharted Waters
- Barriers to the Preclinical Development of Therapeutics that Target Aging Mechanisms
- Evaluating Health Span in Preclinical Models of Aging and Disease: Guidelines, Challenges, and Opportunities for Geroscience
- Resilience in Aging Mice
- Frameworks for Proof-of-Concept Clinical Trials of Interventions That Target Fundamental Aging Processes
- Strategies and Challenges in Clinical Trials Targeting Human Aging

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 00, No. 00, 1–7
doi:10.1093/gerona/glw112
Advance Access publication August 16, 2016

OXFORD

Special Issue: Moving Geroscience into Uncharted Waters: Perspective

Barriers to the Preclinical Development of Therapeutics that Target Aging Mechanisms

Christin E. Burd,[1,2,*] Matthew S. Gill,[3,*] Laura J. Niedernhofer,[3] Paul D. Robbins,[3] Steven N. Austad,[4] Nir Barzilai,[5,6] and James L. Kirkland[7]

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Received March 22, 2016; Accepted June 2, 2016

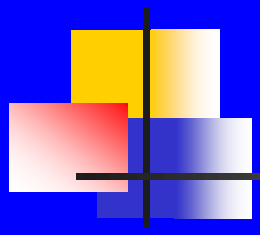
Decision Editor: Rafael de Cabo, PhD

Retreat 1

Barriers to the Pre-Clinical Development of Therapeutics that Target Aging Mechanisms

May, 2014, the Scripps Research Institute, Jupiter, FL

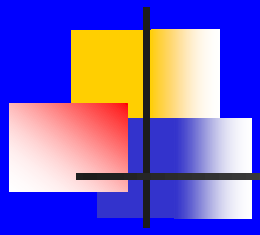
1. drug discovery
2. lead compound development
3. translational pre-clinical biomarkers
4. funding
5. integration between researchers and clinicians



Aging researchers had varied and strong perceptions of the ideal preclinical pipeline

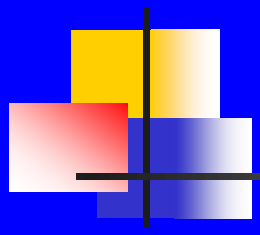
Funding

- $ for high risk but potentially transformative translational science
- Review of translational proposals



Infrastructure

- Early phase forward and reverse translational infrastructure:
- accessible biobanks
- help with IND's
- communication channels: shared protocols, SOP's, coordination

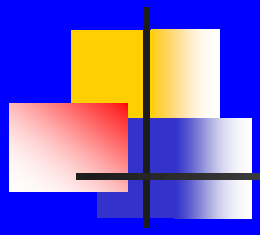


Competition

As they move to translation, fields tend to move from collaboration and openness to competition and secrecy

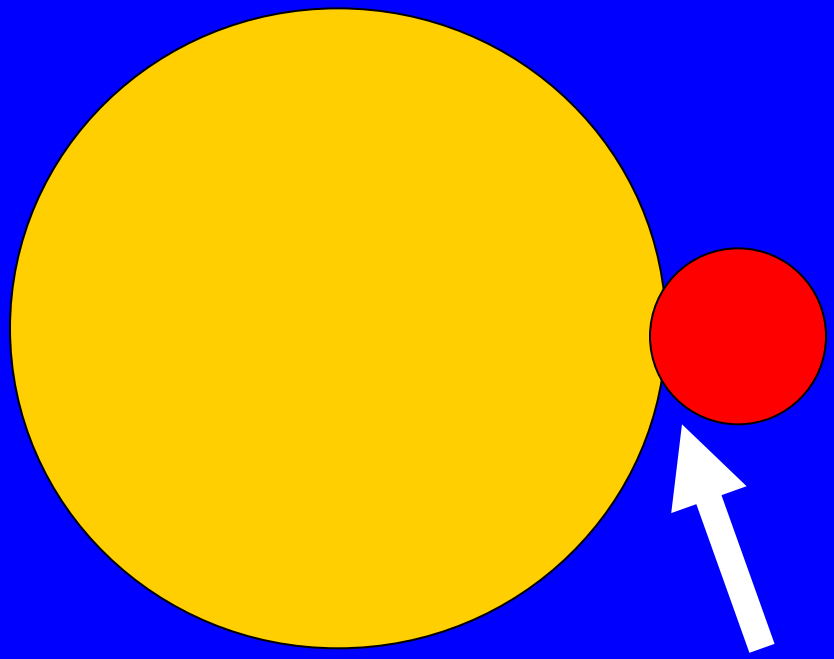
Competition and secrecy make doing collaborative, multi-center academic clinical trials difficult

Secrecy can interfere with sharing information about potential new indications and side-effects



Personnel with sufficient grasp of basic aging biology, IND clinical trials design, and geriatrics

Basic/Clinical Divide



- 7,000 geriatricians in US (board-certified)
- <12 have Division of Aging Biology, NIH R01's
- Few basic aging researchers attend clinical geriatrics meetings
- Few geriatricians attend basic aging meetings
- Few geriatricians have completed INDs

Solutions

More training for clinicians in the basic biology of aging and basic scientists in translation

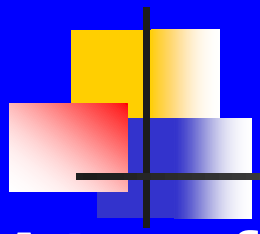
Formation of clinical trials networks

Recognition for team science rather than individuals

Outcomes and Directions

- Trans national network of aging centers
- Formal links with EU networks
- Formal links with NCATS
- Meetings with FDA, particularly about preclinical registration study strategies
- Formal links with the ITP and other NIA programs
- Development of a national preclinical studies network to follow on from this R24. Bridge between the basic biology of aging community and application

How will Geriatric Medicine be Practised in the Future?



A transformation in geriatrics is possibly close

Currently:

- **Tertiary prevention**
- **Complications of chronic diseases**
- **Aides and devices**
- **Geriatric syndromes, frailty, social consequences**

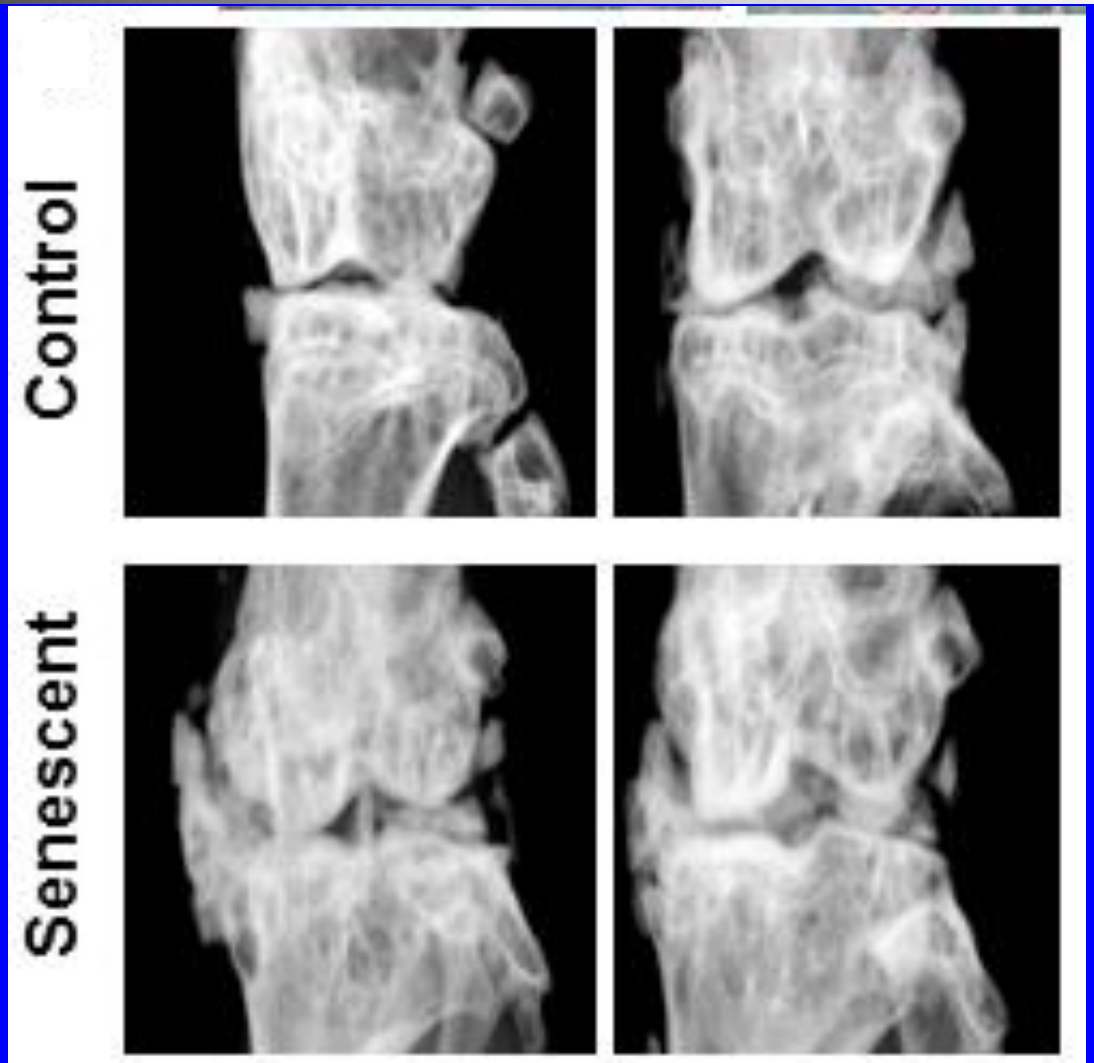
In 10 years:

Delay of chronic diseases and geriatric syndromes with compression of morbidity using interventions based on recent advances in the biology of aging

Is There a Point at Which it is Too Late to Intervene?

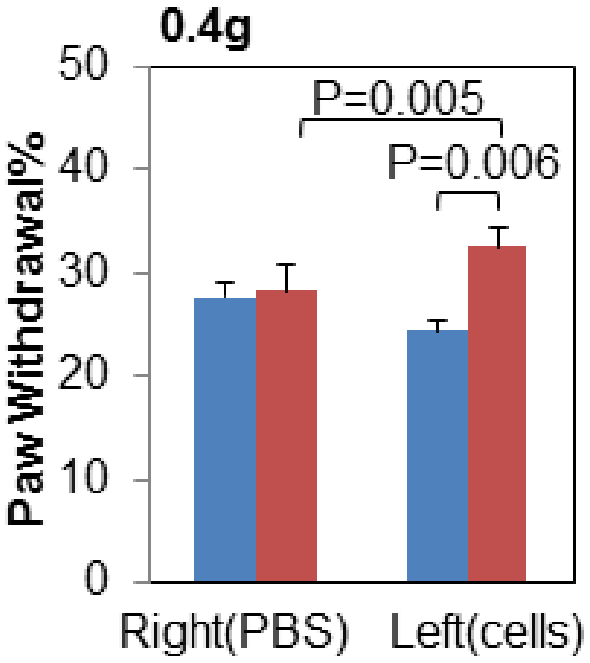
- A prevailing view in the field has been that interventions targeting fundamental aging processes will only be useful if administered preventively before beginning of disability
- However, these interventions may have a role in older individuals with multiple morbidities

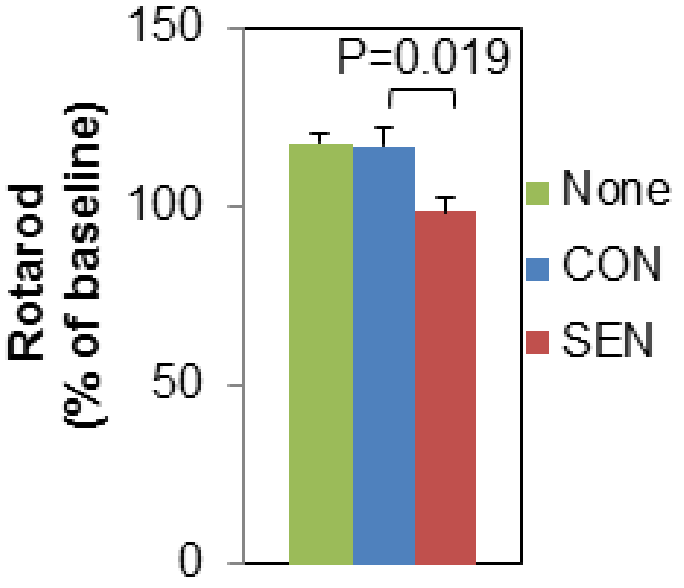
Transplanting Senescent Cells Into Knees Causes Osteoarthritis-Like Joint Destruction

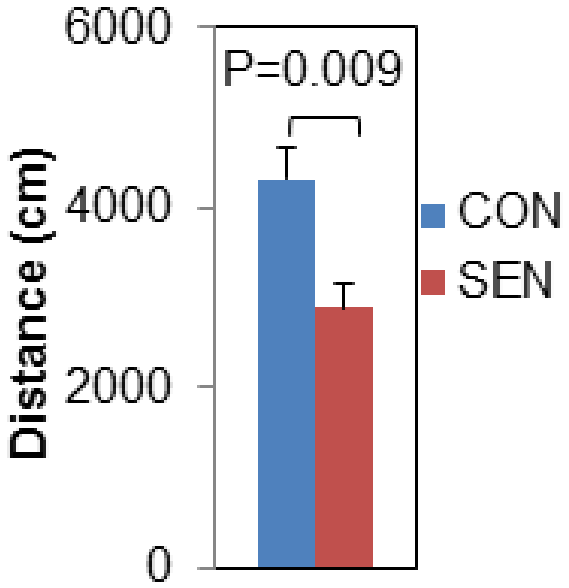


J. Gerontol.
In Press

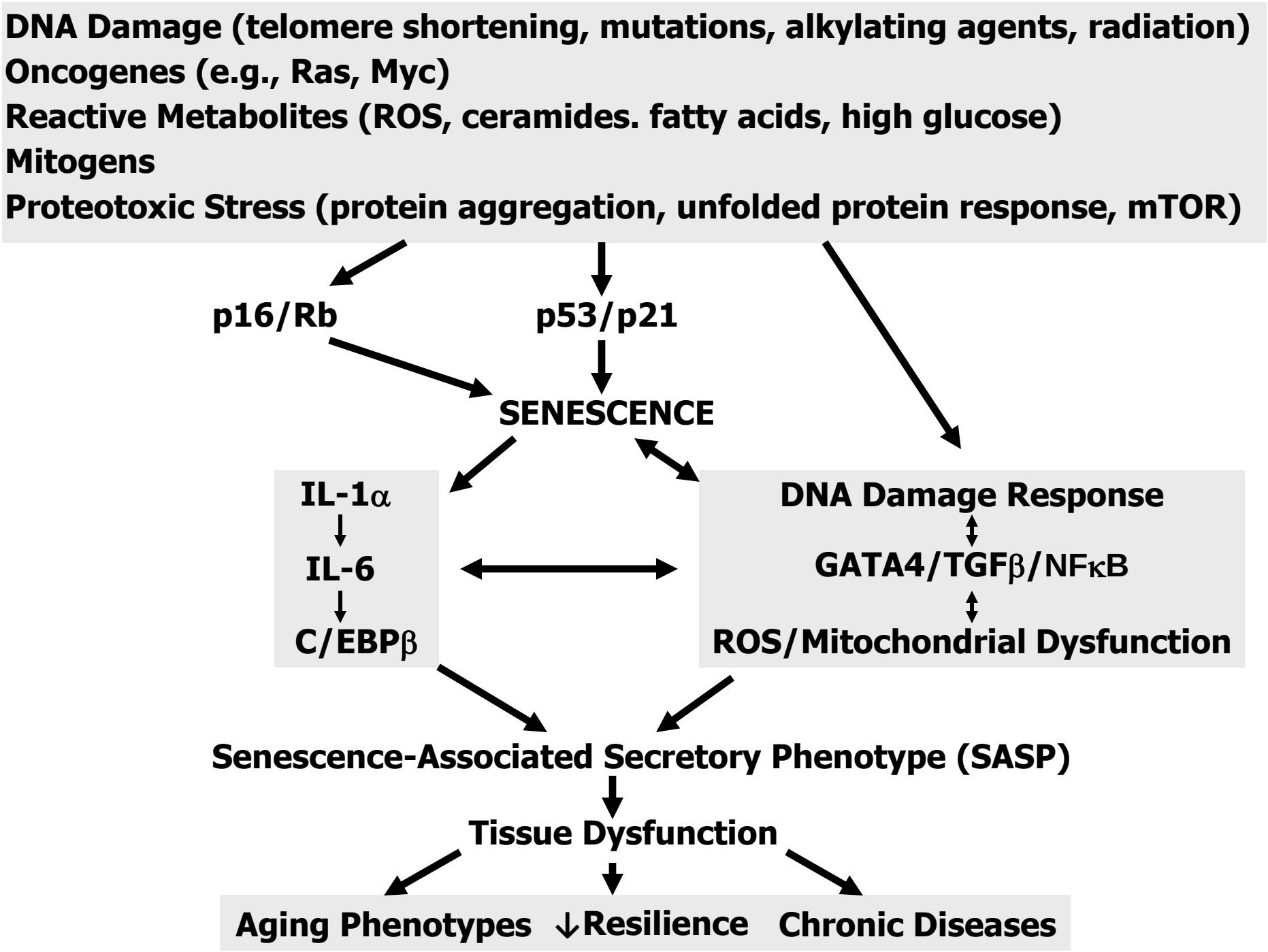
Transplanting Senescent Cells Into Knees Causes Pain and Decreased Mobility



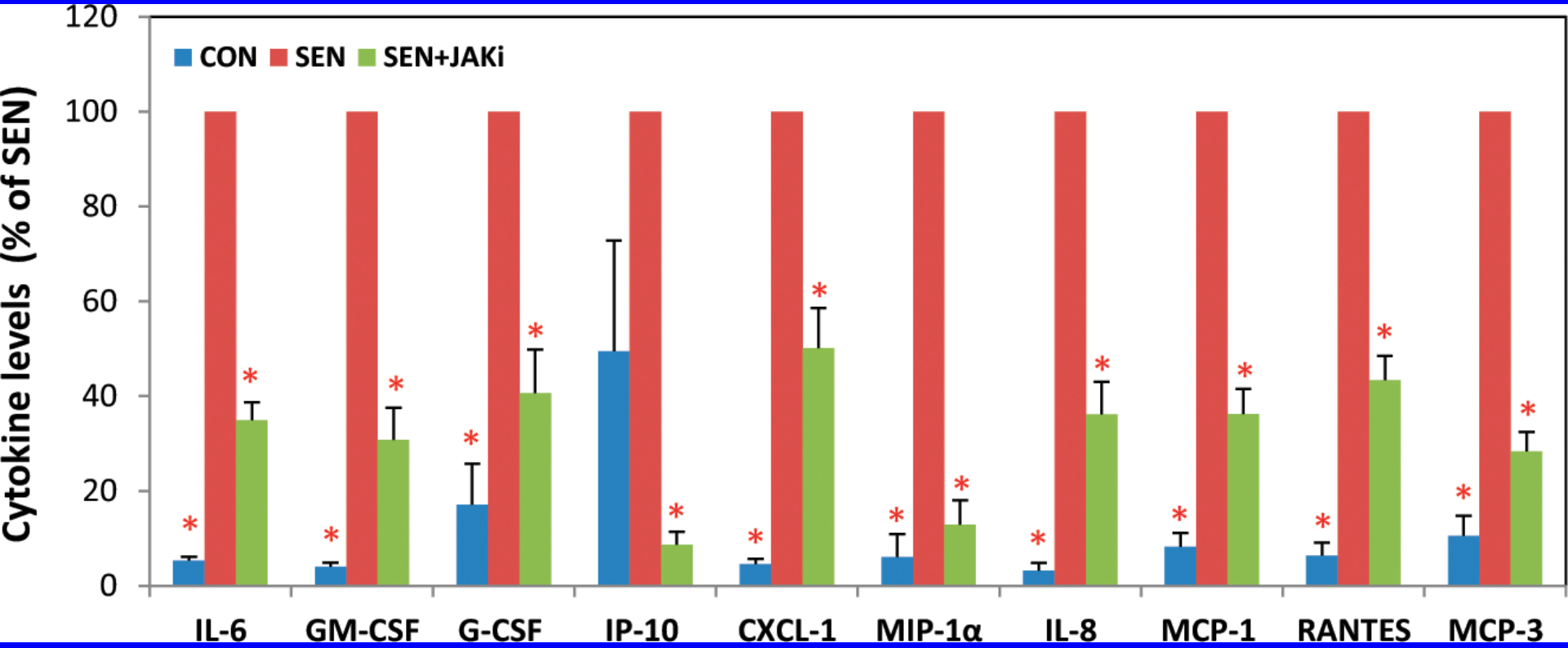




J. Gerontol. In Press


DNA Damage (telomere shortening, mutations, alkylating agents, radiation)
Oncogenes (e.g., Ras, Myc)
Reactive Metabolites (ROS, ceramides. fatty acids, high glucose)
Mitogens
Proteotoxic Stress (protein aggregation, unfolded protein response, mTOR)
p16/Rb
p53/p21
SENESCENCE
IL-1α
IL-6
C/EBPβ
DNA Damage Response
GATA4/TGFβ/NFκB
ROS/Mitochondrial Dysfunction
Senescence-Associated Secretory Phenotype (SASP)
Tissue Dysfunction
Aging Phenotypes
↓Resilience
Chronic Diseases

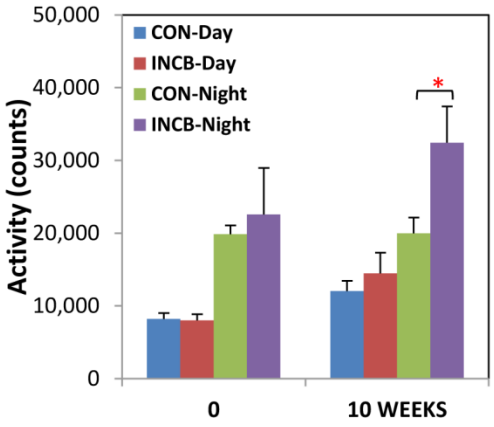
JAK Inhibitors Blunt the SASP in Senescent Human Preadipocytes

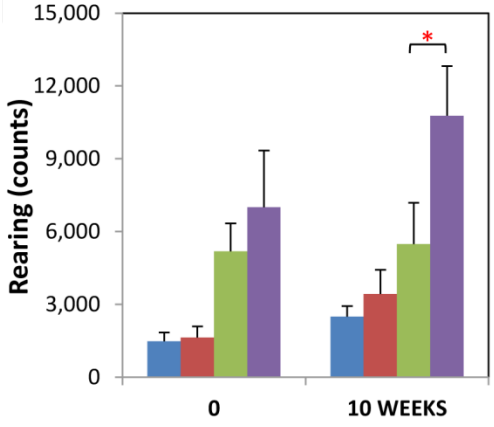


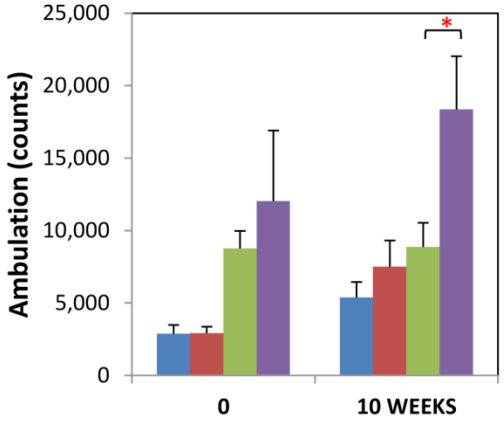
*P < 0.05 compared with SEN; n = 6

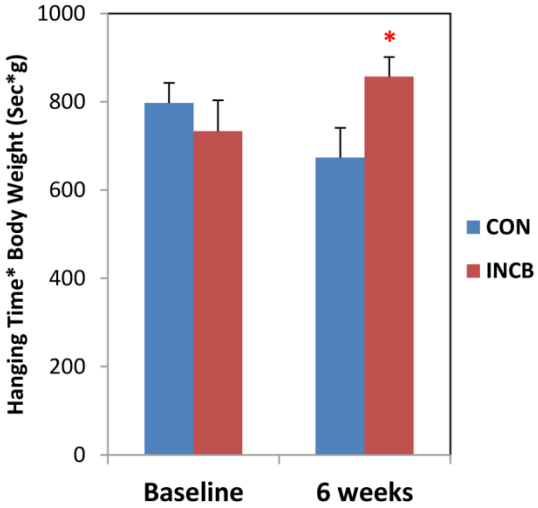
PNAS, 2015

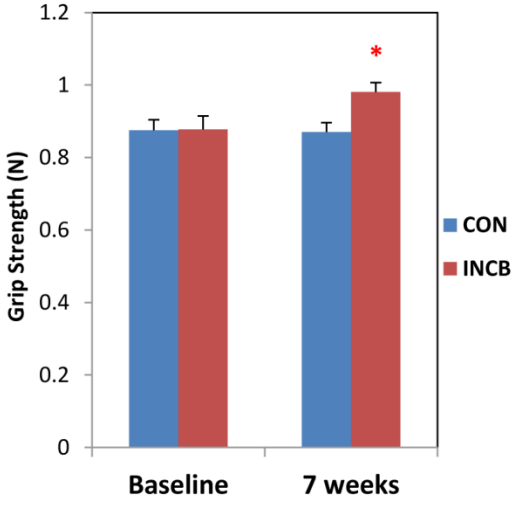
Inhibiting JAK1/2 Alleviates Frailty in Old Mice

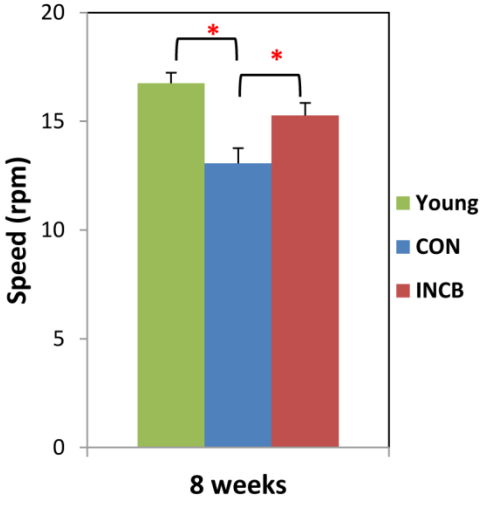












60 mg/Kg ruxolitinib daily gavage for 10 weeks in 24 month old mice

PNAS, 2015

Resilience Clinical Trial: Rapamycin Enhances Flu Vaccine Response in the Elderly

RESEARCH ARTICLE

IMMUNOLOGY

mTOR inhibition improves immune function in the elderly

Joan B. Mannick,[1]* Giuseppe Del Giudice,[2] Maria Lattanzi,[2] Nicholas M. Valiante,[3] Jens Praestgaard,[4] Baisong Huang,[1] Michael A. Lonetto,[1] Holden T. Maecker,[5] John Kovarik,[6] Simon Carson,[7] David J. Glass,[1] Lloyd B. Klickstein[1]

Inhibition of the mammalian target of rapamycin (mTOR) pathway extends life span in all species studied to date, and in mice delays the onset of age-related diseases and comorbidities. However, it is unknown if mTOR inhibition affects aging or its consequences in humans. To begin to assess the effects of mTOR inhibition on human aging-related conditions, we evaluated whether the mTOR inhibitor RAD001 ameliorated immunosenescence (the decline in immune function during aging) in elderly volunteers, as assessed by their response to influenza vaccination. RAD001 enhanced the response to the influenza vaccine by about 20% at doses that were relatively well tolerated. RAD001 also reduced the percentage of CD4 and CD8 T lymphocytes expressing the programmed death-1 (PD-1) receptor, which inhibits T cell signaling and is more highly expressed with age. These results raise the possibility that mTOR inhibition may have beneficial effects on immunosenescence in the elderly.

Sci Transl Med. 2014 Dec 24;6(268):268ra179.

Conclusions

- Were considerable differences in perceptions about developing interventions between the basic biology of aging and clinical communities
- These reduced quite dramatically as the retreat process progressed
- Next steps include:
  1) creating a small translational geroscience network
  2) completing a few small-scale trials
  3) developing infrastructure in a network of a few institutions that want to collaborate with each other
  4) training programs for basic science/clinicians with expertise in translational studies