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

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GEMSSTAR Models and Studies of Aging
Bethesda
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Aging is at the Nexus of Chronic Disease
Incidence of Multimorbidity Increases with Age

Rochester Epidemiology Project
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

1. Description
2. Mechanism
3. Intervention
4. Translation
5. 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

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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
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• 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
Special Issue: Moving Geroscience into Uncharted Waters: Perspective

Barriers to the Preclinical Development of Therapeutics that Target Aging Mechanisms

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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
• 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
Transplanting Senescent Cells Into Knees Causes Pain and Decreased Mobility
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)

Senescence
- Associated Secretory Phenotype (SASP)

Senescence-Associated Secretory Phenotype (SASP)
- Tissue Dysfunction
- Aging Phenotypes ↓ Resilience
- Chronic Diseases

DNA Damage Response
- GATA4/TGFβ/NFκB
- ROS/Mitochondrial Dysfunction

IL-1α
↓
IL-6
↓
C/EBPβ

p16/Rb

p53/p21

SENESCENCE
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
mTOR inhibition improves immune function in the elderly

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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.
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