Interventions: Moving from Preclinical to Phase III Trials: Phases I & II

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GEMSSTAR Models and Studies of Aging

Bethesda

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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
Critical Illness Myopathy

Do We Have Interventions That Work?

Interventions that appear to be effective in mice:

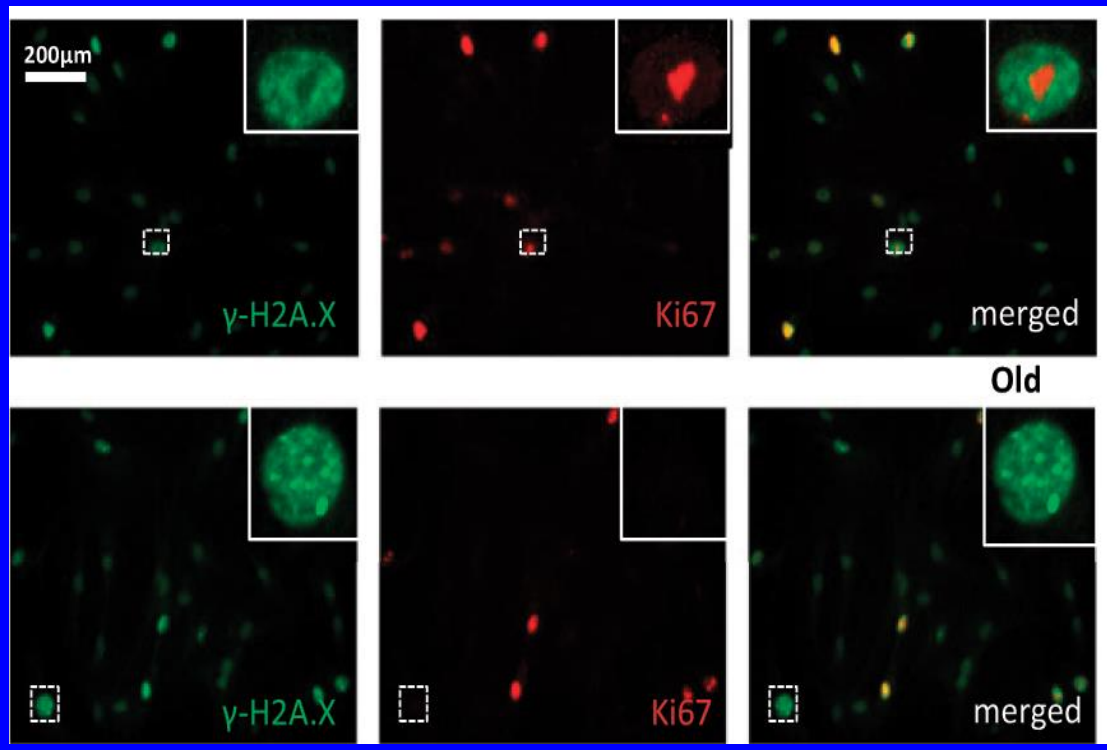
Lifespan and healthspan
- **Caloric restriction**
- **Exercise**
- **Rapamycin**
- **α-estradiol**
- **ACE inhibitors, ARB's**
- **Metformin**
- **Senolytics: Dasatinib, Quercetin, Navitoclax, others**

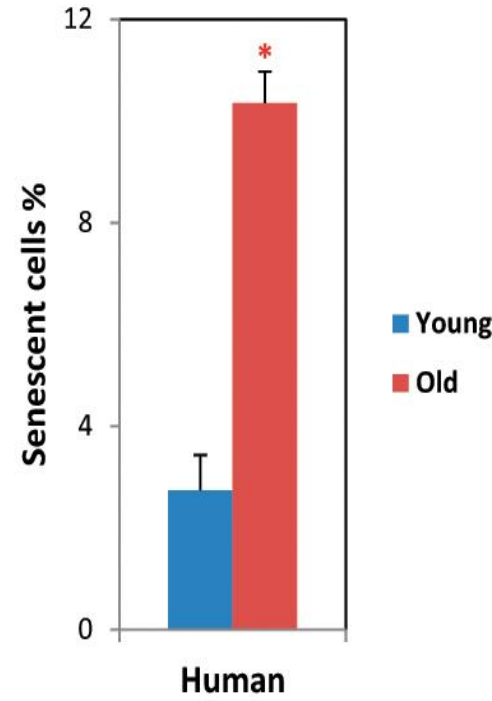
Healthspan
- **Flavonoids/Resveratrol/Sirtuin activators**
- **Senescence-associated secretory phenotype (SASP) inhibitors:**
  - **Ruxolitinib, Rapamycin, Metformin**

Lifespan
- **Acarbose**
- **NDGA (Nordihydroguaiaretic Acid; median lifespan only)**
- **Protandim**
- **Methionine restriction**
- **Aspirin (median lifespan only), salicylic acid, salsalate (?)**

Potential
- **GDF8, GDF11 (?)**
- **Protein aggregation inhibitors**
- **Others (at least 35 potential strategies)**

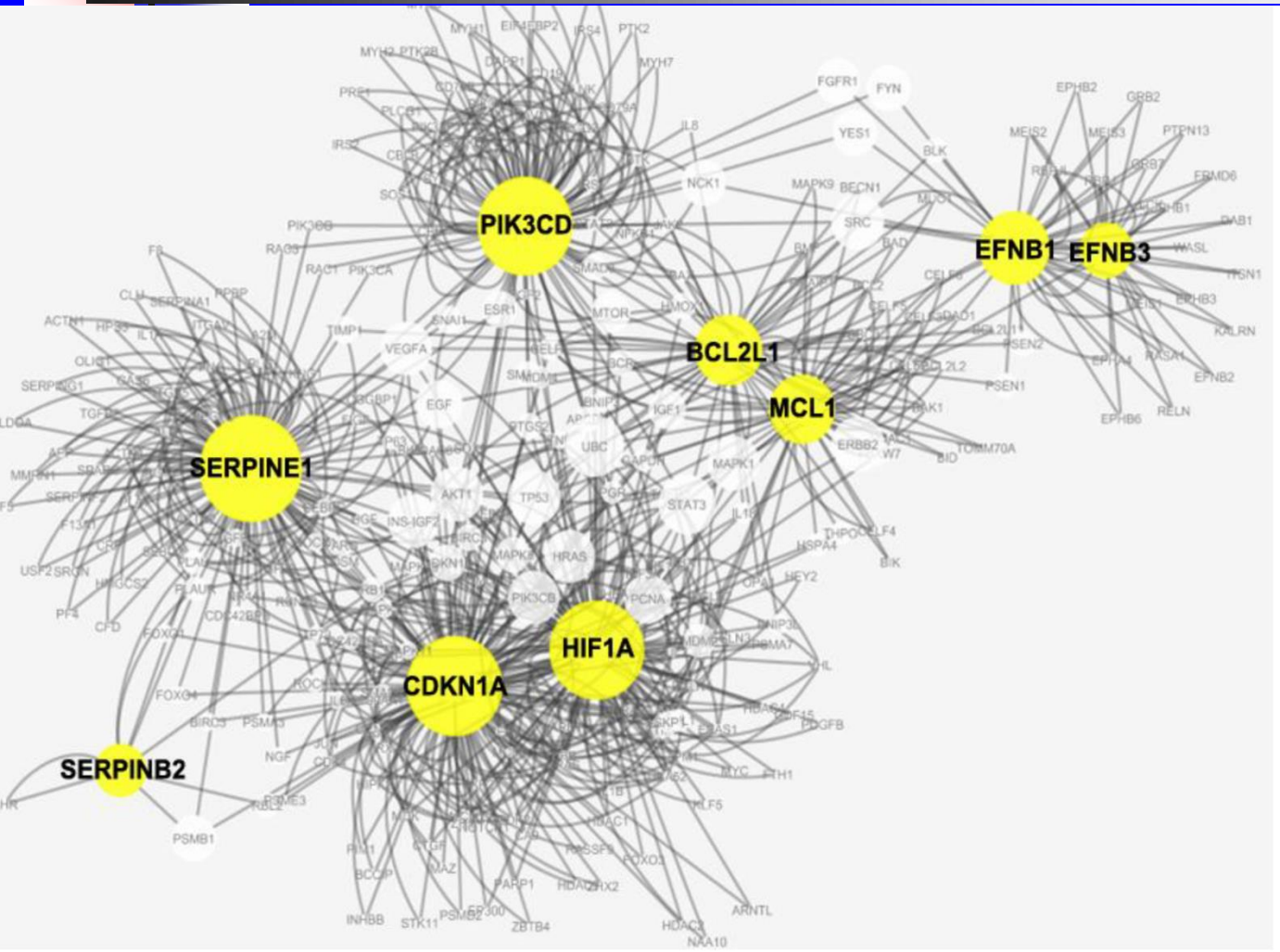
Senescent Preadipocytes Accumulate in Human Adipose Tissue with Aging





4 younger (31 ± 5 y) and 4 older (71 ± 2 y) healthy male volunteers. *P < 0.05

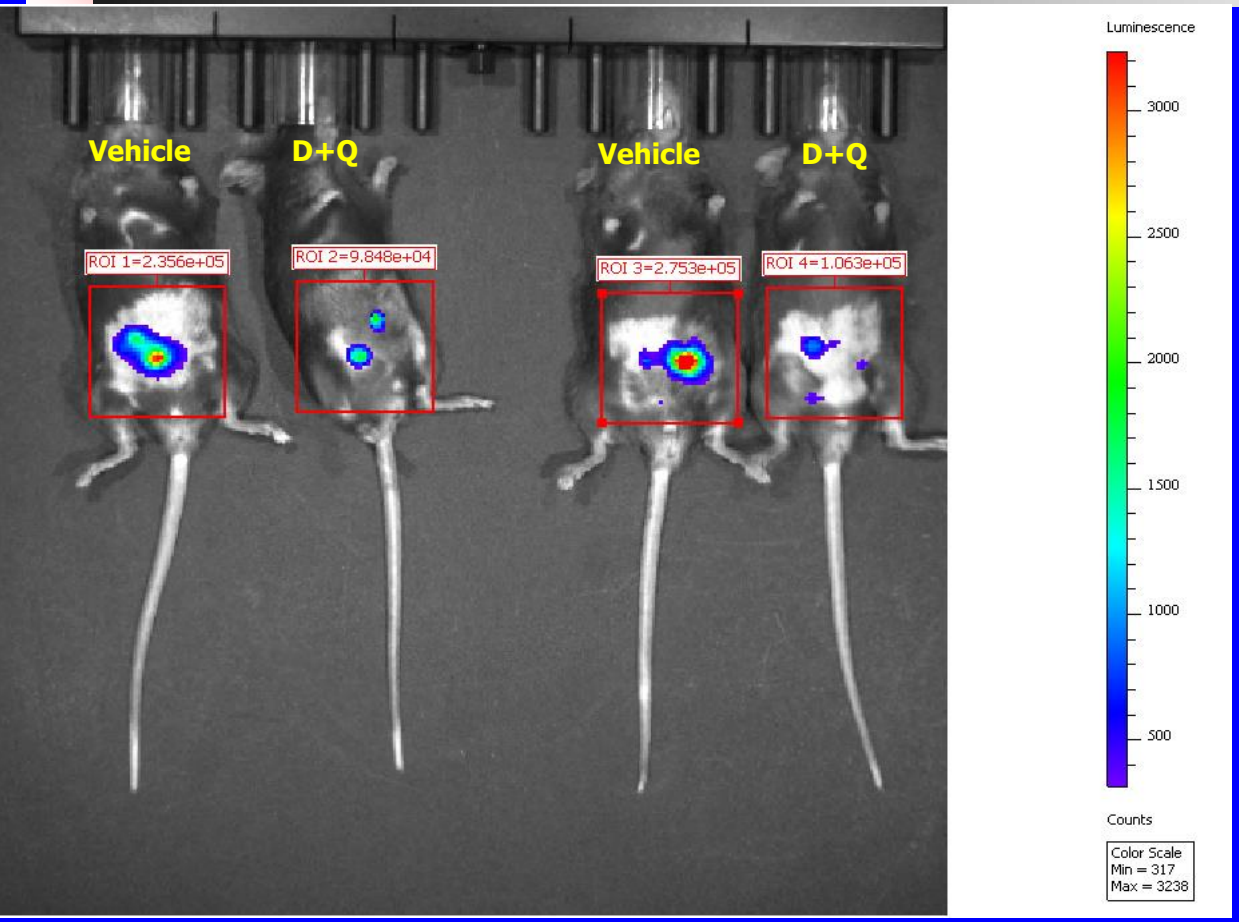
Networks of Anti-Apoptotic Regulators Conferring Resistance to Apoptosis in Senescent Cells



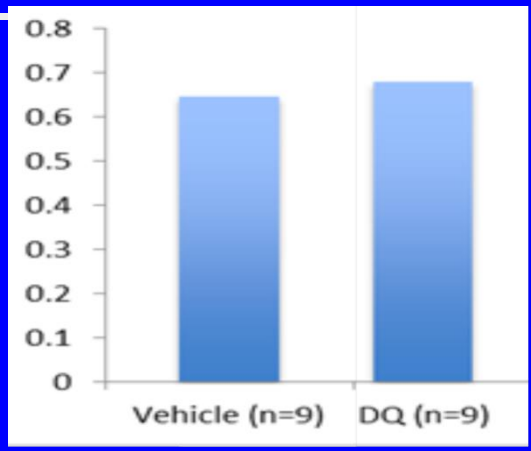
Pathways: Ephrins/ dependence receptors, PI3Kδ/ Akt/ Metabolic, Bcl-2 (Bcl-xl, Bcl-2, Bcl-w), p53/ p21/ serpine (PAI-1&2), HIF-1α

Aging Cell March, 2015

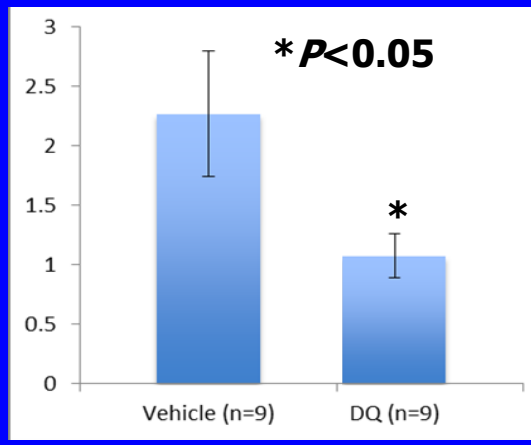
D+Q Clears Transplanted Luciferase-Expressing Senescent Preadipocytes



SFFV Promoter-Luciferase; 10^5 Cells Transplanted/ Mouse

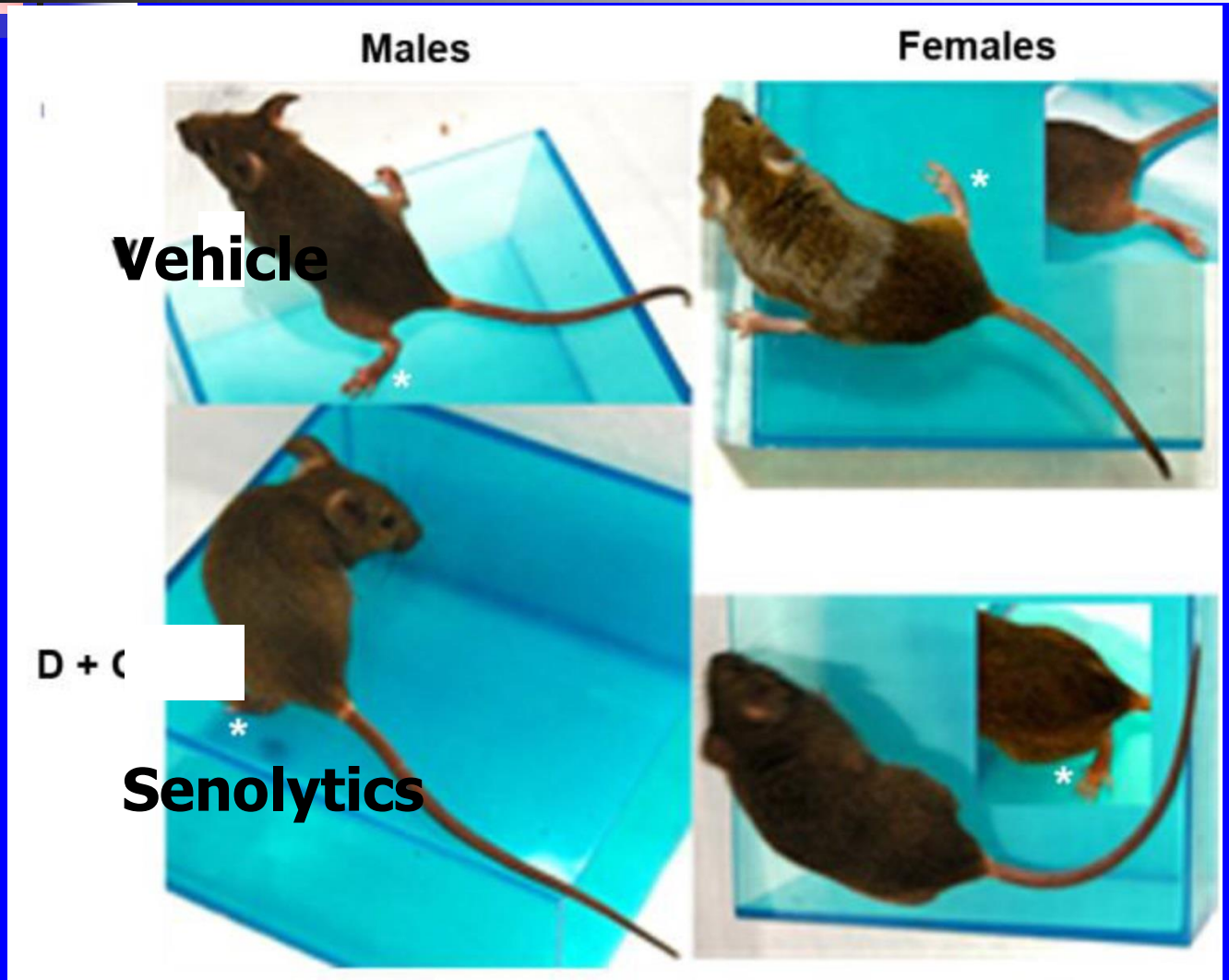


Non-senescent cell-transplanted



Senescent cell- transplanted

Senolytics Delay Neurologic Dysfunction in Progeroid Mice



L Niedernhofer

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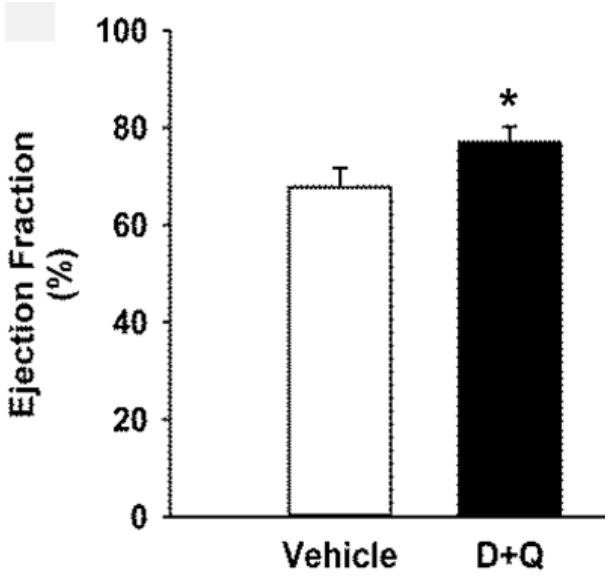
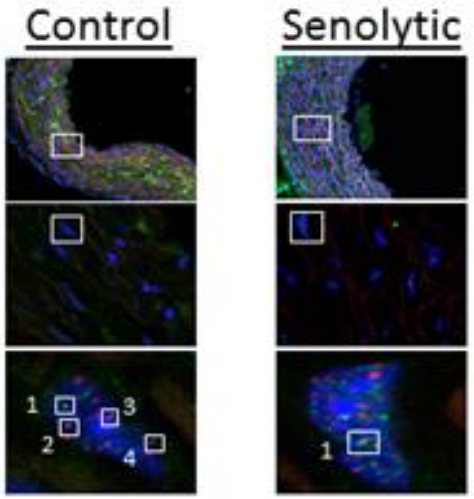
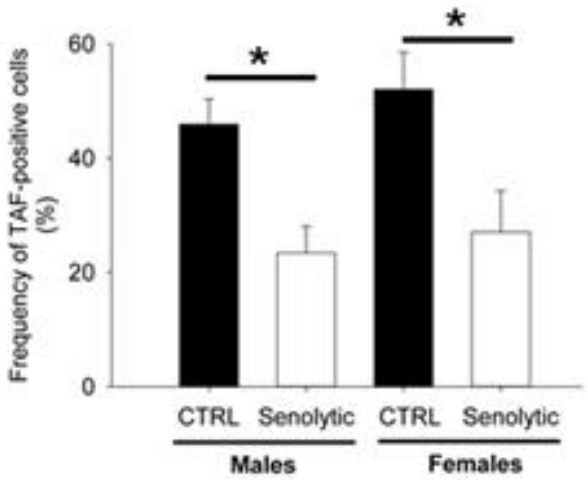
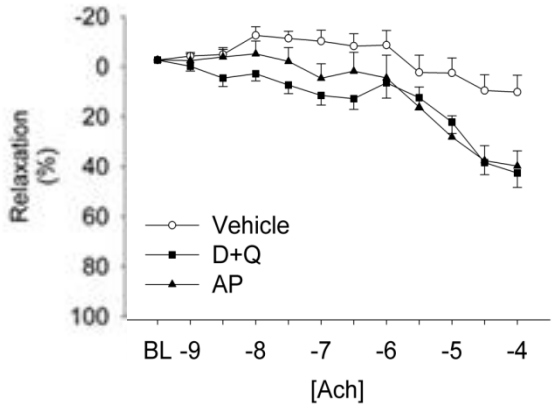
Senolytics Enhance Cardiac and Vascular Function in Old Mice

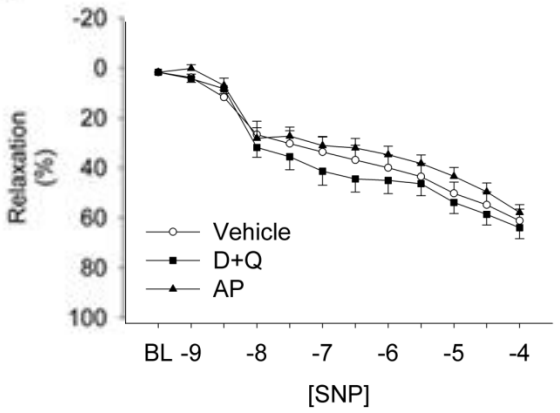


24 month old mice



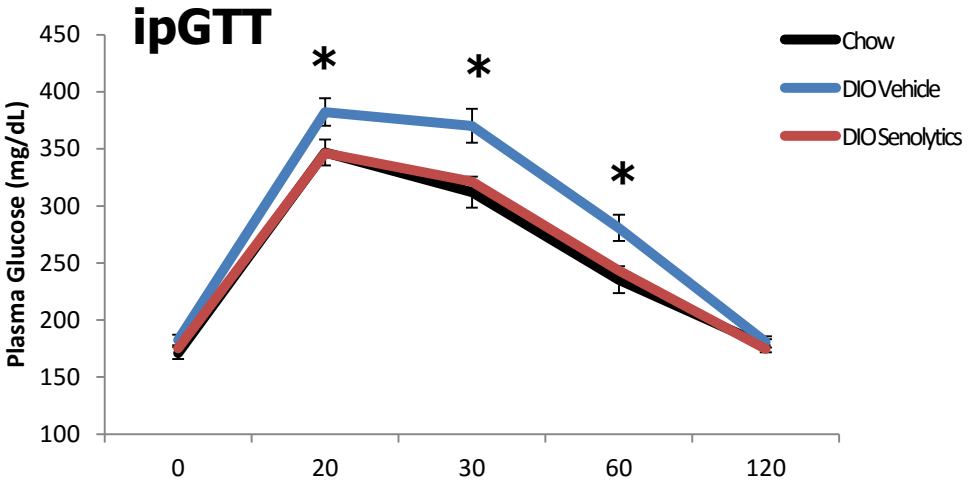


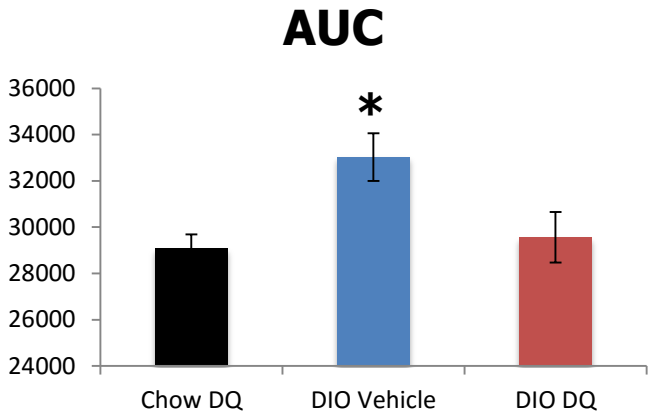


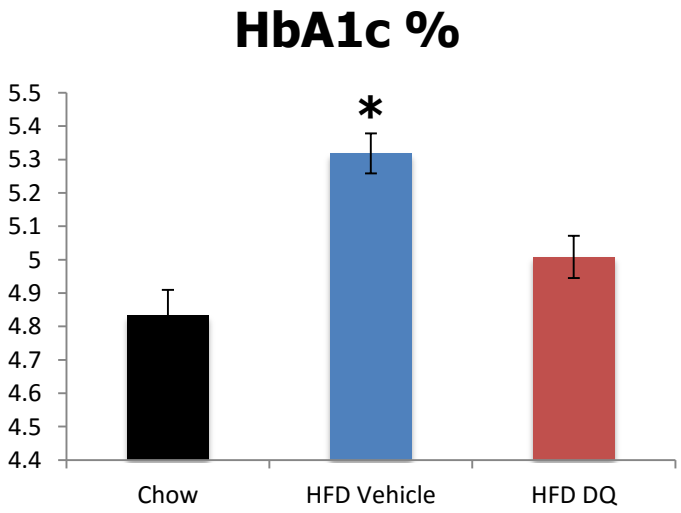


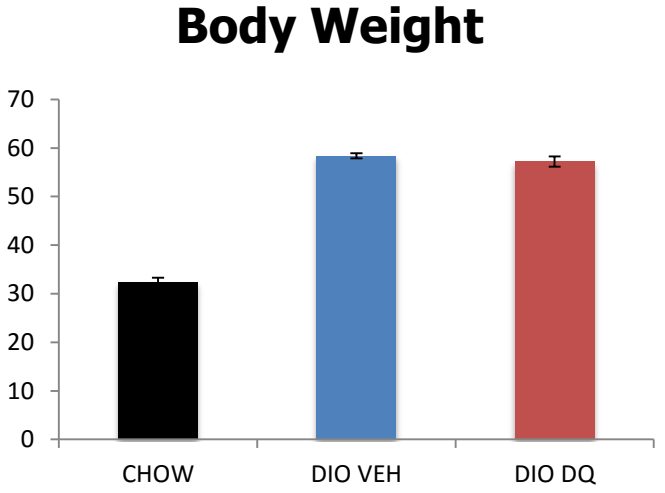
J Miller
Aging Cell March, 2015; Feb., 2016

Senolytics Alleviate Glucose Intolerance in DIO Mice

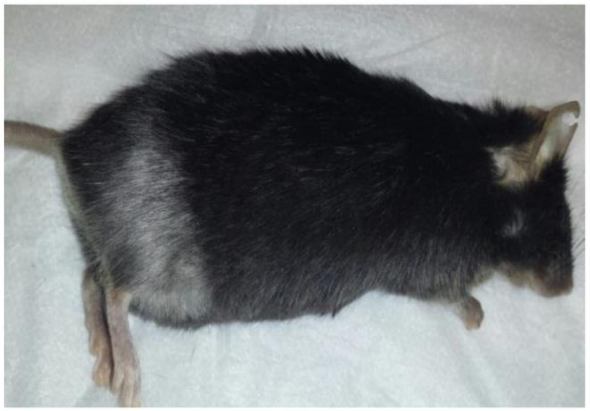


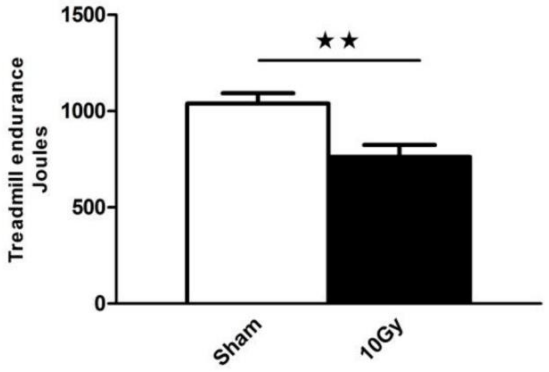






A Single Dose of Senolytics Alleviates Radiation-Induced Gait Disturbance for 7 Months





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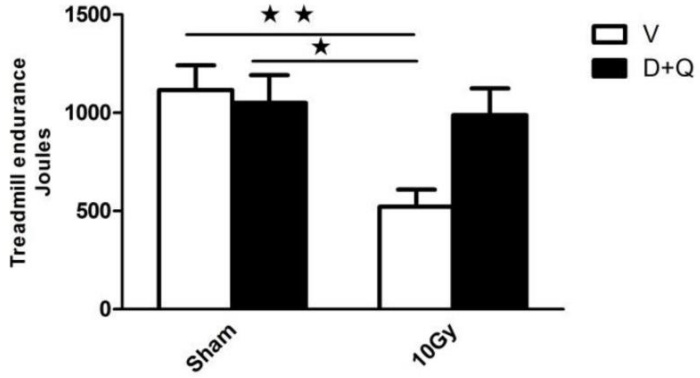

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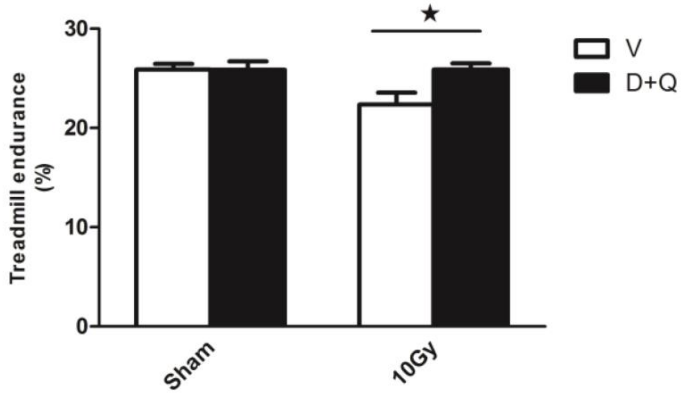


N=6-9 mice/ group;
* *P*<0.05;
** *P*<0.001

Aging Cell March, 2015

Emerging Evidence for Effects of Senescent Cells or Their Removal On:

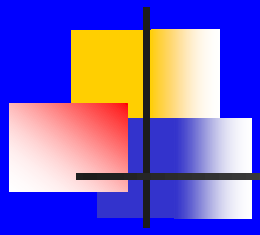
Diabetes/ Obesity
Age-Related Lipodystrophy
Cardiac Dysfunction
Vascular Hyporeactivity/ Calcification
Aortic Lipid Deposits
Frailty/ Sarcopenia
Response to Chemotherapy
Response to Radiation
Cancer
Sequellae of Bone Marrow Transplantation
Cognition/ Alzheimer's/ Parkinson's/ ALS
Renal Dysfunction
Osteoporosis/ Osteoarthritis
COPD/ Idiopathic Pulmonary Fibrosis/ Tobacco
Primary Biliary Cirrhosis
Progerias
Cataracts/ Macular Degeneration/ Glaucoma
HIV
Prostatic Hypertrophy
Skin Disorders
Stem Cell Activation

Animal Models for Testing Interventions

- Translationally relevant animal models (for this particular use; not to the exclusion of animal models to discover aging mechanisms)
- Old animals, frail animals, old animals with geriatric syndromes
- Resilience, including animals exposed to clinically-relevant insults
- Age-related chronic disease animal models
- Animal models for testing mechanism
- Animal models acceptable to the FDA for preclinical registration studies

Clinical Trials Considerations

- Measurable, clinically-relevant outcomes appropriate for older populations
- Symptomatic or imminently at-risk
- Short-term
- Compelling clinical need
- Benefit that justifies risk
- Multiple co-morbidities



Phases

Phase 0: Pharmacodynamics and pharmacokinetics particularly oral bioavailability and half-life

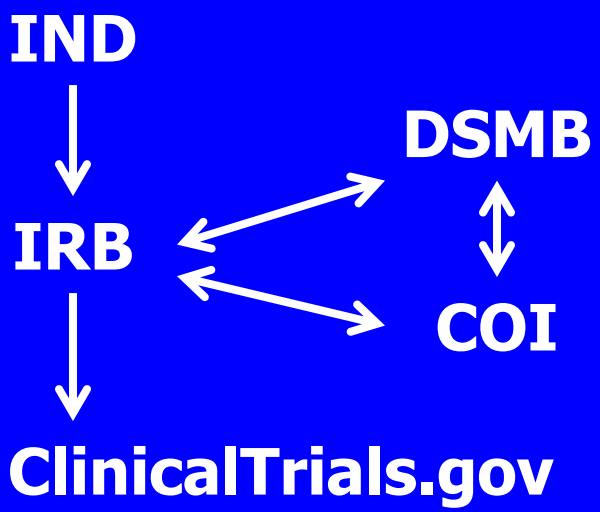
Phase I: Dose-ranging (healthy volunteers)

Phase II: Efficacy and safety

Phase III: Efficacy, effectiveness, and safety

Phase IV: Post-marketing surveillance

Approvals and Oversight



Biomarkers for Studies Targeting Fundamental Aging Processes

Dosing and Pharmacokinetics Biomarkers

Pharmacodynamic Biomarkers

Mechanism Biomarkers

Surrogate Endpoint Biomarkers

Toxicity

- Need to test in age-appropriate animals based on indication
- Reverse antagonistic pleiotropy: Some drugs that are beneficial in older individuals may be harmful in younger individuals (*e.g.*, rapamycin)
- Short *vs.* long-tern toxicity: duration of toxicity studies depends on indication and is longer for new chemical entities

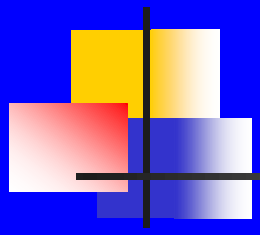
Academic *vs.* Commercial

Academic: new pathways or paradigms natural products, repurposed, off-patent or limited patent life

Commercial: lower financial risk or high potential return, medicinal chemical refinements of effective candidates that are patentable

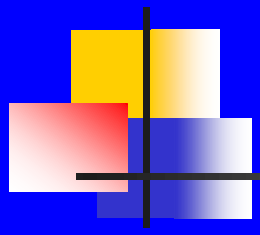
IND

- Pre-clinical effectiveness data
- (Mechanism)
- Manufacturing (certificates for all reagents, assays for compound at each step, assays for contaminants, GMP)
- Contracts with suppliers
- Safety data
- Toxicology
- ADME
- Trial protocol



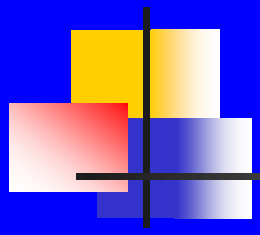
FDA Inspection

- Very likely if a new class, indication, or new chemical entity
- Unannounced
- Actually inspect labs, equipment, records
- Wise to do mock inspections



IRB

Benefits and Risks
Scientific Justification
Statistical Power
IND
DSMB
Consent
SOP
Insurance
Data Security
Personnel
Conflicts of Interest
Means of Contact
Reimbursement

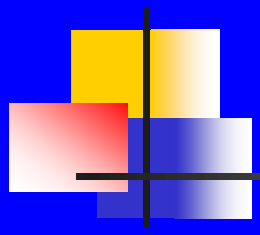


Phase IA

- New chemical entities or natural products where dosing and safety data are limited
- Currently, dose-ranging testing of drug on healthy volunteers, but need to consider conducting in older subjects with multimorbidity
- Often sub-therapeutic, but with ascending doses
- A small number of participants, usually three, are entered sequentially at a particular dose, and if safe, progress with another 3 at the next dose
- Determines whether drug is safe before checking for efficacy

Phase IB

- Pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability
- Subjects receive multiple low doses, while samples (blood and other fluids) are collected at various times to acquire information on how the drug is processed
- We need to consider doing these studies in older populations
- Dose is subsequently escalated in further groups, up to a predetermined level



Food Effect

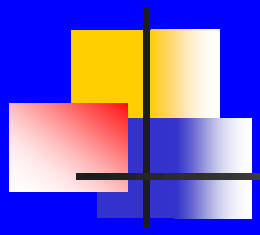
- Short trial to investigate differences in absorption caused by eating before the drug is given
- Usually a crossover study, with volunteers being given identical doses of the drug while fasted and after fed

Phase IIA

- Evaluate whether the drug has any biological activity or effect
- Phase IIA is specifically designed to assess dosing requirements

Phase IIB

- Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s))
- Open label or randomized. Randomized Phase II trials have far fewer subjects than Phase III trials
- Phase IIA and B are performed in larger groups (100-300)
- Some trials combine Phases I and II, and test both efficacy and toxicity



Efficacy *vs.* Effectiveness

- **Efficacy: whether the drug given in the specific manner described in the study is able to influence an outcome of interest (*e.g.*, tumor size) in the chosen population (*e.g.*, cancer patients with no other ongoing diseases)**

- **Effectiveness: whether a treatment will influence the disease. In an effectiveness study, subjects are treated as they would be when the treatment is prescribed in actual practice**

Clinical Scenarios for Testing Agents That Target Aging Processes (*e.g.*, Cellular Senescence or the SASP)

Simultaneous Alleviation of Co-Morbidities

- 3 or more of: diabetes, atherosclerosis, hypertension, MCI, sarcopenia, osteoarthritis, etc.
- Delay in 2nd or later co-morbidities (TAME)

"Accelerated Aging" Conditions

- Childhood cancer survivors
- Bone marrow transplant survivors
- Progeroid syndromes
- Diabetes due to obesity
- HIV (dementia, frailty)

Conditions with Localized Cellular Senescence

- Osteoarthritis
- Fracture non-union
- Atherosclerotic plaques
- Radiation
- Idiopathic pulmonary fibrosis
- COPD/ tobacco
- Glaucoma

J. Clin. Invest. 123:966-972, 2013
J. Gerontol. 48:1-5, 2013
Exp. Gerontol. 2014

Clinical Scenarios for Testing Agents That Target Aging Processes (*e.g.*, Cellular Senescence or the SASP)

Otherwise Fatal Conditions

- Idiopathic pulmonary fibrosis
- Primary biliary cirrhosis
- Cancers
- HIV dementia

Resilience/ Clinical Stresses in Pre-frail Subjects

- Chemotherapy
- Radiation
- Elective surgery
- Bone marrow transplantation
- Rehabilitation after MI
- Immunization
- Recovery after pneumonia

Frailty

- Slow gait/ decreased strength/ sarcopenia
- Loss of independence in moderately frail subjects

J. Clin. Invest. 123:966-972, 2013
J. Gerontol. 48:1-5, 2013
Exp. Gerontol. 2014

Conclusions

- Clinical trials could lead to provision of human tissues across the age range and before and after interventions to basic biology of aging labs
- Exciting new agents that target fundamental aging mechanisms alleviate frailty and enhance lifespan and healthspan in mice
- These could lead to clinical interventions in humans – if pre-clinical studies demonstrate effectiveness and low toxicity and if we can establish the right clinical study approaches, obtain resources, and prepare personnel