WEBINAR:

Inflammation and Aging
Tuesday, October 1, 2019
2-3pm ET (11am-12pm PT)

Luigi Ferrucci, MD, PhD
National Institute on Aging
NORMAL INFLAMMATORY REACTION AND CHRONIC INFLAMMATION

Normal Inflammatory Reaction

Dysregulated Chronic Inflammation

IL-6
CRP

IL-6
CRP

Stress/Infection
Response
Healing

Time
The Mild Pro-Inflammatory State of Aging

Periodontal disease associates with higher brain amyloid load in normal elderly


High CAL3

Low CAL3

Apo-E4 Carriers

High CAL3

Low CAL3

Apo-E4 Non Carriers

Standard Uptake Value Ratio
Interleukin-6 Serum Levels Predict Incident Disability
A Case Cohort Study Nested in the EPESE

Ferrucci et al. JAGS 1999;47: 639-44
IL-6 is a Cross-Sectional and Longitudinal Predictor of Comorbidity

- High baseline IL-6 and faster increase of IL-6 Over Time
- High baseline IL6
- REFERENCE

Potential Causes (top) and Consequences (bottom) of Inflammageing.
Inflammation, Aging, and Senolytics

James L. Kirkland, M.D., Ph.D.,
Noaber Foundation Professor of Aging Research Director, Mayo Clinic Kogod Center on Aging

Webinar: Inflammation and Aging
Nathan Shock Centers of Excellence
AFAR/ NIH
October 1, 2019
Consequences of Fundamental Aging Processes

**Fundamental Aging Mechanisms**

- Inflammation (chronic, low-grade, sterile), Fibrosis
- Macromolecular/ Organelle Dysfunction (DNA, protein aggregation, autophagy, AGE’s, lipotoxicity, mitochondria)
- Stem Cell and Progenitor Dysfunction
- **Cellular Senescence**

**Phenotypes**

- Geriatric Syndromes: Sarcopenia, Frailty, Immobility, MCI
- Chronic Diseases: Dementias, Cancers, Atherosclerosis, Diabetes, Osteoporosis, Osteoarthritis, Renal dysfunction, Blindness, Chronic lung disease
- Decreased Resilience: Infections, Delirium, Delayed wound healing, Slow rehabilitation, Chemotherapy toxicity, ICU Care
Cellular Senescence

Senescence Associated β-Galactosidase

γH2A.X
25th passage human abdominal subcutaneous preadipocytes
Senescent Cells Accumulate in Human Adipose Tissue with Aging

4 younger (31 ± 5 y) and 4 older (71 ± 2 y) healthy male volunteers. *P < 0.05
Transplanting Senescent Cells Causes Physical Dysfunction and Decreases Survival

Xu et al., Nature Medicine, 2018
D+Q Clears Transplanted Luciferase-Expressing Senescent Preadipocytes

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

Xu et al., Nature Medicine, 2018

Non-senescent cell-transplanted

* P<0.05

Senescent cell-transplanted
Diabetes is Alleviated in Obese Mice Treated with Senolytics

Lean
Obese
Obese D+Q

ipGTT
Palmer et al., Aging Cell, 2019
Emerging Evidence for Benefits of Senolytics On:

- Diabetes/ Obesity
- Age-Related Lipodystrophy
- Cardiac Dysfunction
- Vascular Hyporeactivity/ Calcification/ AV Fistulae
- Frailty/ Sarcopenia
- Response to Chemotherapy
- Response to Radiation
- Cancer
- Sequellae of Bone Marrow Transplantation
- Sequellae of Organ Transplantation
- Cognition/ Alzheimer’s/ Parkinson’s/ ALS/ Anxiety
- Renal Dysfunction
- Osteoporosis/ Osteoarthritis
- COPD/ Idiopathic Pulmonary Fibrosis/ Tobacco
- Hepatic Steatosis
- Liver Cirrhosis
- Primary Biliary Cirrhosis
- Progerias
- Cataracts/ Macular Degeneration/ Glaucoma
- Prostatic Hypertrophy
- Skin Disorders
- Stem Cell Activation
- Lifespan
Senolytics Alleviate Physical Dysfunction in Old Mice

Xu et al., Nature Medicine, 2018
Abdominal subcutaneous adipose biopsies at baseline (BL) and 11 days after the last dose (PT) of a 3 day course of D+Q; N=9 subjects

ClinicalTrials.gov identifier: NCT02848131
First-in-Human Trial of Senolytics: D+Q for Idiopathic Pulmonary Fibrosis

- No severe adverse events
- 9 doses/ 3 wks
- Functional measures 1 wk after last dose

 Justice et al., eBioMed., 2019
Conclusions

• The target of senolytics is senescent cells, not a single molecule or biochemical pathway

• Senolytics alleviate progenitor dysfunction

• Senolytics attenuate tissue inflammation

• Intermittent treatment may be effective

• Senolytics delay or alleviate multiple chronic diseases and enhance healthspan and lifespan in mice

• These agents could lead to interventions for humans that delay, prevent, or alleviate senescence- and age-related conditions – if clinical trials continue to demonstrate effectiveness and low toxicity
Dawn Bowdish, Ph.D.
Associate Professor of Pathology and Molecular Medicine, McMaster University
The microbiota and age-associated inflammation.

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Immune education
Metchnikov’s theory of aging
Does the composition of the aging microbiota influence age associated inflammation?

Take care of your microbiome (it may be key to a long, healthy life)
Life expectancy in **richer** neighbourhoods

**men**: 81

**women**: 84

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In **poorer** neighbourhoods

**men**: 76

**women**: 82

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- Intestinal permeability
- Low Fat Diet = low LPS
- Increased permeability
- **(Different) Stress**, Exercise, Safe jobs, safe environment = Less inflammation

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- Intestinal permeability
- High Fat Diet = LPS
- Increased Permeability
- Chronic Disease
- Chronic Stress, Inactivity, Smoking, Environmental exposures = Systemic inflammation

- Low Fibre, High Fat = Microbial dysbiosis