INFLAMMATION AND AGING

NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

WEBINAR

October 1, 2019

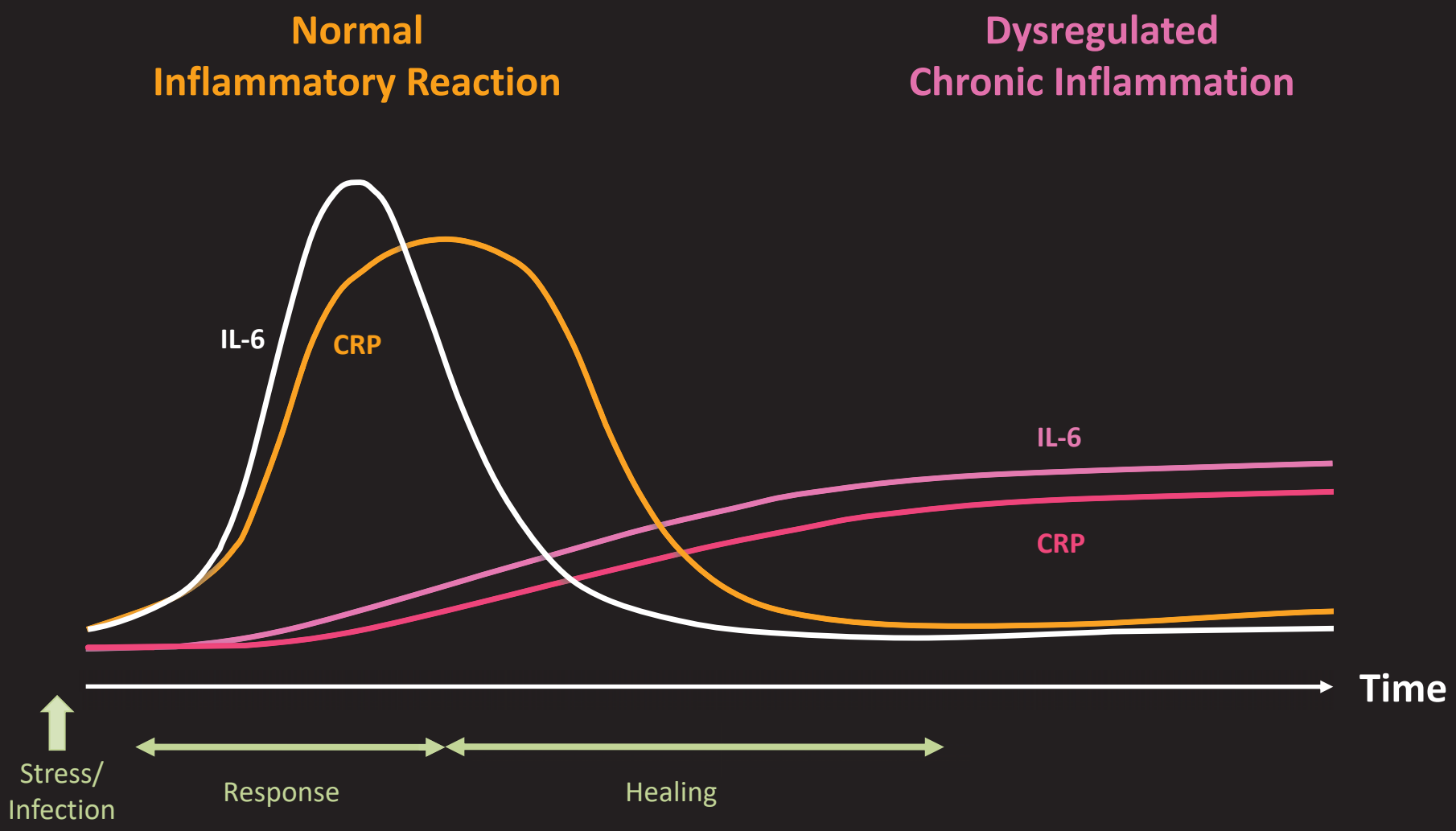
NATHAN SHOCK CENTERS
OF EXCELLENCE IN THE
BASIC BIOLOGY OF AGING

WEBINAR:

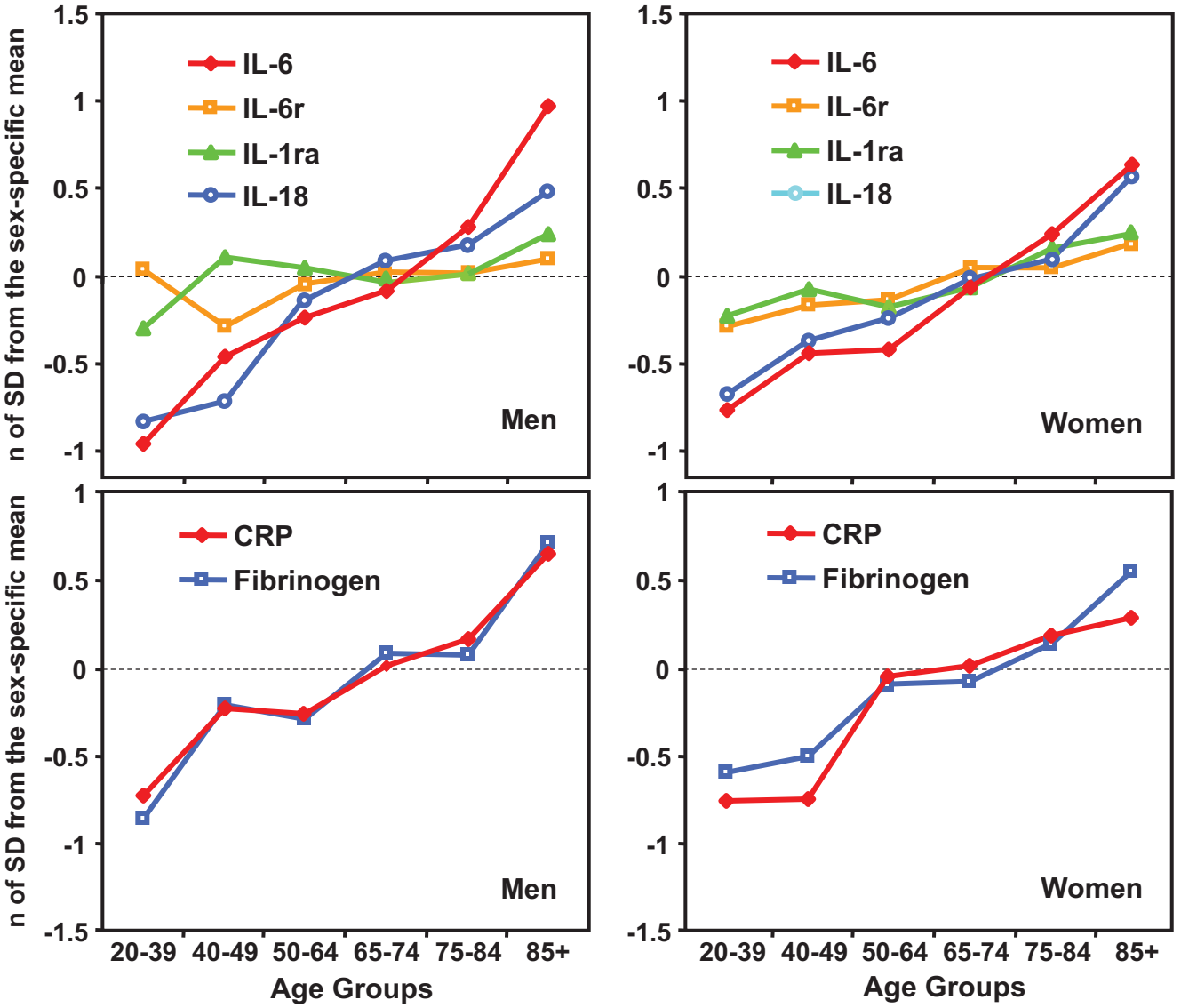
Inflammation and Aging
Tuesday, October 1, 2019
2-3pm ET (11am-12pm PT)

Luigi Ferrucci, MD, PhD
National Institute on Aging

Normal Inflammatory Reaction and Chronic Inflammation



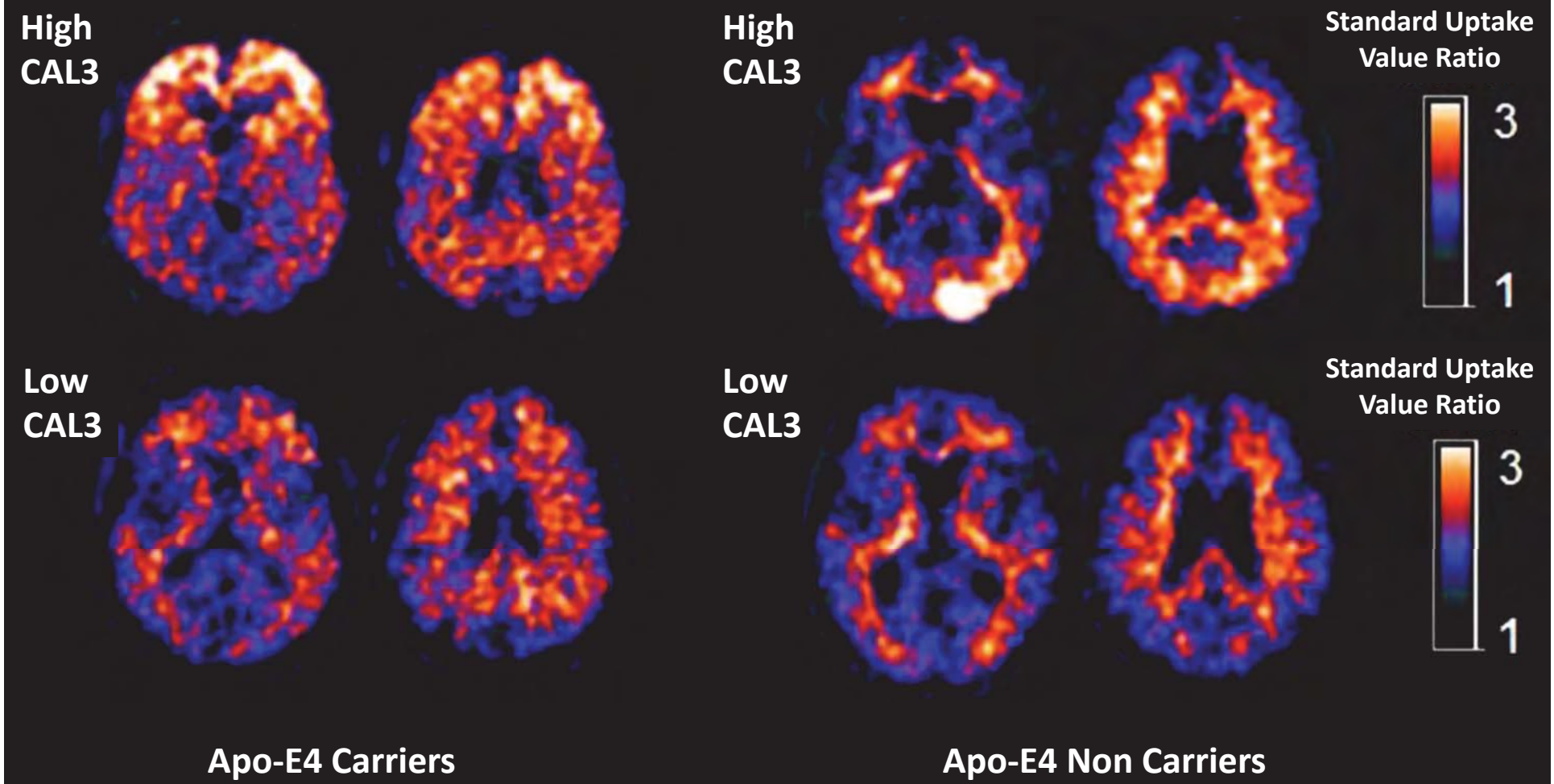
The Mild Pro-Inflammatory State of Aging



Ferrucci L et al. Blood. 2005;105:2294-9.

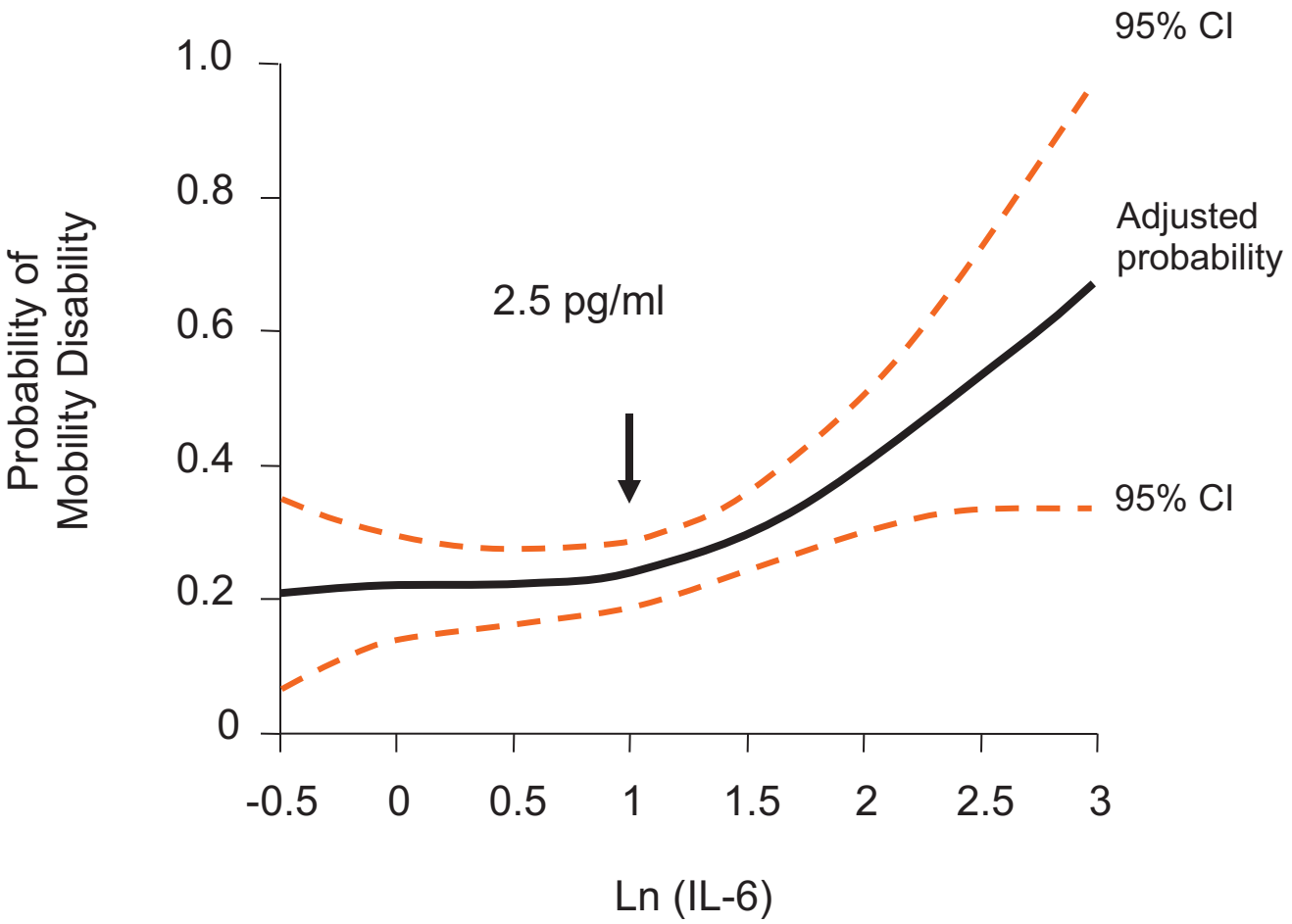
Periodontal disease associates with higher brain amyloid load in normal elderly

Angela R. Kamer et al. Neurobiol Aging. 2015 February ; 36(2): 627–633



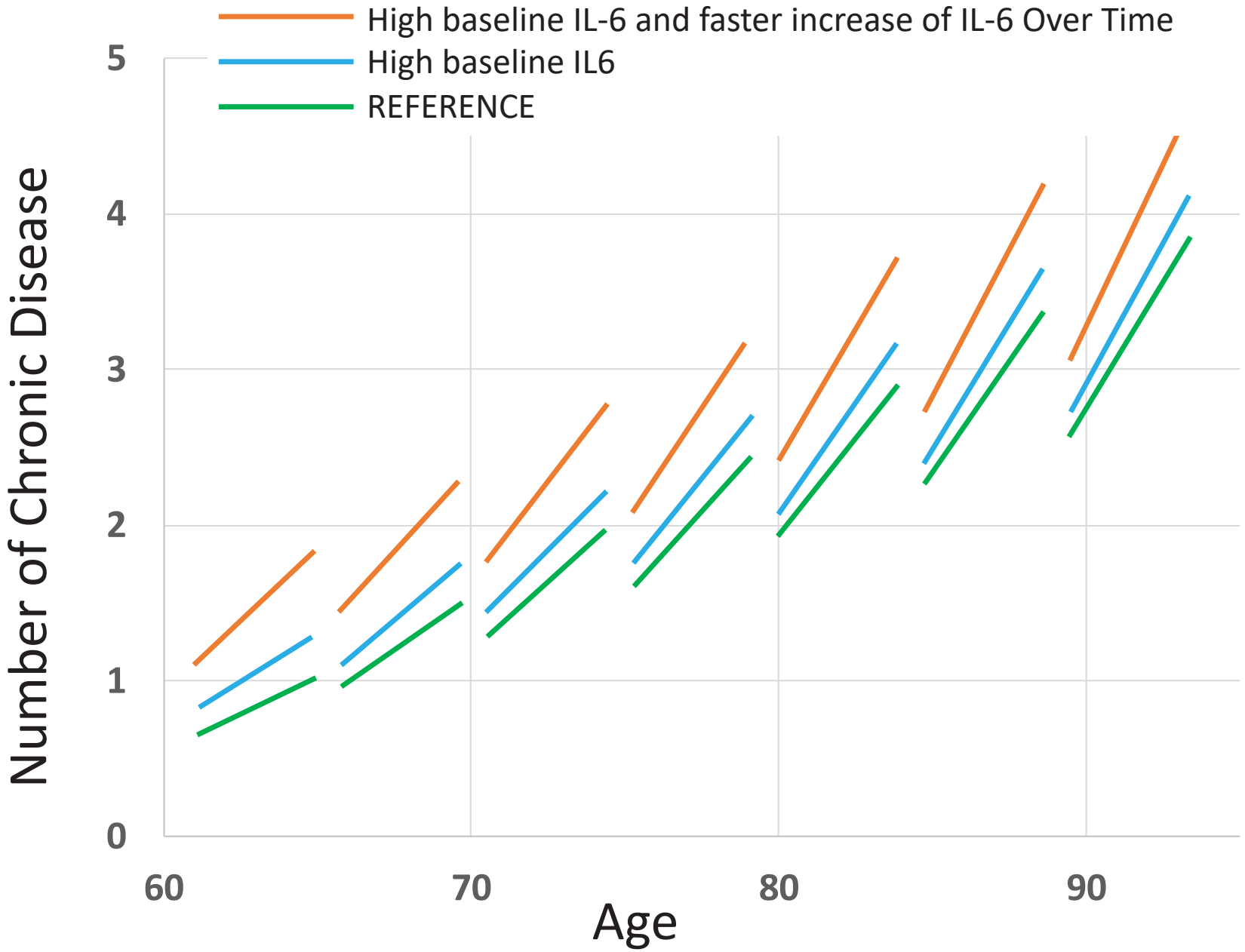
Interleukin-6 Serum Levels Predict Incident Disability

A Case Cohort Study Nested in the EPESE



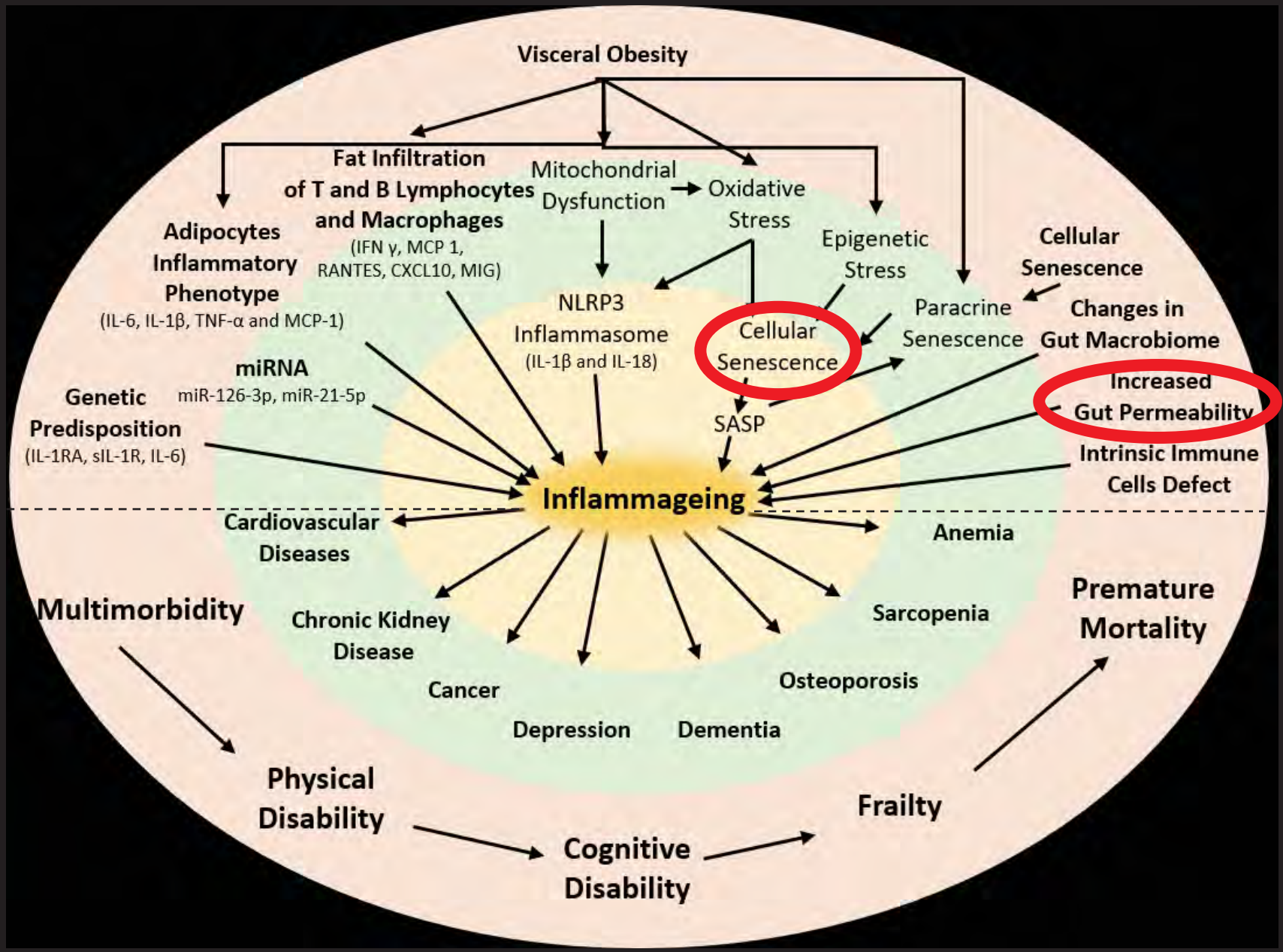
Ferrucci et al. *JAGS 1999;47: 639-44*

IL-6 is a Cross-Sectional and Longitudinal Predictor of Comorbidity



Fabbri E et al. J Gerontol A Biol Sci Med Sci. 2015 Jan;70(1):63-70. doi: 10.1093/gerona/glu127.

Potential Causes (top) and Consequences (bottom) of Inflammaging.



Ferrucci L, Fabbri E. Nat Rev Cardiol. 2018 Sep;15(9):505-522

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

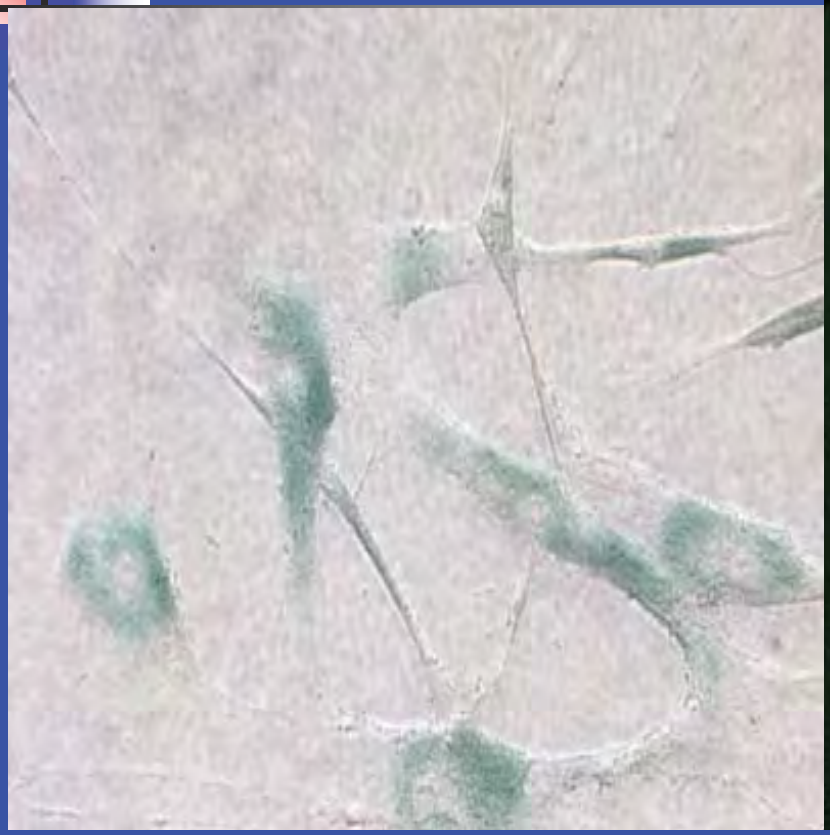
Phenotypes

Geriatric Syndromes:
Sarcopenia
Frailty
Immobility
MCI

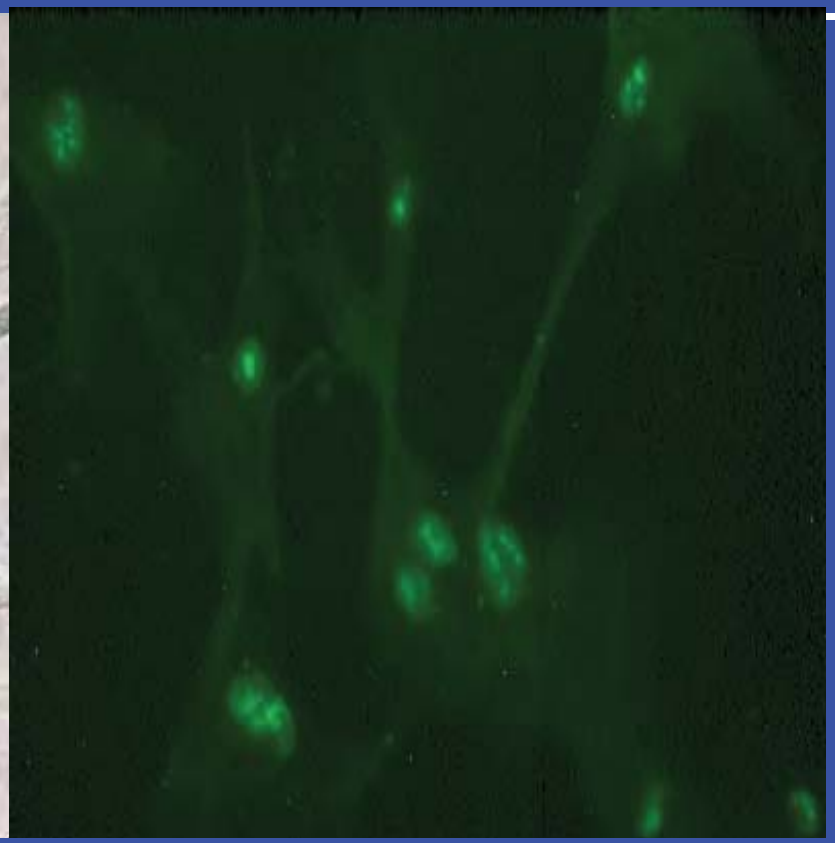
Chronic Diseases:
Dementias
Cancers
Atherosclerosis
Diabetes
Osteoporosis
Osteoarthritis
Renal dysfunction
Blindness
Chronic lung disease

Decreased Resilience:
Infections
Delirium
Delayed wound healing
Slow rehabilitation
Chemotherapy toxicity
ICU Care

Cellular Senescence



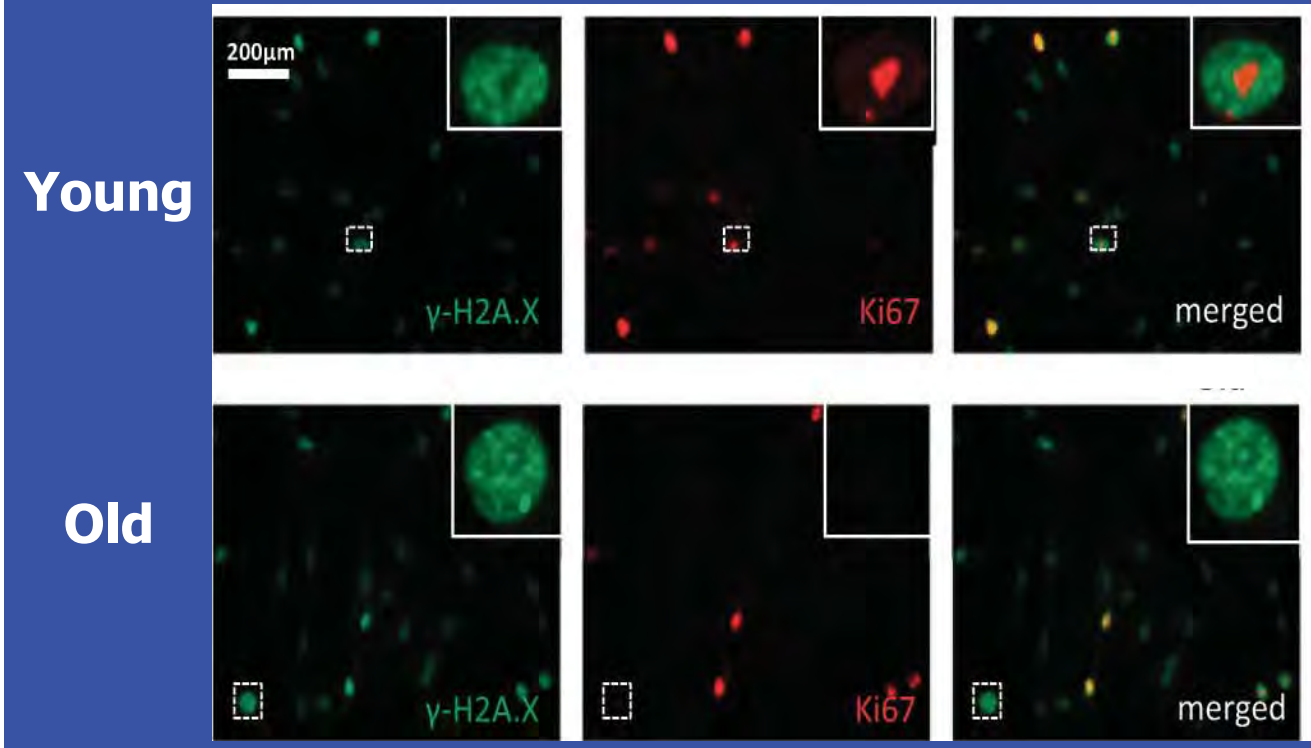
Senescence Associated β-Galactosidase

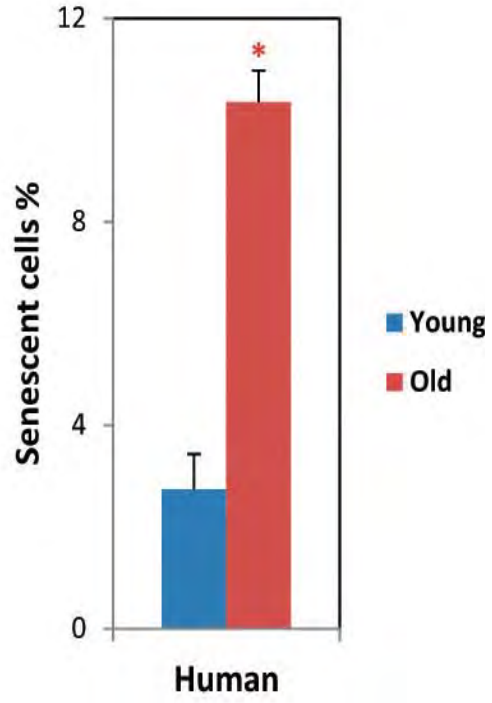


γH2A.X

25th passage human abdominal subcutaneous preadipocytes

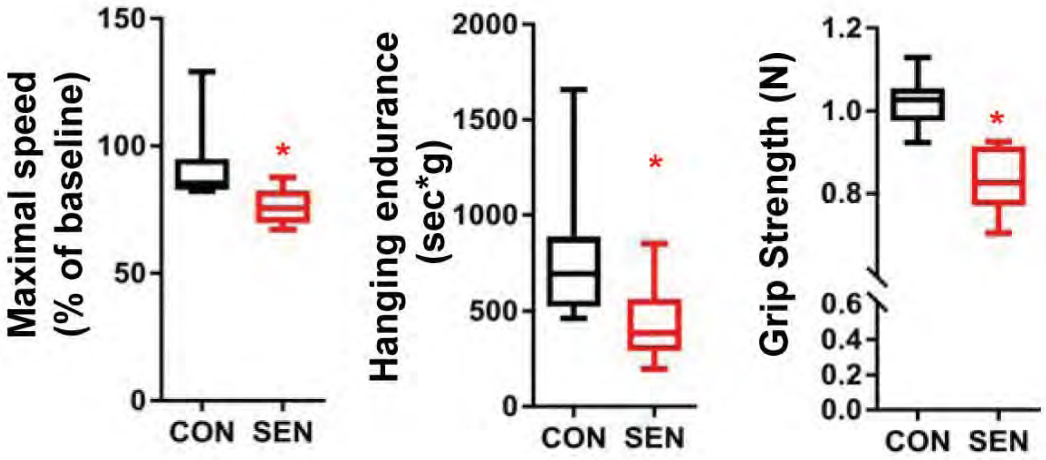
Senescent Cells Accumulate in Human Adipose Tissue with Aging

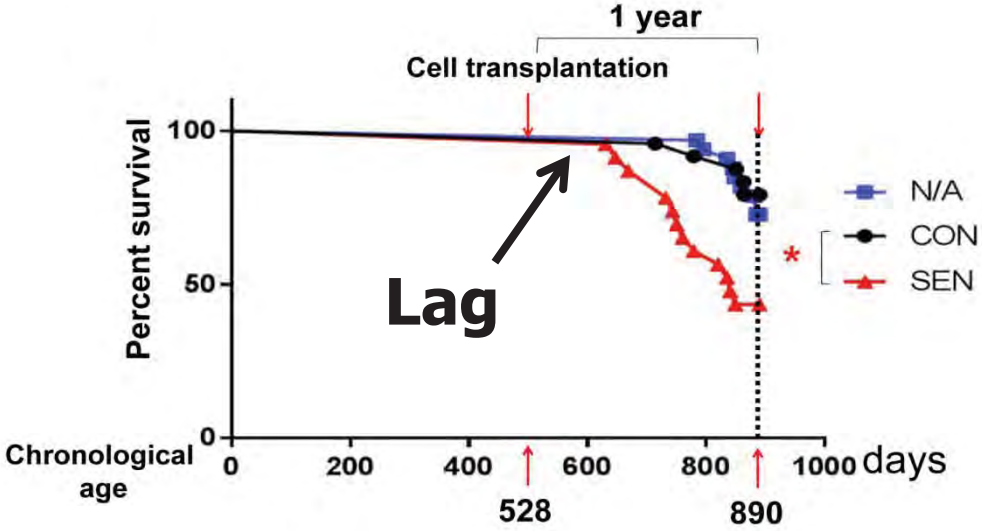




4 younger (31 ± 5 y) and 4 older (71 ± 2 y) healthy male volunteers. *P < 0.05

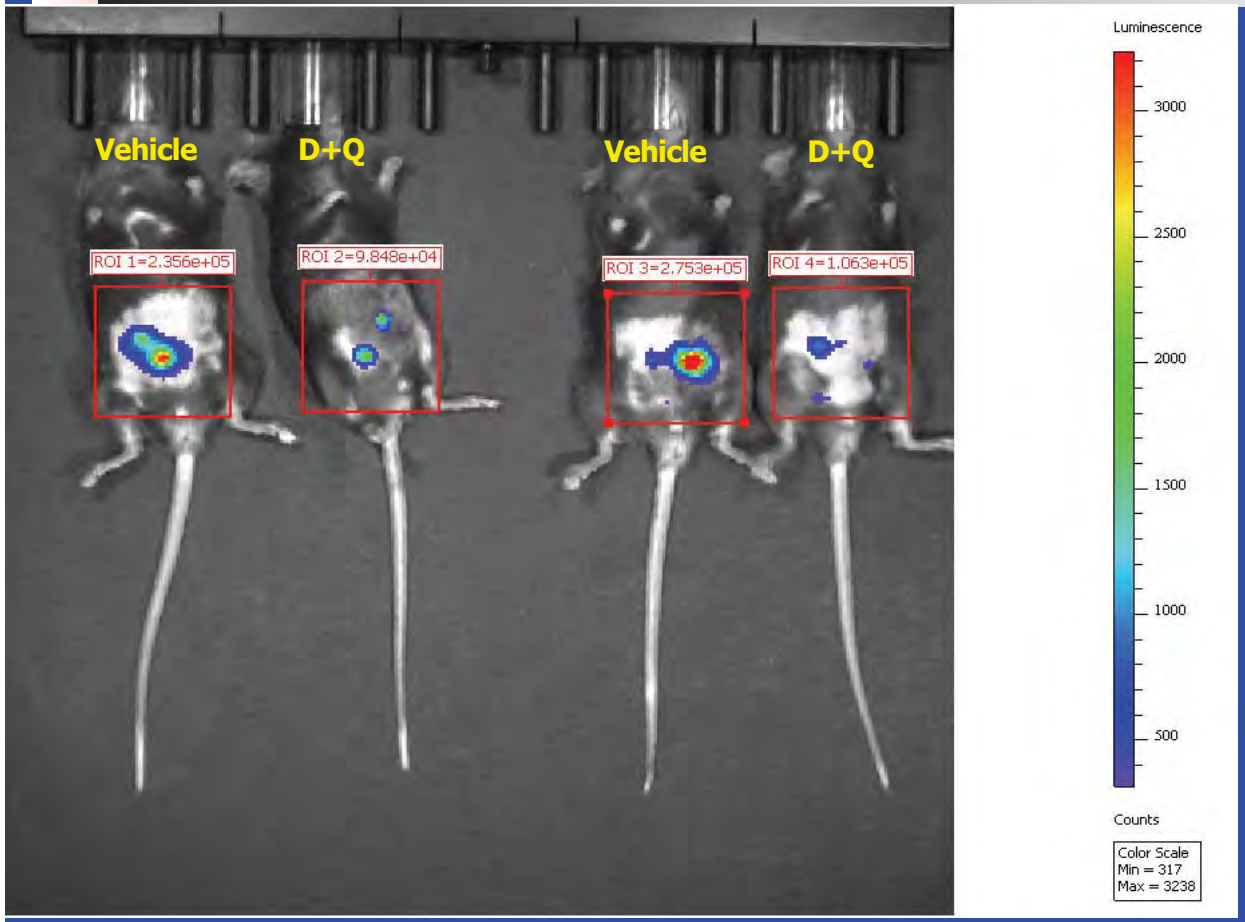
Transplanting Senescent Cells Causes Physical Dysfunction and Decreases Survival

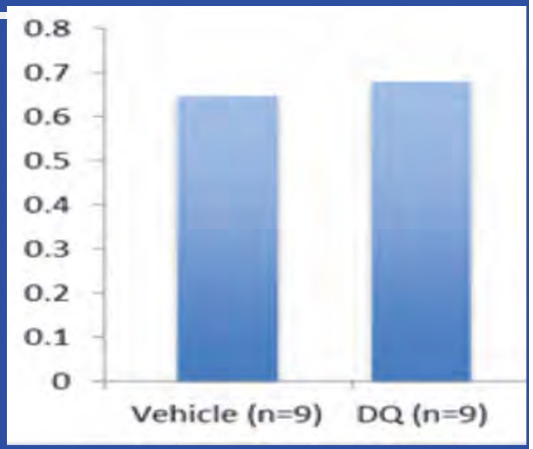




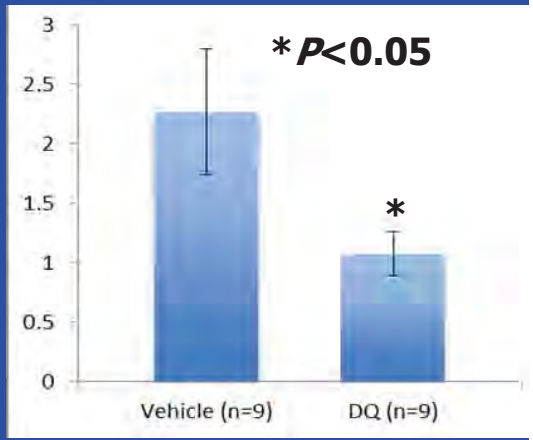
Xu *et al.*, Nature Medicine, 2018

D+Q Clears Transplanted Luciferase-Expressing Senescent Preadipocytes





Non-senescent cell-transplanted

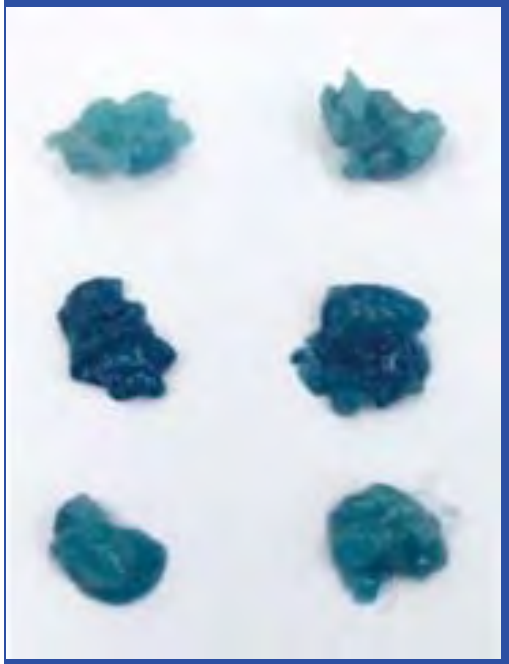


Senescent cell-transplanted

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

Xu *et al.*, Nature Medicine, 2018

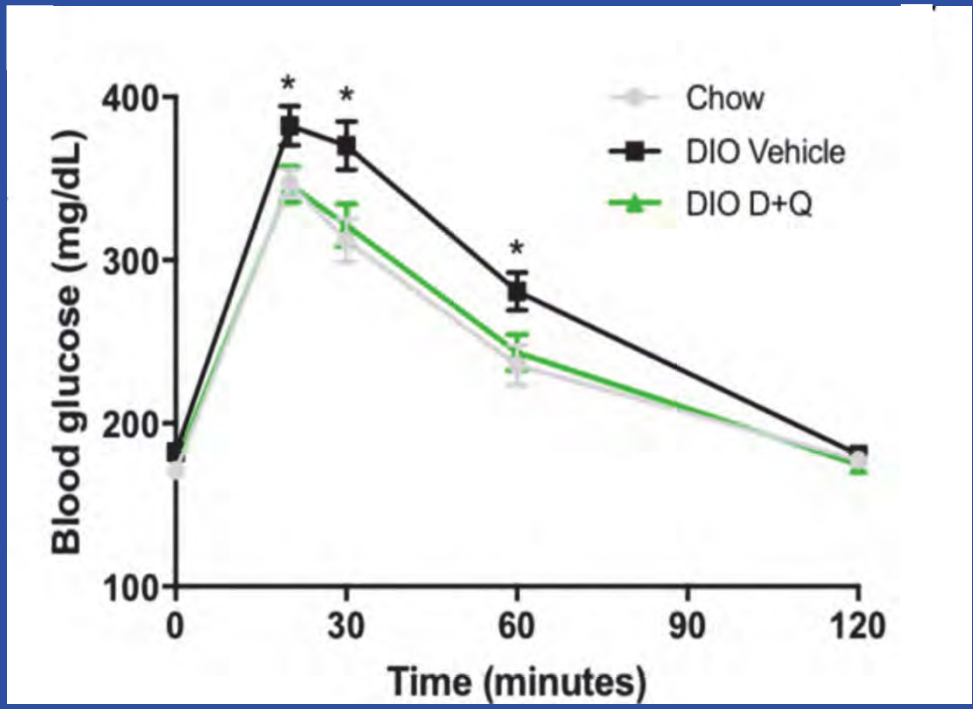
Diabetes is Alleviated in Obese Mice Treated with Senolytics



Lean

Obese

Obese D+Q



ipGTT

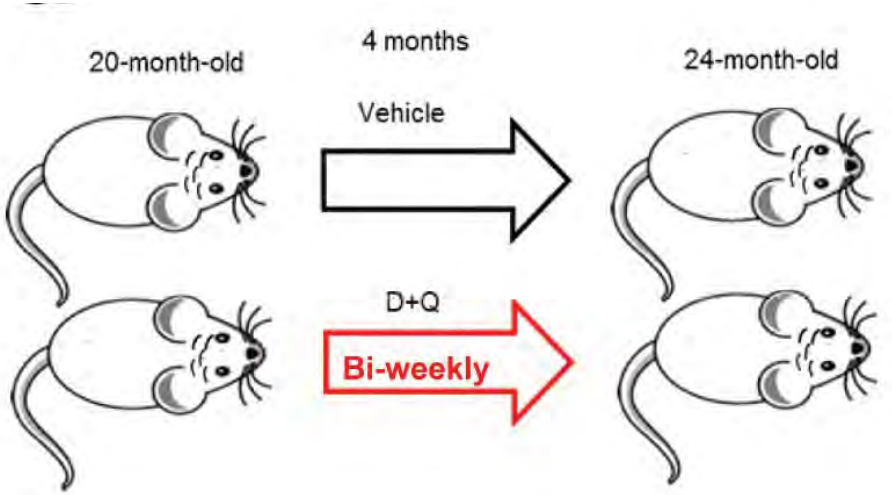
Palmer *et al.*, Aging Cell, 2019

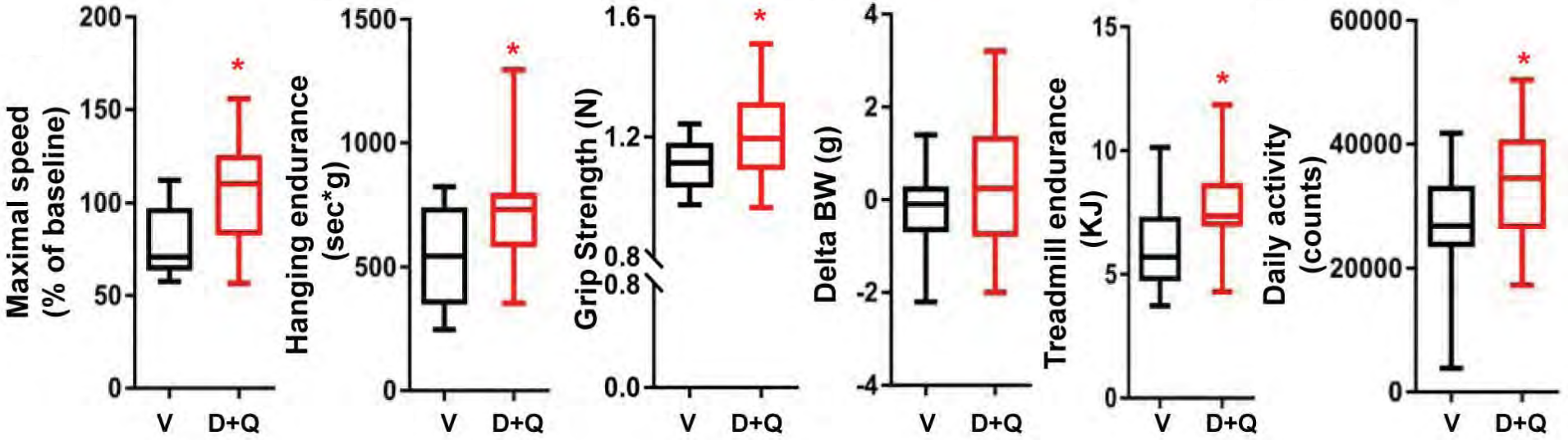
Emerging Evidence for Benefits of Senolytics On:

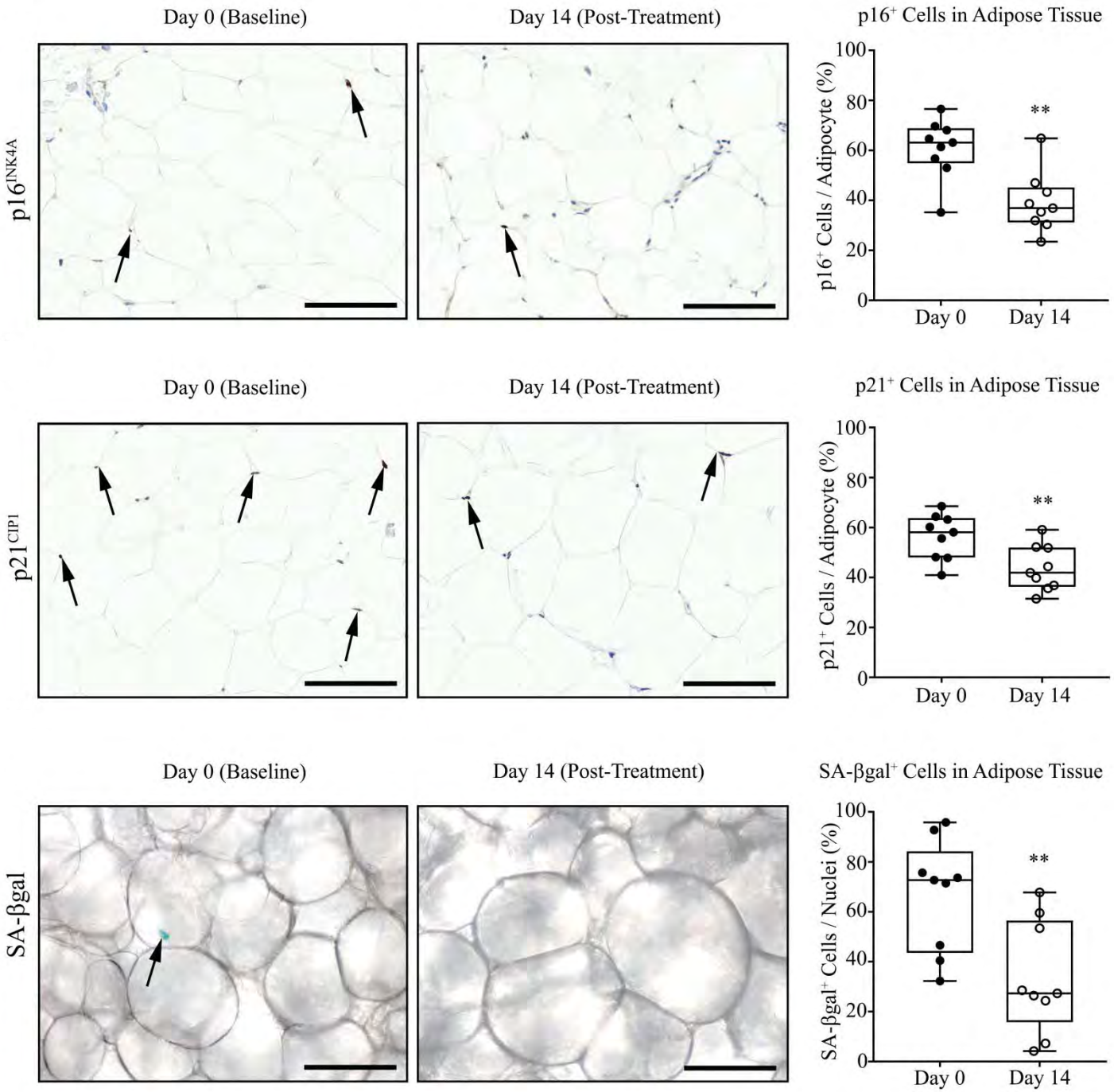
Diabetes/ Obesity
Age-Related Lipodystrophy
Cardiac Dysfunction
Vascular Hyporeactivity/ Calcification/ AV Fistulae
Frailty/ Sarcopenia
Response to Chemotherapy
Response to Radiation
Cancer
Sequellae of Bone Marrow Transplantation
Sequellae of Organ Transplantation
Cognition/ Alzheimer's/ Parkinson's/ 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



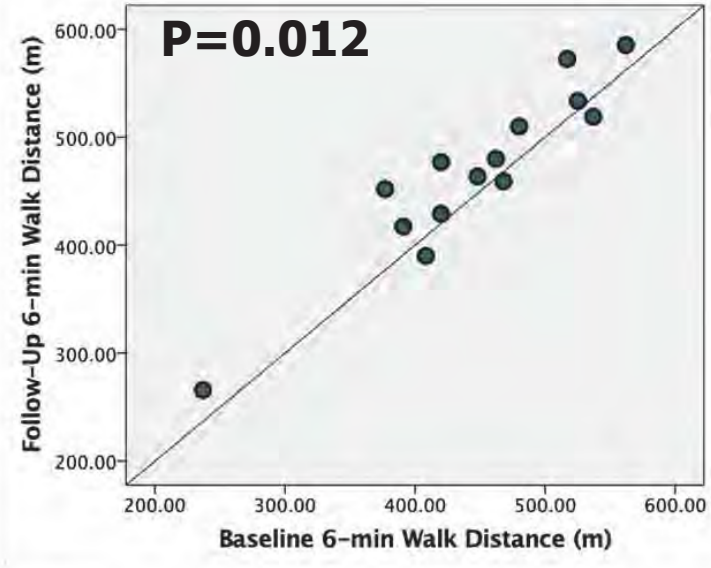


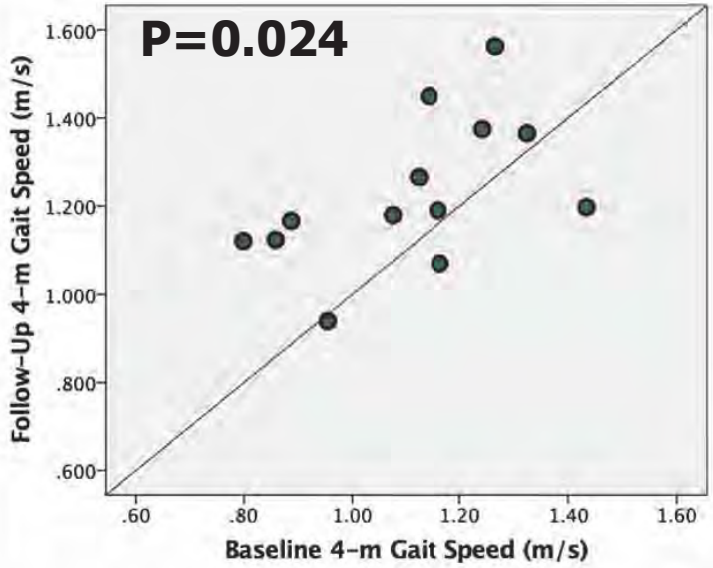


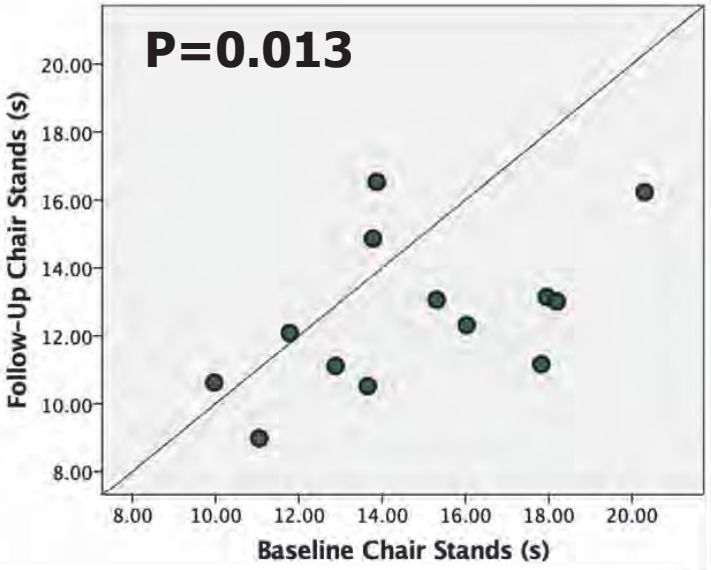
Abdominal subcutaneous adipose biopsies at baseline (BL) and 11 days after the last dose (PT) of a 3 day course of D+Q; N=9 subjects

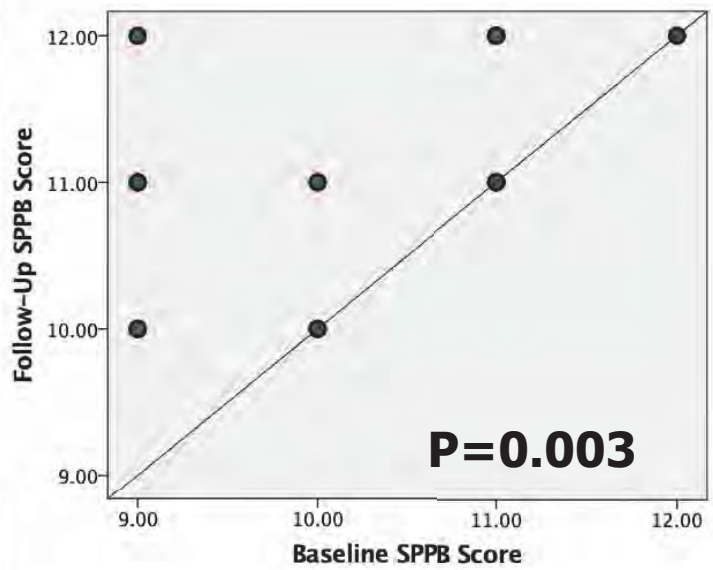
ClinicalTrials.gov identifier: NCT02848131

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

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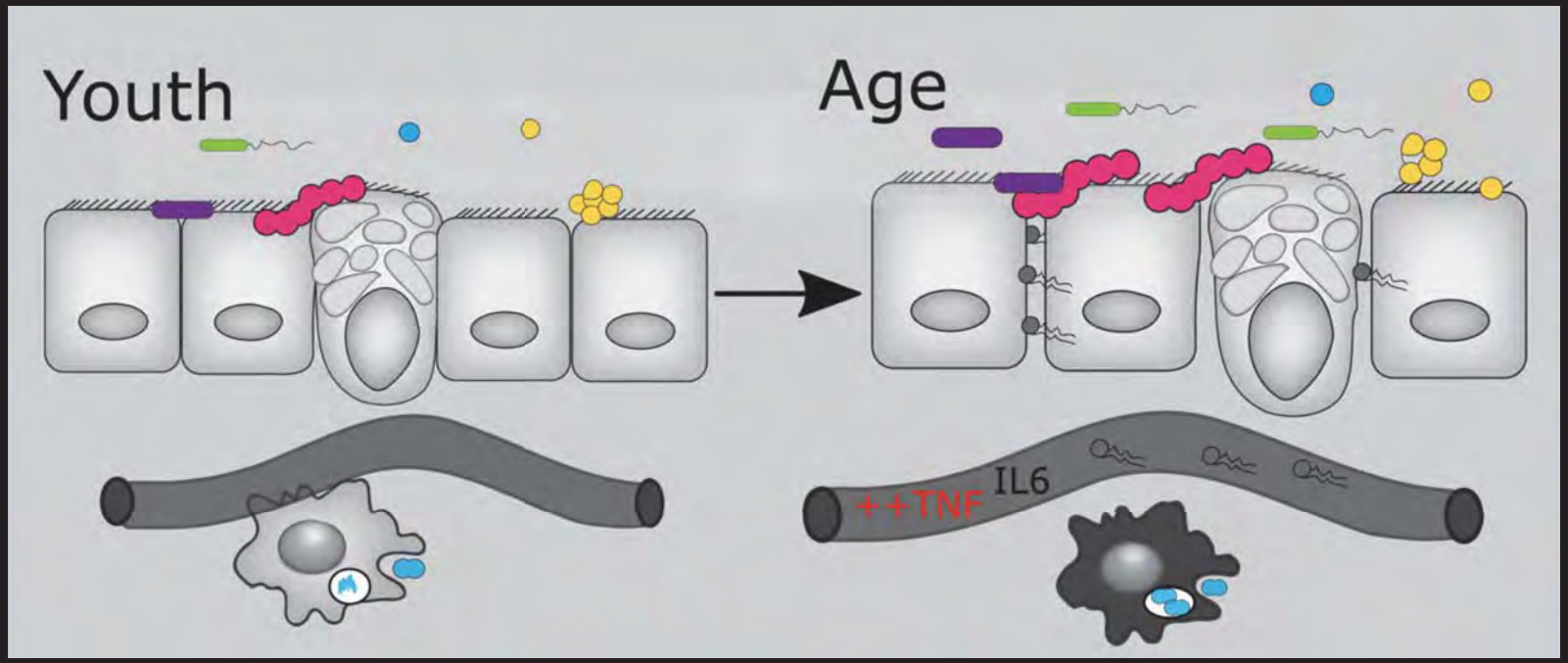
WEBINAR
October 1, 2019

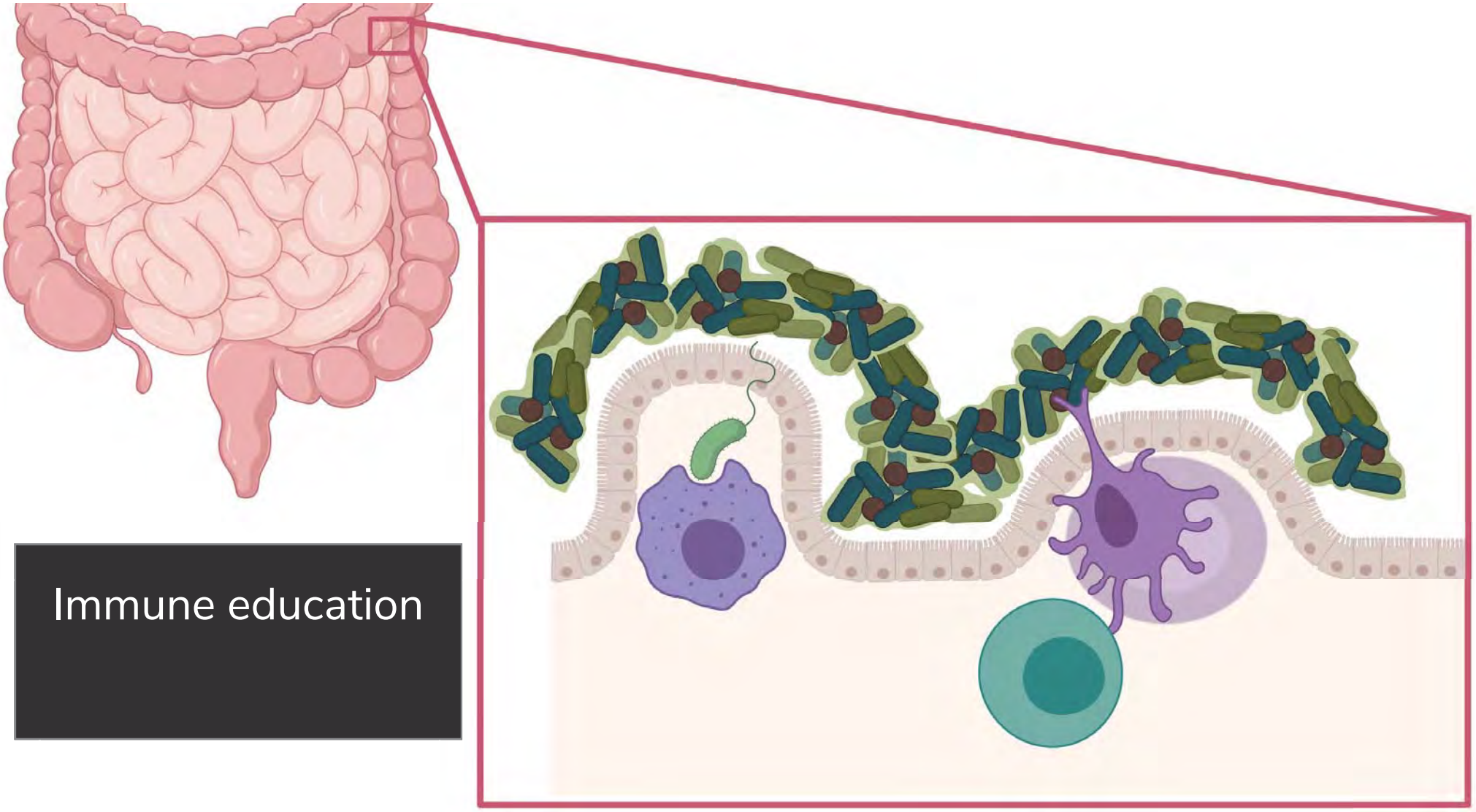
Dawn Bowdish, Ph.D.

Associate Professor of Pathology
and Molecular Medicine,
McMaster University



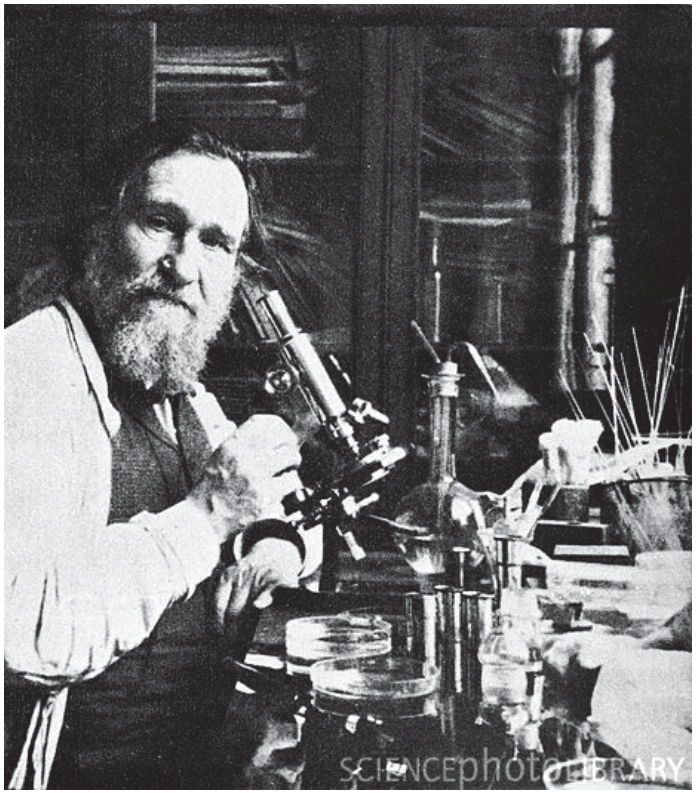
The microbiota and age-associated inflammation.

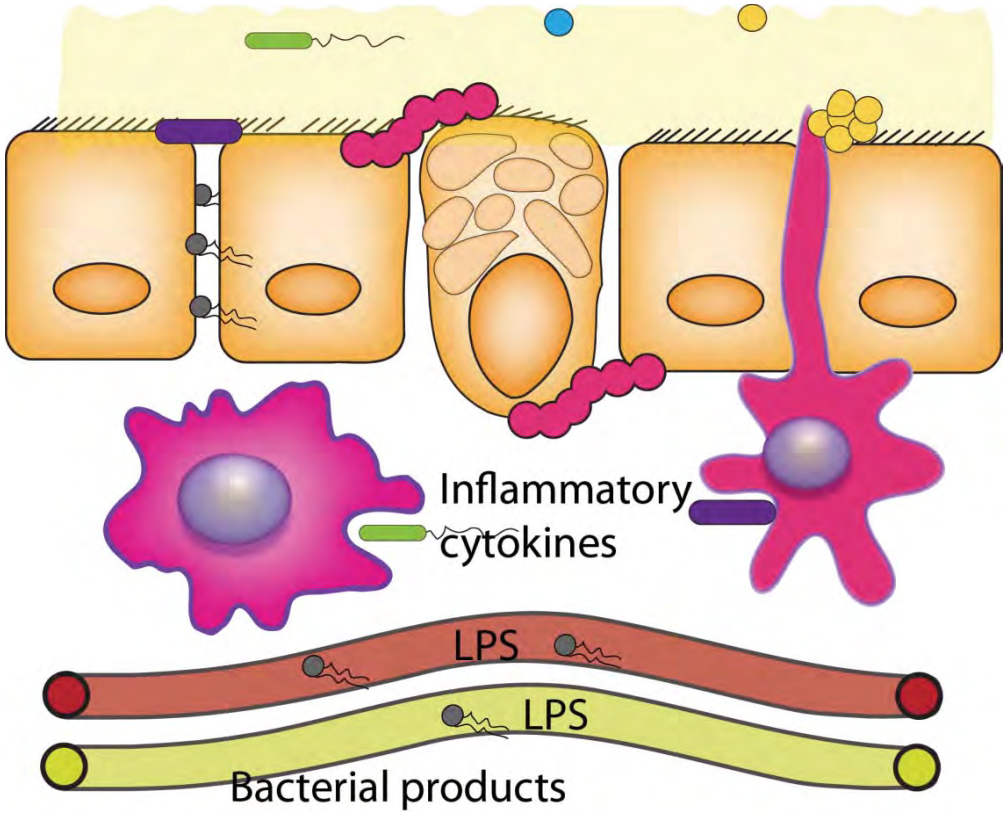
Dr. Dawn Bowdish
McMaster University
bowdish@mcmaster.ca
www.bowdish.ca
@MsMacrophage
house.macrophage



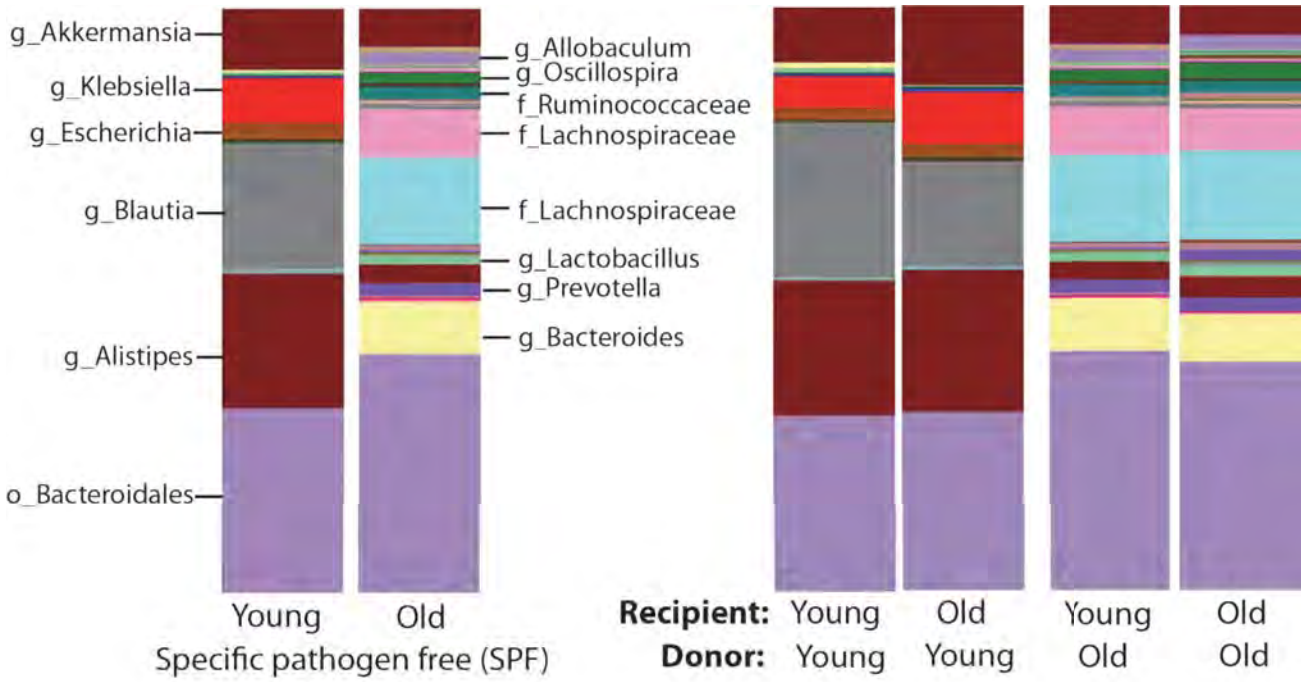
Immune education

Metchnikov's theory of aging



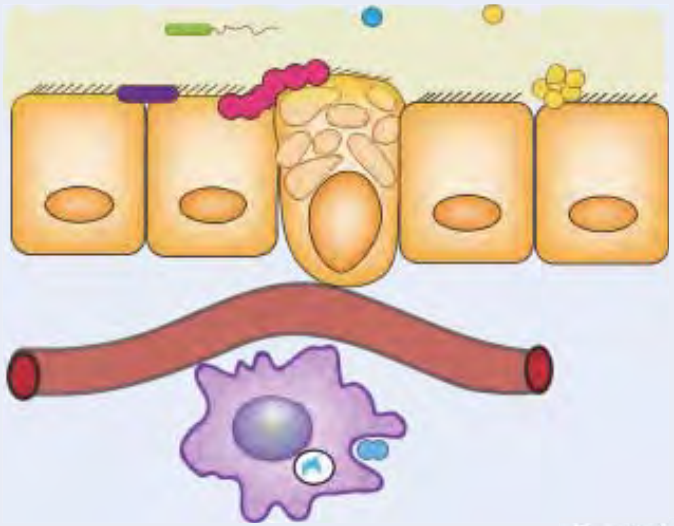


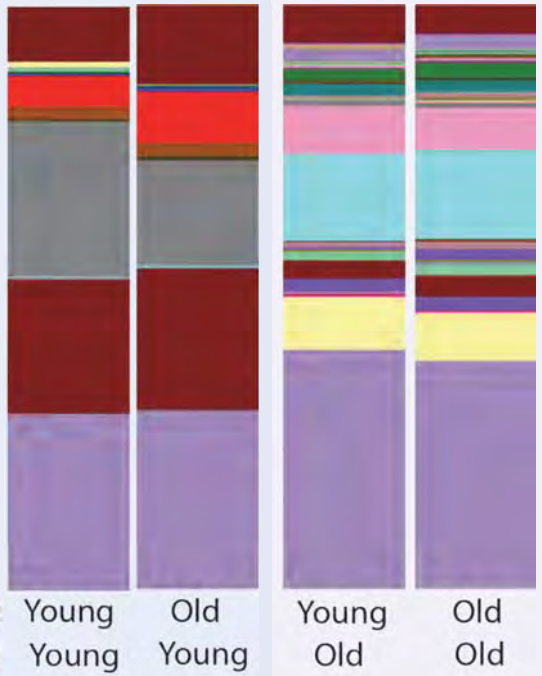
Does the composition of the aging microbiota influence age associated inflammation?



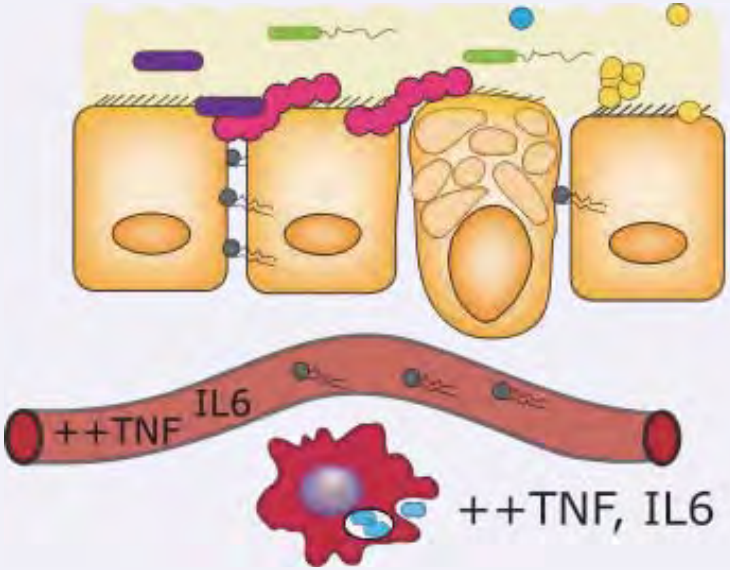
Cell Host Microbe. 2017 Apr 12;21(4):455-466.e4.

Young Microbiome



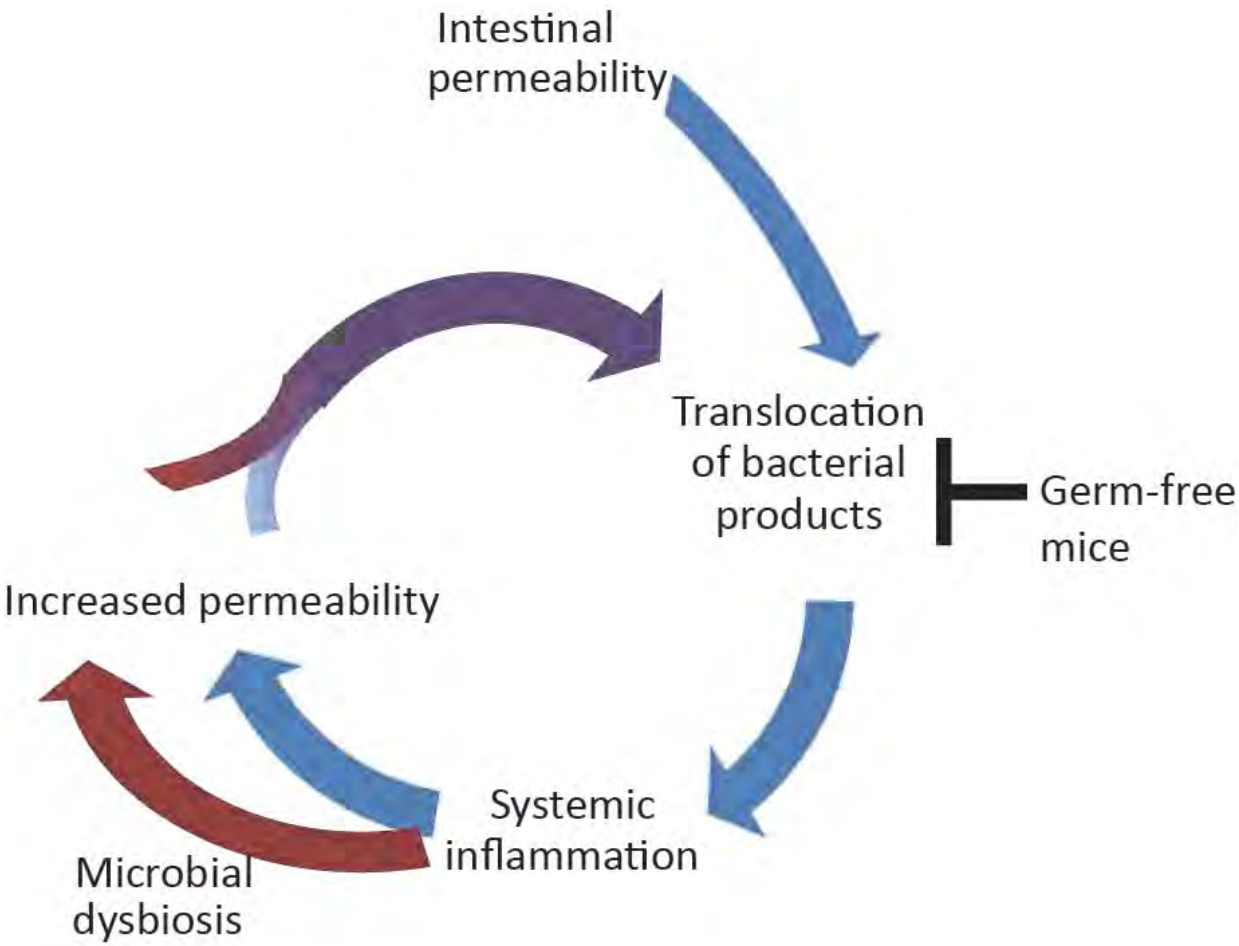


Old Microbiome



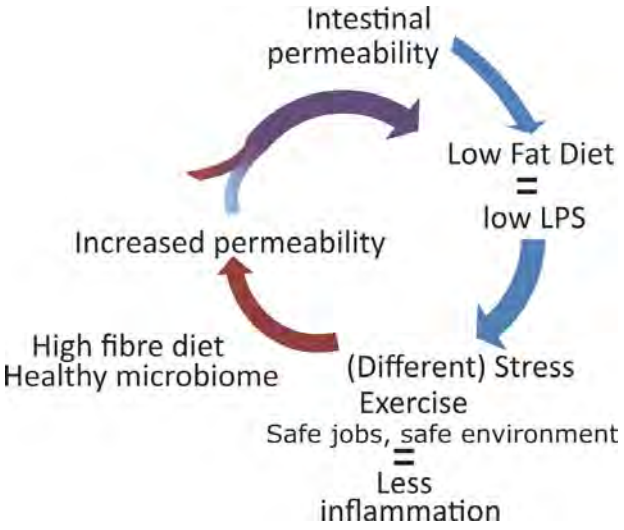
Cell Host Microbe. 2017 Apr 12;21(4):455-466.e4.

Take care of your microbiome
(it may be key to a long, healthy life)



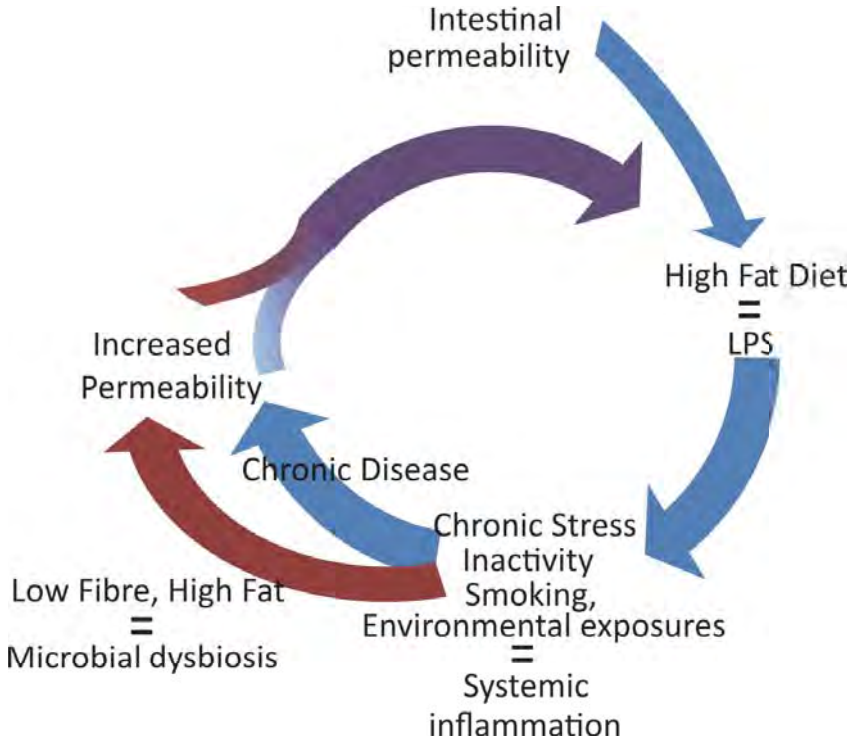
Life expectancy in **richer** neighbourhoods

men 81 women 84



In **poorer** neighbourhoods

men 76 women 82



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