Plasma Infusions and Regenerative Medicine in Aging

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Plasma infusions and Regenerative Medicine in Aging

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The following potential conflict of interest relationships are germane to my presentation.

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NA/Non-Clinical

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Note: This lecture has been peer reviewed to ensure fair balance and evidence based medicine

Objectives

- Understanding the relationship of Stem Cells, Inflammation and the Immune System

- Immune Dysfunction with Aging and Chronic Diseases

- The Use of Plasma Derived from Mobilized Stem Cells to Improve Immune Dysfunction and Chronic Diseases of Aging

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Extending Healthspan is Our Dream

- Healthy aging patterns

- High quality of life into late stages of our life span, with few daily living impairments

- And none or a near absence of age-related disease

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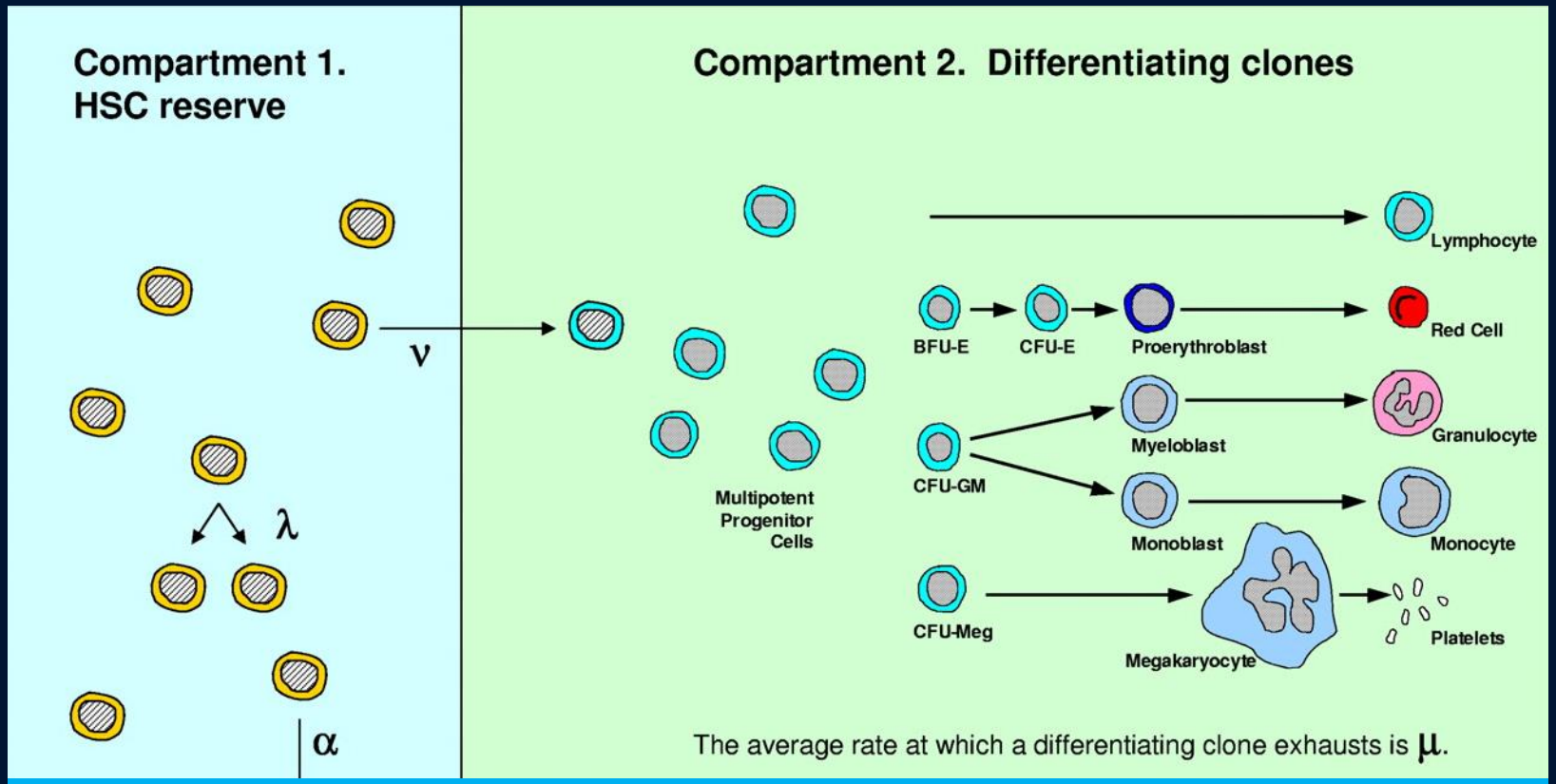
THE FOUNTAIN OF YOUTH



- *New Scientist:* study author, Henne Holstege, thinks stem cells could be key.
- How might her study help the rest of us to live longer and healthier is a central one.
- Her results raise the possibility of rejuvenating aging bodies by injecting people with stem cells saved from early in their lives.

115-Year-Old Woman's Blood Reveals Limits on Longevity. New Scientist

THE DEVELOPMENT OF BLOOD CELLS FROM STEM CELLS (HSCs)



Catlin, Sandra N., et al. "The replication rate of human hematopoietic stem cells in vivo." *Blood* 117.17 (2011): 4460-4466.

blood

EVIDENCE OF THE IMMUNE RISK PROFILE

Experimental Gerontology
Volume 42, Issue 8, August 2007, Pages 753–761

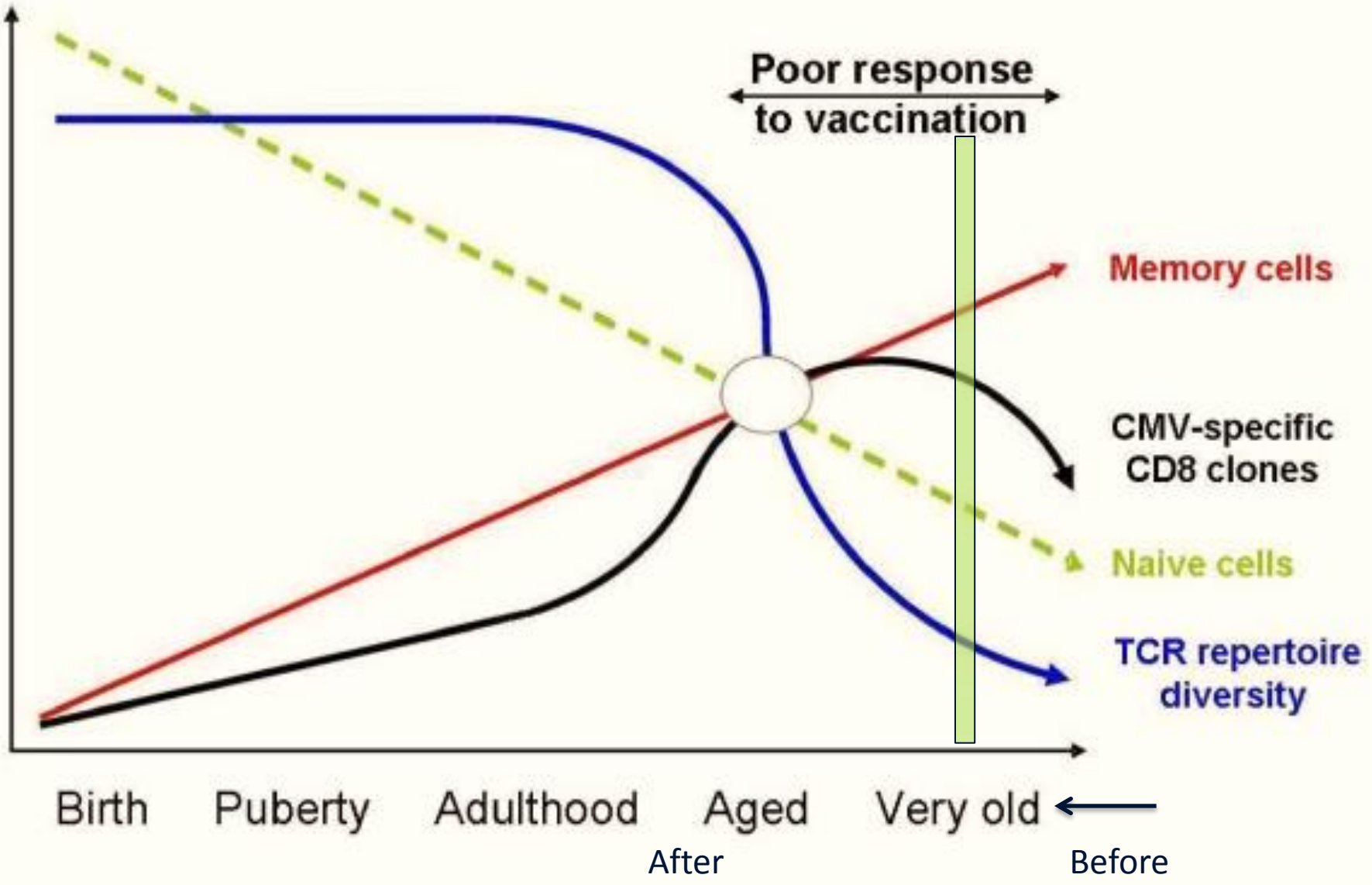


No Immune Risk Profile among individuals who reach 100 years of age: Findings from the Swedish NONA immune longitudinal study

Jan Strindhall[a], Bengt-Olof Nilsson[b], Sture Löfgren[c], Jan Ernerudh[d], Graham Pawelec[e], Boo Johansson[f, g], Anders Wikby[a,]

- These results confirm the importance of the IRP as a major predictor of mortality in the very old.
- Moreover, the results suggested that survival to the age of 100 is associated with individuals with an “inverted” IRP that was stable across time, i.e., maintenance of a high CD4/CD8 ratio and low numbers of CD8+CD28− cells.

MODEL FOR THE EVOLUTION OF T-CELLS IMMUNITY OVER THE HUMAN LIFESPAN



AGING OF THE IMMUNE SYSTEM (IMMUNOSENESCENCE)

A decreased immune response due to aging causes an increased incidence and severity of:

Chronic Inflammatory Disorders

Infections

Cancers

Frailty

Autoimmune Disorders

Slowness
Weakness
Weight loss
Low activity
Fatigue

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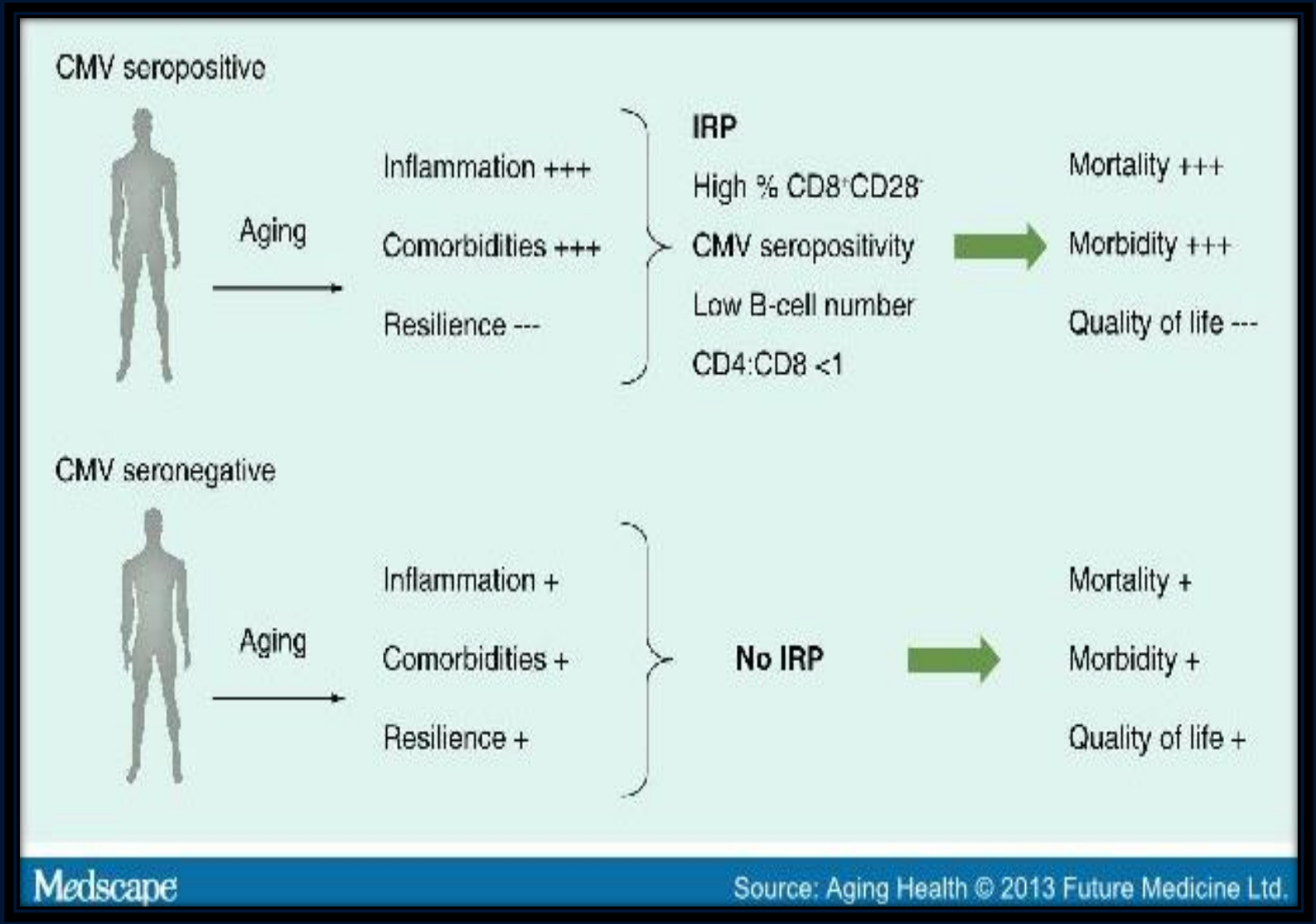
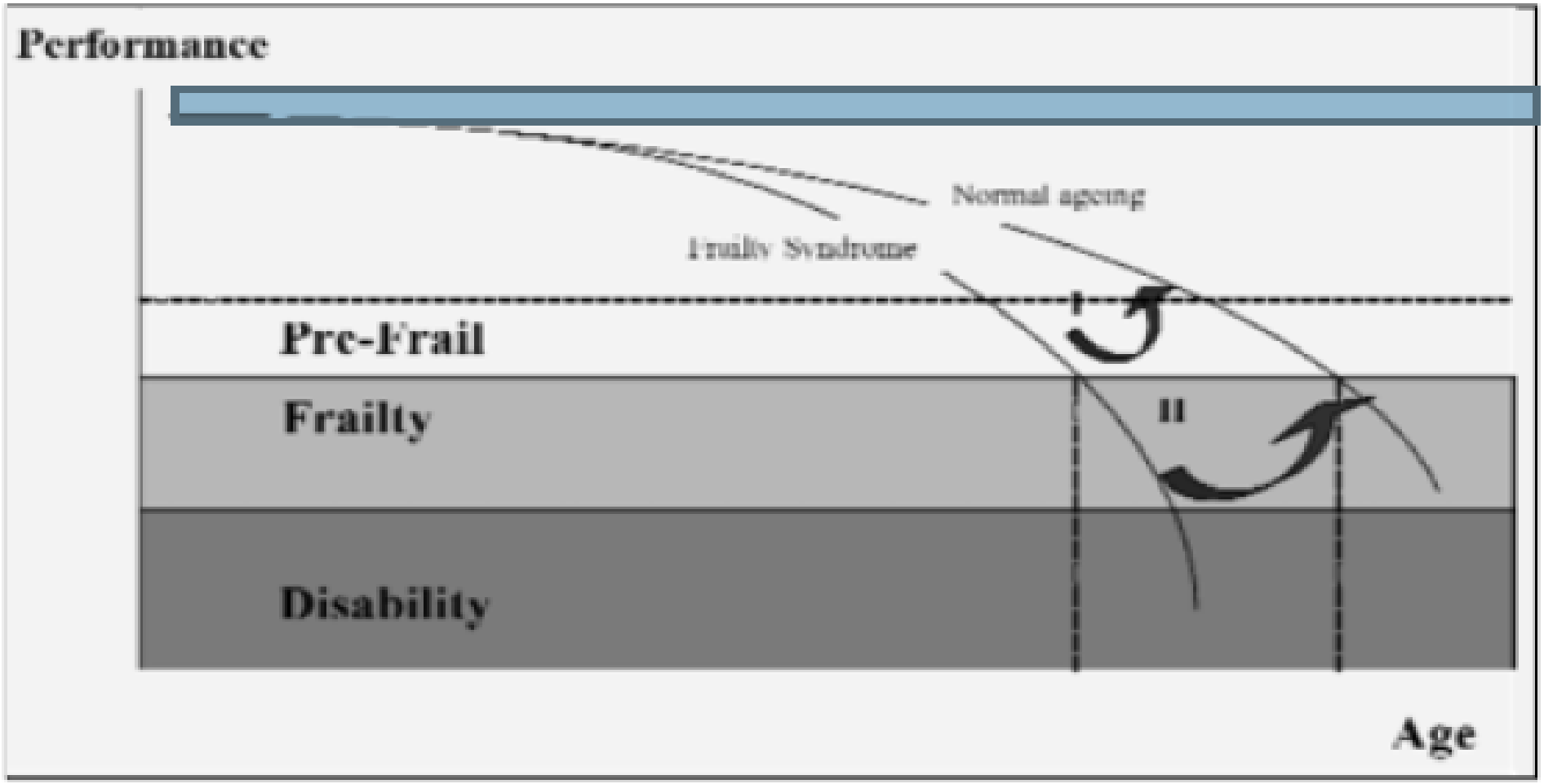
SIGNIFICANCE OF THE IMMUNE RISK PROFILE



FRAILTY SYNDROME

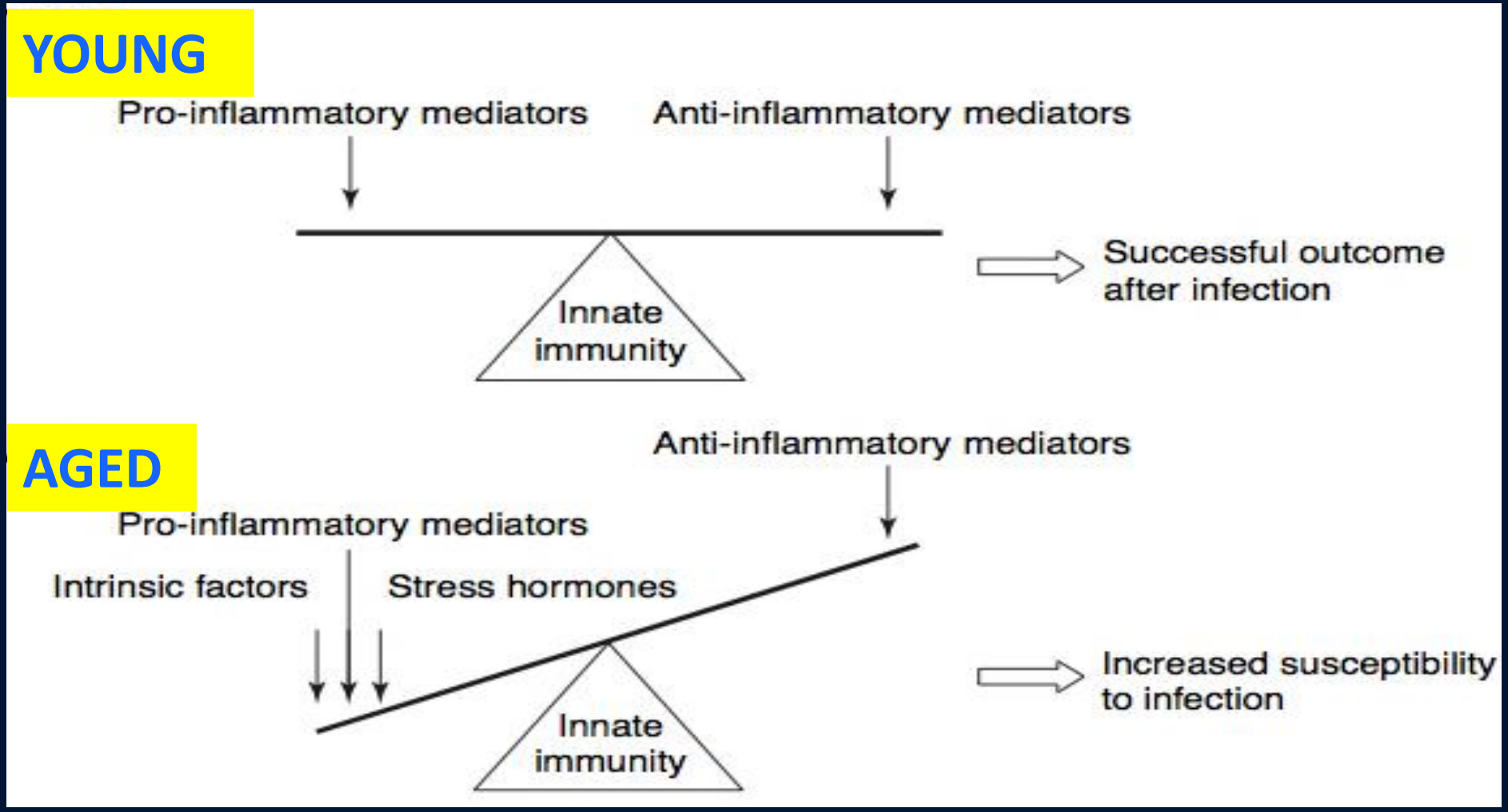


I stands for primary interventions and II for secondary interventions

INFLAMMATION…



AGING:
THE IMMUNE SYSTEM VS. INFLAMMATION



Experimental Gerontology 38 (2003) 981–987

INFLAMMATION / FLAME / FIRE

Controlled







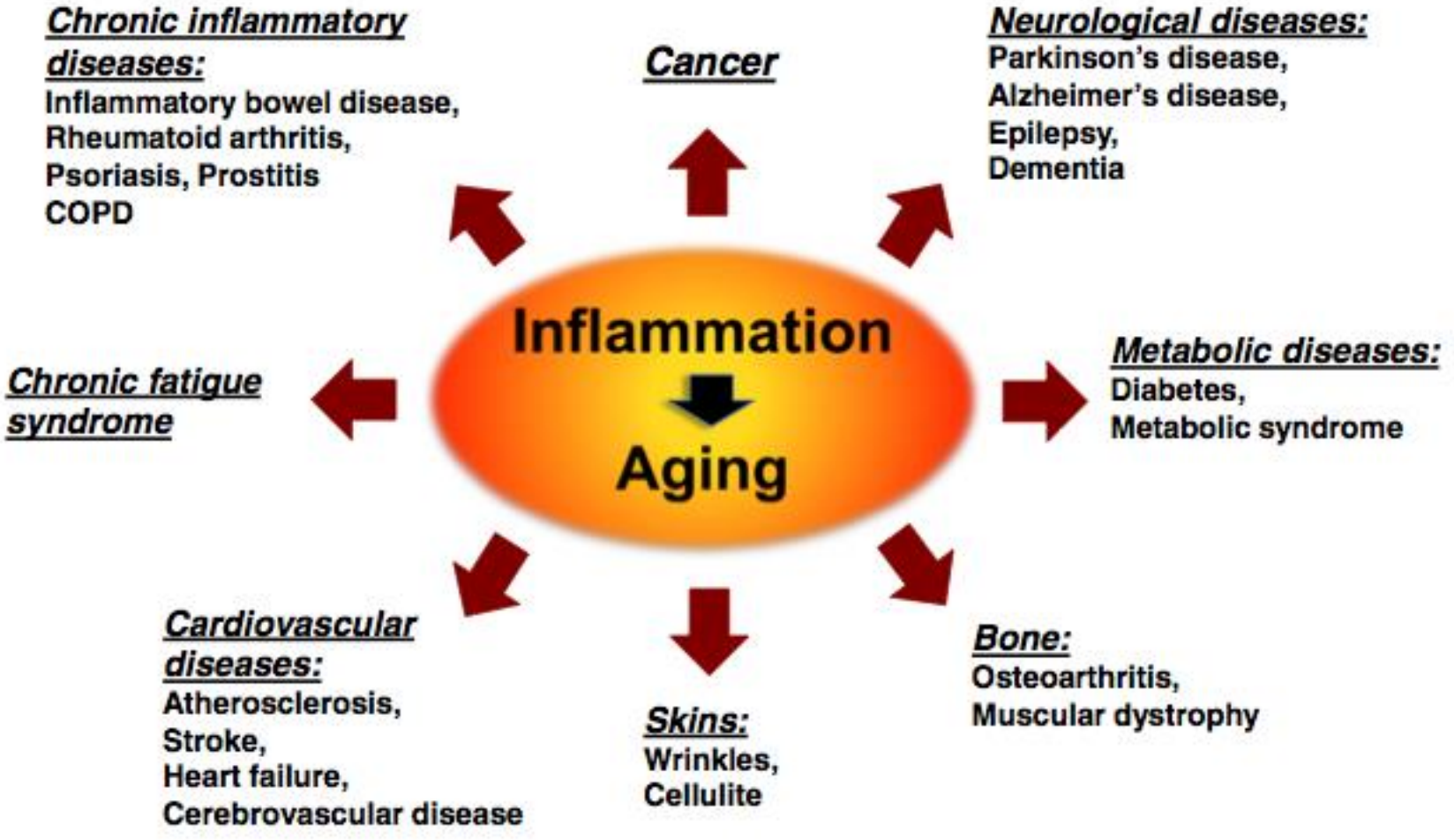
Uncontrolled







AGING ASSOCIATED CHRONIC DISEASES REGULATED BY INFLAMMATION



S32S. Prasad et al. / Preventive Medicine 54 (2012) S29–S37

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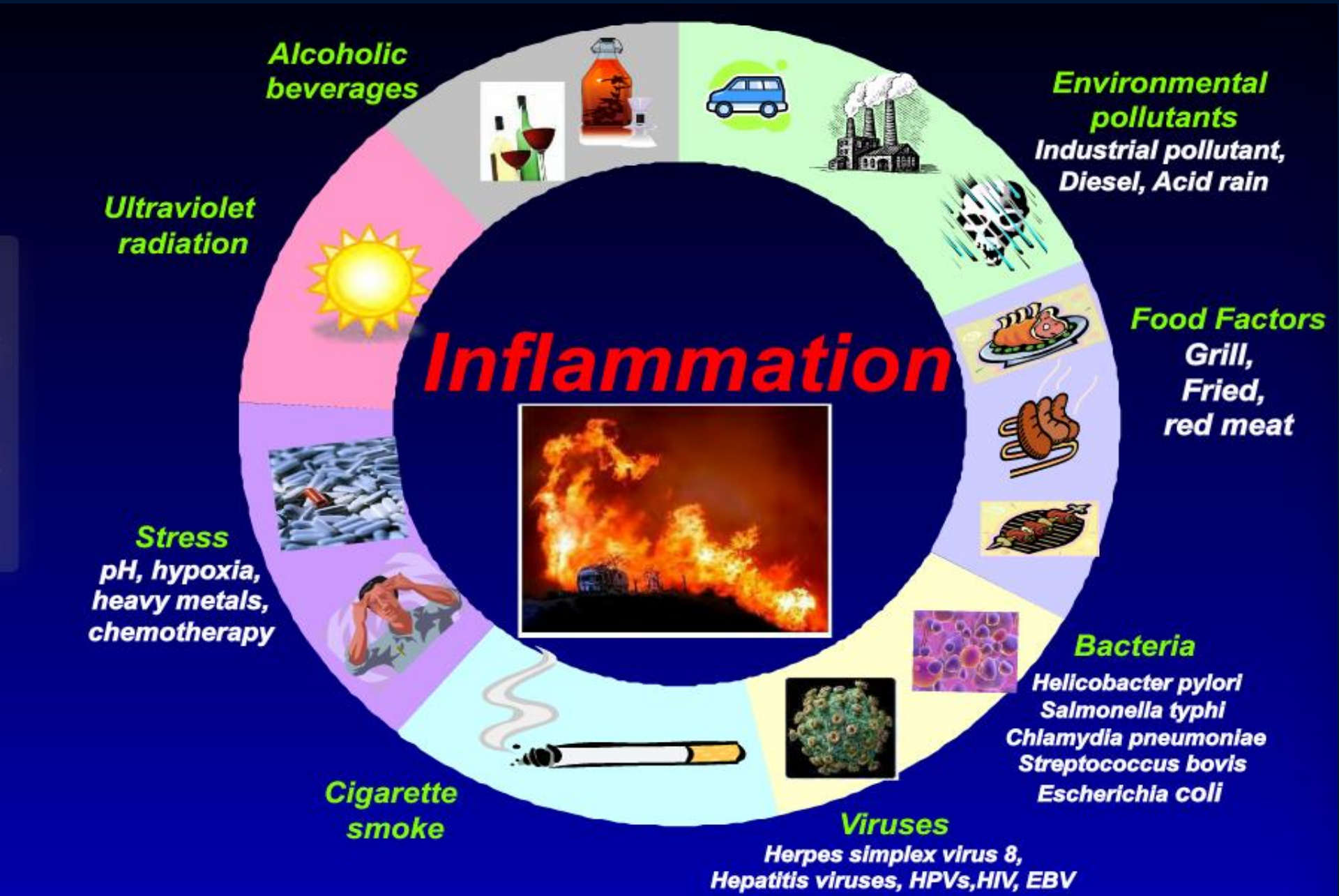
POTENTIAL SOURCES OF INFLAMMATION



INFLAMMATION AND AGING

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians

Yasumichi Arai [a,1], Carmen M. Martin-Ruiz [b,1], Michiyo Takayama [c], Yukiko Abe [a], Toru Takebayashi [d], Shigeo Koyasu [f,g], Makoto Suematsu [a,e], Nobuyoshi Hirose [a,*,2], Thomas von Zglinicki [b,**,2]

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[e] *Department of Biochemistry, Keio University School of Medicine, and JST, ERATO, Suematsu Gas Biology Project, Tokyo, Japan*
[f] *Laboratory for Immune Cell Systems, RIKEN Centre for Integrative Medical Sciences (IMS), Yokohama, Kanagawa, Japan*
[g] *Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo, Japan*

Problem

- The older adult population is currently growing at an unprecedented rate.

- Health disparities in those aged 50 and older are becoming more prevalent.

- Healthcare spending will continue to increase, largely due to the aging population.

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Reality

- An unhealthy aging trajectory
- Associated with the onset of comorbid diseases
- Diminished quality of life
- An increased mortality risk

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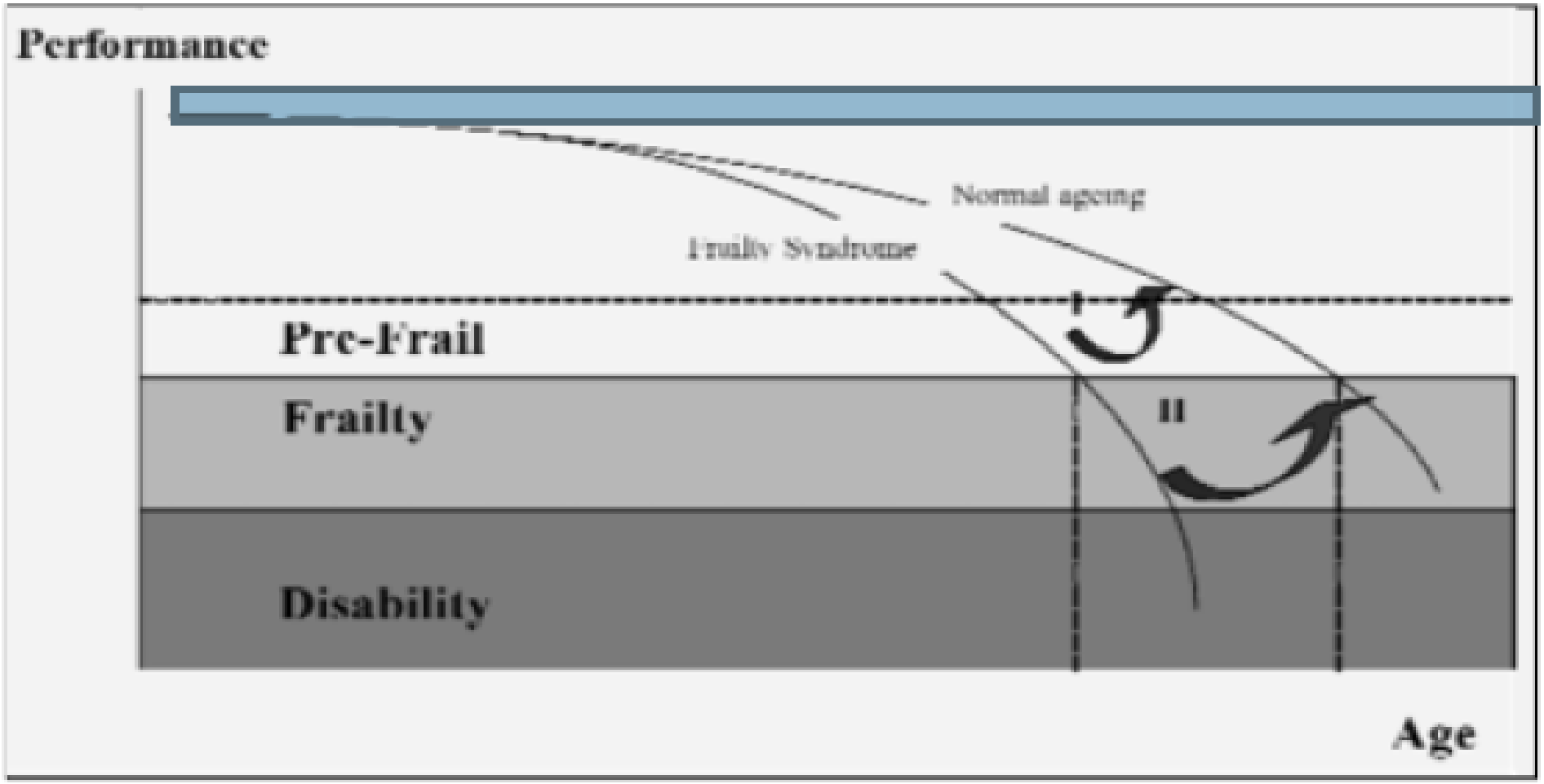
FRAILTY SYNDROME



I stands for primary interventions and II for secondary interventions

Chronic Critical Illness

- 100,000 U.S. patients at any one time
- 5 to 10% survive catastrophic illness or surgical procedure
- Left with a prolonged need for (>21 days) need for mechanical ventilation
- Recurrent infections, organ dysfunction, profound weakness and delirium
- 50% mortality in 1 year, of others <12% at home and functionally independent
- Healthcare costs: $20 Billion Annually

N ENGL J MED,3702 Jan 9,2014

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ACP Internist Weekly | DEMENTIA | DECEMBER 19, 2017

No interventions proven to prevent late-life dementia, systematic reviews find

The reviews examined physical activity, prescription medications, cognitive training, and over-the-counter vitamins and supplements.

EXTENDING HEALTHY LIFE SPAN

- In 16 trials, the reviewers found insufficient evidence to draw conclusions about the effectiveness of aerobic training, resistance training or tai chi for improving cognition
- The trials reviewed three dementia medications, 16 antihypertensive agents, four diabetes medications, two NSAIDs or aspirin, 17 hormones, and seven lipid-lowering agents. The evidence did not support use of any of the treatments for cognitive protection
- For cognitive training, 11 trials with low or medium risk of bias, six enrolling healthy adults with normal cognition and five enrolling adults with mild cognitive impairment, provided insufficient evidence that cognitive training exercises could prevent dementia

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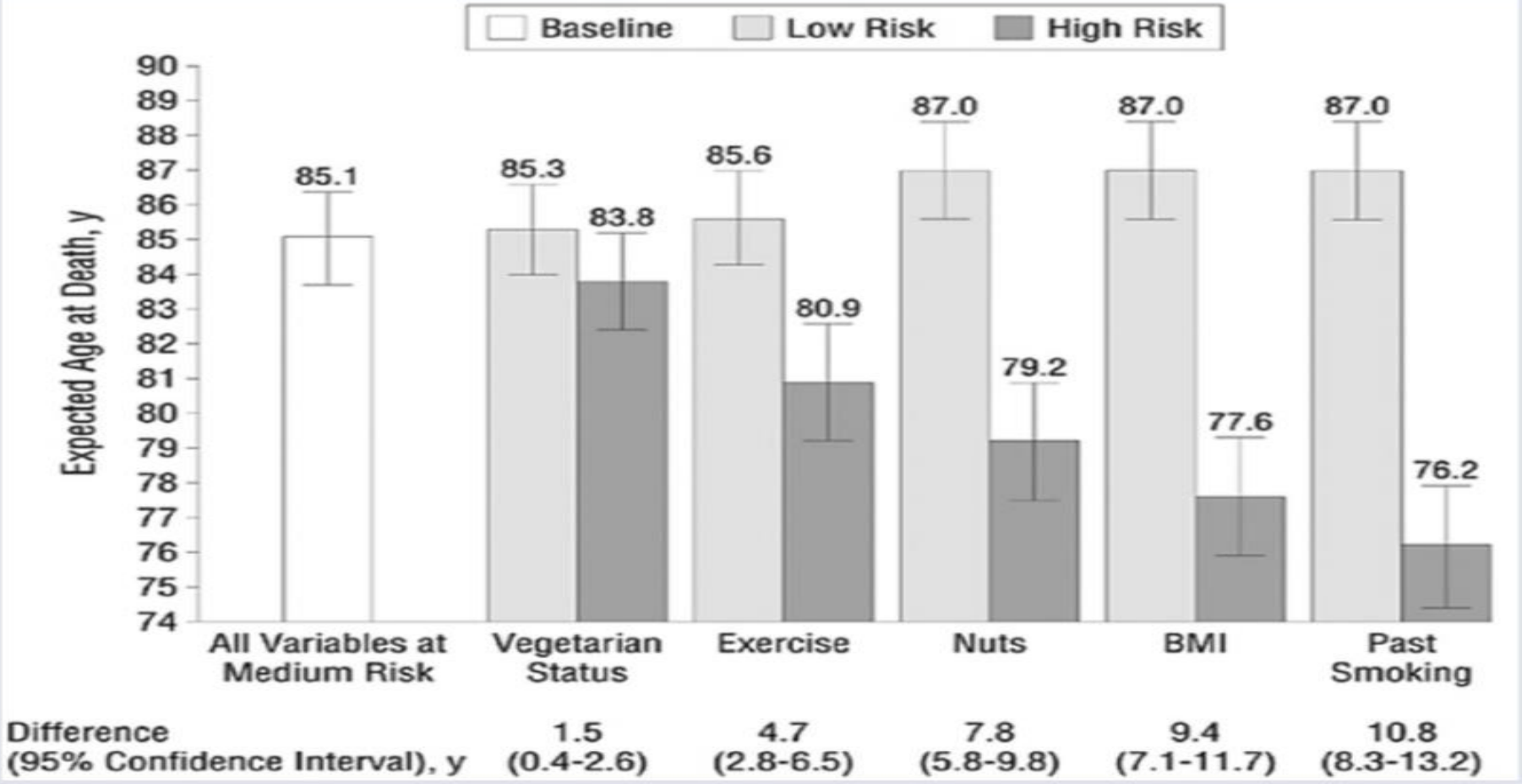
EXTENDING HEALTHY LIFE SPAN

Expected Ages at Death (95% Confidence Intervals) in Men With Jointly High- or Low-Risk Values for the Risk Factor in a Particular Column and Those to Its Left (Other Variables at Medium-Risk Values).



BMI, body mass index.
Source: Fraser and Shavlik.[49]

EXTENDING HEALTHY LIFE SPAN

- For OTC vitamins and supplements, a review included 38 trials comparing OTC supplements, including omega-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or beta carotene, multi-ingredient supplements, with placebo or other OTC interventions for preventing or delaying cognitive decline, mild cognitive impairment, or clinical Alzheimer-type dementia. The reviewers found insufficient evidence that any of the supplements reduced the risk for cognitive decline.

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TREATMENTS FOR AGING

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SO WHY NOT INVENT TREATMENTS FOR AGING?

- Google's **Calico** Operation founded in 2013 is funded by hundreds of millions of dollars for anti-aging research.
- Craig Venter, the genetics entrepreneur, has launched a company called **Human Longevity** to find genes that lead to long life.
- A recent study uses **Metformin** for Anti-aging effects.
- **Elysium**, a nutraceutical company, utilizes specific natural precursors and herbs to increase NAD^+ levels and allow cells to function at their potential.
- A 2017 paper published in *Cell* reviewed **a peptide that could genetically clear senescent cells** via cell-intrinsic apoptosis by inhibiting transcriptional regulators that act as pivots in their viability.

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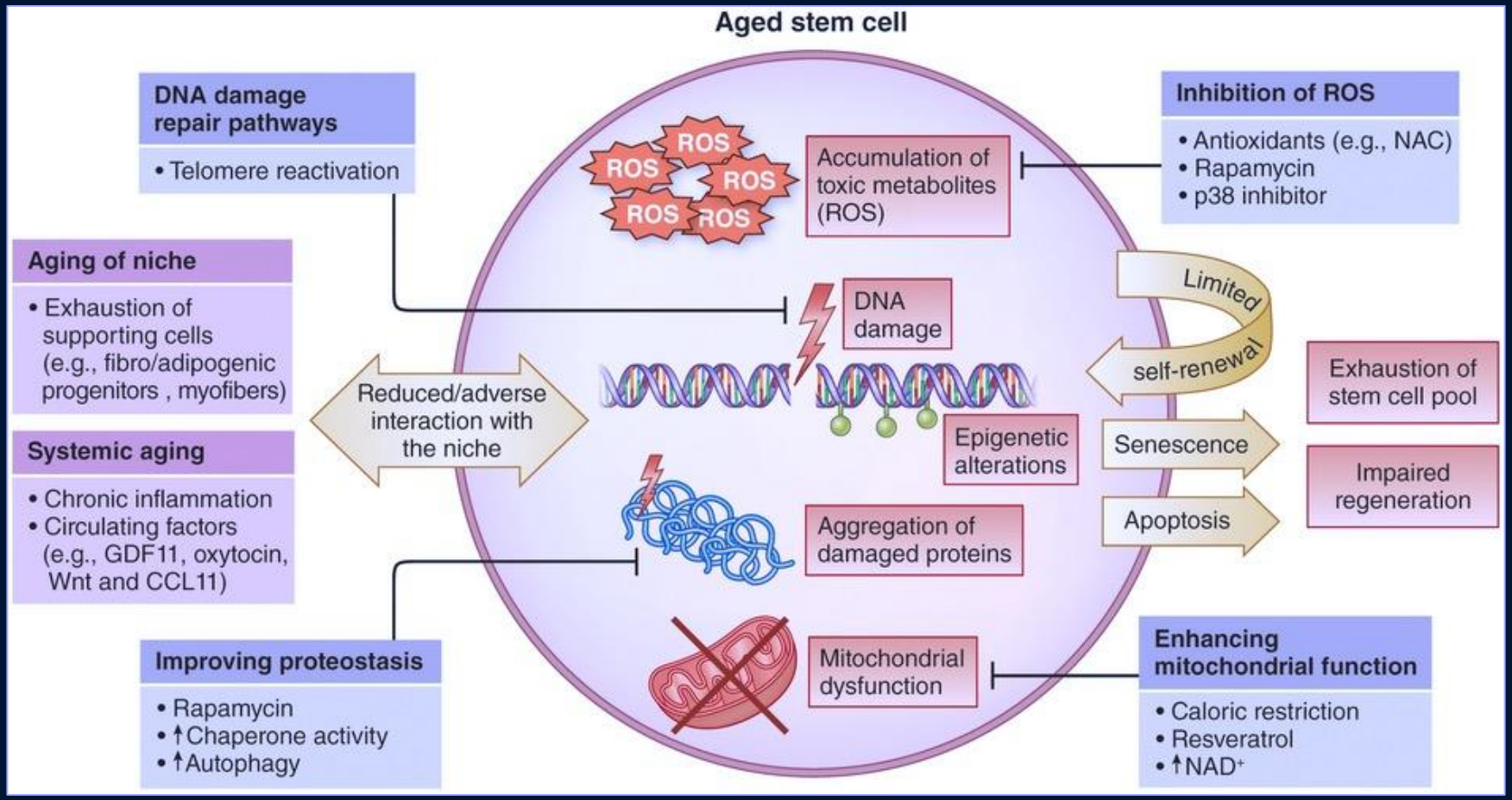
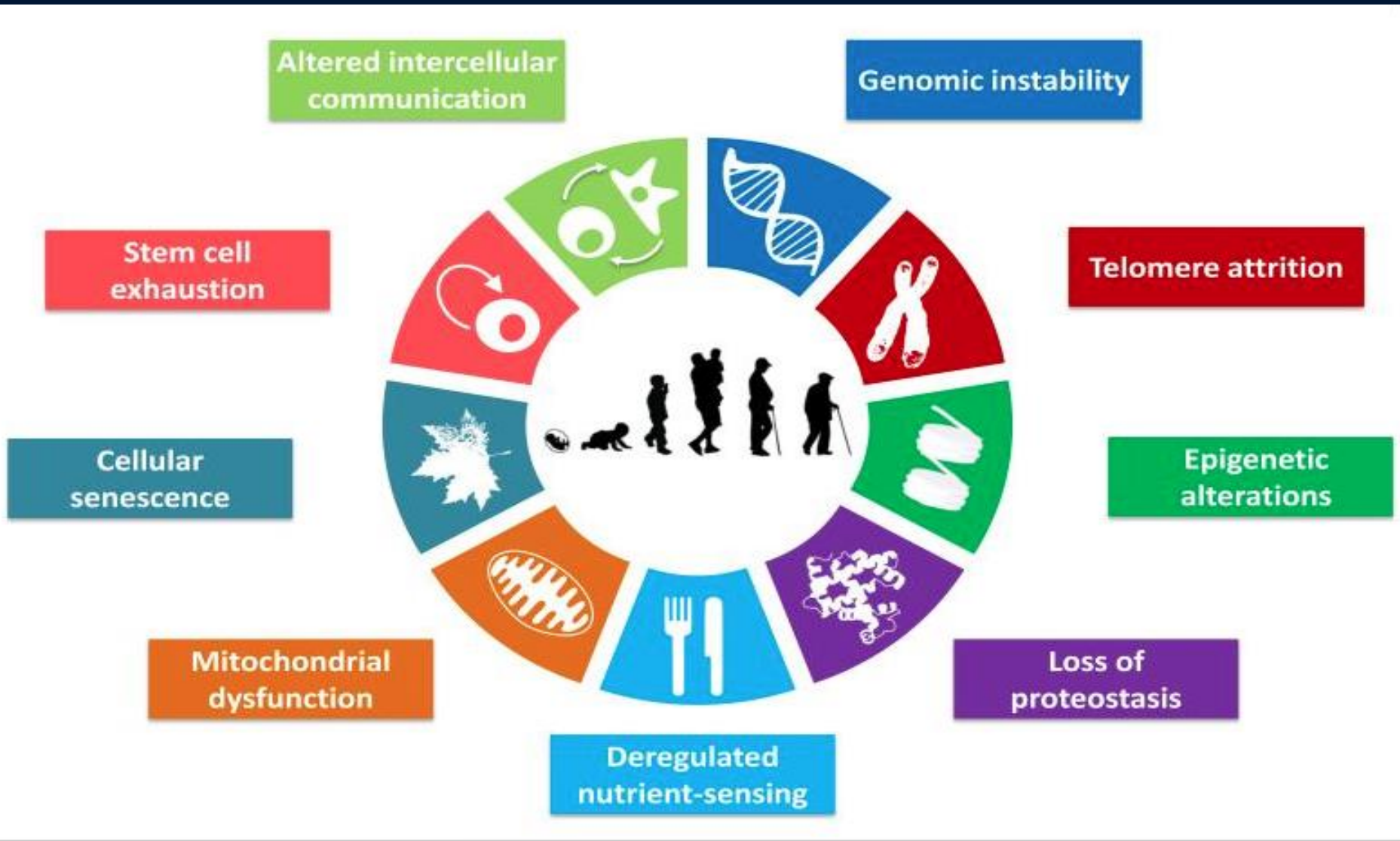
MECHANISMS CONTRIBUTION TO STEM CELL AGING AND DYSFUNCTION



MECHANISMS CONTRIBUTION TO STEM CELL AGING AND DYSFUNCTION



THE REDUCTIONIST APPROACH TO SLOW AGING

DNA damage repair pathways

- Telomere reactivation

Improving proteostasis

- Rapamycin
- ↑Chaperone activity
- ↑Autophagy

Enhancing mitochondrial function

- Caloric restriction
- Resveratrol
- ↑NAD^+

Inhibition of ROS

- Antioxidants (e.g., NAC)
- Rapamycin
- p38 inhibitor

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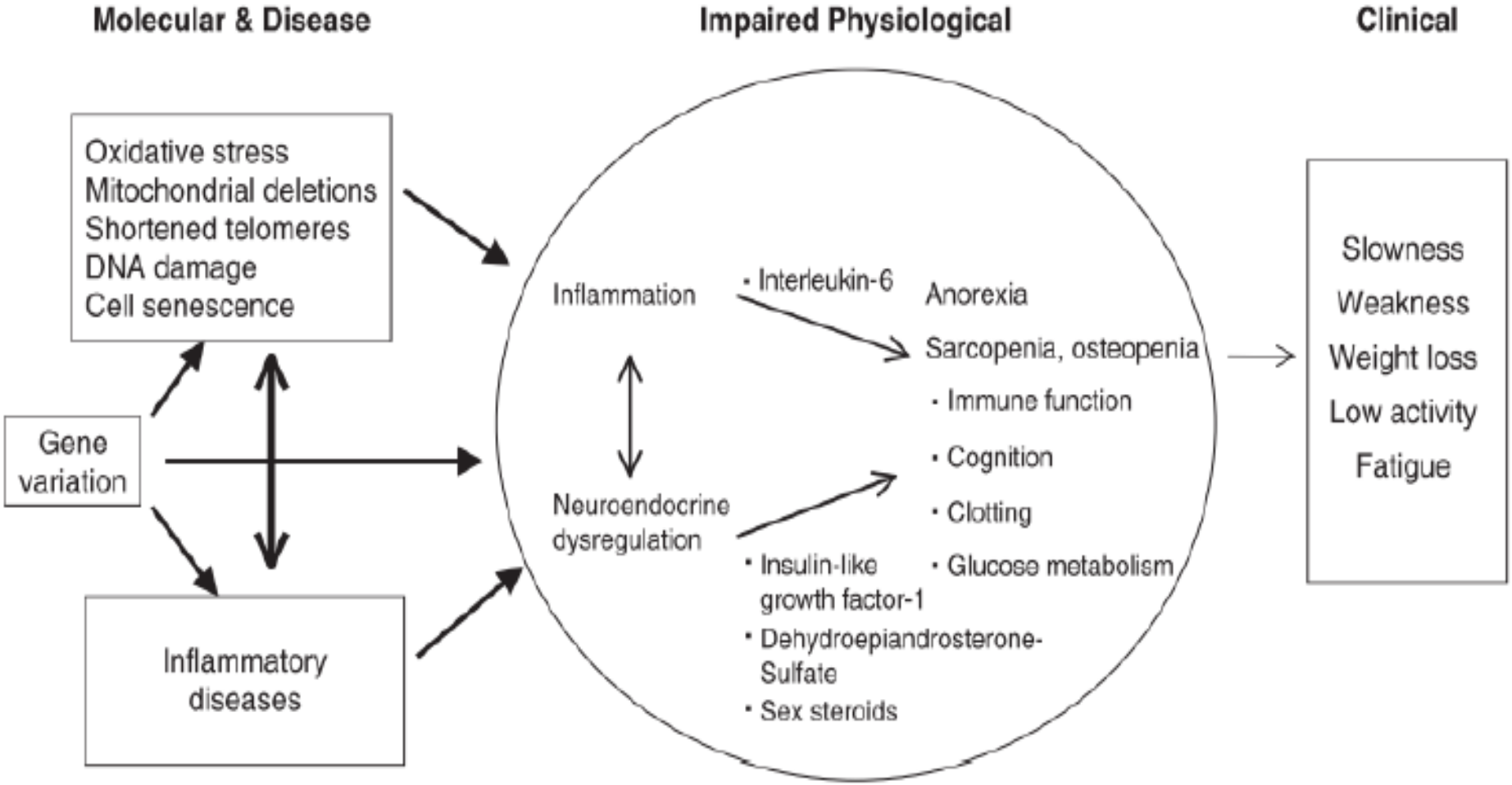
Overview of molecular, physiological, and clinical pathway to frailty.

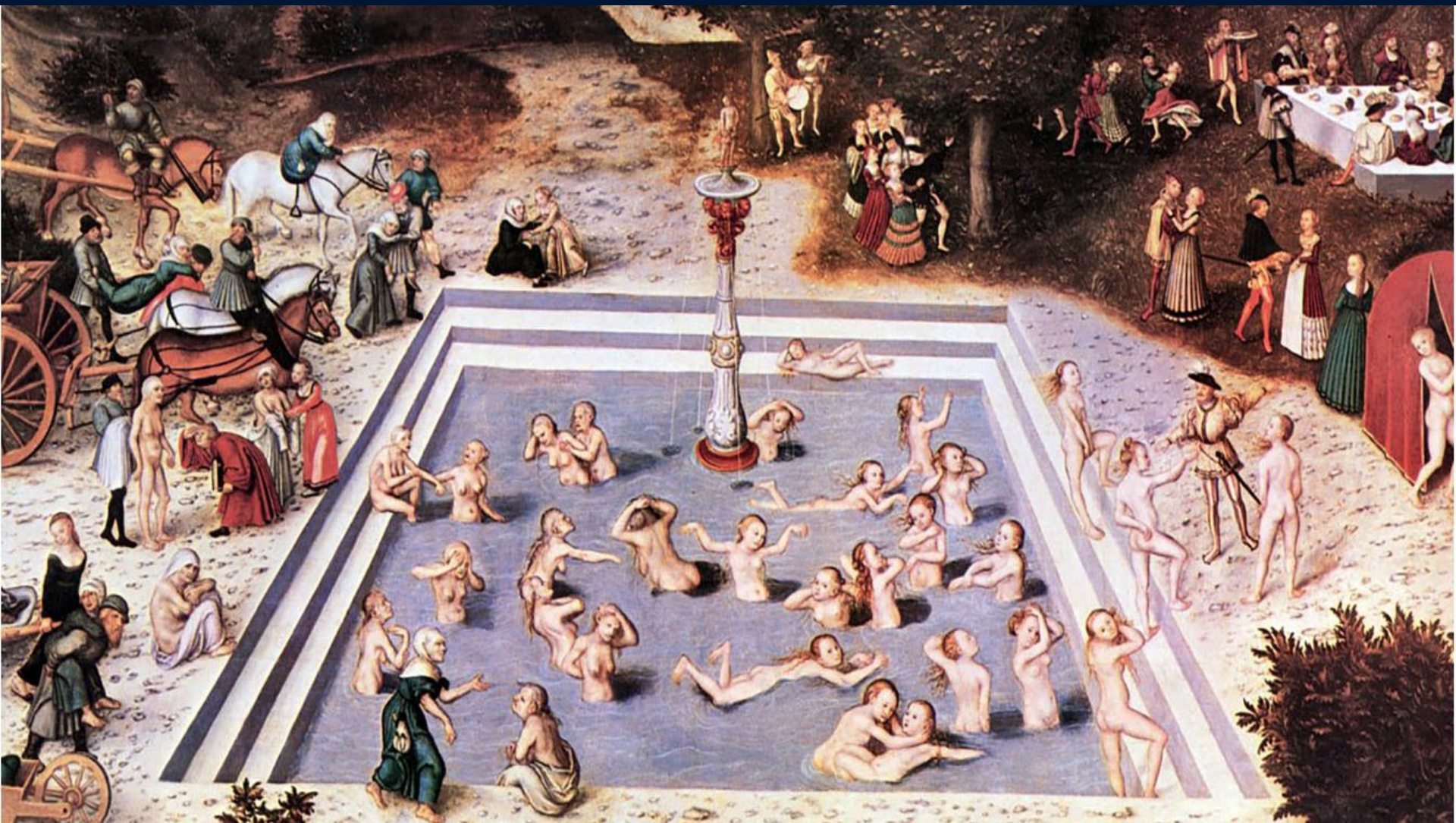


YOUNG BLOOD FOR AGING





THE FOUNTAIN OF YOUTH
Lucas Cranach The Elder



HISTORY OF YOUNG BLOOD FOR AGING IN HUMANS

- In 1615, Andreas Libavius proposed connecting the arteries of an old man to those of a young man.
- In 1660 Robert Boyle in London in 1660, wrote “The Prolongation of Life”. This might be achieved, he hoped, by replacing old blood with new.
- **In October 2009 , Maharaj: FDA,IND for infusion of young donor white cells for treating Cancer, a disease of aging.**
- In October 2014 ,Wyss-Coray: “In blood there are factors that orchestrate the aging process”.

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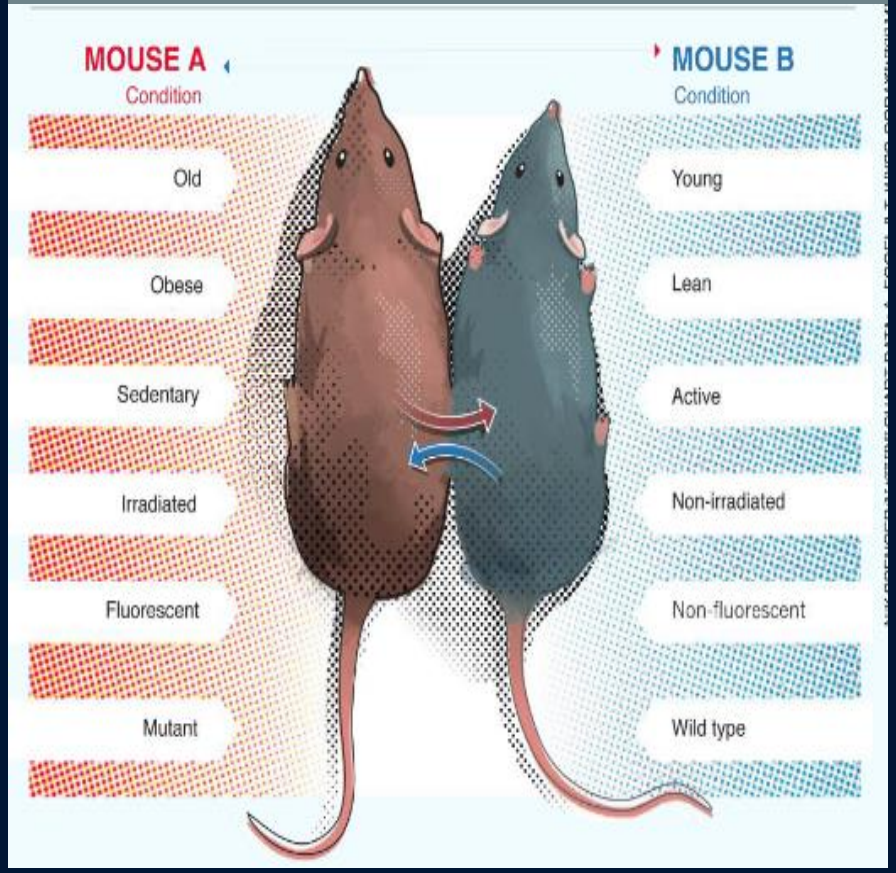
SHARE AND SHARE ALIKE



- **Parabiotic experiments, in which two animals share a common bloodstream were first attempted in the 1860s.**
- **Recently researchers have looked at old and young mouse pairs to understand how young blood helps to repair many tissues.**

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YOUNG STEM CELL MOBILIZED PLASMA: A NOVEL THERAPY FOR AGING/FRAILTY

Live Longer Live Well

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SIZE OF THE PROBLEM

It is estimated that there will be 2 billion people over the age of 65 worldwide by 2050

Clegg, A., et al (2013), “Frailty in elderly people”, Lancet, 381(9868), 752-762.

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YOUNG BLOOD TO TREAT CANCER A DISEASE OF AGING

Heliyon

ELSEVIER

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24 October 2017

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Heliyon 3 (2017) e00438.
doi: 10.1016/j.heliyon.2017.e00438

CrossMark

Young donor white blood cell immunotherapy induces extensive tumor necrosis in advanced-stage solid tumors

Dipnarine Maharaj [a,*], **Pedro G. Vianna** [a,b], **Wendy Ward** [a], **Anthony J. Messina** [a], **Trevor Rayborn** [a], **Jacqueline V. Gouvea** [a], **Richard D. Hammer** [c], **Zheng Cui** [d]

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[b] *Department of Medicine, Stanford University School of Medicine, Stanford, California 94305, USA*

[c] *Department of Pathology, University of Missouri School of Medicine, Columbia, Missouri 65212, USA*

[d] *Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157, USA*

METHOD OF REPAIRING AGE AND DISEASE IMMUNE DYSFUNCTION AND CELLULAR SENESCENCE WITH LYMPHOID STEM CELLS AND THEN RE-APPLYING THOSE FOR THERAPEUTIC USE

SERIAL NUMBER **14/274,224**

Dr. Dipnarine Maharaj

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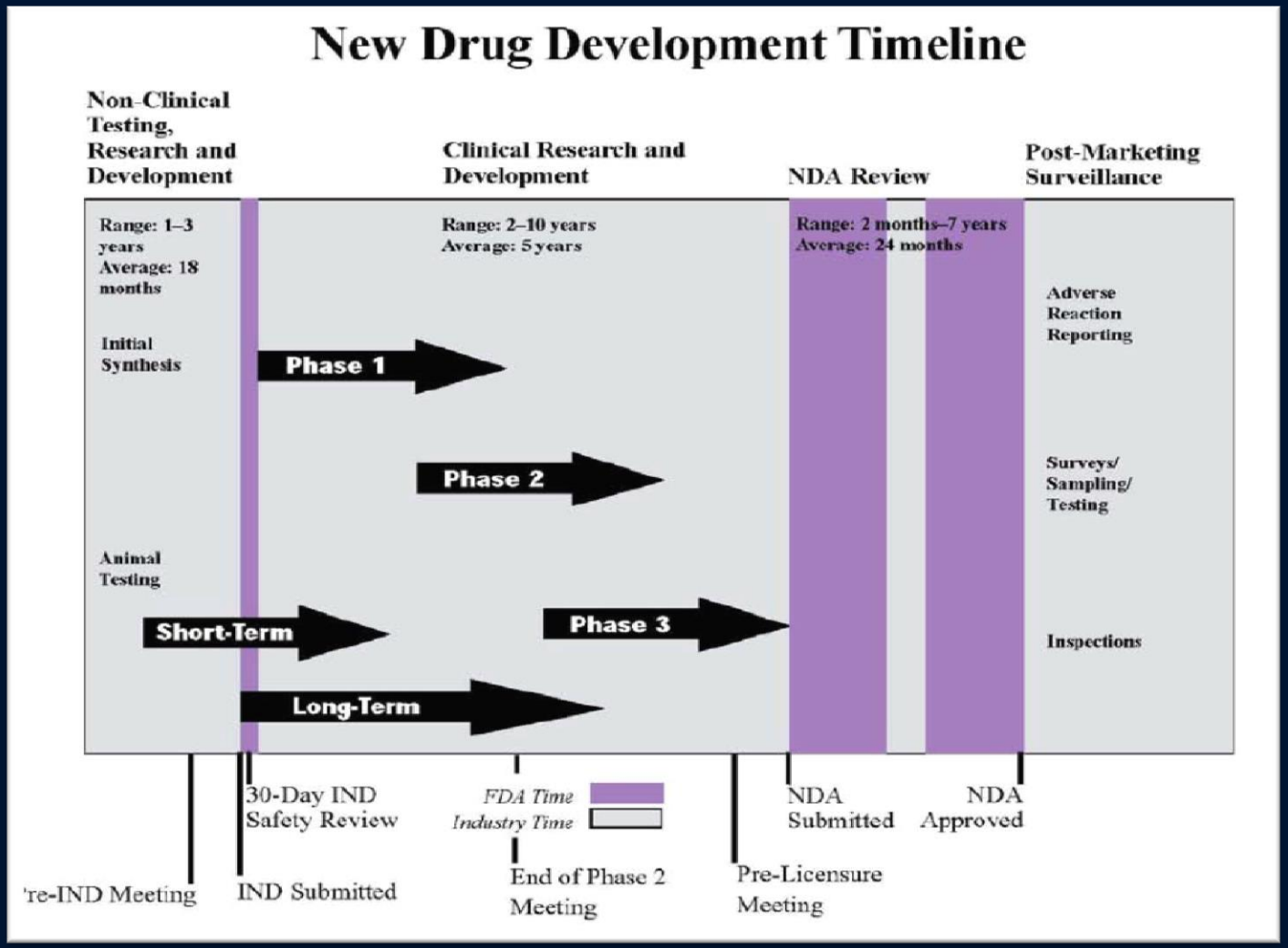
PROTOCOL FOR AGING/FRAILTY DEVELOPMENT TIMELINE



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WHY YOUNG BLOOD?

- **When we are born, our blood is awash with hundreds of proteins that help our tissues grow and heal.**

- **In adulthood, the levels of these pro-youthful proteins plummet.**

- **As these pro-youthful proteins vanish from the blood, tissues around the body start to deteriorate, causing chronic inflammation that damages cells and accelerates aging.**

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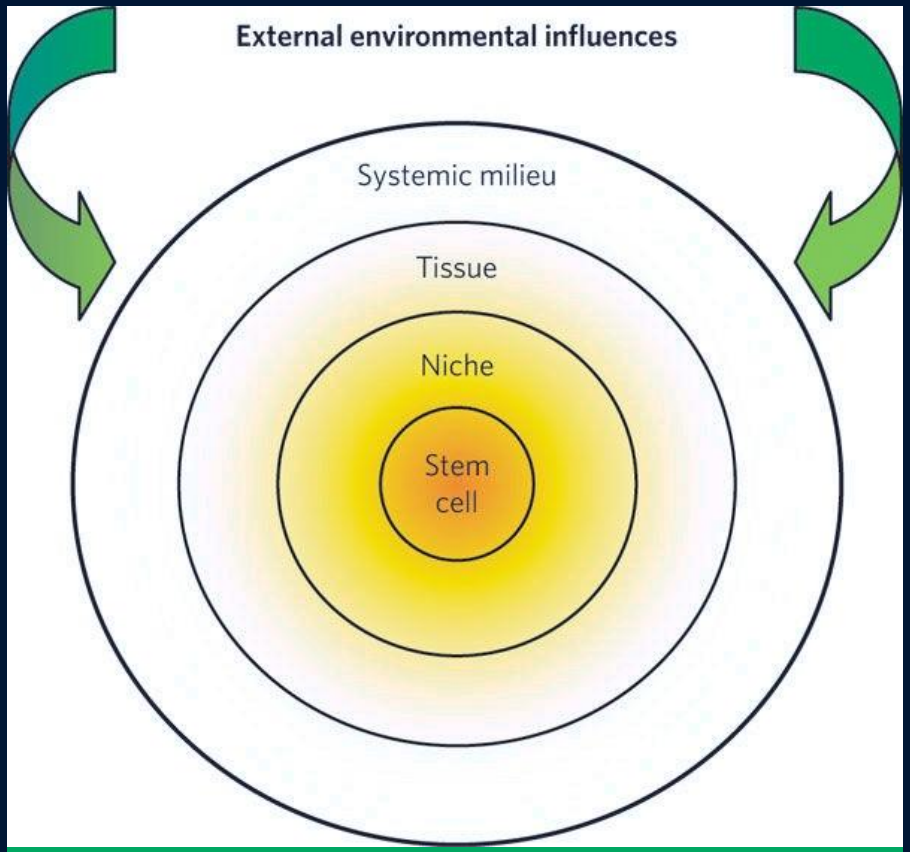
STEM CELLS ARE RESPONSIBLE FOR NORMAL TISSUE HOMEOSTASIS AND REPAIR



Rando, Thomas A. "Stem cells, ageing and the quest for immortality." *Nature*441.7097 (2006): 1080.

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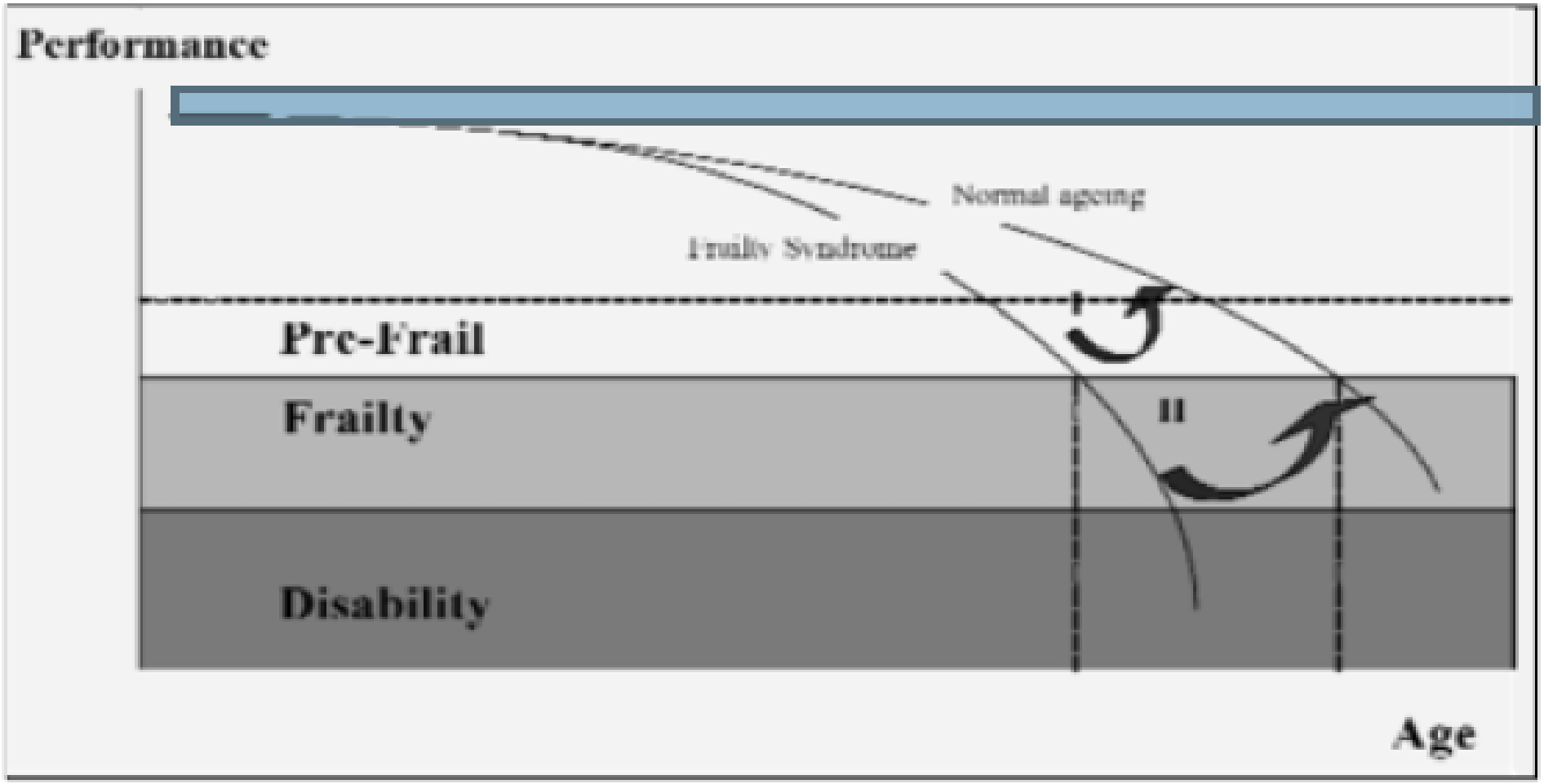
FRAILTY SYNDROME



I stands for primary interventions and II for secondary interventions

FRAILTY

- Nutritional Status (Weight Loss)
- Energy (Exhaustion)
- Physical Activity (Leisure time activity)
- Mobility (Gait Speed)
- Strength (Grip Strength)
- Cognition
- Mood
- Mental Health

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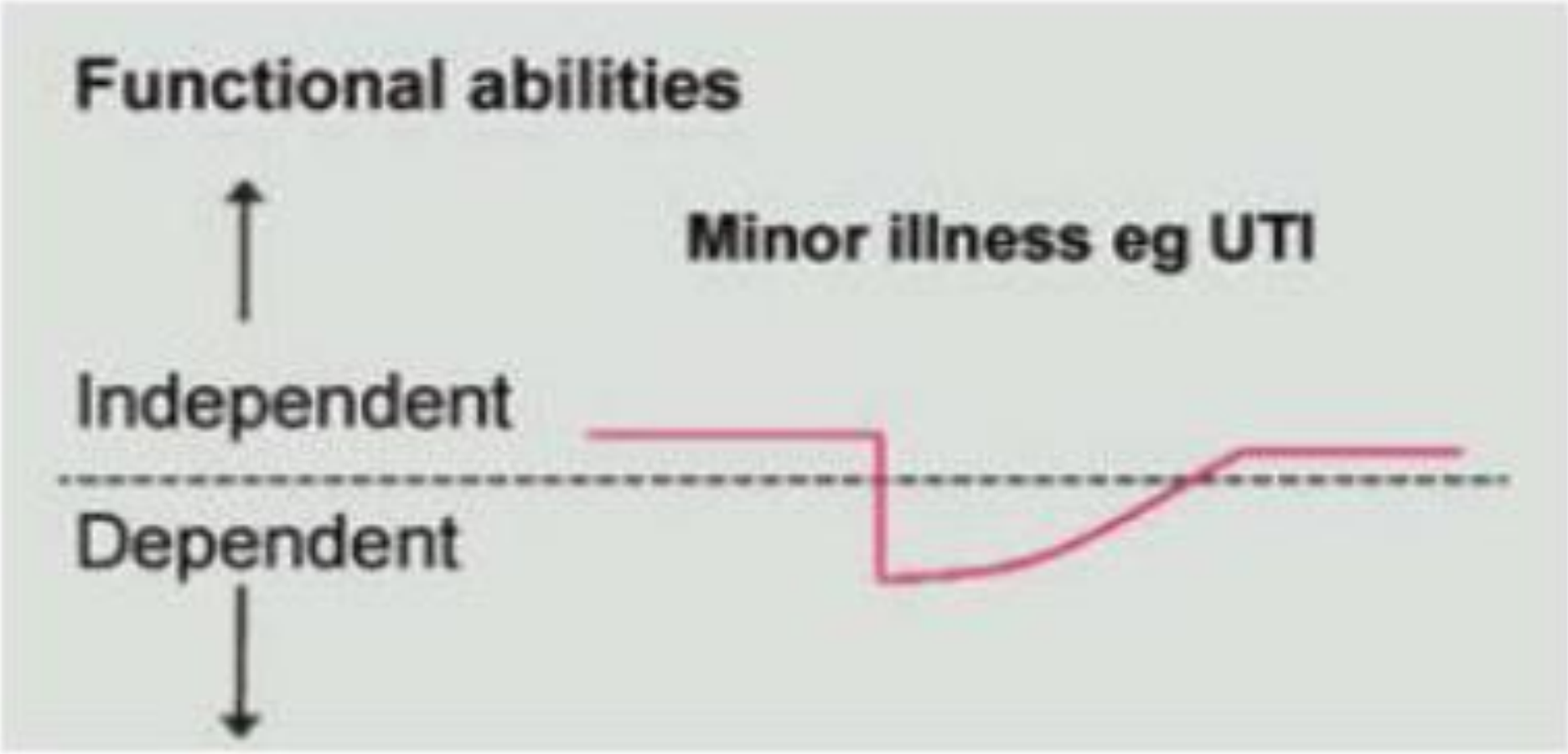
Vulnerability to sudden change in health due to reduced functional reserve in frail older people



Trial finds blood-plasma infusions for Alzheimer's safe, promising

NOV. 2017

Stanford University School of Medicine investigators have reported success in an early-phase clinical trial examining the safety, tolerability and feasibility of administering infusions of blood plasma from young donors to participants with mild to moderate Alzheimer's disease.

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Trial finds blood-plasma infusions for Alzheimer's safe, promising

On two of three different assessments of functional ability, participants showed statistically significant improvement

The capacity to perform basic tasks essential to independent daily life, such as remembering to take medications and being able to pay bills and prepare one's own meals.

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Breakthrough Stem Cell Study Offers New Clues to Reversing Aging

NATURE | ARTICLE

日本語要約

Hypothalamic stem cells control ageing speed partly through exosomal miRNAs

Yalin Zhang, Min Soo Kim, Baosen Jia, Jingqi Yan, Juan Pablo Zuniga-Hertz, Cheng Han & Dongsheng Cai

Affiliations | Contributions | Corresponding author

Nature **548**, 52–57 (03 August 2017) | doi:10.1038/nature23282

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By Dana P. Goldman, David Cutler, John W. Rowe, Pierre-Carl Michaud, Jeffrey Sullivan, Desi Peneva, an
S. Jay Olshansky

Substantial Health And Economic Returns From Delayed Aging May Warrant A New Focus For Medical Research

DELAYED AGING VS DISEASE-SPECIFIC RESEARCH

- Slowing the aging process is a realistic goal
- The Economic value of delayed aging is 7.1 trillion dollars over 50 years
- Greater investment to delay aging would:
  - Forestall Disease
  - Extend Healthy Life and
  - Improve Public Health

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ACP Internist Weekly | HEALTH SPENDING | OCTOBER 17, 2017

Frail elderly account for majority of potentially preventable Medicare spending

Among subpopulations of high-cost Medicare beneficiaries,

frail elderly patients account for the majority of potentially preventable spending, according to a new study.

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Association of Patient Frailty With Increased Morbidity After Common Ambulatory General Surgery Operations

Carolyn D. Seib, MD, MAS[1]; Holly Rochefort, MD[1]; Kathryn Chomsky-Higgins, MD, MS[1]; et al

» Author Affiliations

JAMA Surg. Published online October 11, 2017. doi:10.1001/jamasurg.2017.4007

Key Points

Question Is frailty associated with perioperative morbidity in patients undergoing ambulatory hernia, breast, thyroid, or parathyroid surgery?

Findings In this cohort study, an increasing National Surgical Quality Improvement Program modified frailty index was associated with a stepwise increase in the incidence of 30-day complications; an intermediate modified frailty index (2-3 frailty traits) and a high modified frailty index (≥4 frailty traits) were significantly associated with any type of complication and with serious complications, respectively, in multivariable analysis adjusting for other risk factors and clustering by operation. Anesthesia with local and monitored anesthesia care was the only modifiable covariate associated with decreased odds of serious 30-day complications.

Meaning Frailty is independently associated with perioperative morbidity in patients undergoing common ambulatory general surgery and should be considered in patient selection and counseling.

AGING V. DISEASE-SPECIFIC RESEARCH



COSTS OF AGING

DOI: 10.1377/hlthaff.2013.0052
HEALTH AFFAIRS 32,
NO. 10 (2013): 1698–1705
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The People-to-People Health
Foundation, Inc.

By Dana P. Goldman, David Cutler, John W. Rowe, Pierre-Carl Michaud, Jeffrey Sullivan, Desi Peneva, and S. Jay Olshansky

Substantial Health And Economic Returns From Delayed Aging May Warrant A New Focus For Medical Research

ABSTRACT Recent scientific advances suggest that slowing the aging process (senescence) is now a realistic goal. Yet most medical research remains focused on combating individual diseases. Using the Future Elderly Model—a microsimulation of the future health and spending of older Americans—we compared optimistic "disease specific" scenarios with a hypothetical "delayed aging" scenario in terms of the scenarios' impact on longevity, disability, and major entitlement program costs. Delayed aging could increase life expectancy by an additional 2.2 years, most of which would be spent in good health. The economic value of delayed aging is estimated to be $7.1 trillion over fifty years. In contrast, addressing heart disease and cancer separately would yield diminishing improvements in health and longevity by 2060—mainly due to competing risks. Delayed aging would greatly increase entitlement outlays, especially for Social Security. However, these changes could be offset by increasing the Medicare eligibility age and the normal retirement age for Social Security. Overall, greater investment in research to delay aging appears to be a highly efficient way to forestall disease, extend healthy life, and improve public health.

Dana P. Goldman (dana.goldman@usc.edu) is a professor of public policy and pharmaceutical economics and the director of the Schaeffer Center for Health Policy and Economics at the University of Southern California, in Los Angeles.

David Cutler is a professor of economics at Harvard University, in Cambridge, Massachusetts.

John W. Rowe is a professor of health policy and management at Columbia University, in New York City.

Pierre-Carl Michaud is a professor of economics at the University of Quebec, in Montreal.

ffrey Sullivan is director of tic consulting at n Health Economics, in s.

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