I’ve Collected Blood, Now What?

Incorporating Geroscience into Clinical Research

JEREMY D. WALSTON, MD
RAYMOND AND ANNA LUBLIN PROFESSOR OF MEDICINE
JOHNS HOPKINS UNIVERSITY
WWW.FRAILTYSCIENCE.ORG
Overview

- Modeling Physical Frailty and Resiliency
- Feasible Measures of Physiology and Biology
- Inflammatory/Immune System Measures
- Suggested Guidelines
Scientific/Gerontological Models

Physical Frailty
Physical Resiliency
Chronic Inflammation
Complex Pathway to Physical Frailty

Potential Triggers
- Molecular Aging
- Mitochondrial decline
- DNA Methylation
- Apop/Necroptosis
- ↑ Senescent Cells
- ↑ Altered autophagy
- Genetic Variation
- Environment
- Chronic Diseases
  - Depression
  - Cognitive Decline
  - Cancer
  - Chronic Infection
  - Cardiovascular
  - Diabetes/Obesity

Physiology
- ↑ Inflammation
- ↑ HPA Axis
- ↑ Sympathetic nervous system
- ↑ Angiotensin system action
- ↓ Energy production
- Altered Anabolic Hormones

Clinically Apparent
- Weakness
- Fatigue
- Weight loss
- Slowness

Outcomes
- Dependence
- Disability
- Chronic Diseases
- Cognitive Decline
- Mortality

Walston J, 2016
Clinically Apparent vs. Invisible Frailty Measures

- Weakness
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Dynamic physical property declines
- Anemia
- Increased clotting factors
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
- Low activity
- Slow gait
- Increased clotting factors
- Clinically Apparent
- Low IFG-1 Glucose intolerance
- Altered Energy Metabolism & Endocrine Systems
- Low DHEA-S
- Clinically Apparent vs. Invisible Frailty Measures
- Fatigue
- Immune/Inflammation
- HPA axis
- Altered Stress Response Systems
- Autonomic nervous system
- Mitochondrial dysfunction
- Epigenetic alterations
- Weight loss
- Mild cognitive impairment
- Low albumin & cholesterol
- Fatigue
Biomarkers from Stimulus-Response Experiments in Physical Resiliency

- ACTH Stimulation
- Diurnal Salivary Cortisol Profile
- Oral Glucose Tolerance Test
- Holter Monitoring
- Dynamic ex-vivo response of immune cells
- Orthostatic Blood Pressure
**CI Definition**

Chronic inflammation (CI) is a heterogeneous, low grade activation of the innate immune system that remains ‘on’ after activation.

Acute inflammation is high grade activation of innate immune system that targets specific acute injury or illness and shuts down after acute condition resolves.
Consequences of CI in Older Adults

Worsening Chronic Disease States

Functional decline
- Sarcopenia, fibrotic tissue replacement
- Satellite Cell Decline

Cognitive decline
- Neurodegeneration and MCI

Physical Frailty
- Poor response to vaccines
- Altered Stress Response Systems and Energy Metabolism
Intrinsic or Age-Related Etiologies (Geroscience)

Necrotosis-related Cellular Debris (immune modulating)
Senescent Cells (fat, fibroblasts)
Altered Immune System (senescent, clonal cells)
Altered Gut Wall and Microbiome
Gene Variation (contributory or preventative)
Mitochondrial damage and oxidative stress
Intrinsic (Ageing) Alterations in the Innate Immune System

**Changes due to aging**

- Increased production of proinflammatory cytokines
- Chronic Inflammation
- Increased activity at the basal state

**SPECIFIC STIMULATION**

- Neutrophils
  - Impaired chemotaxis, phagocytosis, and NET formation
  - ↓ Signal transduction, e.g., to TLR-1, GM-CSF
  - ↑ PI-3 kinase signal transduction

- Monocytes
  - ↓ TLR1/2-dependent IL-6 and TNF-α production
  - Impaired expression of costimulatory proteins
  - ↑ TLR-5-induced cytokine production
  - ↑ in IL-10 production

- Dendritic cells
  - ↓ TLR-induced cytokine production
  - ↓ IFN gene expression
  - ↑ Basal cytokine production

- NK cells
  - ↑ CD56dim CD16+ cytotoxic cells
  - ↓ Expression and function of cytotoxicity receptors
Best Serum Markers of CI to Date

1. **TNF-alpha R1** (*validated, less variable, biologically relevant)
2. **IL-6** (*validated, quite variable with illness)
3. **CRP** (utilized in clinical practice, distal signal, more vascular)

** cytokines have good evidence of consequential biological activity
## Cytokines and Mortality over 10 Years in CHS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>logCRP</td>
<td>72</td>
<td>&lt;.0001</td>
<td>1.22</td>
</tr>
<tr>
<td>logIL6</td>
<td>287</td>
<td>&lt;.0001</td>
<td>1.44</td>
</tr>
<tr>
<td>logTNFRI</td>
<td>274</td>
<td>&lt;.0001</td>
<td>1.48</td>
</tr>
<tr>
<td>logIL18</td>
<td>24</td>
<td>&lt;.0001</td>
<td>1.12</td>
</tr>
<tr>
<td>logIL1RA</td>
<td>56</td>
<td>&lt;.0001</td>
<td>1.19</td>
</tr>
<tr>
<td>age</td>
<td>772</td>
<td>&lt;.0001</td>
<td>1.80</td>
</tr>
<tr>
<td>WSS</td>
<td>281</td>
<td>&lt;.0001</td>
<td>1.47</td>
</tr>
<tr>
<td>PCS</td>
<td>237</td>
<td>&lt;.0001</td>
<td>1.43</td>
</tr>
<tr>
<td>IIS</td>
<td>433</td>
<td>&lt;.0001</td>
<td>1.64</td>
</tr>
</tbody>
</table>

Varadhan R et al, JGMS, 2014
Chronic Inflammation and Future MCI

Gross A. et al, 2019, Frontiers in Neurology
IL-6 and Multisystem Dysregulation

Rhesus monkeys injected with low dose IL-6 developed multisystem changes

- 10% lean body mass decline by DEXA within 30 days
- Anemia & osteopenia
- Decreased albumin & cholesterol
- Increased CRP, alkaline phosphatase

Binkley, NC, et al. 1994 and Ershler & Keller, 2000
Chronic TNF-Alpha R1

- Contributes to necroptosis signaling and DAMP release
- DAMP drives further inflammatory pathway activation
- Accelerates cell loss in frailty
Indoleamine 2,3-dioxygenase (IDO)

↑ Chronic Inflammation
IL-6, TNFα, INFγ
Summary

- Use Modeling to Develop Clinical Connections to Aging Phenotypes and Measurement Priorities
- Consider Physiology and Biology Measures
- Think Feasibility and Tight Focus for Present Projects
- Absolutely Store Samples for Broader Future Opportunities
- Think Intervention Development!! (feasible diagnostics, treatment monitoring, in addition to clinical measures)
Acknowledgments

Claude D. Pepper Older Americans Independence Center
National Institute on Aging, P30-AG021334

Characterizing Resiliencies to Physical Stressors in Older Adults: A Dynamical Physiological Systems Approach, UH3AG056933
## Acknowledgements

<table>
<thead>
<tr>
<th>Peter Abadir</th>
<th>Nick Miclik</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor Bopp</td>
<td>Lolita Nidadavolu</td>
</tr>
<tr>
<td>Tae Chung</td>
<td>Esther Oh</td>
</tr>
<tr>
<td>Neal Fedarko</td>
<td>Sadra Sapheri</td>
</tr>
<tr>
<td>Jackie Langdon</td>
<td>Jeremy Walston</td>
</tr>
<tr>
<td>Sean Leng</td>
<td>Reyhan Westbrook</td>
</tr>
<tr>
<td>Thomas Laskow</td>
<td>Yuqiong Wu</td>
</tr>
<tr>
<td>Huifen Li</td>
<td></td>
</tr>
</tbody>
</table>