

American Geriatrics Society
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**Research Agenda for Frailty in Older Adults:
Towards a Better Understanding of Physiology and Etiology**
Tuesday, January 27 - Friday, January 30, 2004
Admiral Fell Inn, Historic Fell's Point
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Conference Organizers

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Stephanie Studenski, MD, MPH, Visiting Prof., Department of Medicine, University of Pittsburgh, Pittsburgh, PA
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Attendees

Mark Bach, MD, PhD, Director, Clinical Research, Endocrinology & Metabolism, Merck & Co., Inc., Rahway, NJ
Ludovico Balducci, MD, H. Lee Moffitt Cancer Center Research Institute, Tampa, FL
Brock Beamer, MD, Assistant Professor, Johns Hopkins University School of Medicine, Baltimore, MD
Howard Bergman, MD, Canadian Initiative on Frailty and Aging, Montreal, Canada
Caroline Blaum, MD, Assoc. Prof. of Internal Medicine Geriatrics, Univ. of Michigan Med School, Ann Arbor, MI
Vilhelm Bohr, MD, PhD, National Institute on Aging/GRC, Baltimore, MD
Cynthia Brown, MD, Assistant Professor, University of Alabama at Birmingham, Birmingham, AL
Judith Campisi, PhD, Lawrence Berkeley National Laboratory, Life Sciences Division, Berkeley, CA
Anne Cappola, MD, ScM, Asst. Prof. of Medicine & Epidemiology, University of Pennsylvania, Philadelphia, PA
Christy Carter, PhD, Wake Forest University School of Medicine, Winston-Salem, NC
Chiara Cavazzini, MD, National Public Health System, Rome, Italy
Richard Cawthon, MD, PhD, University of Utah, Salt Lake City, UT
Aravinda Chakravarti, PhD, Prof. & Director, Institute of Genetic Medicine, Johns Hopkins Univ., Baltimore, MD
Laura Dugan, MD, Assoc. Prof. of Neurology, Anatomy & Neurobiology, Washington University, St. Louis, MO
Hannelore Ehrenreich, MD, DVM, Max-Planck-Institute for Experimental Medicine, Goettingen, Germany
William Evans, PhD, Director, Nutrition, Metabolism & Exercise Pgm, Univ of Arkansas, Little Rock, AR
Neal Fedarko, PhD, General Clinical Research Center, Johns Hopkins Bayview Medical Center, Baltimore, MD
Tom Gill, MD, Associate Professor of Medicine, Yale University School of Medicine, New Haven CT
Brett Goodpaster, PhD, Assistant Professor of Medicine, University of Pittsburgh, Pittsburgh, PA
Mark Hallet, MD, Human Motor Control Section, Medical Neurology Branch, NINDS, Bethesda, MD
Jeffrey Hausdorff, PhD, Assistant Professor of Medicine, Beth Israel Deaconess Med Center, Boston, MA
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Nancy Jenny, PhD, Research Asst Prof, Dept of Pathology, College of Medicine, Univ of Vermont, Colchester, VT
Fran Kaiser, MD, Clinical Professor of Medicine, UT Southwestern & Adjunct Prof of Medicine, St Louis Univ.
Doug Kiel, MD, MPH, Associate Professor of Medicine, Harvard Medical School Division on Aging, Boston, MA
James Kirkland, MD, PhD, MSc, Assoc. Prof. of Medicine, Boston University School of Medicine, Boston, MA
Lewis Lipsitz, MD, Gerontology Division Chief, Beth Israel Deaconess Med Center, Boston, MA
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Mary Tinetti, MD, Professor of Medicine, Epidemiology & Public Health, Yale University, New Haven, CT
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Tuesday, January 27

5:30-8:30 pm The conference will begin with an evening dinner and after-dinner speakers. Those providing introductory remarks will be: **Linda Fried, M.D., M.P.H.** (Welcome Remarks); **T. Franklin Williams, M.D.**; **Evan Hadley, M.D.**

After-dinner presentation: "Dynamics of Stability: The Physiologic Basis of Functional Health and Frailty"
Speaker: **Lewis Lipsitz, M.D.**

Wednesday, January 28

Day 1: Introduction to Frailty in Older Adults

I. The syndrome of frailty, what it is and is not

8:30-9:00 Introduction and Overview: Speaker: **Linda P. Fried, M.D., M.P.H.**

Goals and Content: Overarching perspective and premise of the conference:

- a) Current understanding as to the phenotype(s) of frailty, and areas of disagreement.
- b) Review of organizing hypotheses regarding etiology that set the basis for the program and discussion.
- c) Field is well enough developed to set a research agenda, identify directions needed and applicable models, and, with physiologists and molecular biologists participating, to refine the phenotype through conference discussion and further research

9:00-9:40 Respondents: **Stephanie Studenski, M.D.**; **Luigi Ferrucci, M.D., Ph.D.**; **Anne Newman, M.D.**, **John Morley, M.D.**; and **Mary Tinetti, M.D.** **9:40-9:55** Discussion

Day 1 morning pathophysiology section:

II. Pathophysiologic mechanisms of frailty

Goals and Content: Current evidence supports hypotheses that frailty is a multisystem physiologic dysregulation of aging, with systems at the core of this syndrome being endocrine and immune/inflammatory function, and their, as well as other, effects on muscle, bone and brain, and the cumulative effects of changes in each of these systems on frailty itself. This discussion will begin by providing broad hypotheses as to the linkage of phenotypic components of frailty to underlying pathophysiologic pathways. Then, the focus for the following presentations will be on the evidence for expressions of loss of physiologic reserve, manifestation in the presence of stressors, multisystemic dynamics, cumulative systems affected, and potential unifying hypotheses. The conference will also consider whether evidence for involvement of multiple physiologic systems sheds light on underlying mechanisms that are affecting multiple systems.

9:55-12:30 Pathophysiologic mechanisms, Part 1:

9:55-10:00 Introduction: Lewis Lipsitz, M.D.

Evidence for dysregulation and decrements in physiologic reserve, which are latent until the system is stressed.

10:00-10:20 Clotting process dynamics: A pathophysiologic stress response: **Russell Tracy, PhD**

10:20-10:30 Discussion

10:30-10:50 Ineffective hematologic responses to chemotherapy in frail older adults: **Lodovico Balducci, M.D.**

10:50-11:00 Discussion

11:00-11:15 Break

11:15-11:35 Responses to anesthesia and surgical stress: **Jeffrey Silverstein, M.D.**

11:35-11:45 Discussion

11:45-12:05 Dysregulation of gait and responses to postural dysequilibrium: **Jeffrey Hausdorff, Ph.D.**

12:05-12:15 Discussion

12:15-12:30 General discussion of relationships of impaired stress responses to frailty

12:30-1:30 Lunch

1:30 Pathophysiologic mechanisms, Part II: Dysregulation of specific physiologic systems (e.g., inflammatory, endocrine, and metabolic) in frailty.

1:30-1:55 Inflammation: evidence for systemic dysregulation in frailty. Speaker: **Jeremy Walston, M.D.**

1:55-2:10 Discussion

2:10- 2:35 Cytokines: application of evidence regarding inflammatory cytokines and frailty. Speaker: **Ronenn Roubenoff, M.D.**

2:35-3:00 Panel discussion: **William Ershler, M.D.; Tamara Harris, M.D., M.S.**

3:00-3:15 Break

3:15 The aging endocrine system

3:15-3:35 Relationship of androgens and estrogens to body composition and other frailty related alterations;

Speaker: **Anne Cappola, M.D., M.Sc.**

3:35-3:50 Discussion

3:50-4:15 Interplay between sex steroids and cytokines; Speaker: **Ronenn Roubenoff, M.D.**

4:15-4:25 Discussion

4:25-4:45 Relationship of growth hormone to body composition and other frailty-related alterations; Speaker: **Doug Kiel, M.D.**

4:45-5:30 Comment and panel-led discussion - Moderator: **Fran Kaiser, M.D.**

Thursday, January 29

Day 2: Body composition in frailty: sarcopenia, tradeoffs of muscle and fat

8:30-8:50 Are muscle quality and strength equal contributors to frailty? Speaker: **Bret Goodpaster, Ph.D.**, University of Pittsburgh.

9:50-9:10 Functional reserve of muscle: changes with age and what we know about determinants. Speaker: **Tamara Harris, M.D., M.S.**, National Institute on Aging

9:10-9:25 Discussion

9:25-9:40 Obesity and Inflammation: Does fat influence frailty? Speaker: **Caroline Blaum, MD**, University of Michigan

9:40-10:00 Does dysdifferentiation of progenitor cells contribute to frailty? Speaker: **James Kirkland, M.D., Ph.D.**, Boston University School of Medicine

10:00-10:15 Discussion

10:15-10:30 Break

II. Subclinical neurological dysfunction as a marker of frailty in older adults

11:00-11:25 Speaker: **Luigi Ferrucci, M.D., Ph.D.**

Description: Previous studies have hypothesized that mobility, muscle strength and fatigue are important components of the frailty syndrome. It has been assumed that these are of cardiopulmonary and endocrinologic/inflammatory origin. However, all three conditions may be caused by primary neurologic damage. The plasticity of the CNS is the basis, as well, for most of the adaptive instrumental and behavioral strategies that an individual develops. The presenter will show data demonstrating that a high percentage of older persons have abnormal neurological signs and that these are associated with reduced physical function. It is hypothesized that potential mechanisms by which such subclinical, "soft" neurological damage may have such an impact could be via triggering the metabolic pathway that is characteristic of the frailty syndrome. To address this, the speaker will ask: a) is there a specific neurological component of the frailty syndrome and how could this contribute to "loss of reserve?" and b) to what extent could the mobility and functional components of the frailty syndrome be caused by primary neurological damage?

11:25- 11:40 Discussion lead by **Mark Hallett, M.D.**

11:45-12:30 Lunch (to be served at meeting)

III. Summary of evidence for multisystem dysregulation

12:30-1:30 Does interplay between systems suggest potential common underlying mechanism? **Brock Beamer, M.D., Neal Fedarko, Ph.D, Hannelore Ehrenreich, M.D., and Bruce Troen, M.D.**

Respondents: **William Ershler, M.D., Ph.D., William Evans, Ph.D., and Jeremy Walston, M.D.** Panelists will

comment on independent mechanisms, and, especially, relationships, interactions between mechanisms and systems. Panelists will integrate information across all discussions and presentations to this point.

1:30-2:00 Break

IV. Exploratory discussion: Theorizing about possible biologic mechanisms

A. Discussions will explore: What is known about the biology of frailty that connects molecular change to altered physiology?

2:00-2:15 Introduction

2:15- 2:35 How cell senescence may impact the development of frailty. Speaker: Judith Campisi, Ph.D.

2:35-2:55 Aravinda Chakravarti, Ph.D.: Lessons from the study of genetics of complex disorders: Can genetic variation be the ultimate cause of frailty?

2:55-3:20 Discussion

3:20-3:40 Break

B. Molecular biology of frailty

Charge to speakers: Could there be some commonality in age-related changes in molecular signaling systems that might impact endocrine, immune and muscle systems? Speakers to speculate on things that "go wrong" in the aging cell that could be related to problems we hypothesize are involved in frailty: mitochondria, energy metabolism, oxidative damage, telomere area. The speakers will consider genetic and molecular mechanisms underlying the phenotypic presentation of frailty.

3:40-3:45 Introduction to this section: **William Ershler, M.D.**

3:45-4:00 Oxidative damage and mitochondria linking cell systems to the whole organism. The speaker will consider how oxidative damage impacts the immune system, neurologic system, muscle, hormones, and, through these systems, frailty: **Laura Dugan, M.D.**

4:00-4:15 DNA repair: **Vilhelm Bohr, M.D., Ph.D.**

4:15-4:30 Gene variation and frailty: **Jeremy Walston, M.D.**

4:30-4:55 Mechanisms of aging and frailty: telomere length and organismal aging applications to frailty.

Speaker: **Richard Cawthon, M.D., Ph.D.**

4:55-5:30 Panel discussion: Putting it all together to show how genetic variation and molecular change contribute to the phenotype of frailty; Moderators: **Judith Campisi, Ph.D., William Ershler, M.D., Neal Fedarko, Ph.D.,** and **Bruce Troen, M.D.**

Friday, January 30

Day 3 I. Concluding synthesis of discussion on pathophysiology of frailty

8:30-9:10 Speakers: **Jack Guralnik, M.D., Ph.D., Linda Fried, M.D., M.P.H., Brock Beamer, M.D.,** and **Russell Tracy, PhD**

This discussion will summarize evidence from prior presentations regarding how people may become frail, in the absence or the presence, of diseases, and suggest directions for potential points of intervention.

9:10-9:30 Discussion: Observational research versus interventional research and models.

II. Animal models that could provide evidence on frailty

9:30-9:40 Introduction and goals of this session: **William Ershler, M.D.**

9:40-10:15 Aging cardiovascular mouse models: Applications in frailty research: **George Taffet, M.D.**

10:15-10:30 Break

10:30- 11:05 Rat model for midlife performance and prediction of longevity: applications to frailty?

Speaker: **Christy Carter, Ph.D.**

11:05-11:40 Panel discussion: **William Ershler, M.D., George Taffet, M.D,** and **Christy Carter, Ph.D.**

III. Potential for pharmacologic and nonpharmacologic interventions: Rationale and strategy for treatment; Exploratory theory and evidence

11:40-11:45 Introduction: **Stephanie Studenski, M.D., M.P.H.**

Speakers will focus on components or aspects of frailty such as strength, loss of muscle, weight loss, fatigue, or neurosensory decrements that might be amenable to being altered by the given intervention and provide very specific support from existing studies.

This talk will pose the following questions for each of the speakers to address:

- a. What is the rationale for this intervention?
- b. Who is the target population for this intervention?
- c. What are the main clinically measurable indicators of the mechanism of effect?

- d. What are the major elements of the clinical intervention?
- e. What key steps must be accomplished prior to initiating a clinical trial of this intervention?

Each speaker will have 15 minutes for presentation and 5 minutes for questions.

11:45-12:05 Nonpharmacologic intervention: physical activity for prevention or amelioration of frailty: **William Evans, Ph.D.**

12:05-12:25 Nonpharmacologic intervention: prehabilitation: **Tom Gill, M.D.**

12:25-12:40 Discussion

12:40-1:30 Lunch

1:30-1:50 Potential use of EPO: **Hannelore Ehrenreich, M.D.**

1:50-2:10 Anti-inflammatory agents: Statins: **Anne Newman, M.D., M.P.H.**

2:10-2:30 ACE inhibitors: **Marco Pahor, M.D., Ph.D.**

2:30-2:50 Growth Hormone: **Mark Bach, M.D., Ph.D.**

2:50-3:10 Testosterone and DHEA: **Anne Cappola, M.D.**

3:10-3:30 Discussion of pharmacologic agents with panel of speakers and audience: **Stephanie Studenski, M.D., M.P.H.** initial respondent and moderator.

3:30-4:00 Closing remarks: This will include a summary of the evidence re: animal models, potential points of intervention, and discussion of proposed research agenda: **William Ershler, M.D.** and **Jeremy Walston, M.D.**

4:00 Close of meeting