

AGING: PREVENTION, REVERSAL AND SLOWING



42nd Annual Meeting of the
American Aging Association

PRE-CONFERENCE
AGING AND NUTRITION
MAY 31, 2013

**SHERATON INNER HARBOR HOTEL
BALTIMORE, MARYLAND
JUNE 1-3**

SCHEDULE AT A GLANCE

<p><i>FRIDAY</i> <i>MAY 31, 2013</i></p> <p><i>PRE-PROGRAM</i></p>	<p><u>CHESAPEAKE BALLROOM</u></p> <p>8:30 AM – 8:45 AM OPENING REMARKS</p> <p>8:45 AM – 10:00 AM STUDENT/POST-DOC SUBMITTED ABSTRACT SESSION</p> <p>10:00 AM – 10:30 AM BREAK</p> <p>10:30 AM – 12:30 PM CELLULAR BASIS OF FOOD AND EFFECTS</p> <p>12:30 PM – 1:30 PM LUNCH ON YOUR OWN</p> <p>1:30 PM – 3:30 PM ANIMAL MODELS</p> <p>3:30 PM – 4:00 PM BREAK</p> <p>4:00 PM – 6:15 PM TRANSLATIONAL RESEARCH</p> <p>6:30 PM -8:00 PM AGE WELCOME RECEPTION</p>
--	---

*SATURDAY
JUNE 1, 2013*

*AGING:
PREVENTION,
REVERSAL AND
SLOWING*

CHESAPEAKE BALLROOM

8:15 AM – 8:30 AM
OPENING REMARKS

8:30 AM – 9:30 AM
KEYNOTE ADDRESS: STEPHEN HELFAND, MD

9:30 AM – 10:35 AM
LONGEVITY AND HEALTHSPAN: LESSONS FROM FLIES TO HUMANS

10:35 AM – 11:00 AM
BREAK

11:00 AM – 12:10 PM
LONGEVITY AND HEALTHSPAN: LESSONS FROM FLIES TO HUMANS
CONTINUED

12:10 PM – 1:30 PM
LUNCH ON YOUR OWN

1:30 PM – 2:20 PM

CHESAPEAKE BALLROOM

VINCENT CRISTOFALO AWARD LECTURE
*NUTRIENT SIGNALING PATHWAYS REGULATE AGING AND DISEASES:
FROM YEAST TO HUMANS*

2:30 PM – 3:50 PM

CHESAPEAKE BALLROOM **LOCH RAVEN BALLROOM**
SARCOPENIA: STRATEGIES FOR SUBMITTED ABSTRACTS
PREVENTING, REVERSING AND
SLOWING

3:50 PM – 4:15 PM
BREAK

4:15 PM – 5:45 PM

CHESAPEAKE BALLROOM **LOCH RAVEN BALLROOM**
SARCOPENIA: STRATEGIES FOR SUBMITTED ABSTRACTS
PREVENTING, REVERSING AND
SLOWING

6:00 PM – 7:00 PM

CHESAPEAKE GALLERY
COCKTAIL RECEPTION AND POSTER SESSION I

7:00 PM – 8:30 PM

CHESAPEAKE BALLROOM
SPECIAL STUDENT SESSION

*SUNDAY
JUNE 2, 2013*

*AGING:
PREVENTION,
REVERSAL AND
SLOWING*

CHESAPEAKE BALLROOM

8:00 AM – 10:15 AM
SLOW THE PACE OF AGING: ROLE OF MIMETICS

10:15 AM – 10:45 AM
BREAK

10:45 AM – 12:45 PM
IMPACT OF DIETARY INTERVENTIONS IN PREVENTING, REVERSING,
AND SLOWING BIOLOGICAL AGING PROCESSES

12:45 PM – 2:00 PM
HARBORVIEW BALLROOM
AWARD LUNCHEON AND
DENHAM HARMAN AWARD LECTURE

2:00 PM – 4:15 PM
CHESAPEAKE BALLROOM **LOCH RAVEN BALLROOM**
BENCH TO BEDSIDE TO TRANSATLANTIC
HEALTHCARE SYMPOSIUM

4:15 PM – 4:45 PM
BREAK

4:45 PM – 5:45 PM
CHESAPEAKE BALLROOM
MARK SMITH ADDRESS
RAPAMYCIN: THE FIRST LONGEVITY DRUG?

5:45 PM – 6:15 PM
CHESAPEAKE BALLROOM
SPECIAL LECTURE
IT'S A GIG: THE TRANS-NIH GEROSCIENCE INTEREST GROUP

6:15 PM – 6:45 PM
CHESAPEAKE BALLROOM
AGE BUSINESS MEETING

6:45 PM – 8:00 PM
CHESAPEAKE GALLERY
COCKTAIL RECEPTION AND POSTER SESSION II

*MONDAY
JUNE 3, 2013*

*AGING:
PREVENTION,
REVERSAL AND
SLOWING*

CHESAPEAKE BALLROOM

8:00 AM – 9:45 AM
MECHANISMS TO PROTECT AGAINST BIOLOGICAL AGING AND
DISEASE

9:45 AM – 10:15 AM
BREAK

10:15 AM – 12:35 PM
CHESAPEAKE BALLROOM **LOCH RAVEN BALLROOM**
NATHAN SHOCK EMERGING TECHNOLOGIES
CENTER SYMPOSIUM FOR STUDYING AGING AND
HEALTHSPAN

12:35 PM – 1:00 PM
CHESAPEAKE BALLROOM
AWARDS CEREMONY FOR TRAINEES

TABLE OF CONTENTS

Acknowledgments	1
Conference Program	9
Poster Session outline	24
Award Presentation Abstracts.....	28
Session Abstracts	31
Poster Session Abstracts	56
Membership Directory	86

ACKNOWLEDGEMENTS

The American Aging Association and the College of Clinical Gerontology are grateful to the following sponsors for support of this conference as well as grant support from the National Institute of Aging. Their generous contributions have enabled us to continue a tradition of offering an excellent program of pertinent topics presented by speakers renowned in their fields, providing valuable mentoring opportunities for junior investigators and scholarships for students.

National Institute on Aging

Glenn Foundation for Medical Research

American Federation for Aging Research

British Society for Research on Ageing

Age UK

California Walnut Commission

Ocean Spray

Wild Blueberry Association of North America

U.S. Highbush Blueberry Council

The Buck Institute

Institute for Aging and Alzheimer's Disease Research

UNT Preventable Aging Foundation

California Strawberry Commission

California Dried Plum Board

Springer Science & Business Media

The Gerontological Society of America

Student Data Blitz Sponsors

Student Travel Award Sponsors



NATIONAL INSTITUTES OF HEALTH / NATIONAL INSTITUTE ON AGING

Overview

The National Institute on Aging (NIA), one of the 27 institutes and Centers of the National Institutes of Health, leads the federal government in conducting and supporting research on aging and the health and well-being of older people. The Institute seeks to understand the nature of aging and the aging process, and diseases and conditions associated with growing older, in order to extend the healthy, active years of life. In 1974, Congress granted authority to form NIA to provide leadership in aging research, training, health information dissemination, and other programs relevant to aging and older people. Subsequent amendments to this legislation designated NIA as the primary Federal agency on Alzheimer's disease research.

Mission

The Institute's mission is to:

- Support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging.
- Foster the development of research and clinician scientists in aging.
- Provide research resources.
- Disseminate information about aging and advances in research to the public, health care professionals, and the scientific community, among a variety of audiences.

Programs

NIA sponsors research on aging through extramural and intramural programs. The extramural program funds research and training at universities, hospitals, medical centers, and other public and private organizations nationwide. The intramural program conducts basic and clinical research in Baltimore, MD, and on the NIH campus in Bethesda, MD.

www.nia.nih.gov

PLATINUM SPONSOR



GLENN FOUNDATION
FOR MEDICAL RESEARCH

The purpose of the foundation, which was founded in 1965 by Paul F. Glenn, is to extend the healthy productive years of life through research on the mechanisms of biological aging.

www.glennfoundation.org

GOLD SPONSOR



American Federation for Aging Research

For 27 years, the American Federation for Aging Research (AFAR) has been at the forefront of this revolutionary approach to the science of healthier aging. AFAR has played a major role in providing and advancing knowledge of aging and mechanisms of age-related disease by providing start-up grants to more than 2,400 early-career scientists. To learn more about AFAR, visit our website www.afar.org. We also invite you to visit our web site InfoAging.org for the latest information on the biology of aging, common diseases of aging and healthy lifestyles.

www.afar.org

GOLD SPONSOR

BSRA ***British Society for Research on Ageing***

The British Society for Research on Ageing

The British Society for Research on Ageing (BSRA) promotes research to understand the causes and effects of the ageing process. BSRA encourages publication and public understanding of ageing research, publishes its own journal "Lifespan", a monthly electronic newsletter and holds an annual scientific meeting.

www.bsra.org.uk/index.html

SILVER SPONSOR



SILVER SPONSOR



California Walnut Commission: Eating a handful of walnuts everyday is an easy way to improve your diet and your health. Please visit our booth to learn about heart healthy, versatile and delicious California Walnuts. Visit our website: walnuts.org for more information on our health research program and current scientific studies.

SILVER SPONSOR



SILVER SPONSOR



Wild Blueberry Association of North America
<http://www.wildblueberries.com>

SILVER SPONSOR



SILVER SPONSOR



SILVER SPONSOR



STUDENT TRAVEL AWARD DONATION



The mission of the Preventable Aging Foundation is to promote research on mechanisms of biological aging and to facilitate discovery of chemical, nutritional and lifestyle strategies that enhance health and quality of life during aging.

EXHIBITOR



California Strawberry Commission

EXHIBITOR



California Dried Plums

EXHIBITOR



STUDENT DATA BLITZ DONATION



The Gerontological Society of America is the oldest and largest multidisciplinary scientific organization devoted to the advancement of aging research. Its membership includes more than 5,000 researchers, educators, practitioners, and other professionals. The Society's principal mission is to promote research and education in aging and to encourage their dissemination to others.

STUDENT DATA BLITZ DONATIONS

Robert M. Anson
Christiaan Leeuwenburgh

STUDENT TRAVEL AWARD DONATIONS

Holly Brown-Borg
Donna Holmes
Kevin Perrott
Christian Sell
LaDora V. Thompson
Janko Nikolich-Zugich

MEMBERSHIP DONATIONS

GENERAL DONORS

Arthur Balin
Elliot Bergman

JAMES A. JOSEPH MEMORIAL FUND

Arthur Balin
Elliot Bergman
Marlene Joseph
Kevin Perrott
Frederick and Ann Marie Yule

MARK A. SMITH MEMORIAL FUND

Arthur Balin
Elliot Bergman
Peggy Harris
George Perry

RESEARCH FUND

Arthur Balin

Friday, May 31, 2013

Aging and Nutrition

Chairs: Barbara Shukitt-Hale, PhD and Michael Forster, PhD

Sponsored in Part by:

California Walnut Commission

Ocean Spray

Wild Blueberry Association of North American

U.S. Highbush Blueberry Council

Institute for Aging and Alzheimer's Disease Research

UNT Preventable Aging Foundation

California Strawberry commission

California Dried Plum Board

7:30 am – 8:30 am **Pre-Conference Registration and Continental Breakfast**

8:30 am – 8:45 am **Welcome and Opening Remarks**

Barbara Shukitt-Hale, PhD

Jean Mayer USDA HNRCA at Tufts University, Boston, MA

8:45 am – 10:00 am **Session I**
Student/Post-Doc Submitted Abstract Session

Chair: Paula Bickford, PhD

University of South Florida and VAMC, Tampa, FL

8:45 am – 9:00 am

1. Interaction of ApoE Genotype, Antioxidants and Exercise on Brain Function

Krian Chaudhari

University North Texas Health Science Center, Fort Worth, TX

9:00 am – 9:15 am

2. Assessment of Berry Fruit's Effects on Mobility and Cognition in Aging

Marshall Miller

Jean Mayer USDA HNRCA at Tufts University, Boston, MA

9:15 am – 9:30 am

3. Estrogen's Ability to Protect Against Contraction – Induced Injury in Mouse Skeletal Muscle is Modest

Tara L. Mader

University of Minnesota, Minneapolis, MN

9:30 am – 9:45 am

4. Dietary Methionine and Aging in Long – and Short – Living Growth Hormone Mutant Mice

Joseph Wonderlich

University of North Dakota, Grand Forks, ND

9:45 am – 10:00 am

5. Long Term Consumption of Cranberry Extract Improves *C. elegans* Healthspan in Elderly Populations

Sujay Guha

Clemson University, Clemson, SC

- 10:00 am – 10:30 am** **BREAK**
- 10:30 am – 12:30 pm** **Session II**
Cellular Basis of Food and Effects
Chair: Donald Ingram, PhD
Pennington Biomedical Research Center, Baton Rouge, LA
- 10:30 am – 11:00 am **6. Anti-Aging Effects of Cranberry Consumption Revealed from Multi-Species Studies**
Sige Zou, PhD
National Institute on Aging, Bethesda, MD
- 11:00 am – 11:30 am **7. Cherry Picking Blueberries for Redox State (not ROS) Remediation in Aging and Alzheimer Neurons**
Gregory J. Brewer, PhD
Southern Illinois University, Springfield, IL
- 11:30 am – 12:00 pm **8. Protective Effects of Dietary Polyphenols May Vary with Cell Type and Injury in Neural Cells**
Kiran Panicker, PhD
Beltsville Human Nutrition Research Center, USDA, Beltsville, MD
- 12:00 pm – 12:30 pm **9. Diet and Gene Interactions in Alzheimer Prevention**
Gregory M. Cole, PhD
University of California Los Angeles, Los Angeles, CA
- 12:30 pm – 1:30 pm** **LUNCH ON YOUR OWN**
- 1:30 pm – 3:30 pm** **Session III**
Animal Models
Chair: Donald Ingram, PhD
Pennington Biomedical Research Center, Baton Rouge, LA
- 1:30 pm – 2:00 pm **10. Influence of Timing, Formulation and Combinations on Antioxidant Interventions Outcomes**
Nathalie Sumien, PhD
University of North Texas Health Science Center, Fort Worth, TX
- 2:00 pm – 2:30 pm **11. Antioxidants and Brain Aging: Lessons Learned from Studies in Dogs**
Elizabeth Head, PhD
University of Kentucky, Lexington, KY
- 2:30 pm – 3:00 pm **12. Effects of Berry Diets on Tumorigenesis and on the Disruption of Cognitive Performance Produced by Exposure to Space Radiation**

Friday, May 31, 2013

*Bernard Rabin, PhD
University of Maryland Baltimore County, Baltimore, MD*

3:00 pm – 3:30 pm

13. Dietary Approaches for Regenerative Medicine
*Paula Bickford, PhD
University of South Florida and VAMC, Tampa, FL*

3:30 pm – 4:00 pm

BREAK

4:00 pm – 6:15 pm

**Session IV
Translational Research**
*Chair: Donald Ingram, PhD
Pennington Biomedical Research Center, Baton Rouge, LA*

4:00 pm – 4:30 pm

14. Nutritional Approaches to Ameliorate Age-Related Neurocognitive Decline
*Robert Krikorian, PhD
University of Cincinnati, Cincinnati, OH*

4:30 pm – 5:00 pm

15. Berries, Flavonoids and Health in Aging
*Francine Grodstein, ScD
Brigham and Women's Hospital, Boston, MA*

5:00 pm – 5:30 pm

16. Nutrient Associations with Human Brain Neuropathology and Neural Reserve
*Martha Clair Morris, ScD
Rush Medical University, Chicago, IL*

5:30 pm – 6:00 pm

17. Vascular Aging: The Role of the Diet
*Britt Burton-Freeman, PhD
University of California Davis, Davis CA*

6:00 pm – 6:15 pm

General Discussion
*Chair: Michael J. Forster, PhD
University of North Texas Health Science Center, Fort Worth, TX*

PRE-CONFERENCE ADJOURNS

6:30 pm – 8:00 pm

AGE Welcome Reception
(All attendees are Invited to Attend)

*Sponsored in Part by:
American Federation for Aging Research (AFAR)*

AGING: PREVENTION, REVERSAL AND SLOWING

*Chair: LaDora V. Thompson, PhD, PT
University of Minnesota
President American Aging Association*

7:30 am – 8:15 am **Continental Breakfast**

8:15 am – 8:30 am **Welcome and Opening Remarks**
*LaDora V. Thompson, PhD, PT
President American Aging Association*

8:30 am – 9:30 am **Keynote Address**
*Sponsored by:
The Glenn Foundation*

I'm not Dead Yet – Lessons from Flies and Mice about Healthier Longer Life
*Stephen Helfand, MD
Brown University, Providence, RI*

9:30 am – 12:10 pm **Session I**
*Sponsored by:
The Glenn Foundation*

Longevity and Healthspan: Lessons from Flies to Humans
*Chair: Blanka Rogina, PhD
University of Connecticut Health Center, Farmington, CT*

9:30 am – 9:35 am **Introductory Remarks**
*Blanka Rogina, PhD
University of Connecticut Health Center, Farmington, CT*

9:35 am – 10:05 am 18. **Indy Mutations Maintain Fly Health Homeostasis**
*Blanka Rogina, PhD
University of Connecticut Health Center, Farmington, CT*

10:05 am – 10:35 am 19. **Are Healthspan and Longevity Necessarily Coupled in Rodent Studies?**
*Sarah Mitchell, PhD
National Institute on Aging, Baltimore, MD*

10:35 am – 11:00 am **BREAK**

11:00 am – 11:30 am 20. **Healthspan vs Lifespan: What's up in *Caenorhabditis elegans*?**
*Tom Johnson, PhD
University of Colorado – Boulder, Boulder CO*

Saturday, June 1, 2013

- 11:30 am – 12:00 pm **21. The Mechanism by Which Longevity Genes Protect Against Aging Genes**
Derek M. Huffman, PhD
Albert Einstein College of Medicine, Bronx, NY
- 12:00 pm – 12:10 pm **Panel Discussion**
- 12:10 pm – 1:30 pm** **LUNCH ON YOUR OWN**
- 1:30 pm – 2:20 pm** **Vincent Cristofalo**
Memorial Rising Star Award and Lecture
Sponsored by:
The American Federation of Aging Research (AFAR)
Margaret F. Cristofalo
- Nutrient Signaling Pathways Regulate Aging and Diseases: From Yeast to Humans**
Valter Longo, PhD
University of Southern California, Los Angeles, CA
- 2:30 pm – 5:45 pm** *Sessions IIA and Submitted Abstracts Session IIB are Dual Sessions*
- 2:30 pm – 5:45 pm** **Session IIA**
Sarcopenia: Strategies for Preventing, Reversing, and Slowing
Chair: Esther Dupont-Versteegden, PhD
University of Kentucky, Lexington, KY
- 2:30 pm – 2:35 pm **Introductory Remarks**
Esther Dupont-Versteegden, PhD
University of Kentucky, Lexington, KY
- 2:35 pm – 3:00 pm **22. Muscle Regrowth: Does Age Make a Difference?**
Esther Dupont-Versteegden, PhD
University of Kentucky, Lexington, KY
- 3:00 pm – 3:25 pm **23. Muscle Adaptation to Contractile Activity: Effects of Aging**
Joyce Chen, PhD
Chung Gung University, Kweishan, Tao-Yuan
- 3:25 pm – 3:50 pm **24. Can Nutritional Interventions Slow Sarcopenia or Reverse Muscle Loss?**
Steve Alway, PhD
West Virginia University, Morgantown, WV

3:50 pm – 4:15 pm

BREAK

Session IIA - Continued

Sarcopenia: Strategies for Preventing, Reversing, and Slowing

Chair: Charlotte Peterson, PhD

University of Kentucky, Lexington, KY

4:15 pm – 4:20 pm

Introductory Remarks

Charlotte Peterson, PhD

University of Kentucky, Lexington, KY

4:20 pm – 4:45 pm

25. Structural and Functional Determinants of Muscle Quality

Luigi Ferrucci, MD, PhD

National Institute on Aging, Baltimore, MD

4:45 pm – 5:10 pm

26. Autophagy and Mitochondrial Dysfunction in Muscle and Nerves with Age: Potential Interventions

Christiaan Leeuwenburgh, PhD

University of Florida, Gainesville, FL

5:10 pm – 5:35 pm

27. Human Muscle Aging and Adaptation: Underlying Cellular Mechanisms

Charlotte Peterson, PhD

University of Kentucky, Lexington, KY

5:35 pm – 5:45 pm

Panel Discussion

2:30 pm – 5:45 pm

Sessions II A and Submitted Abstracts Session II B are Dual Sessions

2:30 pm – 5:45 pm

Session IIB : Submitted Abstracts

Advances in Aging Research: Assembling the Pieces from Different Models

Chair: Michael J. Forster, PhD

University of North Texas Health Science Center, Fort Worth, TX

2:30 pm – 2:35 pm

Introductory Remarks

Michael J. Forster, PhD

University of North Texas Health Science Center, Fort Worth, TX

2:35 pm – 2:50 pm

28. Depletion of mTORC2 Impairs the Health and Longevity of Male, but not Female Mice

Dudley W. Lamming, PhD

Whitehead Institute, MIT, Cambridge, MA

Saturday, June 1, 2013

- 2:50 pm – 3:05 pm **29. Patterns of Intraspecific Variability in the Lifespan and Transcriptome Response to Caloric Restriction in Rotifers**
David B. Mark Welsh, PhD
Marine Biological Laboratory, Woods Hole, MA
- 3:05 pm – 3:20 pm **30. The Role of Apolipoprotein E4 Allele, Cancer, CVD and Neurodegenerative Disorders in Human Lifespan**
Alexander Kulminski, PhD
Duke University, Durham, NC
- 3:20 pm – 3:35 pm **31. Protection of Proteasome Activity in the Long-Lived Naked Mole-Rat by a Multiprotein Resistosome**
Karl Rodriguez, PhD
University of Texas Health Science Center San Antonio, San Antonio, TX
- 3:35 pm – 3:50 pm **32. Evaluating Hormesis as a Mechanism in Calorie Restriction**
Carrie Elks, PhD
Pennington Biomedical Research Center, Baton Rouge, LA
- 3:50 pm – 4:15 pm BREAK**
- 4:15 pm – 5:30 pm Session IIB Continued**
Submitted Abstracts
Chair: Rochelle Buffenstein, PhD
University of Texas Health Science Center San Antonio, San Antonio, TX
- 4:15 pm – 4:20 pm **Introductory Remarks**
Rochelle Buffenstein, PhD
University of Texas Health Science Center San Antonio, San Antonio, TX
- 4:20 pm – 4:35 pm **33. How does the Body Know How Old it is?**
Josh Mitteldorf, PhD
MIT, Cambridge, MA
- 4:35 pm – 4:50 pm **34. Does Redox State Matter: A Comparison Among Replicative Senescence, SIPS and Senescence Induced due to Proteostasis Impairment**
Mina Konigsberg, PhD
Universidad Autonoma Metropolitana

- 4:50 pm – 5:05 pm **35. An Age-Related Decline in Nrf2 Protein Synthesis, a Novel Mechanism for the Attenuation of Xenobiotic Detoxification Capacity**
Eric Smith
Linus Pauling Institute - Oregon State University, Corvallis, OR
- 5:05 pm – 5:20 pm **36. Subacute Treatment of Rapamycin Reverses Cardiac Aging by Improving Mitochondrial Energy Metabolism**
Ying Ann Chiao, PhD
University of Washington, Seattle, WA
- 5:20 pm – 5:30 pm **Panel Discussion**
- 6:00 pm – 7:00 pm** **Poster Session I**
Competition for Glenn Award and Nicolai Prize
- 6:00 pm – 7:00 pm** **Cocktail Reception during Poster Session**
- 7:00 pm – 8:30 pm** **Special Student Session**
Organized by:
Rafa de Cabo, PhD, NIA, Baltimore, MD
Christiaan Leeuwenburgh, PhD, University of Florida, Gainesville, FL
- Sponsored in Part by:*
The Gerontological Society of America
Mike Anson, PhD
Christiaan Leeuwenburgh, PhD
- 7:00 pm – 10:00 pm** **AGE Board of Directions Dinner Meeting**

Sunday, June 2, 2013

7:00 am – 8:00 am Continental Breakfast

8:00 am – 10:15 am Session III
Slow the Pace of Aging: Role of Mimetics
Chair: Joseph Baur, PhD
University of Pennsylvania, Philadelphia, PA

8:00 am – 8:05 am **Introductory Remarks**
Joseph Baur, PhD
University of Pennsylvania, Philadelphia, PA

8:05 am – 8:35 am **37. Resveratrol Improves the Skeletal Muscle Metabolic Response to High Fat Feeding in a Nampt-Sirt1 Dependent Manner**
Evi Mercken, PhD
National Institute on Aging, Bethesda, MD

8:35 am – 9:05 am **38. Update from the NIA Aging Intervention Testing Program**
Randy Strong, PhD
University of Texas Health Science Center at San Antonio, San Antonio, TX

9:05 am – 9:35 am **39. Pathways and Small Molecules that Reverse Tissue Aging**
David Sinclair, PhD
Harvard University, Boston, MA

9:35 am – 10:05 am **40. Inhibiting mTOR Signaling: A Strategy to Mimic Caloric Restriction?**
Joseph Baur, PhD
University of Pennsylvania, Philadelphia, PA

10:05 am – 10:15 am **Panel Discussion**

10:15 am – 10:45 am BREAK

10:45 am -12:45 pm Session IV
Impact of Dietary Interventions in Preventing, Reversing, and Slowing Biological Aging Processes
Chair: Luigi Ferrucci, MD, PhD
National Institute on Aging, Bethesda, MD

10:45 am – 10:50 am **Introductory Remarks**
Luigi Ferrucci, MD, PhD
National Institute on Aging, Bethesda, MD

- 10:50 am – 11:20 am 41. **Growth Hormone and Aging: The Role of Nutrient Restriction or Supplementation**
Holly Brown-Borg, PhD
University of North Dakota, Grand Forks, ND
- 11:20 am – 11:45 am 42. **Dietary Interventions for Healthy Aging**
Rafael de Cabo, PhD
National Institute on Aging, Baltimore, MD
- 11:45 am – 12:10 pm 43. **East Meets Mid-West: CR Monkey Studies Face Off**
Julie Mattison, PhD, National Institute on Aging, Bethesda, MD
And
Roz Anderson, PhD, University of Wisconsin, Madison, WI
- 12:10 pm – 12:35 pm 44. **CALERIE Comprehensive Assessment of the Long-Term Effects of Restricted Intake of Energy – Results from a 2 Year Human Calorie Restriction Trial**
Sai Krupa Das, PhD
Tufts University, Boston, MA
- 12:35 pm – 12:45 pm **Panel Discussion**
- 12:45 pm – 2:00 pm** **American Aging Association Denham Harman Award and Luncheon**
(All Attendees are Invited to Attend)
- 1:00 pm – 2:00 pm** **Plenary Session I: Denham Harman Award Lecture**
- Hormones and Aging: Lessons from the Dwarf Mouse**
Holly Brown-Borg, PhD
University of North Dakota, Grand Forks, ND
- 2:00 pm – 4:15 pm** *Sessions VA and VB are Dual Sessions*
Session VA
Bench to Bedside to Healthcare
Chair: Deborah Ferrington, PhD
University of Minnesota, Minneapolis, MN
- 2:00 pm – 2:05 pm **Introductory Remarks**
Deborah Ferrington, PhD
University of Minnesota, Minneapolis, MN
- 2:05 pm – 2:35 pm 45. **Losartan Reverses Age-Related Changes in Mitobiogenesis, Myocardial Function, Oxidative Damage, and Energy Metabolism**
Peter Abadir, MD
Johns Hopkins University, Baltimore, MD

Sunday, June 2, 2013

- 2:35 pm – 3:05 pm **46. Proteomics and Age-Related Macular Degeneration Defining Disease Mechanism and Guiding Treatment Strategies**
Deborah Ferrington, PhD
University of Minnesota, Minneapolis, MN
- 3:05 pm – 3:35 pm **47. Recovery from Acute Events and Strategies for Developing and Testing Interventions to Maximize Recovery?**
Jay Magaziner, PhD
University of Maryland, Baltimore, MD
- 3:35 pm – 4:05 pm **48. Randomized Clinical Trials and Public Policy: Improving Population Health**
Mary McGrae McDermott, MD
Northwestern University Feinberg School of Medicine, Chicago, IL
- 4:05 pm – 4:15 pm **Panel Discussion**
- 2:00 pm – 4:15 pm** *Sessions VA and VB are Dual Sessions*
Session VB
Transatlantic Symposium
Chair: Richard Faragher, PhD
University of Brighton, Brighton, UK
- Sponsored by:*
British Society for Research on Ageing (BSRA)
Age UK
- 2:00 pm – 2:05 pm **Introductory Remarks**
Richard Faragher, PhD
University of Brighton, Brighton, UK
- 2:05 pm – 2:30 pm **49. PKC Alpha and Wound Healing in Older People**
Helen Thomason, PhD
University of Manchester, Manchester, UK
BSRA KORENCHEVSKY AWARD
- 2:30 pm – 2:55 pm **50. Better Health by Workplace Design: Addressing the Challenges for Ageing Construction Workers**
Diane Gyi, PhD
Loughborough University, Leicestershire, UK
- 2:55 pm – 3:20 pm **51. A New *Caenorhabditis elegans* Model of Adult-Onset Neurodegeneration with Potential for Neuroprotective Drug Screening**
Alan Morgan, PhD
University of Liverpool, Liverpool, UK

3:20 pm – 3:45 pm **52. New Insights into the Premature Ageing Werner's Syndrome in the Nematode Worm *C. elegans***
Hayley Lees, PhD
University of Oxford, Oxford, UK

3:45 pm – 4:10 pm **53. TBA**
Sarah E. MacPherson, PhD
University of Edinburgh, Edinburgh, UK

4:05 pm – 4:15 pm **Panel Discussion**

4:15 pm – 4:45 pm BREAK

4:45 pm – 5:45 pm Plenary Session II: Mark Smith Address
Rapamycin: The First Longevity Drug?
Arlan Richardson, PhD
Barshop Institute for Longevity and Aging Studies
University of Texas Health Science Center At San Antonio

Sponsored by:
James Joseph and Mark Smith Memorial Fund
American Aging Association

5:45 pm – 6:15 pm Special Lecture
It's a GIG: The Trans-NIH Geroscience Interest Group
Felipe Sierra, PhD
National Institute on Aging, Bethesda, MD

6:15 pm – 6:45 pm AGE Business Meeting – Open to all AGE Members

6:45 pm – 8:00 pm Poster Session II
Competition for Glenn Award and Nicolai Prize

6:45 pm – 8:00 pm Cocktail Reception during Poster Session

Monday, June 3, 2013

7:30 am – 8:00 am **Continental Breakfast**

8:00 am – 10:15 am **Session VI**
Mechanisms to Protect Against Biological Aging and Disease

Chair: Holly Brown-Borg, PhD
University of North Dakota, Grand Forks, ND

8:00 am – 8:05 am **Introductory Remarks**

Holly Brown-Borg, PhD
University of North Dakota, Grand Forks, ND

8:05 am – 8:35 am **54. Calorie Restriction and Essential Amino Acid Restriction Contribute Additively to the Benefits of Short-Term Dietary Restriction in Mice**

James Mitchell, PhD
Harvard University, Boston, MA

8:35 am – 9:05 am **55. Differential Stress Resistance and Sensitization in Cancer Treatment**

Valter Longo, PhD
University of Southern California Los Angeles, Los Angeles, CA

9:05 am – 9:35 am **56. Mitochondrial-Derived Peptides and Their Role in Aging**

Pinchas Cohen, MD
University of Southern California, Los Angeles, CA

9:35 am – 9:45 am **Panel Discussion**

9:45 am – 10:15 am **BREAK**

10:15 am – 12:35 pm *Sessions VIIA and VIIB are Dual Sessions*
Session VIIA

Sponsored by:
NIA and Nathan Shock Center

Nathan Shock Center Symposium

Chair: Felipe Sierra, PhD
National Institute on Aging, Bethesda, MD

10:15 am – 10:20 am **Introductory Remarks**

Felipe Sierra, PhD
National Institute on Aging, Bethesda, MD

- 10:20 am – 10:45 am **57. Glucocorticoids Exacerbate Cognitive Deficits in TDP-25 Transgenic Mice via a Glutathione Mediated Mechanism: Implications for Aging, Stress and TDP-43 Proteinopathies**
Salvatore Oddo, PhD
University of Texas Health Science Center San Antonio, San Antonio, TX
- 10:45 am – 11:10 am **58. Hypothalamic Regulation in Crowded Litter Mice: Early Life Control of Aging and Longevity**
Marianna Sadagurski, PhD
University of Michigan, Ann Arbor, MI
- 11:10 am – 11:35 am **59. Genetic Tools for Analysis of Lifespan and Healthspan in Mice**
Luanne Peters, PhD
The Jackson Laboratory, Bar Harbor, ME
- 11:35 am – 12:00 pm **60. Targeting Central and Peripheral IGF-1 Signaling for Healthy Aging and Longevity**
Derek M. Huffman, PhD
Albert Einstein College of Medicine, Bronx, NY
- 12:00 pm – 12:25 pm **61. HIF-1 Modulates Longevity Through a Complex Pathway Involving Xenobiotic Metabolism**
Scott Leiser, PhD
University of Washington, Seattle, WA
- 12:25 pm – 12:35 pm **Panel Discussion**
- 10:15 am – 12:35 pm** *Sessions VIIA and VIIB are Dual Sessions*
Session VIIB
Sponsored in part by:
Buck Institute
- Emerging Technologies for Studying Aging and Healthspan**
Chair: Edgar Arriaga, PhD
University of Minnesota, Minneapolis, MN
- 10:15 am – 10:20 am **Introductory Remarks**
Edgar Arriaga, PhD
University of Minnesota, Minneapolis, MN
- 10:20 am – 10:50 am **62. Teasing Apart Age Related Sub Cellular Complexity**
Edgar Arriaga, PhD
University of Minnesota, Minneapolis, MN

Monday, June 3, 2013

- 10:50 am – 11:20 am **63. FGF Signaling Restores Asymmetric Division and Loss of Self-Renewal in Aged Skeletal Muscle Stem Cells**
Brad Olwin, PhD
University of Colorado-Boulder, Boulder, CO
- 11:20 am – 11:50 pm **64. Single Cell Gene Expression Profiling of Bone**
Simon Melov, PhD
The Buck Institute, Navato, CA
- 11:50 pm – 12:20 pm **65. Functional Metabolomics Opens a New Window on Aging Mitochondria *in vivo***
Kevin Conley, PhD
University of Washington, Seattle, WA
- 12:20 pm – 12:35 pm **Panel Discussion**
- 12:35 pm – 1:00 pm AWARDS CEREMONY FOR TRAINEES**
- 1:00 pm MEETING ADJOURNS**

Poster Sessions

Saturday June 1 and Sunday June 2, 2013

66	Decreased Recent Thymic Emigrant Number and Shortened Telomere Length in Obese A-Bomb Survivors Kengo Yoshida (P), Yoshiko Kubo, Mika Yamaoka, Tomonori Hayashi, Waka Ohishi, Yoichiro Kusunoki
67	Independent Chemical Regulation of Health- & Senescent-Spans in Drosophila Robert Arking (P)
68	Age-Related Change of Protein Degradation in Mouse Liver Parenchymal Cells Yuki Kishimoto (P), Akiko Amano, Naoki Maruyama, Akihito Ishigami
69	Short-Term Caloric Restriction Initiated at Different Ages had Minimal Effect on Nrf-2 Activation Nopporn Thangthaeng (P), Nathalie Sumien, Michael J. Forster
70	“Who wants to Live Forever?”- Chromatinome RNAi Screen for Longevity in <i>C. elegans</i> K.Chocian, H.Lees, H.Cantwell, J.Mellor and A. Woollard
71	The Paternal Age Effect: A Role for p53 Activation in Regulating AP Endonuclease 1 Abundance with Increased Paternal Age Jamila R. Momand (P,G) and Christi A. Walter
72	An Examination of Age-Dependent Inter-Individual Variation in Gene Expression in Three Species Produces Surprising Results R. Michael Anson (P) and Arielle Charmaine Holliday
73	A Multi-Organism Approach to Selecting Strong Candidates for Mammalian Longevity Genes George L. Sutphin (P,G), Shannon Bean, Matt Kaeberlein, Ron Korstanje
74	Pcsk2 may Co-Regulate Female Sexual Maturation and Longevity Through the Regulation of Circulating IGF1 Dan Gatti, Rebecca Krier, Luanne Peters, David E. Harrison, Beverly Paigen, Gary A. Churchill, Rong Yuan (P)
75	Deregulation of Alternative Splicing in Human Aging Alice Holly (P), David Melzer, Luke Pilling, Luigi Ferrucci, Lorna Harries
76	A Tumor Suppressor Complex with GAP Activity for the Rag GTPases that Signal Amino Acid Sufficiency to mTORC1 Liron Bar-Peled (P,N), Lynne Chantranupong, Andrew D. Cherniack, Walter Chen, Kathleen A. Ottina, Brian Grabiner, Eric A. Spear, Scott Carter, Matthew Meyerson, David M. Sabatini
77	Thioredoxin 2 Overexpression and Thioredoxin 1 Down-Regulation Attenuate Aging Through Independent and Common Mechanisms Sara Dube, Lisa C. Flores, Madeline Roman, Yiqiang Zhang, Adam Salmon, Shuko Lee, Holly Van Remmen, Arlan Richardson, Gene B. Hubbard, Yuji Ikeno (P)
78	Mechanisms that Extend Lifespan in Sprague-Dawley Rats by Cu/ZnSOD Overexpression Madeline Roman, Lisa Flores, Adam Salmon, Sara Dube, Nicolas Musi, Shuko Lee, Gene B. Hubbard, Holly Van Remmen, James Kirkland, Tamar Pirtskhalava, Tamar Tchkonja, Arlan Richardson, Yuji Ikeno(P)
79	Effects of Short-Term Phytoestrogen Supplementation on Cognitive Function in Male and Female Mice Akram Sidhu (P,N), Michael J. Forster, Nathalie Sumien
80	Systemic Effects of Decreased Neuronal mTOR Signaling Stacy A. Hussong (P,G), Jonathan J. Halloran, Raquel R. Burbank, Ai-Ling Lin, Vanessa Y. Soto, Veronica Galvan
81	Identifying and Quantifying Mitochondrial DNA Damage with the Progression of Age-Related Macular Degeneration Deirdre Manion-Fischer (P), Rebecca Kappahn, Deborah Ferrington, Edgar Arriaga
82	Human Aging System Diagram - A New Stage of the Analysis of Complex Problems Anna Vladimirovna Kremetsova (P), Danila A. Medvedev, Alex A. Moskalev, Boris A. Kaurov, Elena V. Tereshina, Valery B. Mamaev, Igor V. Artyuhov, Elena G. Pasyukova

Poster Sessions
Saturday June 1 and Sunday June 2, 2013

83	Regulation of PGC-1α Levels by GSK-3b as a Mediator of Aging-Related Disease Karl Miller (P), Albert Budhipramono, Porsha Howell, Michael Polewski, Monica Chou, Rozalyn Anderson
84	Habitual Physical Activity Improves Neutrophil Function in the Elderly: The Physical Activity and Healthy Ageing Study (PAHA) David B. Bartlett (P,N), Clare L. McNulty, Oliver Fox, Laura Murphy, Elizabeth Sapey, Anton J.M. Wagenmakers, Janet M. Lord
85	Inflammation and Human Aging: Transcriptome-Wide Mediators in Blood Leukocytes David Melzer (P), Luke Pilling, Lorna Harries, William Henley, Dena Hernandez, Andrew Singleton, Luigi Ferrucci
86	Skeletal Muscle Power Generation with Aging and Inactivity Jong-Hee Kim, Ted G. Graber, and LaDora V. Thompson
87	The Effect of Visceral Fat Removal on Insulin Signaling in Ames Dwarf Mice Vinal Menon (P), Xu Zhi, Michal Masternak
88	Altered Gene Expression in the Brain of Senescence-Accelerated Mouse During Postnatal Development Ryoya Takahashi (P) and Keiko Odera
89	Withdrawn
90	Degenerative Changes in Neurons and Interstitial Cells of Cajal in Mouse Internal Anal Sphincter During Aging M. Jill Saffrey (P), Prasanna P.K.M. Gamage, Heather A. Davies, Frances M. Colyer, Bhavik A. Patel, Mark S. Yeoman, Richard N. Ranson
91	Insulin-like Growth Factor (IGF-1), Neurogenesis and Synaptogenesis Lalida Rojanathammanee (P,G), Sharlene Rakoczy, Holly Brown-Borg
92	Stress Test and Redox Interventions to Determine the Relative Importance of GSH and NAD(P)H in Aging and AD-Like Neurons Debolina Ghosh (P,N), Kelsey R. LeVault, Gregory J. Brewer
93	Impaired Protein Homeostasis in ALS Mice: A Role for Mutant SOD1 in Peripheral Myelin Protein 22 Aggregation Ryan T. Hamilton (P,G), Rochelle Wei, Amanda L. Jernigan, Arunabh Bhattacharya, Asish R. Chaudhuri, Holly Van Remmen
94	TOR And NO As Regulators of Brain Vascular Function in a Mouse Model of AD Veronica Galvan (P), Ai-Ling Lin, Wei Zheng, Jonathan Halloran, Raquel Burbank, Stacy Hussong, Matthew J. Hart, Martin Javors, Eric Muir, James D. Lechleiter, Peter T. Fox
95	Associations between Physical Activity, Inflammation and Cardiovascular Function in an Elderly Cohort Clare L. McNulty (P), David B. Bartlett, Nicola Crabtree, Janet M. Lord, James P. Fisher, Anton J. Wagenmakers
96	Cardiac Aging in the Extremely Long-Lived Naked Mole-Rat Kelly Grimes (P,N) and Rochelle Buffenstein
97	Ovariectomy and Vitellogenin-RNAi Extend Lifespan via Overlapping but Distinct Physiologies in Grasshoppers John D. Hatle (P), Alicia G. Linqvist, Jacob Burnett, Katherine A. Veleta, Derek R. Tokar, Joseph Canzano
98	Protection of Protein Structure and Function in the Longest Lived Animal Stephen Treaster (P,N), Asish Chaudhuri, Steven Austad
99	Enhanced Protein Homeostasis Mechanisms in Naked Mole Rats Cells Harrison Pride, Yiqiang Zhang, Rochelle Buffenstein, Peter Hornsby, Arlan Richardson, Viviana I. Perez (P)
100	Cytoprotection, Longevity, and Cancer Resistance in the Naked Mole-Rat Kaitlyn N. Lewis (P,N) and Rochelle Buffenstein

Poster Sessions

Saturday June 1 and Sunday June 2, 2013

101	C57BL/6 Lifespan Study: Age-Related Changes in Muscle Power Production and Contractile Velocity Ted G. Graber (P,N), Jong-Hee Kim, LaDora V. Thompson
102	A Novel Approach for the Quantification of Olfactory Acuity in a Murine Model Keith Maslin (P,N), Samantha Rendon, Steven Austad
103	Regulation of Mitochondrial Proteostasis by the Protein Oxidation Repair Enzyme MsrA JennaLynn Styskal, Daniel Pulliam, Holly Van Remmen, Arlan Richardson, Adam Salmon (P)
104	Mitochondrial Overexpression of the Protein Oxidation Repair Enzyme MsrA Prevents Insulin Resistance JennaLynn Styskal Hunnicutt (P,G)
105	Heat Therapy Preserves Muscular Endurance in Aged Mice Kylie Kavanagh (P), Marnie Silverstein, Ashley T. Wylie, Daniel C. Files, Carol E. Milligan, Stephen B. Kritchevsky
106	Growth Hormone Receptor Knockout Mice Display Differences in DNA Methyltransferases and Interspersed Repeats Armstrong, VA (P,N), Rakoczy, S, Brown-Borg, HM
107	The Age-Related Decline in Hemoglobin Concentration in Mice is Primarily Determined by Genetic Regulation of RBC Count Kevin Flurkey (P), Rong Yuan, Gary A. Churchill, Luanne L. Peters
108	Role of Mitochondrial Matrix Protease Clpp in Mitochondrial Homeostasis, Metabolism and Aging Deepa Sathyaseelan (P), Daniel Pulliam, Shauna Hill, JennaLynn Styskal, Michael Walsh, Yun Shi, Holly Van Remmen
109	QTL Analysis of Lifespan in a Mouse Model Gary A. Churchill (P), Dan Gatti, Luanne Peters, Rong Yuan
110	Compensatory Responses to Mitochondrial Complex IV Dysfunction in the Long-Lived Surf1 Knockout Mouse Daniel Alan Pulliam (P,N), Deepa Sathyaseelan, Yuhong Liu, Shauna Hill, Holly Van Remmen
111	Long-Term Administration of Losartan Ameliorates Several Pathologies Associated with Sarcopenia in Mice Tyesha N. Burks (P,G), Ruth Marx-Rattner, Christopher W. Ward, Peter M. Abadir, Jeremy D. Walston, Ronald D. Cohn
112	Simple Syntheses of Diverse Polyphenolic Compounds – Facilitating Dissection of Multiple Modes of Activity Vishal Birar, Angela Sheerin, Richard G.A. Faragher, Lizzy Ostler (P)
113	Development of a Frailty Index in Aging Mice Haiming Liu (P,N), Ted G. Graber, Lisa Ferguson-Stegall, LaDora V. Thompson
114	Functional Genomics of Stress Resistance and Longevity in Mice Wallace S. Chick (P)
115	A Novel Role for the Immunoproteasome in Cellular Stress Response Marcela Maldonado (P,G), Rebecca J. Kapphahn, Neal Heuss, Dale S. Gregerson, Ching Yuan, Deborah A. Ferrington
116	Reproductive Mode Versus Environmental Temperature in the Senescence Switch of <i>H. oligactis</i> Samantha Rendón (P,N), Vanessa Y. Soto, Natalia Podlitskaya, Kathleen E. Fischer, and Steven N. Austad
117	Mice Harboring a Complex IV Mutation have a Distinct Metabolic Phenotype Shauna Hill (P,N), Daniel Pulliam, Deepa Sathyaseelan, Yuhong Liu, Holly Van Remmen
118	Short-Term Dietary Restriction Prevents Neurogenic Muscle Atrophy Through a Novel ROS/HDAC4 Mediated Mechanism Michael E. Walsh (P,N), Yuhong Liu, Holly Van Remmen

119	2013 Wild Blueberry Health Study Report: Web Measurements are Able to Detect 0.2% Annual Memory Changes at 95% Confidence H.A. Raphaelson, D.J. Burns, R.J. Coppings, D.L. Doiron, K.E. Gerstmann, K. Hull, A.C. Kokesh, B.S. Kristal, A. Pruchnicki, B. Sachs, R. Schnoll, J.H. Vogelman, A. Wetherell, R.J. Martin (P)
120	2013-2014 Study Protocol To Determine If High-Polyphenol, Wild Maine Blueberries Can Postpone Frailty And Aging D.J. Burns, B.S. Kristal, A. Pruchnicki, A. Raphaelson, B. Sachs, R. Schnoll, J.H. Vogelman, A. Wetherell, R.J. Martin (P)
121	Longevity Patterns of Four Long-Lived US Populations: Chinese-, Japanese-, Cuban- And Spanish-Americans R.J. Martin (P), H.A. Raphaelson, J.W. Ashford
122	Systems Biology of Human Aging - Network Model 2013 John D. Furber (P)
123	Effect of Dietary Restriction from Old on the Age-Related Changes of Skeletal Muscle Keiko Odera (P) and Ryoya Takahashi
124	A Mitochondrial ATP Syntase Interacts with Macronutrients to Modulate Lifespan in Drosophila Xiaoping Sun (P,G), Yolitz Jason, Yaning Sun and Sige Zou
125	Flipping the Switch: How Hormetic Stress Resistance Proteins Influence Metabolism Sophia Rose Levan (P,N), Evi Mercken, Jess Curtis, Michel Bernier, Rafael de Cabo
126	The Stress Response Gene “Fit” for Lifespan Regulation in Drosophila Jinhwan Lim (P,G), Xiaoping Sun and Sige Zou
127	Cranberry Interacts with Dietary Macronutrients to Modulate Lifespan in Drosophila Yaning Sun (P,G), Cecilia Wang, Jason Yolitz, Xiaoping Sun, Thomas Alberico, Mara Laslo and Sige Zou
128	Metformin Improves Healthspan and Lifespan in Mice Hector H. Palacios (P,N), Alejandro Martin-Montalvo, Evi M. Mercken, Sarah J. Mitchell, Michel Bernier and Rafael de Cabo
129	Cytochrome B5 Reductase 3 Increases Lifespan Through the Poly-unsaturation of Fatty Acids and Improvement of Mitochondrial Performance Vincent Gutierrez (P,N), Alejandro Martin-Montalvo, Hector H. Palacios, Michel Bernier and Rafael de Cabo
130	Improved Glucose Homeostasis by NQO1, A New Insulin Receptor Target Alejandro Martin-Montalvo (P,G), Hector H. Palacios, Vincent Gutierrez, Jessica M. Curtis, Sophie Levan, Michel Bernier and Rafael de Cabo
131	Are Healthspan and Longevity Necessarily Coupled in Rodent Studies? Sarah Mitchell(P,G) and Rafael de Cabo
132	The SIRT1 Activator SRT1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet Michel Bernier (P), Sarah Mitchell, Alejandro Martin-Montalvo, Evi M. Mercken, James Ellis, George Vlasuk, Rafael de Cabo
133	Resveratrol Improves Adipose Insulin Signaling And Reduces The Inflammatory Response In Adipose Tissue Of Rhesus Monkeys On A High-Fat, High-Sugar Diet Irene Alfaras (P,G), Yolanda Jimenez-Gomez, Julie A. Mattison, Kevin J. Pearson, Alejandro Martin-Montalvo, Hector H. Palacios, Joseph A. Baur, Jonathan S. Bogan, Michel Bernier, and Rafael de Cabo
134	Resveratrol Supplementation Offers Neuroprotection in Rhesus Macaques Fed a High-Fat, High-Sugar Diet Shakeela J. Faulkner (P,N), Joanne S. Allard, Julie A. Mattison, Kevin J. Pearson, Jessica Curtis, Michel Bernier, Rafael de Cabo
135	Regulation Of Skeletal Muscle Regeneration By Diet And Age Jessica Curtis(P,G), Shakeela Faulker, Vincent Gutierrez, Cuong Nguyen, Robert Wersto, Amy Wagers, Luigi Ferrucci, and Rafael de Cabo
136	No Longer Limber: A Sarcopenic Tale in Mammals Jordan J Licata (P,N), Evi M Mercken, Julie A Mattison and Rafael de Cabo

KEYNOTE ADDRESS

I'm not Dead Yet – Lessons from Flies and Mice about Healthier Longer Life

Stephen Helfand, MD

Brown University, Providence, RI

Decreasing the activity of the *Indy* gene (*I'm not dead yet*) in flies extends life span without a decline in fertility, physical activity, flight velocity or metabolic rate. Worldwide natural variants in *Indy* modify *Indy* expression, increasing reproduction and longevity, and demonstrating that alterations in *Indy* expression in the wild imparts significant improvement in fitness and longevity. Found most abundantly at the plasma membrane of adult fat body, oenocytes and midgut cells, the primary sites of intermediary metabolism in the fly, the *Indy* gene codes for a high-affinity dicarboxylate/citrate plasma membrane transporter. The hypothesis that decreases in *Indy* might be affecting metabolism in a manner similar to calorie restriction (CR) is supported by the findings that CR down-regulates *Indy* in normal flies, and that *Indy* long-lived flies share phenotypes with long-lived CR flies, including decreased insulin-like signaling, lipid storage, weight gain, resistance to starvation, and increased spontaneous physical activity.

A mouse knock-out of a mammalian homolog of *Indy* (mINDY; SLC13A5) protects mice from age-related or high-fat-feeding-related insulin resistance and adiposity, and promotes phenotypes similar to those seen in CR. The mINDY-deleted mice exhibit increased hepatic mitochondrial biogenesis, lipid oxidation, and energy expenditure, as well as decreased hepatic de novo lipogenesis, activation of hepatic AMPK, induction of PGC-1alpha, inhibition of ACC-2, and reduction of SREBP-1c. The mINDY-deleted mice have reduced body weight, and preserve normal insulin signaling during aging or on high-fat diets, demonstrating that some of the positive effects of *Indy* in flies can be extended to mammals. *Indy's* effect on mammalian energy metabolism suggests *Indy* is a potential target for treatment of obesity and type 2 diabetes, and that understanding of its regulation could lead to new agents for extending healthy life span and provide valuable insight into the genetic mechanisms of normal aging.

VINCENT CRISTOFALO MEMORIAL RISING STAR AWARD AND LECTURE

Nutrient Signaling Pathways Regulate Aging and Diseases: From Yeast to Humans

Valter Longo, PhD

University of Southern California, Los Angeles, CA

Longevity studies in simple organisms have greatly accelerated our understanding of the fundamental mechanisms of aging but this contribution requires validation in mammals. A combination of both biased and unbiased studies in the unicellular *S. cerevisiae* allowed us to identify the Ras/cAMP/PKA as the glucose response pro-aging pathway and the Tor-S6K as the amino acid response pro-aging pathway. Either starvation, deletion of genes in these pathways, or both caused a two to ten fold chronological lifespan extension as well as remarkable protection against a wide variety of toxins. Inactivation of these pathways has been confirmed to affect longevity and healthspan in higher eukaryotes including mice. Based on our results showing that Tor-S6K yeast mutants are dwarf and those by others showing that dwarf mice with deficiencies in the growth hormone-IGF-I axis are long-lived and protected from diseases we studied a population of humans with Growth Hormone Receptor deficiencies. We show that these short stature individuals rarely develop cancer or diabetes, analogously to the findings in mice. These results suggest that there is a fundamental and conserved relationship between sugars and amino acids, the activation of the cAMP/PKA and Tor/S6K pathways, aging and diseases.

DENHAM HARMAN AWARD LECTURE

Hormones and Aging: Lessons from the Dwarf Mouse

Holly Brown-Borg, PhD

University of North Dakota, Grand Forks, ND

Endocrine mutants have provided remarkable insight into the role of GH and IGF-1 in aging and longevity. The GH-deficient Ames dwarf mouse lives significantly longer than their wild type siblings. Understanding the mechanisms that lead to lifespan extension has been the focus of our work. We found that these mice exhibit elevated antioxidative enzymes, glutathione levels, detoxification enzymes and reduced oxidative damage. In addition, methionine metabolism is altered in dwarf mice such that transmethylation and transsulfuration are increased in comparison to age-matched wild type mice. Administration (in vivo and in vitro) and overexpression of GH suppresses antioxidative enzymes, increases oxidative damage and alters methionine metabolism.

We believe that GH is involved in the regulation of these pathways and that the hormone deficiency in Ames mice contributes to both enhanced stress resistance and longevity. The selective sensitivity of the GH system to methionine may ensure that the drive to grow is modulated not by general amino acid availability, but by the amino acid least available in the nutrient supply. Thus, when the demand for growth is absent (no GH), the resources shift toward factors that increase survival such as stress resistance and repair processes.

MARK A. SMITH AWARD LECTURE

Rapamycin: The First Longevity Drug?

Arlan Richardson, PhD

Barshop Institute for Longevity and Aging Studies
University of Texas Health Science Center at San Antonio

Since 2009, several groups have shown that giving mice rapamycin, an inhibitor of the mTOR pathway, extended both median and maximal lifespan. The ability of rapamycin to increase lifespan strongly suggests that it might be the first anti-aging drug. To determine if rapamycin increases lifespan by retarding/delaying aging, our group has studied the ability of rapamycin to: (1) retard or reduce age-related diseases [e.g., cancer, atherosclerosis, and neurodegeneration] and (2) improves physiological functions that decline with age. Feeding rapamycin prevented the development of various human cancer models in mice, e.g., colon cancer in a transgenic mouse model ($Apc^{Min/+}$) of adenomatous polyposis. We also found that feeding rapamycin attenuated the development and progression of atherosclerotic lesions in $ApoE^{-/-}$ mice fed a high fat diet. Most striking was the effect of rapamycin on neurodegeneration. Using two transgenic mouse models of Alzheimer's disease, we showed that feeding mice rapamycin rescued cognitive deficits and ameliorated A β and tau pathology. Increased autophagy as a result of feeding rapamycin appears to be important in the rapamycin-mediated reduction in A β levels; however, we also found that rapamycin improved cerebral blood flow and vascularization. Rapamycin was also observed to improve the decline in cognition in older normal mice, and mice fed rapamycin showed decreased anxiety and depressive-like behavior. Therefore, rapamycin appears to have substantial effects on the central nervous system in mice.

We have also studied potential negative side-effects of rapamycin. In a detailed analysis of the effect of long-term rapamycin on immune function we found that rapamycin: (1) is not an immunosuppressor, rather it is an immunomodulator, e.g., it enhances some immune functions, reduces others, and has no effect on other functions, (2) has no negative effect on the response of mice to an antigen, and (3) has little if any effect on susceptibility of mice to infectious agents. However, we find that rapamycin feeding can induce insulin resistance on certain diets. Currently, we are studying the effect of feeding rapamycin to a non-human primate, the common marmoset to evaluate the potential of taking rapamycin treatment as an anti-aging therapy to a primate model.

SPECIAL LECTURE

It's a GIG: The Trans-NIH Geroscience Interest Group

Felipe Sierra, PhD

National Institute on Aging, Bethesda, MD

Geroscience represents a trans-disciplinary conceptual framework that links the biology of aging to a vast array of age-related chronic diseases. The Geroscience Interest Group (GSIG) is a collaborative effort across several NIH Institutes to support the notion that aging is the major risk factor for these diseases and as such, basic aging biology represents a valuable approach in biomedicine. By pooling resources and expertise across the entire NIH, the GSIG identifies major cross-cutting areas of research and proposes coordinated approaches to identify hurdles and envision solutions to the health problems of our burgeoning elderly population. While most of the effort of the GSIG focuses on increasing awareness within and across the NIH, some activities are also open to the scientific community at large, and these will be discussed.

AGE PROGRAM SPEAKER ABSTRACTS

Abstract Number corresponds to speaker presentation number in the program schedule

(P) Denotes Presenter (G) Denotes Post-doctoral Candidate for Glenn Award

(N) Denotes Pre-Doctoral Candidate for Nicolai Award

1. Interaction of ApoE Genotype, Antioxidants and Exercise on Brain Function

Kiran Chaudhari (P,N), Jessica Wong, Philip Vann, Nathalie Sumien

University of North Texas Health Science Center and IAADR, Fort Worth, Texas

The $\epsilon 4$ allele of apolipoprotein E (ApoE) has been associated with increased risk for development of late-onset Alzheimer's disease (AD). To prevent appearance of brain dysfunction, a healthy lifestyle, such as exercising and eating antioxidants, is often recommended. Physical activity has been shown to have an allele-specific beneficial effect on cognition in humans and rodents. Antioxidant therapy is often suggested to improve brain function, as increased oxidative stress has been correlated with brain dysfunction, especially in $\epsilon 4$ carriers. Health conscious individuals are likely to combine exercise with antioxidant intake to increase protection, however recent studies have indicated a negative interaction of these two factors. In some cases, antioxidant intake abolished the beneficial effects of exercise. Our study aimed at determining the nature of the interaction between exercise and antioxidants on functional outcomes in a model of increased AD risk. Young male and female mice, expressing the human ApoE3 or E4, were placed under one of the treatment: Sedentary/control diet (SedCon), Sedentary /antioxidant-rich diet (Vitamins E and C; SedEC), Exercise/control diet (EXCon), Exercise/antioxidant-rich diet (EXEC), for 8 weeks prior to behavioral testing. In a coordination test, the E3 mice performed better than the E4 mice, and a significant improvement was observed with the ExEC treatment in males E3 and females E4. Better spatial learning was detected with EXEC in E3 females but not in E4. In males EX impaired learning index in E3 males. In active avoidance acquisition session, learning performance was improved with EX and EXEC treatment in E3 male, and with EXCon treatment in female E4, whereas cognitive flexibility was improved in both male and female in E3 by all the treatments but not in E4. These results in young mice provide an indication that genotype and sex are critical determinants in the functional outcomes of the treatment.

2. Assessment of Berry Fruit's Effects on Mobility and Cognition in Aging

Marshall G. Miller¹ (P,N) and Barbara Shukitt-Hale²

¹Tufts University / Human Nutrition Research Center on Aging; ²USDA/ARS/HNRCA

Changes in aging, in both animals and humans, include parallel decrements in mobility and cognition, even in the absence of degenerative disorders such as Parkinson's or Alzheimer's diseases. Diet has long been known to influence aging; however, specific whole foods are now being investigated for their effect on the aging brain. Research, conducted in our lab, has shown that dietary berry fruit can improve mobility and cognition in aged rodents, in part due to reduced levels of oxidative stress and inflammation. A recent study in our laboratory established a methodology for assessing the effects of dietary interventions on age-related declines in mobility and cognition among older adults. Importantly, this study used methodology which parallels behavioral tasks employed in our rodent model. Results indicate increases in postural sway and declines in gait speed, spatial navigation, and executive function. Preliminary results from our ongoing study expand this methodology to investigate the effects of a dietary blueberry intervention on healthy older adults (60-75 years of age).

Research funded by the USDA and the U.S. Highbush Blueberry Council

3. Estrogen's Ability to Protect Against Contraction-Induced Injury in Mouse Skeletal Muscle is Modest

Tara L. Mader (P,N), Allison M. Kosir, Kristen A.

Baltgalvis, Dawn A. Lowe

University of Minnesota, Minneapolis, MN

Aging is associated with decreased skeletal muscle function and increased susceptibility to injury. This is in part attributed to changes in the quality of the contractile unit. Loss of estrogen has been implicated as a mediator of age-associated changes in muscle quality and has been suggested to be protective from injury as well. We hypothesized that loss of estrogen would accentuate skeletal muscle injury. Injury was induced in wildtype mice in vivo by 150 eccentric contractions but the strength loss that resulted was not significantly different between control mice and estrogen

deficient mice ($P \geq 0.19$). To probe the question further, mdx mice, a model that is known to be highly susceptible to injury, was investigated. Mdx mice were randomly assigned to ovariectomy or sham treatment at six weeks of age. At 12 weeks of age, in vivo torque production and susceptibility to eccentric injury of the posterior crural muscles were assessed. There was no difference in maximal isometric torque production between estrogen deficient (ovariectomized) and sham mice ($p=0.235$). However, estrogen deficient mice exhibited 13% more severe torque loss following a series of eccentric contractions than mice with normal estrogen levels ($p=0.001$). These results suggest that estrogen is modestly protective against contraction-induced injury. A large unanswered question now becomes, to what extent and by what mechanisms might estrogen help muscle to recover from injury. This is important to understand when considering the loss of estrogen experienced by women at the time of menopause.

4. Dietary Methionine and Aging in Long- and Short-Living Growth Hormone Mutant Mice

Joseph Wonderlich (P), Sharlene Rakoczy, Debbie Raasakka, Lalida Rojanathammanee, Vanessa Armstrong, Nicole Raasakka, Holly BrownBorg
University of North Dakota School of Medicine & Health Sciences, Grand Forks, ND

Dietary methionine restriction (MR) extends mean and maximum lifespan in rats and mice and decreases the incidence of age-related disease. Reductions in growth hormone (GH)/ insulin-like growth factor 1 (IGF1) signaling also results in significant longevity in comparison to wild type controls. The objective of this study is to determine the relationship between circulating GH/IGF1 status, dietary methionine and lifespan. GH-deficient Ames dwarf, GH-resistant GH receptor knock out (GHRKO) and GH overexpressing transgenic (GH tg) mice were subjected to diets with altered methionine levels beginning at eight weeks of age. Body weights were recorded at least monthly throughout the ongoing study. Food consumption was monitored for six weeks in each of the nine groups of mice. Wild-type siblings of Ames dwarf mice on three different methionine (MET) diets showed a significant increase in median lifespan (0.16% MET: 798.5 days, 0.43% MET: 581 days, and 1.3% MET: 556 days). Similarly, differences between mutant species and their wild-type siblings have also been observed. Current data suggests there is no significant difference in median lifespan when comparing the Ames dwarf to wild-type mice provided a 0.16%

methionine diet, as opposed to the 0.43% diet ($p < 0.0001$) and the 1.3% diet ($p < 0.0001$). GH tg and wild-type mice administered a 0.16%, 0.43%, and a 1.3% methionine diet displayed significantly different median life spans ($p < 0.0001$). The early results of this study indicate that lifespan is extended in short-living GH tg mice on methionine restriction but not those low methionine or methionine-enriched diets (0.16%: 568 days, 0.43%: 357 days, 1.3%: 387 days, $p < 0.0001$). The results to date suggest that the level of lifetime circulating GH interacts with the methionine level in the diet and alters aging in mice.

5. Long-Term Consumption of Cranberry Extract Improves *C. elegans* Healthspan in Elderly Populations

Sujay Guha (P,N), Yuqing Dong, Ryan Kane, Cole Murbach
Clemson University

Extensive studies have demonstrated the ability of many nutraceuticals to alleviate the symptoms of aging and stress. We recently reported that cranberry extract (CBE) supplementation at an optimum concentration could prolong *Caenorhabditis elegans* (*C. elegans*) lifespan – dependent upon *daf-16* and *osr-1*. Considering that aging is a progressive degeneration of physiological functions, it is intriguing to know if CBE consumption interferes with age-related degenerative changes in animals. Thus, we examined the effect of CBE consumption on the healthspan of *C. elegans* populations of different ages and with varying age-related disorders. Our results suggest that long-term CBE supplementation led to a profound extension of lifespan, which is associated with the enhancement of cognitive skills and the reduction of muscular degeneration for aged worms. In *C. elegans* models of human proteotoxic disease, we further found that CBE supplementation may maintain protein homeostasis by preventing protein aggregation or misfolding, which are common age-related pathologies in aged cells. Additionally, we compared the effect of cranberry upon the motility, behaviors, and stress response of worms at different ages and found positive mediation by CBE. Together, our findings suggest that cranberry has profound benefits on the aging process in *C. elegans*, prompting the development of diet (cranberry) intervention against aging and age-related disorders.

6. Anti-Aging Effects of Cranberry Consumption Revealed from Multi-Species Studies

Cecilia Wang, Min Zhu, Yaning Sun, Jason Yolitz, Xiaoping Sun, Edward Spangler and Sige Zou (P)
Translational Gerontology Branch, National Institute on Aging, Baltimore, MD

Nutraceuticals derived from plants possess known bioactive elements and supplementation of diets with nutraceuticals has been shown to be an effective intervention for promoting healthy aging. Similarly, dietary macronutrients are critical environmental factors that modulate health and lifespan. Here we will discuss our studies on determining whether and how dietary macronutrient composition influences the longevity effect of nutraceuticals. Specifically we investigated the effect of a cranberry-containing nutraceutical on health and lifespan in flies and rodents. Animals were fed diets containing 2% cranberry for 12-18 months for rodents or the entire adult life of flies. We then measured changes in pancreatic cells of rats, immune and morphological changes in the brains of a mouse model of Alzheimer's disease (AD), and lifespan in flies. We found that cranberry supplementation delayed age-related loss of pancreatic beta-cells and improved insulin secretion in rats. Cranberry supplementation reduced expression of immune response proteins and delayed age-related accumulation of A β aggregates in the brain of the AD mice. We also found that cranberry could extend lifespan in flies. This lifespan extension, however, depends on diet composition since cranberry only extended lifespan in flies fed a high sugar-low protein diet but not a low sugar-high protein diet. These findings suggest that cranberry supplementation can be an effective intervention for promoting healthy aging. Moreover, our findings stress the importance of taking diet composition as well as dietary customs into account when developing aging interventions for humans. This study was supported by the IRP of NIA.

7. Cherry Picking Blueberries for Redox State (not ROS) Remediation in Aging and Alzheimer Neurons

Greg Brewer¹ (P), Debolina Ghosh¹, James A Joseph²
¹*Southern IL Univ Sch. of Med. Springfield IL;* ²*USDA-HNRC, Tufts U., Boston, MA (deceased)*

Neurons from aged rodent brains maintain an aging phenotype of increased susceptibility to stressors. We previously found that a blueberry extract (BB) was equally neuroprotective against beta-amyloid

toxicity at all ages. Simultaneous labeling for ROS with DCF and for glutathione with monochlorobimane showed a mechanism of BB action to involve transient ROS generation with an increase in glutathione through Nrf2 induction (Nuclear erythroid-related factor 2). No individual component was as effective as the crude BB. These results suggest that the beneficial effects of BB polyphenols involve transient stress signaling and redox protection (hormesis) for improved cognition.

In another approach we used rational small molecules to provide both an NADH energy precursor (nicotinamide) and a Nrf2 redox control inducer (18 α -glycyrrhetic acid; GA) to protect neurons from old and 3xTg-AD mice. We further determined whether glutathione (GSH) loss or increased ROS was more important to neurodegeneration under stress. We observed that GSH depletion with BSO increased neuronal death of 3xTg-AD cultured neurons at increasing rates across the age-span, while non-transgenic (nTg) neurons were resistant to GSH depletion until old age. Remarkably, the rate of neuron loss with ROS did not increase in old age and was the same for both genotypes, which indicates that age-related cognitive deficits in the AD-model were not caused by ROS. Therefore, we targeted the redox-sensitive transcription factor, Nrf2, with GA to stimulate a number of redox enzymes. GA restored Nrf2 and GCL levels in 3xTg-AD compared to nTg neurons. The combination of GA with nicotinamide additively increased survival against beta-amyloid or BSO stress. These treatments suggest that the redox environment is more important to neuron survival than ROS and supports our epigenetic oxidized redox shift (EORS) theory of aging. The dual neuroprotective treatment with nicotinamide and a Nrf2 inducer indicates that these age-related and AD-related changes are reversible.

8. Protective Effects of Dietary Polyphenols may Vary with Cell Type and Injury in Neural Cells

Kiran S. Panickar^{1,2} (P)

¹*Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD;* ²*Diet, Genomics, & Immunology Lab, Beltsville Human Nutrition Research Center, USDA, Beltsville, MD*

Ischemic stroke is caused by an interruption of cerebral blood flow, which can lead to vascular leakage, inflammation, tissue injury, and necrosis. Brain edema is an important consequence of cerebral ischemia and oxidative stress and inflammation have been implicated in its pathogenesis. Astrocyte

(glial) swelling is a major component of cytotoxic brain edema in ischemia and, along with vasogenic edema, may contribute to increased intracranial pressure, brain herniation, and additional ischemic injuries. Neuronal and endothelial swelling may contribute to brain edema. Considerable interest has focused on polyphenols because of their antioxidant and anti-inflammatory properties. C6 glial, SK-N-SH neuronal, and bEnd3 brain endothelial cultures were exposed to oxygen-glucose deprivation (OGD) for 5 hr. Cell swelling was examined in the presence or absence of polyphenols. Flavonoids including quercetin, myricetin and hesperidin attenuated cell swelling in glial cultures. Green tea extract (GTE), cinnamon extract, and a type A polyphenol trimer from cinnamon (MW 864) also attenuated cell swelling in glial cells. Neuronal swelling was blocked by GTE but at a higher concentration than that required for glial cultures. However, such swelling was not blocked by myricetin or quercetin. A polyphenol-rich extract from green tea (GT) and a polyphenol trimer, but not cinnamon extract, prevented cell swelling in endothelial cells. Resveratrol, which did not prevent cell swelling in C6 glial or neuronal cells post-ischemia, prevented cell swelling in endothelial cells. Effects of these polyphenols on mitochondrial function were also varied depending on the cell type or the phase of the injury (during or post-ischemia). Black tea extract did not protect glial swelling but protected neuronal swelling. OGD-induced reduction in glutamate uptake was ameliorated by cinnamon and myricetin but not quercetin. However, most polyphenols attenuated the OGD-induced rise in intracellular calcium. These results indicate that the protective effects of polyphenols may vary with the neural cell type or the cellular mechanism associated with ischemic injury.

9. Diet and Gene Interactions in Alzheimer Prevention

Gregory M. Cole (P) and Sally Frautschy
Easton Center, University of California Los Angeles and Greater LA VA GRECC

Mediterranean diet has proven preventive benefits for cardiovascular disease (CVD) and shares risk factors with Alzheimer disease (AD). Genetic risk factors for AD like ApoE4 accelerate beta amyloid deposition to have their primary effect on age of onset rather than clinical progression. Similarly, CVD and AD dietary risk factors (antioxidants, omega-3) reduce amyloid in models but typically fail to impact progression in trials. Omega-3 associate with lower human beta amyloid blood

levels, but they also reduce tauopathy and have neuroprotective activities suggesting possible treatment effects. Neuroprotective effects of DHA and its metabolites in animals include protection against neuronal death pathways, synaptic marker loss and electrophysiological dysfunction while epidemiological studies link Omega-3 intake with protection from regional brain shrinkage and white matter damage. However, trials have failed or suggested Omega-3 treatment effects only in subjects with minor memory problems but not with AD. Other approaches including Omega-3 and antioxidant-based cocktails have some modest success in early stage patients raising hopes for improved cocktails with broader activity. Our group is testing cocktails including a bioavailable formulation of curcumin, a polyphenolic with potent anti-amyloid and anti-inflammatory activity in multiple AD models and now in clinical trials. One large DHA clinical trial and 3 epidemiological studies suggest a cognitive benefit only in non-ApoE4 carriers. Based on this, we are investigating ApoE x dietary PUFA interactions in plaque forming ApoE3 or 4 knock-in mice with FAD mutations. We find that ApoE4 carriers have distinct amyloid, immunoregulatory and tau kinase responses to dietary PUFA that may help explain limited clinical trial success with Omega-3. Our research argues that understanding how ApoE4 interacts with environmental risk factors including nutrients and how to modulate that interaction may be central to a successful and cost-effective AD prevention effort.

10. Influence of Timing, Formulation and Combinations on Antioxidant Intervention Outcomes

Nathalie Sumien (P) and Michael J. Forster
University North Texas Health Science Center, Fort Worth, TX

The study of antioxidants as an anti-aging intervention strategy has a long history and has yielded variable, often conflicting outcomes regarding their effectiveness in both human subjects and mammalian animal models. The variability in the functional outcomes may be due to one or several factors. Here, we summarized how some of these factors may influence the functional outcomes of vitamins E and C, and Coenzyme Q₁₀ supplementation in the most common mouse model of aging: C57BL/6 mice. We determined whether the timing of the intervention during life is an important factor influencing the final outcome by comparing life-long versus senescence-initiated supplementation.

We also compared different formulation for vitamin E and Coenzyme Q₁₀ and clarified whether it changed the functional outcomes. And lastly, we compared single versus combinations of antioxidants on functional and biochemical outcomes. The results from these studies provided clear indication that timing, formulation and nature of the antioxidant intervention during aging are all critical determinants of the functional outcome.

11. Antioxidants and Brain Aging: Lessons Learned from Studies in Dogs

Elizabeth Head (P)

University of Kentucky, Sanders-Brown Center on Aging, Lexington, KY

Aging dogs naturally develop learning and memory decline and also exhibit human-like individual variability in the aging process. Impaired frontal function is also a consistent feature of aging in the dog as measured by reversal learning, which reflects response inhibition. The neurobiological basis for cognitive dysfunction may be related to the progressive accumulation of beta-amyloid (A β – identical in dogs and humans), mitochondrial dysfunction and/or cumulative oxidative damage to proteins, lipids and DNA/RNA as observed in human brain. Thus, we hypothesized that reducing oxidative damage and mitochondrial dysfunction through a diet rich in antioxidants and mitochondrial co-factors would reduce cognitive decline in aging dogs. We completed a study of aging beagles (>9 years) treated for a period of 2.9 years) with a diet enriched in vitamin E, C, fruits and vegetables and mitochondrial co-factors (lipoic acid, carnitine). We observed rapid and robust improvements in learning. Memory improvements occurred after an extended period of treatment suggesting a possible reversal of memory impairments. The addition of behavioral enrichment (social, environmental and cognitive) further enhances learning and memory improvements in response to an antioxidant diet. Interestingly, these effects appear to be selective only for aging and not young dogs. Neurobiologically, an antioxidant enriched diet prevented but did not reverse existing A β in the brain and reduced oxidative damage. However, when mitochondrial co-factors were tested separately from cellular antioxidants as was combined in the first study, we did not observe the same robust effects as in the combination study. These results suggest that the combination of mitochondrial cofactors with cellular antioxidants is critically important to improving brain function and reducing pathological signs of aging in the

brain. Given the very modest benefits of antioxidants reported in human clinical trials, particularly those in Alzheimer's disease patients, it may be useful to consider combinations of antioxidants rather than single compound supplementation.

12. Effects of Berry Diets on Tumorigenesis and on the Disruption of Cognitive Performance Produced by Exposure to Space Radiation

Bernard M. Rabin (P)

Department of Psychology, UMBC, Baltimore, MD

As is the case with all types of radiation, exposure to the types of radiation (particles of high energy and charge [HZE particles], protons and alpha particles) that will be encountered on exploratory class missions to other planets can lead to the development of tumors. In addition, space radiation is unique in that exposure to HZE particles and protons also produces neurochemical and cognitive/behavioral changes similar to those that characterize the aging process, including deficits in spatial learning and memory, object recognition memory and operant responding on an ascending fixed-ratio schedule. As such, it has been proposed that exposure to space radiation produces “accelerated” aging. It is possible that the aging-like changes in neural and behavioral functioning may result from radiation-induced oxidative stress. If oxidative stress is the mechanism underlying “accelerated” aging from space radiation, then treatment with antioxidant diets should prevent the neuronal and behavioral changes that accompany exposure to HZE particles. To evaluate this possibility, rats were maintained on diets containing strawberry or blueberry extract for 2-8 weeks prior to exposure to 56Fe particles, a prominent component of space radiation. Compared to rats maintained on control diets, the rats maintained on the antioxidant diets did not show deficits in cognitive performance, although the effectiveness of the different diets in preventing performance decrements depended upon the specific behavioral task. Both diets were equally effective in reducing the frequency of occurrence of radiation-induced tumors. These results support the role of oxidative stress in the development of performance decrements produced by exposure to space radiation and suggest that antioxidant berry diets may be effective countermeasures, possibly reducing both tumorigenesis and performance decrements on exploratory class missions.

Supported by NASA Grants: NNX08AM66G and NNX13AB73G

13. Dietary Approaches for Regenerative Medicine

Brent J. Small, Patrick Bradshaw, Paula C. Bickford (P)
James A Haley Veterans Hospital and Center of Excellence for Aging and Brain Repair, USF Morsani College of Medicine, School of Aging Studies, USF; Department of Cell Biology, Microbiology and Molecular Biology, USF, Tampa, FL

Aging is a complex process that involves cellular senescence, a gradual loss of tissue homeostasis and declines in organ function. Denham Harman first proposed the free radical theory of aging in 1956. This theory now includes the mitochondrial theory of aging. Mitochondria, as the power source of the cell, have important control over metabolic function, which has been a major focus of aging research in recent years. Disruption of mitochondrial energy metabolism is linked to diverse aspects of aging including brain aging and Alzheimer's disease. Emerging evidence suggests that stem cell niches within the body may be particularly sensitive to aging and may, in part, be an underlying cause of aging as stem cells are important in maintaining and repairing tissue and organ function. We show that dietary approaches are capable of increasing stem cell function in aged animals. One of high interest is NT-020 a proprietary blend of blueberry, green tea, carnosine and Vitamin D3. Our previous studies have shown that this intervention increases neurogenesis in the aged rat brain and improves cognitive behaviors. We now further show that some of these changes can lead to increased health span and the effect may be mediated by increased mitochondrial energy metabolism in the stem cell niche. We have also completed a double blind placebo controlled clinical trial with normal elderly subjects with a mean age of 73. Subjects were screened with the MMSE and the mean MMSE was 29. Subjects were randomized to placebo (n = 53) or control (n = 52) and their cognitive functioning was assessed at baseline and 2 months. In this highly functioning elderly population we observed a significant improvement in two timed tests, identical pictures and number completion. This reflects an improvement in processing speed, a measure sensitive to aging and thought to underlie performance on other higher order cognitive tests.

14. Nutritional Approaches to Ameliorate Age-Related Neurocognitive Decline

Robert Krikorian (P)
University of Cincinnati, Cincinnati, OH

With the expansion of the aging population and increase in chronic age-related disease conditions,

the prevalence of dementia, especially Alzheimer's disease, is projected to reach epidemic proportions. There is no effective therapy for AD and prospects for a curative agent are uncertain. However, preventive strategies, as opposed to disease cure, may be more effective in reducing the burden of dementia. Dietary interventions are promising (albeit under-utilized) approaches because they have the potential to influence fundamental pathophysiological factors. In particular, dietary approaches can ameliorate metabolic disturbance and downstream mechanisms that promotes neuropathology. We will discuss the basis for utilizing diet manipulation and dietary supplementation in the context of age-related memory decline and review the results of recent human trials with aging adults. These initial human studies have shown enhancement of neurocognitive function with both metabolic manipulation and berry fruit supplementation, and there are indications that these approaches may produce common beneficial effects. These research findings comprise an emerging database translating results from preclinical studies and indicate that such interventions have potential as preventive interventions in the context of increasing dementia prevalence.

15. Berries, Flavonoids and Health in Aging

Francine Grodstein (P)
Brigham and Women's Hospital, Boston, MA

OBJECTIVE: Berries are high in flavonoids, and improve cognition in animal models. However, limited research has addressed flavonoid or berry intake in humans. Thus, we prospectively evaluated whether greater long-term intakes of berries and flavonoids are associated with slower rates of cognitive decline in older women. **METHODS:** We utilized data from the Nurses' Health Study for this research. Beginning in 1980, a validated, semiquantitative food frequency questionnaire was administered every 4 years to Nurses' Health Study participants. In the late 1990s, we began measuring cognitive function in the oldest Nurses' Health Study participants, 16,010 women aged 70 years and older. Follow-up cognitive assessments were conducted twice, at 2-year intervals. For the purposes of these analyses, we ascertained long-term diet by averaging dietary reports from 1980 through the initial cognitive interview. Using multivariate-adjusted, mixed linear regression models, we then estimated mean differences in slopes of cognitive decline according to categories of long-term berry and flavonoid intakes. **RESULTS:** We found strong relations of

greater berry, anthocyanidin, and flavonoid intakes with better cognitive health. Specifically, greater intakes of blueberries and strawberries were associated with slower rates of cognitive decline (eg, for a global score averaging all 6 cognitive tests in our battery, for blueberries: mean difference = 0.04 standard units, 95% confidence interval [CI] = 0.01-0.07, comparing extreme categories of intake, p-trend = 0.014; for strawberries: mean difference = 0.03, 95% CI = 0.00-0.06, comparing extreme categories of intake, p-trend = 0.022), after adjusting for multiple potential confounders. These effect estimates were equivalent to those we found for approximately 1.5 to 2.5 years of age in our cohort; that is, berry intake appears to delay cognitive aging by up to 2.5 years. Additionally, in further supporting evidence, greater intakes of anthocyanidins and total flavonoids were associated with slower rates of cognitive decline (p-trends = 0.015 and 0.053, respectively, for the global cognitive score). **CONCLUSION:** Higher intake of flavonoids, particularly from berries, appears to improve rates of cognitive decline in older adults.

16. Nutrient Associations with Human Brain Neuropathology and Neural Reserve

Martha Clair-Morris (P)

Rush Medical University, Chicago, IL

Dementia is characterized by greater brain neuropathology including amyloid plaques and neurofibrillary tangles (hallmarks of Alzheimer's disease), macro- and micro-infarcts (hallmarks of vascular dementia), and Lewy bodies (hallmarks of Parkinson's disease) as well as lower neural reserve through decreased neurons and synaptic proteins. Animal models have demonstrated altered neural reserve and neuropathology through dietary manipulations of vitamin E and of n-3 fatty acids. Whereas epidemiological studies have examined these nutrients in relation to the development of dementia, no human study has investigated the impact of nutrients on brain pathologies and reserve. The Memory and Aging Project (MAP) is a prospective clinical, neuropathological study of dementia in which all participants are dementia free at enrollment and agree to organ donation at their death. As part of the study, we analyzed brain tocopherol levels in 115 deceased MAP participants and related these to markers of neuropathology and neural reserve. Tocopherols were analyzed in two cortical and two subcortical brain regions. α -tocopherol represented approximately 70% of total tocopherols and γ -tocopherol, 30%. Overall levels of γ -tocopherol

were related to both lower amyloid load ($\beta = -2.10$; $p = .002$) and neurofibrillary tangle severity (lower Braak scores) ($\beta = -1.12$; $p = .02$). Concentrations of α -tocopherol in the brain were not associated with either AD neuropathology, except for a statistical interaction with γ -tocopherol. High α -tocopherol was associated with *higher* amyloid load when levels of γ -tocopherol were intermediate or low, and with lower amyloid levels when γ -tocopherol levels were high (P-value for interaction = 0.03). Higher concentrations of the tocopherols were significantly associated with increased concentrations of pre-synaptic proteins, including complexin I ($\beta = 0.62$; $p = .004$), complexin II ($\beta = 0.73$; $p = .0003$), synaptophysin ($\beta = 1.00$; $p = .002$), and the SNARE proteins, syntaxin ($\beta = 1.01$; $p = .001$) and SNAP-25 ($\beta = 1.21$; $p = .0001$). In models that included concentrations of α -tocopherol and γ -tocopherol simultaneously, only α -tocopherol was independently associated with pre-synaptic protein concentration.

17. Vascular Aging: The Role of the Diet

Britt Burton-Freeman (P)

University of California Davis, Davis CA

Plant foods, including fruits, vegetables, herbs and spices and certain oils have been consistently identified as key components of dietary patterns that reduce risk for the development of chronic diseases, including atherosclerotic cardiovascular disease, Alzheimer's disease, type II diabetes mellitus and some cancers. All of these chronic diseases have an independent age component, such that even in the healthiest individuals, age-related declines and development of disease will ensue. Oxidative stress is a leading hypothesis of chronic / age-related diseases. Aging is associated with enhanced production of oxidative stress factors and declining ability to restore balance leading to cellular and tissue damage and dysfunction. In the vascular world, aging is characterized by progressive losses in *endothelial function* accompanied by functional losses in blood pressure regulation, increased vessel atherogenicity and instability, and increased thromboembolic disease risk. The Western dietary pattern is a risk factor for vascular disease. It is rich in refined carbohydrate and animal fat and lacking in fruits, vegetables and fiber promoting oxidative stress and inflammation. The repeated stress of the Western diet may be the perfect recipe for premature aging. Alternatively, the Mediterranean dietary pattern, rich in fruits and vegetables, nuts, olive oil and moderate wine consumption is associated with lower rates of cardiovascular disease among other

metabolic and degenerative age-related diseases. Various research suggests it is the (poly)phenols of this dietary pattern that contribute favorably to the diet-disease relationship, presumably through their ability to modulate processes of oxidative stress/damage and inflammation. Consumption of anthocyanins and other flavonoids are among those compounds showing systemic biological activity and protective vascular effects. This presentation will discuss processes underlying disease, such as oxidative stress and inflammation and their relationship to cardiovascular disease development, dietary sources and inducers of oxidative stress as well as dietary sources and probable protectors from pre-mature aging of the vasculature.

18. *Indy* Mutations Maintain Fly Health Homeostasis

B. Rogina¹(P), R.P. Rogers¹, N. Neretti², P.-Y. Wang³, S.L. Helfand²

¹University of Connecticut Health Center, Farmington, CT; ²Brown University, Providence, RI; ³National Chengchi University, Taipei City

Indy (*I'm not dead yet*) encodes the fly homologue of a mammalian transporter of di and tricarboxylate components of the Krebs cycle intermediates. Mutations in the *Indy* gene extend life span of the fruit fly. In flies, *INDY* is predominantly expressed in places where intermediary metabolism takes place, such as gut, fat body and oenocytes. Others and our data suggest that *Indy* mutations mimic calorie restriction and extend longevity by related mechanism. This hypothesis is supported by the similarities in physiology of calorie-restricted flies with *Indy* mutant flies on high calorie diet. Our new findings suggest that one of the most important energetic changes caused by the *Indy* mutation are changes in the gut. This is supported by findings that life span returns to normal only when *INDY* levels in the gut return to wild type. Changes in gut energy metabolism result in preservation of ISC homeostasis characterized by a decrease in age-associated accumulation of ISCs. Our studies show a direct connection between changes in energy metabolism, caused by the *Indy* mutation and preservation of ISC homeostasis. Therefore we suggest that *Indy* mutations preserve homeostasis in tissues that contribute extended health and longevity.

19. Are Healthspan and Longevity Necessarily Coupled in Rodent Studies?

Sarah Mitchell (P) and Rafael de Cabo

Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD

Aging results in a progressive decline in all organ systems having a negative impact on reproductive, cognitive, physical, metabolic function and survival. Understanding the mechanisms underlying these processes has become one of the primary focuses in the field of gerontology. For decades the goal of rodent studies was to identify interventions that lead to increases in both mean and maximal lifespan paying little attention to the impact of that particular intervention on overall health and wellbeing of the organism. The aim of all these studies was to ultimately translate these findings to humans. However, whether healthspan and lifespan are necessarily coupled in rodent studies is the question that this talk will address. Here we will present an overview of various rodent studies conducted in our laboratory using different dietary manipulations that had a positive impact on healthspan, lifespan and both. Results include responses to oral glucose tolerance tests, locomotor activity in behavioral testing and the effects of the interventions on longevity.

Funded by the NIA/NIH Intramural Research

20. Healthspan vs Lifespan: What's up in *Caenorhabditis elegans*

Thomas E. Johnson (P), Breanne Newell, James R. Cypser, David Kitzenberg, Pat Tedesco, Lindsey Beverly
Institute for Behavioral Genetics, Department of Integrative Physiology, University of Colorado, Boulder

Model organisms such as *C. elegans* play a large role in the study of human health. Herein we address the question of whether life-extending interventions also extend the fraction of life considered healthy (i.e. "health-span"). These studies have profound implications both for research on aging and for public policy regarding healthcare, specifically as regards sarcopenia (the age-related loss of muscle function) and overall individual mobility. We have tested the health-span effects of several life-extending interventions in the nematode model, including many genetic mutations (especially *daf-2*, *age-1*, *daf-16* and other genes in the insulin-like response pathway). We have also used multiple environmental interventions: drugs approved for human use [Trolox and valproic acid], and two forms of dietary restriction. We assessed several measures of late-life health, spontaneous movement, provoked movement, Class C response, and lifespan. Dietary restriction, in both tested forms, extended health-span in proportion to lifespan. The

daf-2 mutation increased both health-span and lifespan, but health-span to a greater proportion. The *hpa-1* mutation probably modulates health-span via a physiological mechanism related to dietary restriction. This work was supported by a BIG grant from the American Federation for Aging Research and by gifts from Elsevier and the Son² Foundation.

21. The Mechanism by Which Longevity Genes Protects Against Aging Genes

Derek M. Huffman (P)

Albert Einstein College of Medicine, Bronx, NY

Aging is the major risk for diseases such as cancer, AD, type 2 Diabetes mellitus and cardiovascular disease. We hypothesize that a progress in preventing these diseases will occur only if we can understand the reason people age at different rates, and develop strategy to delay aging. We established a unique cohort of individuals with exceptional longevity (~550 Ashkenazi Jews ages 95-112) and their offspring (approximate age 70 years) and age- and sex-matched controls without a family history of unusual longevity. This matched group of offspring of exceptional longevity-proband and their controls are a powerful tool for identifying genetically controlled longevity traits. Our analysis is based on a very large selection that occurs between ages 60 and 112 (when most humans are dead). This selection is an opportunity to follow which genotypes have been under represented with aging ('killing' genotypes) and which have been overrepresented (longevity genotypes). Using a candidate gene approach we identified several common genotypes to lipid, thyroid, IGF-1 R, FOXO3a and adiponectin genes. By employing gene-to gene interactions we have identified aging genotypes and explored how these are buffered by the longevity genes above. Using an un-biased approach we performed GWAS we discovered several SNPs in non-candidate genes that have been mostly unexplored in humans. Many others genotypes with a lower p value can be used in various way to rescue potential false negatives. We have also found novel interactions between longevity and aging genotypes. These analyses will allow us to discover that are the target for longevity genes and develop drugs that will delay aging and will prevent several age related diseases.

22. Muscle Regrowth: Does Age Make a Difference

Esther E. Dupont-Versteegden (P)

Div. Physical Therapy, College of Health Sciences, University of Kentucky, KY

The recovery or maintenance of muscle mass after and during a period of disuse is impaired at old age. Underlying mechanisms for this attenuated regrowth response are currently unknown; we have investigated the role of satellite cells, intracellular signaling pathways, as well as interactions of skeletal muscle with immune system-related cells. In our studies we have used Fisher 344/BN rats between the ages of 6 and 33 months and soleus and gastrocnemius muscle atrophy was induced by hind limb suspension (HS). Reloading (RE) after HS or intermittent reloading (IR) during HS has been utilized to investigate the regrowth response. Satellite cell fusion appears to occur during attenuation of atrophy in young animals and is absent in aged muscle, but this deficiency is not reflected in changes in myonuclear number. Apoptosis is elevated at old age, but its contribution to atrophy of the regrowth response is unclear since no changes in nuclear number are observed. Lower serum IGF-1 levels with HS are not recovered in aged RE rats, unlike young, indicating an attenuated response in protein synthesis could be responsible for the impaired regrowth. However, intracellular markers of the protein synthesis pathway respond similar in young and old rats. Markers of proteasome-regulated protein degradation also exhibited the same levels in young and old and autophagy-related proteins did not show a difference in the response to HS and RE in muscles from young and old rats. ED2 macrophages were elevated in aged muscle and decreased upon HS which did not occur in young rats; with RE the numbers however recovered in aged. We conclude that muscles from aged rats have the capability to respond appropriately to a muscle growth stimulus, but a larger stimulus, such as exercise, is likely needed in the aged to regrow muscle to similar extent as in young.

23. Muscle Adaptation to Contractile Activity: Effects of Aging

Joyce Chen (P)

Chung Gung University, Kweishan, Tao-Yuan

Skeletal muscles become smaller and weaker as we age, resulting in the frailty of the elderly. To date, high intensity exercise (muscle contractions) is considered the best method to prevent or improve the age-related muscle dysfunction. However, studies found that the adaptive responses of the elderly to high intensity exercise are blunted compared to young adults. The mechanisms underlying the blunted adaptation of aged muscles with contractions could be due to the impaired protein synthesis and/or the impaired myogenesis

in the old animals. In this symposium, I will introduce the current research on age-related changes in protein synthesis with muscle contractions. In addition, I will describe our ongoing research that tries to understand whether the myogenesis of skeletal muscles to contractions are impaired in old animals.

24. Can Nutritional Interventions Slow Sarcopenia or Reverse Muscle Loss?

Steve Alway (P)

West Virginia University, Morgantown, WV

Sarcopenia is the age-associated loss of muscle mass and function. It begins before the age of 50 and progresses quickly after the age of 70. Sarcopenia impairs mobility and increases the susceptibility to muscle injury, thereby leading to a decrease in the independence and the quality of life in the elderly. While the cause of sarcopenia is multifactorial, oxidative stress has been postulated as a potential trigger for muscle loss. Oxidative stress occurs when an increase in oxidant production exceeds an organisms' capacity to buffer them, via a complex coordination of the endogenous antioxidant defense system, leading to greater cell death. This has been shown to play a role in the events that lead to muscle loss with aging. Although dietary supplements have been used for many years as a potential combatant for aging-associated conditions, less is known about the efficacy of nutritional compounds to slow or reverse sarcopenia after muscle loss by disuse or aging per se. Several compounds have been studied by our laboratory in aged rodents, and each has been shown to have a role in reducing the cell signaling events that surround sarcopenia. For example, resveratrol is a naturally occurring polyphenol found in grapes, peanuts and mulberries. We have found that resveratrol reduced the levels of oxidative stress and improved antioxidants in muscles of senescent rodents that had undergone disuse. Similarly, a metabolite of the essential branched-chain amino acid leucine, and green tea, which contains a highly antioxidant catechin, had marked reductions in cell loss during disuse, improved muscle strength, and also improved muscle repair after the period of muscle loss in rodents. However, the effectiveness of the nutritional supplements was greatest during the periods of rapid muscle loss (e.g., muscle disuse) rather than the slower loss of aging with maintaining normal activity. Although nutritional intervention did not appear to be a strong enough stimulus to reverse muscle sarcopenia, it appears to

have a significant potential to reduce muscle loss especially during periods of prolonged disuse.

25. Structural and Functional Determinants of Muscle Quality

Luigi Ferrucci (P) and Rafael De Cabo

National Institute on Aging, Baltimore, MD

Changes in body composition and in physical performance occur in virtually all aging individuals, suggesting they are directly connected. Although, the idea that a decline in muscle mass is directly responsible for a decline in strength -which would be one of the main causes of functional impairment and, ultimately, disability- has recently been challenged by studies showing that age associated decline in strength is higher than expected by changes in muscle mass. Perhaps even more important, strength only explains a small fraction of physical performance. This data suggest that aging is associated with a decline in muscle quality, although a clear operational notion of the term "muscle quality" is still controversial. Theoretically, muscle quality can be expressed by the ratio between mass and strength, namely "the amount of force generated by a unit of muscle mass". However, in practice there are many ways to assess mass and strength and the calculated ratio may be affected by factors other than muscle tissue quality. For example, the ratio between CT-estimated thigh cross-sectional area and knee extension torque is not a generalizable parameter because it is higher in taller persons than in shorter persons, possibly because taller individuals have a wider pennate angle of the muscle and less difference between the functional and the anatomical cross-sectional area. Operationalizing the concept of muscle quality is essential to start investigating possible causes of muscle quality decline with aging. Candidate mechanisms for muscle quality decline with aging include denervation, motor unit remodeling, impaired micro-vascular response, energetic metabolism and architectural deterioration of the sarcomeric structure. Some evidence that these mechanisms are implicated in deteriorating muscle quality is accumulating in animal models and it is starting to be translated to humans. New technological developments are emerging that can substantially improve our ability to study correlation of muscle quality in humans.

26. Autophagy and Mitochondrial Dysfunction in Muscle and Nerves with Age: Potential Interventions

Christiaan Leeuwenburgh (P)

University of Florida, Department of Aging and Geriatric Research, Institute on Aging, Gainesville, FL

Sarcopenia involves the loss in muscle mass, strength and function with age. Besides losses in myocytes, sarcopenia is extensively characterized by a decline in peripheral nerve (PN) function and damage. *Peripheral Nerves an Overlooked Area in Aging Research*. Less attention has been paid to loss in myelin and the declining function of PN with age. We showed in aged animals a drastic decline in the expression of glial and neuronal proteins important for myelination and function of PN. The age-related decline of PN was markedly ameliorated by lifelong calorie restriction. We also noted an improvement in nerve architecture with caloric restriction due to a sustained expression of protein chaperones, markers of the autophagy-lysosomal pathway and a marked reduction in oxidative stress and inflammation. *Human Skeletal Muscle with Age*. In muscle of humans, we recently examined key mitochondrial (Mt) regulatory proteins from elderly subjects classified as high- or low functioning and compared these with young subjects. Mitochondrial respiration rates, PGC-1 α , a Mt regulator for Mt biogenesis, Sirt3, a mitochondrial deacetylase, the Mt fusion protein Opa1, were all markedly suppressed in both high and low functioning subjects compared to young controls. *Interventions to Improve Muscle Quality*. We examined whether a combination of diet and exercise has a beneficial effects on autophagy, protein quality control and Mt biogenesis in human muscle. A six month weight loss program combined with moderate-intensity exercise was completed to determine the changes in cellular quality control mechanisms of autophagy, ubiquitin-proteasome system, and mitochondrial function, in the skeletal muscle of older obese women. The age-related decline in functional molecules benefitting mitochondrial function (including impaired mitochondrial regulatory pathways) and autophagy (including alterations in other cellular protein homeostatic mechanisms) play a major role to cellular dysfunction. Other potential interventions will be discussed such as resveratrol and promising botanicals as well as pharmacological compounds to attenuate the functional decline observed in humans. (1-7)

¹Dutta, D., Xu, J., Kim, J.S., Dunn, W.A., Jr., and Leeuwenburgh, C. 2013. *Autophagy* 9; ²Marzetti, E., Lees, H.A., Manini, T.M., Buford, T.W., Aranda, J.M., Jr., Calvani, R., Capuani, G., Marsiske, M., Lott, D.J., Vandenborne, K., et al. 2012. *PLoS one* 7:e32829; ³Joseph, A.M., Adhihetty, P.J., Buford, T.W., Wohlgemuth, S.E., Lees, H.A., Nguyen, L.M., Aranda, J.M., Sandesara, B.D., Pahor, M., Manini, T.M., et al. 2012. *Aging cell* 11:801-809; ⁴Wohlgemuth, S.E., Lees, H.A., Marzetti, E., Manini, T.M., Aranda, J.M., Daniels, M.J., Pahor,

M., Perri, M.G., Leeuwenburgh, C., and Anton, S.D. 2011. *Rejuvenation research* 14:315-324; ⁵Opalach, K., Rangaraju, S., Madorsky, I., Leeuwenburgh, C., and Notterpek, L. 2010. *Rejuvenation research* 13:65-74; ⁶Rangaraju, S., Hankins, D., Madorsky, I., Madorsky, E., Lee, W.H., Carter, C.S., Leeuwenburgh, C., and Notterpek, L. 2009. *Aging Cell* 8:178-191; ⁷Wohlgemuth, S.E., Seo, A.Y., Marzetti, E., Lees, H.A., and Leeuwenburgh, C. 2010. *Experimental Gerontology* 45:138-148.

27. Human Muscle Aging and Adaptation: Underlying Cellular Mechanisms

Charlotte A. Peterson, (P)

College of Health Sciences, University of Kentucky, Lexington, KY

Aging is associated with the loss of muscle mass and strength, and a blunted and variable ability to increase mass in response to resistance exercise training. Impaired muscle stem cell (satellite cell) function has been proposed to contribute to these age-associated deficits. In humans, a correlation among satellite cell abundance, myonuclear accretion and growth in response to training has been reported. To directly test these ideas, a genetic mouse model was generated in which satellite cells were effectively ablated in adult muscle. Results show that lifelong satellite cell depletion has no effect on muscle maintenance or on the extent of growth in response to overload that mimics resistance exercise. Thus, satellite cell loss does not play a causal role in muscle wasting during aging, or in diminished muscle adaptability observed with age. Recent data from human resistance exercise training studies suggest that resident macrophages, and the local muscle inflammatory environment, may play a more important role in muscle adaptation in the elderly.

28. Depletion of mTORC2 Impairs the Health and Longevity of Male, but not Female Mice

Dudley W. Lamming¹ (P,G), Pekka Katajisto¹, Maria Mihaylova¹, Omer Yilmaz¹, Amanda Hutchins¹, David Sabatini^{1,2}

¹Whitehead Institute; ²Massachusetts Institute of Technology, Cambridge, MA

Rapamycin, an inhibitor of mechanistic target of rapamycin complex 1 (mTORC1), extends the lifespans of many organisms including mice. We have found that rapamycin disrupts a second mTOR complex, mTORC2, in vivo, and that mTORC2 disruption is an important mediator of the effects of rapamycin. In *C. elegans* decreased mTORC2 signaling promotes longevity, but in mammals the effects of decreased mTORC2 signaling may not be as beneficial. We have found that mTORC2 action is required for the insulin-mediated suppression of hepatic gluconeogenesis,

and mice lacking hepatic Rictor, an essential protein component of mTORC2, are glucose intolerant. In order to determine the effect of decreased mTORC2 signaling on longevity, we have examined three different mouse models of decreased mTORC2 signaling; mice in which one copy of Rictor has been deleted, mice lacking hepatic Rictor, and mice in which Rictor has been depleted in the adult mouse by means of a tamoxifen-inducible Cre. We find that depletion of Rictor negatively impacts the longevity of male mice, but does not impair survival in females. Surprisingly, the effect of Rictor depletion on longevity is separable from the impact of Rictor on glucose homeostasis, as *ric1^{+/-}* mice have reduced lifespan but normal glucose homeostasis. Furthermore, we find that mTORC2 may also be critical in the pro-longevity effect of calorie restriction. Our results implicate mTORC2 signaling as critical in the survival of male mice, and suggest that the inhibition of mTORC2 by rapamycin negatively impacts longevity.

29. Patterns of Intraspecific Variability in the Lifespan and Transcriptome Response to Caloric Restriction in Rotifers

David B. Mark Welch (P) and Kristin E. Gribble
Marine Biological Laboratory, Woods Hole, MA

Caloric restriction (CR) is one of the most reliable means of increasing lifespan across a wide range of animals, although the proximal and ultimate causes of CR are poorly understood. Monogonont rotifers, common aquatic microinvertebrates, are an emerging system for studies of aging, due in part to their small size (~0.5mm), short lifespan (14-28 days), and ease of culturing. We are working with a group of closely related monogononts, the *Brachionus plicatilis* cryptic species complex, that differ in their responses to stimuli such as CR despite their genetic similarity. Isolates from this complex provide a comparative system of natural mutants with which to investigate the origins and causes of CR-mediated lifespan extension. We tested the effects of chronic caloric restriction (CCR) and of intermittent fasting (IF) in twelve isolates and found that variation in lifespan under non-restricted conditions dictated the degree of lifespan extension under CR: longer-lived isolates were less likely to have a significant increase in lifespan under CCR, and were more likely to have a significantly shortened lifespan under IF. While CCR generally increased both lifespan and total fecundity, IF caused increased, unchanged, or decreased lifespan, depending upon the isolate, and generally decreased total fecundity. A lack of

trade-off between lifespan and fecundity under CCR, and differences in lifespan and fecundity under CCR and IF suggests that longevity changes are not always directly determined by energy intake and that varied CR regimens extend lifespan through diverse genetic mechanisms. Differential gene expression between three isolates that respond differently to CCR and IF suggest the underlying genetic mechanisms responsible for changes in lifespan under CR.

30. The Role of the Apolipoprotein E4 Allele, Cancer, CVD and Neurodegenerative Disorders in Human Lifespan

Alexander Kulminski (P), Irina Culminkaya, Konstantin Arbeev, Liubov Arbeeva, Svetlana Ukraintseva, Anatoli Yashin
Duke University, Durham, NC

Enduring interest to the apolipoprotein E (APOE) polymorphism is ensured by its evolutionary-driven uniqueness in humans and its prominent role in lifespan and risks of major human diseases. We use large samples of participants of the Framingham Heart Study original (FHS, N=1258 with 1056 deaths) and offspring (FHSO, N=3924 with 741 deaths) cohorts followed for up to 60 years to characterize sex-specific effect of the APOE e4 allele on lifespan. We also investigate whether or not cardiovascular disease (CVD, N=1790), cancer (N=1303), and neurodegenerative disorders (ND, N=378) mediate the effect of this allele on lifespan. The analyses show that the e4 allele is significantly associated with women's lifespan but not with men's lifespan. The risks of death for women carrying the e4 allele are higher in the FHSO (relative risk [RR]=1.59 and $p=2.4 \times 10^{-4}$) than in the FHS (RR=1.25, $p=0.027$). The effect of the e4 allele on women's lifespan in the FHS is limited to ages younger than about 95 years (RR_{<95}=1.37, $p=1.7 \times 10^{-3}$ vs. RR_{≥95}=0.94, $p=0.794$). Major human diseases including CVD, ND, and cancer, which risks are shown to be sensitive to the e4 allele, do not explain the association of this allele with women's lifespan (RR_{<95}=1.41, $p=5.6 \times 10^{-4}$ when adjusted for all these diseases in the FHS). Our results show that the APOE e4 allele can affect human lifespan in sex- and age-specific manner independently of CVD, cancer, and ND.

31. Protection of Proteasome Activity in the Long-Lived Naked Mole-Rat by a Multiprotein Resistasome

Karl Rodriguez (P,G), Anson Pierce, Pawel Osmulski, Maria Gaczynska, Rochelle Buffenstein
University of Texas Health Science Center San Antonio

Oxidative damage to proteins may cause conformational changes, cross-linking and toxic aggregate formation leading to a loss of protein function. This is causatively linked to the age-related physiological decline and many age-related diseases. Removal of damaged proteins via autophagy or the ubiquitin proteasome system is assisted by molecular chaperones [HSPs] that traffic damaged proteins to the proteolytic machineries and is critical for maintenance of protein quality control and good health during aging. We hypothesized that since naked mole-rats [NMRs] maintain good health for ~75% of their extraordinary lifespan, proteasome activity is more efficient and better protected than that of mice. Proteasomes of NMRs [NMRPRS] are catalytically more active than those of mice [MSPRS]. Curiously, unlike MSPRS, NMRPRS maintain function when subjected to the oxidative stressor 4-hydroxynonenal [HNE]. Similarly, NMRPRS are resistant to several proteasome-specific inhibitors, e.g., the NMRPRS IC50 for bortezomib is 165-fold greater than that of MSPRS. We found that a multi-protein complex, the "resistasome", resides in the cytosol of liver lysates, and protects NMRPRS from inhibition. Moreover, the resistasome-enriched NMR cytosolic extract protects partially purified MSPRS and purified human 26S PRS from inhibition, and modulates their activity even in the absence of inhibitors. We determined that this resistasome-enriched extract contains unusually high levels of HSP70, and that depletion of HSP70 with either HSP70-specific antibodies or HSP-70 specific chemical inhibitors abolishes resistasome effects. These findings leads us to hypothesize that NMRs employ a previously unreported mechanism that contributes to the exceptional efficacy of their proteasomes, both during aging and in response to stress, and that this involves proteasome interactions with a multi-protein chaperone complex enabling then to maintain proteostasis and overcome the many challenges to their somatic integrity over their extraordinary lifespan.

32. Evaluating Hormesis as a Mechanism in Calorie Restriction

Carrie M. Elks¹ (P,G), Anand Nair², Rahul Dange², Joseph Francis², Donald K. Ingram¹

¹Pennington Biomedical Research Center; ²Louisiana State University School of Veterinary Medicine

Past studies have documented that long-term calorie restriction (CR) reduces damage due to reactive oxygen species (ROS) and enhances antioxidant protective systems. The overall

reduction in oxidative stress (OS) remains as a major hypothesis explaining the anti-aging effects of CR, although recent studies in genetically modified mice manipulating key antioxidant pathways have questioned the centrality of this hypothesis. In the current preliminary studies, we have begun to assess hormesis as a key mechanism of CR. As it applies to aging, hormesis has been defined as beneficial effects resulting from cellular responses to mild repeated stress. Hormesis has been proposed as a unifying concept in attempting to explain the anti-aging, anti-disease effects of not only CR but also exercise, and botanicals high in polyphenols. Using both rat and mouse models, we have observed increased production of reactive oxygen and nitrogen radicals (RONS) measured by electroparamagnetic resonance as well as a spike in blood pressure (BP) following during the early initiation of a 40% CR regimen. Additionally, we have noted an age-related decline in this hormetic response in mice that is mirrored in specific molecular signaling events. For example, using PCR to measure gene expression, we found major increases in NFkB, Nrf2, and eNOS in young (3-4 mo) mice after 2 days of CR that were absent in aged mice (23-24 mo). Most importantly, we have shown that feeding of the antioxidant, a-tocopherol (4X control level), prior to or at the time of CR initiation, will block evidence of hormesis. Thus, the key question to be pursued is whether this initial mild OS is necessary to activate protective pathways, including antioxidant defenses, and whether feeding of a high level of an antioxidant will attenuate the beneficial effects of long-term CR?

33. How does the Body Know How Old it is?

Josh Mitteldorf (P)

MIT, Cambridge, MA

In recent decades, a picture of aging has emerged as an active process, regulated according to a schedule. But there are no theories about how the schedule is enforced. A traditional hypothesis would be that the body is simply responding to the current state of damage or deterioration, and changes in metabolism and gene expression with age are an adaptive compensation to lost competences. But there are broad experimental reasons to think that biological reality is stranger than this. In fact, evidence points to one or more "aging clocks" which control the timing of the senescent phenotype. Telomere length declines with age in many vertebrate species, and telomeres have been proposed as an aging clock. But telomere length cannot be the only clock in the

body because there are species in which telomeres do not shorten with age, but that senescence nevertheless. Another hint is provided by the fact that, like aging, development and maturation also unfold on a schedule, although no separate developmental clock has been identified, and we have little understanding of how development is timed. Our hypothesis, then, is that development and aging are driven by one and the same clock, and that the reason no clock has been discovered is that the clock is not separate from the changes in gene expression that characterize different developmental stages. The picture we propose is that the epigenetic state of the body is a Markov process that functions as a kind of self-modifying clock mechanism. The genome's methylation state encodes a record of the body's age, drives the physiology of development and senescence, and also loops back to modify itself gradually over time. Methylation state has the right degree of persistence, and the ability to self-modify; it is thus a logical candidate for the body's primary aging clock.

34. Does Redox State Matter: A Comparison Among Replicative Senescence, SIPS and Senescence Induced due to Proteostasis Impairment

Mina Konigsberg¹ (P), Luis Angel Maciel-Barón¹, Salvador Tello-Solis¹, Sonia Galván-Arzate², Norma Edith Lopez-Diazguerrero¹, Armando Luna-Lopez³, Susana Castro-Obregón⁴, Viridiana Yazmin González-Puertos¹

¹Universidad Autonoma Metropolitana; ²Instituto Nacional de Neurología y Neurocirugía, SSA; ³Instituto Nacional de Geriatria; ⁴Instituto de Biotecnología, UNAM

It is known that cells can achieve the senescence state as a response to different stimuli, such as telomere shortening (Replicative Senescence, RS) or oxidative stress (Stress Induced Premature Senescence, SIPS). Furthermore, recent studies have suggested that other alterations in cellular homeostasis such as mitophagy impairment or the loss of protein homeostasis (proteostasis) are also capable of inducing premature senescence. However little is known about the similarities and differences in the mechanisms that induce senescence, particularly oxidative stress role. Hence, the aim of this work was to induce premature senescence in primary mice lung fibroblasts by inhibiting proteasome activity, using sub lethal doses of the proteasome inhibitor epoxomicin and compare it with SIPS and RS. Senescence classic parameters like cellular proliferation, DNA synthesis and β -Galactosidase

activity assay (SA- β -Gal) were determined. In order to determine the importance of redox state in the senescence induction pathways, we evaluated the GSSG/GSH ratio in a comparative study between RS, SIPS and senescence induced due proteostasis impairment, at three different culture stages: at the beginning, in the pre-senescent state and during the established senescence. To elucidate the proteasome inhibition effect and its relationship with the changes in cellular redox state during the senescence induction, the proteasome activity was also determined at the same time points. Results are discussed in terms of integrating the senescence state as a cellular response to homeostasis loss.

The authors would like to thank MVZ Rocío González Vieira for providing the animals used in this study. And Dr. Claudio Torres, from Drexel University for his suggestions. Maciel-Barón L is a CONACYT scholarship holder. This work is supported by CONACYT grant No. CB-2012-1-178349

35. An Age-Related Decline in Nrf2 Protein Synthesis, a Novel Mechanism for the Attenuation of Xenobiotic Detoxification Capacity

Eric Smith (P,N)

Linus Pauling Ins - Oregon State University, Corvallis, OR

Aging results in an inadequate response to a variety of environmental stress, which increases risk for overt pathophysiology. Our lab previously identified that the Nrf2 transcription factor, which regulates the expression of >200 antioxidant and detoxification genes, is partly responsible for diminished stress resistance (PNAS 2004). The objectives of the present work seek to identify mechanism(s) associated with the decline in Nrf2-mediated stress response. Using cultured hepatocytes from young (3 mo) and old (24-26 mo) rats, we now show that steady-state Nrf2 levels markedly (~60%) decline with age and overexpressing nrf2 results in remediation of lower antioxidant gene expression (e.g. gclc, gclm). These results suggest that the aging lesion resides at maintenance of Nrf2 levels, and not from dysregulation of antioxidant gene expression per se. In further exploring the mechanism(s) involved in lower Nrf2 steady-state levels, we show no significant age-related differences in Nrf2 mRNA levels or its protein half-life. However, measurement of Nrf2 protein synthesis was markedly diminished in aged hepatocytes vs. controls. A polysome profile confirmed that Nrf2 mRNA was associated with fewer ribosomal subunits. Furthermore, the age-related loss of protein synthesis appears to stem from decreased cap-independent utilization of the internal

ribosomal entry site of the Nrf2 message. These results thus point to a marked decline in Nrf2 protein synthesis on an age basis. Taken together, our results show a novel mechanism for the age-related decline in Nrf2 protein levels and consequently, its ability to initiate an adequate response to oxidative and xenobiotic insults.

36. Subacute Treatment of Rapamycin Reverses Cardiac Aging by Improving Mitochondrial Energy Metabolism

Ying Ann Chiao¹ (P), Pabalu P. Karunadharm¹, Dao-Fu Dai¹, Nathan Basisty¹, Haiwei Gu², Simon C. Johnson¹, Danijel Djukovic², Daniel Raftery², Michael J. MacCoss³, Peter S. Rabinovitch¹
¹Department of Pathology, University of Washington;
²Department of Anesthesiology and Pain Medicine, University of Washington; ³Department of Genome Sciences, University of Washington

Calorie restriction of mice is known to attenuate age-related impairment in diastolic function. Rapamycin, a calorie restriction “mimetic”, is protective in models of cardiac hypertrophy and heart failure, but the effect of rapamycin on cardiac aging has not been previously established. The objective of this study is to determine the effects of subacute rapamycin treatment on cardiac aging. We monitored cardiac function in old C57BL/6/CR mice (24 month old at baseline) fed with diet containing 14ppm encapsulated rapamycin, the dose previously shown to extend murine lifespan, or control diet for 10 weeks. By tissue doppler imaging, Ea/Aa increased from 1.00 to 1.26 in mice fed with rapamycin after 10 week, indicating improvement in diastolic function. Surprisingly, this improvement began as early as 4 weeks. Also, mice fed with rapamycin showed a trend of reduced MPI, while fractional shortening did not change with rapamycin treatment. We observed lower LVMI and normalized heart weights in mice treated with rapamycin compared to old control mice, suggesting that 10 week rapamycin treatment can regress age-related cardiac hypertrophy. These results indicate that relatively short-term rapamycin treatment can reverse cardiac aging phenotypes in old mice. LC-MS/MS proteomic analysis showed that the age-related reduction of mitochondrial proteins in control hearts, including multiple subunits of the electron transport chain complexes, was restored to higher levels in hearts of old rapamycin-treated mice. Heavy isotope labeled proteomic analysis of protein turnover using a diet containing deuterated leucine indicated that these proteins are longer lived in rapamycin-treated mice. In addition, preliminary LC-MS/MS targeted metabolic analysis revealed an increase in multiple

TCA cycle intermediates in old rapamycin-treated hearts. These changes suggest that proteomic and metabolomic remodeling after subacute rapamycin treatment results in improved mitochondrial energy metabolism, contributing to the improved cardiac aging phenotypes observed in 10 week rapamycin-treated old mice.

37. Resveratrol Improves the Skeletal Muscle Metabolic Response to High Fat Feeding in a Nampt SirT1 Dependent Manner

Evi M Mercken¹ (P), James G. Ryall², Marcella Fulco², Vittorio Sartorelli² and Rafael de Cabo¹
¹Laboratory of Experimental Gerontology, Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD;
²Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis, and Musculo-Skeletal and Skin diseases, National Institutes of Health, Bethesda, MD

Skeletal muscle insulin resistance plays a key role in the pathogenesis of type 2 diabetes. The NAD⁺-dependent deacetylase SIRT1 is a critical regulator of mitochondrial biogenesis and has been implicated in the regulation of glucose metabolism and insulin sensitivity. Resveratrol, a proposed SIRT1 activator, has been shown to improve health and lifespan in mice fed a high fat diet (HFD). However, there is controversy on the relevance of SIRT1 in lifespan and whether resveratrol's health effects are due to SIRT1 activation. Interestingly, the majority of studies so far have shown the role of SIRT1 at the whole-organism level. We generated SIRT1(i)skm^{-/-} mice in which SIRT1 ablation is selectively induced in adult skeletal muscle to test whether SIRT1 is central to the health benefits of resveratrol on a standard and under HFD conditions. SIRT1(i)skm^{-/-} mice were metabolically similar to littermate control mice under basal conditions; however, following 24 weeks of HFD feeding, SIRT1(i)skm^{-/-} mice were more susceptible to diet-induced obesity (DIO), developing glucose intolerance and peripheral insulin resistance. Consistent with previous reports, resveratrol prevented most of the metabolic effects induced by HFD in wild type (WT) mice while it had no benefits in SIRT1(i)skm^{-/-} mice, indicating that SIRT1 in skeletal muscle plays a pivotal role in resveratrol's whole-body effects in glucose metabolism and insulin sensitivity. In addition, WT mice treated with resveratrol showed increased mitochondrial biogenesis and function in skeletal muscle, whereas these adaptations were abrogated in SIRT1(i)skm^{-/-} mice highlighting the importance of skeletal muscle mitochondria in the development of insulin resistance and glucose

intolerance. Interestingly, we found that resveratrol induced the expression of nicotinamide-phosphoribosyltransferase (Nampt), the rate-limiting enzyme of the NAD⁺ salvage pathway in a SIRT1-dependent fashion suggesting a possible positive feedback loop between SIRT1 and Nampt in the perpetuation of the effects of resveratrol.

38. Update from the NIA Aging Intervention Testing Program

R. Strong¹ (P), D.E. Harrison², N. Nadon³ and R.A. Miller⁴

¹*Department of Pharmacology and Barshop Institute for Longevity and Aging Studies, University of Texas Health Sciences Center and GRECC South Texas Veterans Health Care System, San Antonio TX;* ²*The Jackson Laboratory, Bar Harbor, ME;* ³*Division of Aging Biology, National Institute on Aging, Bethesda, MD;* ⁴*Department of Pathology and Geriatrics Center, University of Michigan, Ann Arbor, MI*

The National Institute on Aging Interventions Testing Program (ITP) was established to evaluate agents that are hypothesized to increase lifespan and/or healthspan in genetically heterogeneous mice. Recent findings, in particular sex-specific outcomes, are summarized. NDGA (nordihydroguaiaretic acid) was shown to increase lifespan preferentially in males. It was subsequently found that there were differences in NDGA blood levels in males and females fed the same dose of NDGA. We repeated the study at different doses of NDGA and found that at a dose of NDGA that gave equivalent blood levels in both males and females, lifespan was extended only in males. Thus, the differential effects of NDGA on lifespan of males and females are not related solely to NDGA blood levels. We also assessed the effects of three doses of rapamycin, the original dose and doses 3 times higher or 3 times lower than used in our first study, on lifespan and age-associated traits. We found a dose-dependent effect of rapamycin on lifespan that was greater in females than in males. Rapamycin also attenuated selected age-sensitive traits in a dose-dependent manner. Acarbose (ACA), an α -glucosidase inhibitor that delays digestion of carbohydrates to sugars, and 17- α -estradiol (EST), a non-feminizing form of estrogen, were also tested. Feeding mice ACA in chow led to a 22% increase in median lifespan in male mice ($p < 0.0001$), and a 5% increase ($p = 0.01$) in females. Maximum lifespan was significantly increased ($p < 0.001$) in each sex. EST led to a smaller, but significant increase (12%, $p = 0.002$) in males using the pooled data set and had no effect on lifespan in females, but the extent of the effect varied among sites.

Supported by U01-AG022303 to RAM, U01-AG022308 to DEH and U01-AG022307 to RS

39. Pathways and Small Molecules that Reverse Tissue Aging

Ana P. Gomes^{1,2,3}, Nathan L. Price¹, Eric L. Bell⁴, Alvin J.Y. Ling¹, Joao S. Teodoro^{2,3}, Evi Mercken⁵, Carlos M. Palmeira^{2,3}, Rafael de Cabo⁵, Anabela P. Rolo^{2,6} and David A. Sinclair¹ (P)

¹*Glenn Labs for the Biological Mechanisms of Aging, Harvard Medical School, Boston, MA;* ²*Center for Neurosciences and Cell Biology, Coimbra, Portugal;* ³*Department of Life Sciences, Faculty of Science and Technology, University of Coimbra, Coimbra, Portugal;* ⁴*Paul F. Glenn Laboratory and Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA;* ⁵*Laboratory of Experimental Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, MD;* ⁶*Department of Biology, University of Aveiro, Aveiro Portugal*

Metabolic reprogramming of cells away from aerobic respiration towards glycolysis is a hallmark of cancer but its role in aging has not been deeply explored. During aging, mitochondrial function declines and metabolism shifts towards glycolysis and the production of lactate, changes that may play a role in the development of age-related diseases including metabolic syndrome. SIRT1 is a nuclear NAD⁺-dependent deacetylase that protects against age-related diseases, in part by induction of mitochondrial biogenesis through activation of the transcriptional co-activator PGC-1 α . We show that a decline in NAD⁺ levels in skeletal muscle with age and a loss of SIRT1 activity results in the activation of a PGC-1 α -independent pathway that results in the stabilization of the hypoxia-inducible factor HIF-1 α . The downstream effects include metabolic reprogramming, an imbalance between the nuclear-encoded and mitochondrial-encoded components of the electron transport chain (ETC), and increased lactate production. We further show that increasing NAD⁺ levels in 24-month old mice rescues the metabolic defect and mitochondrial dysfunction with one week of treatment, demonstrating that this aspect of aging – in contrast to DNA mutation - is readily reversible. These changes provide an explanation for known alterations in energy metabolism, muscle type switching, and mitochondrial function observed in old animals. They also highlight an alternative pathway to the canonical PGC-1 α pathway of mitochondrial regulation. We postulate that this activation of a Warburg-like metabolic program in old tissues may predispose to tumorigenesis and other age-related diseases.

40. Inhibiting mTOR Signaling: A Strategy to Mimic Caloric Restriction?

Joseph Baur (P)

University of Pennsylvania, Philadelphia, PA

Caloric restriction (CR) extends lifespan and reduces the incidence of age-related diseases across many species. Because of the difficulty in maintaining such a lifestyle, and because it remains uncertain whether any benefits of CR in humans might be offset by complications such as frailty or compromised immunity, there has been great interest in mimicking the beneficial aspects of CR with drugs. Perhaps the most promising candidate thus far is rapamycin, which inhibits signaling through the nutrient-sensitive mTOR (mammalian target of rapamycin) pathway. Rapamycin extends lifespan in genetically heterogeneous mice, even when treatment is initiated at an advanced age. Unlike CR, however, rapamycin reduces insulin sensitivity, inhibits mitochondrial biogenesis, and worsens cardiovascular risk factors, suggesting that rapamycin cannot simply be considered a “CR mimetic” and might even shorten lifespan in humans. The canonical target of rapamycin is mTOR complex 1 (mTORC1). We find that rapamycin also inhibits mTORC2 *in vivo*, and that this effect is responsible for rapamycin-induced insulin resistance. Therefore, a more specific inhibitor of mTORC1 might promote longevity while avoiding at least some of the detrimental side effects of rapamycin. We are currently investigating the mechanisms by which rapamycin affects mitochondrial function and lipid handling in mice.

41. Growth Hormone and Aging: The Role of Nutrient Restriction or Supplementation

H.M. Brown-Borg (P), S. Rakoczy, L.

Rojanathammanee, Joseph Wonderlich, Deb Raasakka
University of North Dakota, Grand Forks, ND

Endocrine hormones impact aging and aging processes in multiple ways. Circulating growth hormone (GH) affects not only somatic growth and but also drives aspects of metabolism. We have previously shown that GH modulates methionine metabolism in GH-deficient mice. Restricting methionine (MET) in rodent diets has been shown to lower IGF1 and extend lifespan. Our current studies focus on delineating the relationships between dietary methionine, plasma GH status and factors involved in stress resistance. Our working hypothesis is that GH is involved in the regulation of thiol metabolism that in turn, affects an organisms’ resistance to stressors and ultimately impacts lifespan. Ames dwarf, GH transgenic and

respective wild type mice were subjected to dietary methionine restriction or enrichment. Following eight weeks of MET diets, components of the glutathione and methionine metabolic pathways were examined. Plasma IGF1 levels declined with decreasing dietary MET content. Gene expression of MET conserving and catabolizing enzymes was differentially affected by dietary MET level. Underlying growth hormone status also influenced the metabolic responses to altered dietary methionine. Lifespan studies using Ames dwarf and GH transgenic animals subjected to diets restricted or enriched with methionine are currently underway.

42. Dietary Interventions for Healthy Aging

Rafael de Cabo (P)

Translational Gerontology Branch, National Institute on Aging, Baltimore, MD

Aging is the major driving force behind most chronic diseases. Calorie restriction and its mimetics have provided unique targets for underlying mechanisms of aging. Among these targets, SIRT1 has emerged as a good candidate for drug development. SIRT1 has pluripotent that may also turn out to be a benefit given the multifactorial pathogenesis of aging and aging-associated diseases. SIRT1 is an NAD⁺-dependent deacetylase that extends lifespan in lower organisms and has been proposed to delay or prevent age-related diseases in mammals. Here we will be presenting data on two compounds that activate Sirt1 and metformin, a proposed CR mimetic. We show effects on lifespan and healthspan of mice fed either a standard or a high-fat diets. Lifelong treatment with these compounds showed numerous benefits to health including reduced liver steatosis, increased insulin sensitivity, and enhanced locomotor activity and normalization of gene expression profiles and markers of inflammation and apoptosis, all in the absence of any observable toxicity.

Supported by the Intramural Research Program of the NIA. Part of the work that will be presented was performed under a CRADA with SIRTRIS (a GSK company)

43. East Meets Mid-West: CR Monkey Studies Face Off

Julie Mattison¹ (P) and Rozalyn Anderson^{2,3} (P)

¹*Translational Gerontology Branch, Intramural Research Program, NIA, NIH, Baltimore, MD;*

²*Department of Medicine, SMPH, UW Madison, and*

³*GRECC VA Hospital, Madison, WI.*

Caloric restriction without malnutrition extends lifespan and delays the onset of age-associated

disorders in diverse species, from unicellular organisms to laboratory mice and rats. Until recently, the translatability of CR's effects to human health has been a critical gap in CR research. In the late 1980s two parallel rhesus monkey caloric restriction (CR) studies were initiated to determine the effect of CR on resistance to illness and mortality in nonhuman primates. With more than 20 years of longitudinal data accrued, both studies have demonstrated improvements in health in CR animals compared to controls, significant in the University of Wisconsin (UW) study, and approaching significance in the National Institute on Aging (NIA) study. The impact of CR on survival in nonhuman primates; however, is a point of departure in the two studies. In 2009, the UW study reported improved survival for animals on CR. In contrast, the NIA's 2012 report showed no difference in survival between CR and Control monkeys. Here we present a comparison of key differences in study design that could explain differences in survival outcome, including the genetic origin of the study cohort, age of onset for the dietary intervention, dietary composition, feeding regimens, and protocols for animal husbandry. The relative contributions of these differences to study outcomes will be discussed, and NIA and UW perspectives on the impact of these findings on CR research and its potential to reveal insights into human health will be presented.

44. CALERIE Comprehensive Assessment of the Long-Term Effects of Restricted Intake of Energy – Results from a 2 year Human Calorie Restriction Trial

Sai Krupa Das (P)

Tufts University, Boston, MA

There is enormous public interest in ways older adults can help achieve a profile of healthy aging and avoid premature death. Caloric restriction (CR) has been implicated, in research in animals, as an effective method for extending both lifespan and the period of healthy, active life with minimal side effects and has been suggested as a promising non-pharmacological approach to attenuate biological aging. However, the lack of human clinical trials has prevented addressing the question of whether this is a feasible, effective and safe intervention for humans. The NIH-funded CALERIE trial is a 2 year landmark study of the effects of CR on a broad range of biological parameters and safety issues in humans and was completed in 2012. Emerging data on the adherence and practical levels of CR achievable in humans in a randomized

controlled trial, effects of CR on biological variables including metabolic rate, body composition, quality of life and rates of recidivism have been charted in this unique randomized controlled trial and will be presented. These are questions of great scientific importance and of direct practical relevance to national health care and will be reviewed in the context of work in the CALERIE trial and other important work in the field.

45. Losartan Reverses Age-Related Changes in Mitobiogenesis, Myocardial Function, Oxidative Damage, and Energy Metabolism

Peter Abadir (P)

Johns Hopkins University, Baltimore, MD

Background: Aging, changes in the renin-angiotensin system (RAS), and mitochondrial function are closely linked. We hypothesized that angiotensin AT₁ receptor blockade increases mitochondrial biogenesis and energy production and reduces oxidative stress in aging hearts. Methods: Young (20 wks old, n=8), aged (150 wks old, n=9) and losartan-treated aged C57Bl6 mice (n=9) were studied. QPCR was used 1) to calculate CytB /GAPDH ratio for mitochondrial quantification, 2) to calculate expression of mitobiogenesis regulator PGC1a and 3) to calculate expression of mitochondrial survival gene Nampt. Nitrotyrosine immunohistochemistry staining was utilized for measurement of oxidative stress damage. Magnetic resonance spectroscopy was used to measure cardiac energy metabolism (PCr/ATP ratio) and function at baseline and after 4 weeks of losartan (0.6 gm/kg/day). Results: PGC1a was down regulated with aging (0.6±0.06 fold in the old, P<0.009) while NAMPT was increased (2.6±0.3 fold, P<0.009), suggesting an attempt to sustain the current aged mitochondria. Losartan treatment in aged mice increased PGC1a expression (1.5±0.06 fold, P<0.01), and NAMPT remained elevated at 2.46±0.49 fold (P<0.02). Total numbers (CytB /GAPDH ratio) of the mitochondria were slightly reduced in Losartan treated aged hearts (0.9±0.06 fold), despite increased PGC1a. The failure to increase total numbers of mitochondria despite increased formation may suggest increased breakdown of old damaged mitochondria (mitophagy) in Losartan treated aged mice. LV mass was higher in older (120±8 mg) vs. younger (103±9 mg) mice (P<0.002). EF was lower in older (56±2%) vs. younger (63±2%) mice (P<0.002). Losartan reduced LV mass in older mice (from 120±8 mg to 109±4.1 mg P<0.01) and

increased EF in older mice (from $56\pm 2\%$ to $62.7\pm 2\%$, $P<0.01$) Losartan in older animals also reduced oxidative damage as evidenced by reduced nitrotyrosine staining score in cardiomyocytes (2.5 ± 0.5 vs. 1.3 ± 0.4 , old versus old-treated, respectively, $P<0.0009$). Cardiac PCr/ATP was reduced in older animals (1.5 ± 0.2) compared to young mice (2.0 ± 0.3 , $P<0.0004$). Losartan improved energy metabolism from 1.5 ± 0.2 to 1.87 ± 0.4 , $P<0.01$). Conclusions: Our results indicate that AT₁R blockade with Losartan in aging mice increased mitochondrial biogenesis, restored cardiac function, reduced oxidative stress and improved energy production.

46. Proteomics and Age-Related Macular Degeneration Defining Disease Mechanism and Guiding Treatment Strategies

Deborah Ferrington (P)

Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, MN

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in the developed world. Although the cause of AMD has not been clearly defined, risk factors for developing the disease include age, genetics, behavior and environment. Early clinical features include the formation of drusen, an autofluorescent deposit of debris composed of lipids and proteins that accumulate between retinal cells, and an altered appearance in the retinal pigment epithelium (RPE). The RPE is a monolayer of cells between the photoreceptors and choroid that supports retinal function and homeostasis. Our focus has been on defining the molecular changes that occur within the RPE in the absence and presence of AMD. Using human donor eyes phenotyped for the presence and severity of AMD, we have performed a proteome analysis on the RPE and mitochondria from these cells (Nordgaard et al., 2006, 2008). Our results revealed defects in the mitochondria of donors at early stages of AMD. Subsequent analysis of mtDNA showed significantly increased levels of mtDNA damage in the RPE from donors at stages of AMD preceding macular degeneration and vision loss (Karunadharm et al., 2010), suggesting oxidative damage as a potential mechanism in AMD pathology. Our working model is that with AMD, increased mtDNA damage leads to a disruption in mitochondrial bioenergetics and cell signaling, accompanied by accelerated production of reactive oxygen species. These detrimental mitochondrial changes could lead to RPE dysfunction. Current

treatment strategies that reduce the production of mitochondrial free radicals or boost mitochondrial function may slow down or stop disease progress.

47. Recovery from Acute Events and Strategies for Developing and Testing Interventions to Maximize Recovery?

Jay Magaziner (P)

Department of Epidemiology and Public Health, University of Maryland, Baltimore, MD

Using hip fracture as an example, this presentation will provide information on recovery from an acute event in older persons and on how this information on the consequences of the event and patterns of recovery can be used to develop and test new interventions. Evidence on the medical, physiological, functional and psychosocial consequences of hip fracture and patterns of recovery derived from 25 years of research in the Baltimore Hip Studies will be presented, as will efforts to use this information to identify targets for interventions and strategies for developing and testing them. Results from some of these intervention studies will be presented along with information about a new program that is currently being evaluated.

48. Randomized Clinical Trials and Public Policy: Improving Population Health

Mary McGrae McDermott (P)

Northwestern University Feinberg School of Medicine, Chicago, IL

Clinical research has a large impact on population health, when clinical research findings are used to inform public policies, clinical practice guidelines, and insurance coverage. For example, results of clinical trials of breast and colon cancer screening have influenced practice guidelines and Medicare decisions regarding coverage for specific screening services. However, results of clinical trials, clinical practice guidelines, and Medicare/insurance coverage are not always well aligned. Peripheral artery disease is an example of inconsistencies between results of randomized trials and Medicare insurance coverage. Supervised treadmill exercise interventions have been shown consistently to improve treadmill walking performance and quality of life in patients with peripheral artery disease. However, Medicare does not pay for supervised treadmill exercise for people with peripheral artery disease and this is a primary reason that patients with peripheral artery disease do not participate in supervised treadmill exercise interventions. Yet, the costs of functional impairment and decline in patients with peripheral

artery disease are substantial. Impaired functioning is associated with increased rates of hospitalization and institutionalization. Further work is needed to better influence public policy and ensure that resources are available for services that have been shown to significantly improve health outcomes in patients with chronic diseases, such as those with peripheral artery disease.

49. PKC alpha and Wound Healing in Older People

Helen Thomason (P)

*University of Manchester, Manchester, UK
BSRA KORENCHEVSKY AWARD*

50. Better health by Workplace Design: Addressing the Challenges for Ageing Construction Workers

Diane Gyi¹ (P), Alistair Gibb², Stephanie Eaves¹

¹Loughborough Design School, Loughborough University, UK; ²School of Civil and Building Engineering, Loughborough University, UK

Changing demographics and pension policies are reflected in the increasing age of workforces in the UK and globally. Positive perceptions are that older workers are experienced, dedicated and reliable but there are also negative perceptions, such as they have reduced capacity, are slower and tire more easily. Construction environments are particularly challenging for workers due to exposure to risks such as manual handling, constrained and awkward postures, and repetitive tasks, and often under adverse conditions such as noisy, dusty, wet, or high/low temperatures. Older workers in the construction industry want to remain in the job but there is a general acceptance that injury and ill health go hand in hand, and therefore staying fit and healthy for work is a key concern. The ageing workforce creates a demand for research to support evidence-based practice promoting the health and workability of all workers through the life course. Workplace design (e.g. equipment, work layout, environment) can have a substantial influence on this and as workers have a detailed understanding of their job, in many instances they are able to provide useful input into problem solving. With demographic changes transforming today's workforce, there is an urgent need to support the inclusion and wellbeing of older workers in the workforce and optimise health, wellbeing, and safety. This paper will introduce and present the context for research funded by Age UK to investigate the role of older, experienced workers in healthy more thoughtful design in the construction workplace. The belief is that the industry can learn from these workers in

terms of facilitating healthy behaviours by good design and will lead to the co-development of guidance with the Industry.

51. A New *Caenorhabditis elegans* Model of Adult-Onset Neurodegeneration with Potential for Neuroprotective Drug Screening

Alan Morgan (P), James Johnson, Sudhanva Kashyap, Xi Chen, Bob Burgoyne and Jeff Barclay

Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Crown St., Liverpool, UK

As human populations age, neurodegenerative diseases are becoming an increasing burden. However, the underlying mechanisms that cause age-dependent neuronal loss remain unclear and therapies for these debilitating and eventually fatal disorders are lacking. One way to address this problem is by using simple model organisms to understand the mechanisms of neurodegeneration and to screen for neuroprotective drugs. Here we describe a new *C. elegans* model of age-dependent neurodegeneration caused by mutation of the *dnj-14* gene, which is the worm homologue of human *dnajc5*. The *dnajc5* gene encodes cysteine string protein, a neuronal chaperone that prevents the misfolding of presynaptic proteins. Mutations in *dnajc5* cause adult-onset neuronal ceroid lipofuscinosis (ANCL), a human neurodegenerative disease. We show here that mutations in *C. elegans*' *dnj-14* result in reduced lifespan and ageing-dependent defects in chemosensation, which correlate with the loss of sensory neurons in older *dnj-14* animals. A pilot chemical screen identified resveratrol as a compound able to rescue these defects. The protective effect of resveratrol appears to be independent of the worm Sirtuin, *sir-2.1*, as full rescue is seen in *dnj-14;sir-2.1* double mutant animals. Our screen identified a different compound that not only rescued the short lifespan of *dnj-14* mutants, but also rescued a distinct *C. elegans* neurodegeneration model based on expression of mutant human tau. Future studies of the *dnj-14* model may therefore have applications not only for ANCL, but more generally for human neurodegenerative diseases.

52. New Insights into the Premature Ageing Werner's Syndrome in the Nematode Worm *C. elegans*

Hayley Lees (P), Lynne S. Cox, Alison Woollard
Department of Biochemistry, University of Oxford, Oxford,

We must understand the biology of human ageing in order to ameliorate the deleterious consequences of old age. The study of human progeroid disorders - which recapitulate many of the features of normal ageing - have helped to contribute to our understanding of normal human ageing. Werner's syndrome is a canonical progeroid disorder, caused by mutation of the *WRN* gene. *WRN* encodes both exonuclease and RecQ helicase activities, and is known to participate in DNA replication, repair, recombination and telomere maintenance. In addition, several interacting partners have been identified, but the exact molecular function of the *WRN* gene remains largely unknown. In order to dissect the roles of WRN helicase in ageing, we use mutants of the WRN homologue and interacting partners in the nematode worm, *C. elegans*. This organism has been used extensively as a model system for the study of ageing, due to its short and reproducible lifespan, transparent body, ease of using isogenic controls and tractability of genetic manipulations. Reduction of function by RNA interference of the *C. elegans* *WRN* homologue *wrn-1* leads to ageing phenotypes and shortened lifespan [1]. We have shown that mutation of *wrn-1* leads to genomic instability: interestingly, this phenotype is enhanced in a mutant *cep-1* background (the *C. elegans* p53 homologue). Further, lifespan also shows significant modulation, while brood size remains unchanged from that of either single mutant. Therefore we suggest that *cep-1* status has a significant effect upon the role of *wrn-1* helicase in longevity and germline maintenance in worms.

Lee, SJ; Yook, JS; Han, SM; Koo, HS. *A Development*, 2004. 131(11): p. 2565-2575.

53. TBA

Sarah E. MacPherson

The University of Edinburgh, Edinburgh, UK

54. Calorie Restriction and Essential Amino Acid Restriction Contribute Additively to the Benefits of Short-Term Dietary Restriction in Mice

James Mitchell (P)

Harvard University, Boston, MA

Long-term dietary restriction (DR) extends longevity in model organisms from yeast to non-human primates, and protects against a variety of acute insults including oxidative, proteotoxic, and genotoxic stress. Short-term DR can also protect against oxidative stress associated with clinically relevant endpoints such as ischemia reperfusion injury. The nutritional basis of short-term DR, and the relative importance of calorie versus nutrient

restriction, remains unclear in mammals. Previously we found that removal of protein or specific amino acids from the diet can protect against surgical stress independent of reduced calorie intake. Here, we tested the hypothesis that protein restriction and calorie restriction can contribute independently and additively to the benefits of DR. We used protection from surgical ischemic injury to kidney as an experimental endpoint to probe the nutritional basis of one week of DR. We found reduced intake of either a complete or protein free diet was beneficial in a dose-dependent fashion up to ~50% restriction. At low levels of calorie restriction, protein restriction was more potent than carbohydrate restriction. Essential amino acid addition abrogated the benefits of protein deficiency independent of calorie intake. AMPK activation was increased and markers of mTORC1 activity decreased as a function of nutrient/energy restriction. We conclude that calorie and protein restriction can function additively in a preclinical model of elective surgical stress. These findings have mechanistic implications for potentially separable roles of nutrient and energy sensors in short-term DR, and translational implications for evidence-based dietary recommendations before elective surgery and other forms of acute stress.

55. Differential Stress Resistance and Sensitization in Cancer Treatment

Valter Longo (P)

University of Southern California, Los Angeles, Los Angeles, CA

Cancer treatment is moving toward a personalized medicine approach in which treatment is tailored for each patient. Biogerontology research is moving in exactly the opposite direction by proposing to find ways not only to protect everyone from one disease but to identify impersonalized strategies that can protect against both aging and multiple diseases. Based on our findings that starved yeast were protected against a wide variety of toxins and that this protection was negatively regulated by oncogene orthologs, we hypothesized that starvation conditions would protect normal but not cancer cells from chemotherapy toxicity (Differential Stress Resistance). We later showed that mice fasted prior to treatment became resistant to a wide variety of chemotherapy drugs and collected human clinical data indicating that fasting may protect cancer patients undergoing chemotherapy. Based on the knowledge that mutations such as those found in cancer cells are expected to be deleterious to cells,

particularly under extreme environments, we showed that yeast expressing an activated form of Ras became very sensitive to chemotherapy when starved (Differential Stress Sensitization). We later confirmed these effects in mice by showing that fasting combined with chemotherapy but not each alone can lead to 40-60% cancer free survival in a variety of cancer models. Taken together these results suggest that prolonged fasting has the potential to protect patients from chemotherapy toxicity while increasing the efficacy of the treatment.

56. Mitochondrial-Derived Peptides and Their Role in Aging

Pinchas Cohen (P)

University of Southern California, Los Angeles, CA

Mitochondria are involved in energy metabolism and apoptosis, and are central to the pathogenesis of multiple diseases, including diabetes, cancer, neurodegeneration and aging. Mitochondria contain nearly a thousand proteins of nuclear origin, but the mitochondrial-chromosome only encodes 13 proteins. In 2001, humanin; a novel 24-amino-acid peptide proposed to be encoded from the 16S ribosomal RNA region of the mtDNA, was described to be a potent neurosurvival factor. Soon afterwards humanin was shown to bind and antagonize Bax and IGFBP-3 (1, 2). Humanin has been shown to be cytoprotective in vitro and in vivo in models of stroke, ALS, and Alzheimer's and has metaboloprotective activities against both type-1 & type-2 diabetes (3, 4) and atherosclerosis (5, 6). We recently developed a humanin ELISA assay and demonstrated that humanin declines with aging and its levels are altered in states of insulin resistance, diabetes, endothelial dysfunction and neurodegeneration. In vivo administration of humanin reverses pathological processes involved with type-1 and -2 diabetes, atherosclerosis and Alzheimer's disease. We recently identified an additional six peptides encoded from ORFs within the 16S rRNA, which we named SHLPs (small humanin-like peptides). Analysis of their expression reveals that they are transcribed in the mitochondria from mtDNA, are detectable in plasma, and exhibit a tissue-specific distribution. SHLPs 1-5 act as potent bioactive molecules acting to induce cell survival and ROS inhibition (like humanin, via activation of Erk and Stat3 phosphorylation) but with different temporal profiles, suggesting that these peptides may act in concert. SHLP6 has opposing actions, potentially inducing apoptosis. These observations reveal that the mitochondria possess previously unappreciated roles in the

regulation of metabolism and apoptosis that occur via the synthesis of mitochondrial-derived peptides (MDPs). We propose that the mitochondrial peptidome could explain important new aspects of mitochondrial biology and dysfunction with relevance to human biology and disease and that the novel MDPs we describe here may represent retrograde communication signals from the mitochondria.

Supported by a EUREKA Award R01AG034430, and a Transformative-R01-GM090311

¹Ikonen et al. Proc Natl Acad Sci U S A. 2003; 100:13042–13047; ²Yen K, Lee C, Mehta HH, Cohen P. J Mol Endocrinol. 2013; 50:R11-9; ³Muzumdar et al. PLoS ONE. 2009; 4(7): e6334; ⁴Widmer et al. Am J Physiol Heart Circ Physiol. 2013; 304:H393-7; ⁵Hoang et al. Metabolism. 2010; 59:343-349; ⁶Lee C, Yen K, Cohen P. Trends Endocrinol Metab. 2013 Feb 7. [Epub ahead of print]

57. Glucocorticoids Exacerbate Cognitive Deficits in TDP-25 Transgenic Mice via a Glutathione Mediated Mechanism: Implications for Aging , Stress and TDP-43 Proteinopathies

Salvatore Oddo (P)

University of Texas Health Science Center San Antonio, San Antonio, TX

The accumulation of TDP-43 and its 25kDa C-terminal fragment (TDP-25) are hallmarks of several neurodegenerative disorders, including frontotemporal lobar degeneration (FTLD-TDP) and amyotrophic lateral sclerosis (ALS). Growing evidence shows that environmental factors may facilitate the development of these diseases during aging. Here we show that glucocorticoids increase the levels of soluble TDP-25 and exacerbate cognitive deficits. Additionally, we show that the mechanism underlying the glucocorticoid-mediated increase in TDP-25 levels is coupled to changes in the glutathione redox state, which is known to change with age. Overall these data suggest a possible pathway by which aging contributes to TDP-43 proteinopathies.

58. Hypothalamic Regulation in Crowded Litter Mice: Early Life Control of Aging and Longevity

Marianna Sadagurski (P)

University of Michigan, Ann Arbor, MI

Recent work has demonstrated that limiting nutrient availability in the first three weeks of life leads to extension of mean and maximal lifespan in genetically normal mice. The mechanism behind these novel findings is largely unknown. A growing body of evidence points to the hypothalamus as an essential part of the central nervous system, responsive to nutritional

conditions that modulate metabolism throughout the body. Our data imply that nutritional intervention in the first few weeks of postnatal life leads to long-term effects on metabolism through changes in hypothalamic neural circuits, representing a transient window of opportunity during which interventions may have a long lasting effect on disease and mortality rate.

59. Genetic Tools for Analysis of Lifespan and Healthspan in Mice

Luanne Peters (P)

The Jackson Laboratory, Bar Harbor, ME

The Jackson Laboratory Nathan Shock Center uses state-of-the-art genetic analysis in novel mouse populations to identify genes and molecular pathways influencing lifespan and healthspan. Healthspan measures focus on phenotypes associated with common diseases that significantly and adversely impact quality of life in aging humans. These include measures of hematological function; osteoarthritis and osteoporosis; kidney function and urinary incontinence; immune function; loss of muscle mass, strength, and ambulation; cognitive decline, depression, and anxiety. Phenotyping is done in both longitudinal and cross-sectional cohorts of aging mice. Cohorts include a large panel of classical inbred strains, the highly diverse Diversity Outbred population, 2- and 4-way crosses, congenic, and knockout mice. An example of our overall analytical process utilizing multiple mouse resources is our identification of *Nrip1* (nuclear receptor interacting protein) as a potential longevity gene. Studies using a panel of 32 inbred mouse strains confirmed an inverse relationship with IGF1 and median lifespan. Use of congenic strains confirmed that natural alleles that increase IGF1 expression reduce lifespan. Subsequent analysis in inbred females revealed that mean lifespan correlates directly with age of sexual maturation, as judged by age of vaginal patency (AVP). As expected from this result, AVP inversely correlated with IGF1 levels. Analysis of congenic strains confirmed the IGF1-AVP-lifespan relationships. QTL mapping studies using AVP as trait identified *Nrip1* on Chr 16 as the most likely candidate gene. Accordingly, studies in *Nrip1* knockout mice showed reduced IGF1 and delayed onset of female sexual maturation vs. wild type (WT). Lifespan studies of *Nrip1* null vs. WT littermates are currently underway. In similar studies, we have identified and are testing other longevity candidate genes in knockout mice including *Pcsk9*, *Pcsk2*, *Rapgef4*, *Rab27a*, and *Gorasp2*, leveraging the large

resource of knockout mice available through the Jackson KOMP² project to extend both lifespan and healthspan studies.

60. Targeting Central and Peripheral IGF-1 Signaling for Healthy Aging and Longevity

Derek M. Huffman (P)

Albert Einstein College of Medicine, Bronx, NY

While low GH/IGF-1 signaling is beneficial for lifespan in model organisms, it is paradoxically linked to many age-related diseases in humans. Furthermore, we believe that many 'good' effects of IGF-1 can be accentuated in mammals by increasing central, and/or decreasing peripheral IGF-1 signaling. We will describe new models of IGF-1 signaling, with relevance to the possible prevention, slowing and reversal of aging. Novel insights regarding the mechanisms of central insulin and IGF-1 signaling on peripheral metabolism will also be briefly discussed.

61. HIF-1 Modulates Longevity through a Complex Pathway Involving Xenobiotic Metabolism

Scott Leiser (P)

University of Washington, Seattle, WA

The hypoxia inducible factor (HIF) is a conserved protein that regulates the cellular response to low oxygen conditions. Under normal oxygen levels, HIF is negatively regulated by the von Hippel-Lindau (VHL) tumor suppressor protein. Recent data from our lab and others have shown that deletion of *vhl-1* increases lifespan in *C. elegans* through stabilization of HIF-1. Unfortunately, despite HIF-1 and VHL-1 being highly-conserved, VHL-1 deficiency does not increase lifespan in people, but instead results in von Hippel-Lindau syndrome, a disease characterized by angiomas and increased tumor formation. In order to test whether HIF-1's positive effect on worm longevity can be separated from its negative role in mammalian cancer, we are evaluating the tissues and HIF-1 target proteins that modulate worm lifespan. To test the tissues where HIF-1 stabilization affects longevity, we are using worms expressing a non-degradable form of HIF-1 under various tissue-specific promoters. Our results show that stabilizing HIF-1 in specific tissues is sufficient to increase lifespan in nematodes. Concurrently, we have conducted a screen for age-associated autofluorescence in long-lived *vhl-1* mutant worms and have identified several genes downstream of HIF-1 that are necessary for HIF-1-induced longevity. We are testing whether these targets modulate lifespan

directly, and initial results are encouraging. Our data show that at least two HIF-1 targets can increase worm longevity when overexpressed in the absence of HIF-1 stabilization. Interestingly, one of the genes is known to directly regulate HIF-1 activity through a proposed negative feedback loop. The other HIF-1 target gene is a well-conserved xenobiotic enzyme that whose expression is strongly upregulated in *uhl-1* worms and whose overexpression appears to improve worm lifespan and healthspan. Our future work will further elucidate these proteins in order to better understand the HIF-1 pathway and eventually develop new approaches to improve health and longevity in humans.

62. Teasing Apart Age Related Sub-Cellular Complexity

Edgar Arriaga (P) and Chad P. Satori
University of Minnesota, Minneapolis, MN

Alterations in autophagy have been associated with aging and disease. Many studies investigating this association use the protein LC3-II as marker of autophagy, which is commonly tracked using Western blots or proteins constructs of LC3 with a fluorescent protein such as GFP. Usually, these studies cannot distinguish how LC3-II distributes among the various types of organelles involved in autophagy, namely the pre-autophagosomal structure, the autophagosomes and autolysosomes. Our group pioneered the use of capillary electrophoresis coupled to laser induced fluorescence detection (CE-LIF) to detect and quantify properties of individual organelles. This presentation will describe the use CE-LIF to investigate the distribution of fluorescent construct LC3-GFP in individual organelles. First, the presentation will describe some of the basic concepts of individual organelle CE. Second it will describe a strategy to calculate autophagy flux based on individual organelle measurements. Third, it will provide a perspective on how this technique may be used to investigate models of aging and age related diseases.

63. FGF Signaling Restores Asymmetric Division and Loss of Self-Renewal in Aged Skeletal Muscle Stem Cells

Jenii Bernet, Jason Doles, Bradley B. Olwin (P)
MCD-Biology, University of Colorado, Boulder, CO

Skeletal muscle mass and function declines with age beginning at approximately 40 years of age. Severe loss of muscle mass and function is termed sarcopenia, which increases morbidity and health care costs of the elderly. The mechanisms

involved are not well understood but are thought to include changes in skeletal muscle fibers and in the regenerative capacity of skeletal muscle stem cells. Transplantation of FGF-pretreated muscle stem cells into young mice desensitizes the transplanted donor cells from the aging environment as these cells are maintained for the lifetime of the mouse, preserving muscle mass, strength and preventing age-related molecular changes in myofiber size and myosin isoforms in the transplanted muscle. Investigation of age-related changes in muscle stem cells identified a defect in self-renewal that was not rescued by exposing aged muscle stem cells to a local young environment or by transplantation into young muscle. Aged muscle stem cells exhibited reduced asymmetric division frequencies associated with and elevation of p38 α β MAPK signaling, reductions in asymmetric localization of phospho-p38 α β MAPK, and a loss of responsiveness to FGF ligands. Manipulating FGF signaling from FGF receptor 1 restored aged satellite cell self-renewal in culture. Thus, a cell-autonomous deficit in self-renewal of aged muscle stem cells occurs in part from alterations in signaling pathways regulating muscle stem cell activation and cell fate determination.

64. Single Cell Gene Expression Profiling of Bone

Simon Melov (P)
The Buck Institute, Navato, CA

In mice, there is significant heterogeneity in the rate and magnitude of bone loss with aging. In part this is dependent on genetic background, emphasizing the importance of understanding gene expression changes in cell types responsible for the formation of bone such as the osteoblast. A commonly used model for investigating mechanisms of bone loss with aging is the ovariectomy (removal of ovaries, which causes bone loss). Although ovariectomy is a useful model, we know very little about physiological or genetic changes in key cell types within bone following the loss of estrogen. The majority of data generated concerning bone cell function is derived from studies using cell culture models that imperfectly reflect the cells' physiology within the bone and bone marrow milieu. Data generated from such studies may be potentially misleading due to adaptive changes in these cells from in vitro culturing. Understanding the contribution of individual cell types to this multifactorial process is limited using such a conventional approach. Hence there is a need, particularly in this era of personalized medicine, to delineate individual cell

function in the skeleton, and ultimately to potentially target therapeutic options to distinct cell types. I will present our newly developed workflow for evaluating gene expression changes in single osteoblasts isolated from intact bone, and illustrate the usefulness of the technique for evaluating gene expression changes with age.

65. Functional Metabolomics Opens A New Window On Aging Mitochondria *in vivo*

Kevin E. Conley (P), Brandon Flores, Sharon A. Jubrias and Eric O. Shankland

Translational Center for Metabolic Imaging, University of Washington Medical Center, Seattle, WA

Mitochondrial dysfunction is thought to be a key factor in sarcopenia and loss of mobility in age-related disorders. Few tools have been available to characterize mitochondrial changes with age *in vivo* to assess its role in the muscle and functional decline that leads to mobility disability. Here we present a new non-invasive functional metabolomic approach that fills the gap in these tools. This approach is based on a mitochondrial metabolite evident by MR spectroscopy *in vivo* in elderly muscle in MRIs available in medical research centers (humans) or university chemistry departments (mice). This metabolite has long been known to reflect the mitochondrial matrix-cell pH gradient (ΔpH) that drives oxidative phosphorylation in isolated mitochondria and organs. Our new insight is that, this metabolite peak becomes prominent *in vivo* in human and mouse muscle with age and disease. It appears as a peak split from cell inorganic phosphate reflecting an increased pH in mitochondria vs. the cell (ΔpH). We find that ΔpH is elevated in vastus lateralis muscle of healthy, elderly subjects with reduced mitochondrial content and low muscle mass as compared to age-match elderly controls. Remarkably, elevated ΔpH was also associated with slower walking speed and reduced physical functional performance in these otherwise healthy subjects. No muscle tissue pathology was evident as shown by the absence of hypercontracted fibers or disrupted mitochondria in electron micrographs of muscle biopsies. Preliminary data reveal that high ΔpH reflects mitochondrial uncoupling linked to depressed cell metabolism *in vivo*. This altered metabolism may be a link to mitochondria and muscle wasting as well as the functional disability that comes with age. Thus a new biomarker that becomes prominent in muscle *in vivo* with age promises to open a new window on how mitochondrial aging is linked to sarcopenia and loss mobility in the elderly.

AGE POSTER ABSTRACTS

Abstract Number corresponds to presentation number in the program schedule

(P) Denotes Presenter (G) Denotes Post-doctoral Candidate for Glenn Award

(N) Denotes Pre-Doctoral Candidate for Nicolai Award

66. Decreased Recent Thymic Emigrant Number and Shortened Telomere Length in Obese A-bomb Survivors

Kengo Yoshida (P), Yoshiko Kubo, Mika Yamaoka, Tomonori Hayashi, Waka Ohishi, Yoichiro Kusunoki
Radiation Effects Research Foundation

A long-standing theory of aging hypothesizes that aging and age-related diseases can be attributed to the accumulation of molecular damage. One of the environmental factors that can induce such damage is ionizing radiation. Meanwhile, another theory was recently proposed: nutrient-sensing signaling, typically accompanied by cell growth and adipogenesis, drives aging processes (Blagosklonny, *Cell Cycle* 2006). In fact, mouse studies demonstrated that adipogenesis with pro-inflammatory cytokines accelerated aging of the hematopoietic microenvironments in bone marrow and the thymus (Naveiras et al, *Nature* 2009; Yang et al, *Blood* 2009). Attrition of thymic T-cell production is known to lower immunosurveillance in the elderly. This study aimed to elucidate relationships among aging, radiation exposure, obesity, and endpoints for T-cell aging in peripheral blood, i.e., TRECs (reflecting recent thymic emigrants), numbers and percentages of T-cell subsets, and T-cell telomere lengths. Subjects totaled 990 A-bomb survivors who had donated blood samples during the period 2003-2009. TREC numbers in CD4 and CD8 T cells were measured using a real-time PCR-based method, and telomere lengths in naïve CD4, memory CD4, and total CD8 T-cell populations were assessed by Flow-FISH. Preliminary results showed that i) TRECs in both CD4 and CD8 T cells decreased with aging, obesity markers (BMI, HbA1c), diabetes, and fatty liver conditions; ii) TRECs in CD4 T cells negatively correlated with blood CRP levels; iii) the number of TRECs in CD4 T cells positively correlated with both the number and telomere length of naïve CD4 T cells; and iv) telomere lengths of T-cell populations decreased with aging, HbA1c, diabetes, and fatty liver. Radiation effects on telomere shortening were also suggested, but not on TRECs, probably because of elapsed time (more than 60 years). This human population study thus suggests that obesity with enhanced inflammation may be closely involved in the aging of the T-cell immune system.

67. Independent Chemical Regulation of Health- & Senescent-Spans in *Drosophila*

Robert Arking (P)
Wayne State University

Curcumin has multiple biological effects, including histone acetyl transferase (HAT) activity. Larval feeding with curcumin induces an extended health span in a normal-lived Ra strain adult fly with significantly increased median and maximum longevities. This phenotype shows no additive effect on longevity when combined with an adult dietary restriction (DR) diet. Gene expression data shows that the TOR pathway is inhibited in the larvae and the young to midlife adults, although several other genes involved in longevity extension are also affected. The aging rate is slowed so that it is comparable with that of genetically selected long lived La animals. Feeding the drug to adults during only the health span also results in a significantly extended health span with increased median and maximum life span. However, feeding adults with the drug over their whole life, or only during the senescent span, results in a weakly negative effect on median longevity with no increase in maximum life span. The long-lived La strain shows no response to this DR mimetic.

Sodium butyrate (NaBu) is a Class I histone deacetylase inhibitor (HDACI). This chemical decreases longevity of the normal-lived Ra animals when administered over the health span only or over the entire adult lifespan but increases longevity and decreases mortality rates when administered only in the transition or senescent spans. Mostly deleterious effects are noted when administered by either method to the long-lived La strain. A different HDACI (suberoylanilide hydroxamic acid, SAHA) administered to the normal-lived strain showed similar late-life extending effects, suggesting that this is not an isolated effect of one drug.

The health and senescent spans seem to be separately regulated and apparently have different patterns of drug targets. We are testing whether sequential stage-specific administration of these extended longevity inducing chemicals will yield synergistic effects on lifespan.

68. Age-Related Change of Protein Degradation in Mouse Liver Parenchymal Cells

Yuki Kishimoto (P), Akiko Amano, Naoki Maruyama, Akihito Ishigami

Molecular Regulation of Aging, TMIG

Abnormal protein accumulation in several tissues and organs might be one of the causes of aging. One possible cause of abnormal protein accumulation is an age-related change of the imbalance for between protein synthesis and degradation. Therefore, we evaluated the degradation rate of endogenous proteins in hepatocytes derived from various aged mice. Average half-lives of long-lived proteins were 40 h and 65 h in the cells from young (4-7 months-old) and old (23 months-old) mice, respectively. These results suggested that the half-life of endogenous protein degradation in cells from old mice was about 60% longer than that in the cells of young mice. Now we are investigating the relationships between age-related abnormal protein accumulation and proteolysis by autophagy.

69. Short-Term Caloric Restriction Initiated at Different Ages had Minimal Effect on Nrf-2 Activation

Nopporn Thangthaeng (P), Nathalie Sumien, Michael J. Forster

University of North Texas Health Science Center

Long-term caloric restriction (CR) has been reported to provide a multitude of health benefits, including extended lifespan, improved brain function, and enhanced protection from brain injury. These outcomes have been hypothesized to result from a long-term alteration of redox homeostasis and reduced accumulation of oxidative damage. The purpose of this study was to determine if short-term restriction of energy intake could produce such effects directly in mice of different ages, via antioxidant or detoxification responses linked to activation of NF-E2-related factor 2 (Nrf2). Three groups of C57BL/6J males, aged 3, 12 or 19 months, were maintained on ad libitum feeding (AL) or 30 % CR for a period of four months prior to collection of brain tissue for measurement of: (i) nuclear translocation of Nrf-2, (ii) enzymatic activities of the Nrf-2 -targeted gene products glutamate-cysteine ligase (GCL) and glutathione S-transferase (GST), (iii) glutathione concentration, and (iv) protein oxidation via an aldehyde reactive probe. In AL-fed mice, a modest age-related increase was detected for oxidative damage to cytosolic but not nuclear protein, though Nrf-2 translocation did not show significant

change. Activities of GST and GCL were modestly increased with age in cortex, hippocampus, striatum and cerebellum, whereas glutathione concentration did not show significant age-related change in any region. The short-term regimen of CR had little effect on Nrf-2 activation or its downstream effectors, except in CB and CX, where CR increased activity of GST in the absence of clear Nrf-2 activation. The implementation of CR in the different age groups had little or no effect on GSH concentration or the amount of oxidized cytosolic proteins. The current results suggest that both aging and short-term CR promote antioxidant and detoxification responses, primarily in the cerebellum, in the absence of Nrf2 pathway activation.

70. “Who wants to Live Forever?”-

Chromatinome RNAi Screen for Longevity in *C. elegans*

K.Chocian, H.Lees, H.Cantwell, J.Mellor and A.Woollard

Department of Biochemistry, University of Oxford

To aid our understanding of the ageing process and its connection to epigenetics I used a non-biased approach to uncover novel chromatin factors affecting life span in *C. elegans*. To date, there is some evidence that aged organisms and cells display particular epigenetic marks, however, the mechanism by which chromatin is modified and the biological significance of such modifications as we age is unclear. Using the model organism *C.elegans* and a variety of short and long lived mutants available has already been proven to be a successful approach in unravelling some of the mysteries of this process. I performed an RNAi screen for longevity using a chromatinome library and assessed the accumulation of lipofuscin as a biomarker of ageing. Preliminary results are encouraging, with 16 ‘confident hits’ (where lipofuscin accumulation is significantly delayed on both days of screening) and a further 28 genes under investigation. The validity of the screening approach is confirmed by matching several of the hits to factors that have previously been associated with lengthening lifespan in model organisms (e.g. *mes-2*, *T26A5.8*, *F21H12.1*). A further secondary screen with a simple lifespan assay is being undertaken to select genes of particular interest.

71. The Paternal Age Effect: A Role for p53 Activation in Regulating AP Endonuclease 1 Abundance with Increased Paternal Age

Jamila R. Momand (P,G) and Christi A. Walter
The University of Texas Health Science Center at San Antonio

Over the last few decades there was a 30% increase in the number of fathers over the age of 35-years-old. At this age, a father has the potential to transmit twice as many mutations to his child as a 20-year-old father. Paternal mutations continue to double approximately every 16 years, a phenomenon known as the paternal age effect. The driving force of the paternal age effect is mutagenesis. Base excision repair activity is essential for maintaining a low mutant frequency in the male germline. However, spermatogenic cells isolated from old mice display a 50% decrease in base excision repair activity, with a concomitant increase in mutant frequency, as compared to cells prepared from young mice. Reduced base excision repair activity appears to be mediated by reduced AP endonuclease 1 (APE1), a key base excision repair protein. Mice heterozygous for Ape1 show an increased germline mutant frequency as young adults, while APE1 transgenic mice are protected from age-dependent increases in spontaneous mutagenesis. Our objective is to delineate the mechanism/s mediating reduced APE1 abundance in spermatogenic cells with increasing age. In pachytene spermatocytes and round spermatids obtained from old mice, there is a significant 35% and 25% reduction, respectively, in APE1 abundance as compared to young mice. The age-related decrease in APE1 abundance is not accompanied by a reduction in Ape1 transcript abundance, thereby suggesting that post-transcriptional or post-translational regulation is involved. In somatic cells, p53 plays a role in regulating Ape1 abundance. There is a significant increase in p53 activation in spermatogenic cell populations obtained from old mice. APE1 expression is reduced by 40% in spermatogenic populations obtained from p53 null mice, relative to wild-type mice. Combined, these results indicate a strong relationship between APE1 abundance, germline mutagenesis and p53 activation in spermatogenic cells with increasing age.

72. An Examination of Age-Dependent Inter-Individual Variation in Gene Expression in Three Species Produces Surprising Results

R. Michael Anson¹ (P) and Arielle Charmaine Holliday²
¹*CCBC School of Mathematics and Science; Stevenson University;* ²*Stevenson University*

Even in clonal populations raised in controlled environments, lifespans differ among individuals. While death is, at present, the "gold standard" in

evaluating the effectiveness of potentially life-extending interventions, full lifespan studies are prohibitively expensive. The object of the present work was to evaluate age-dependent variability in inter-individual gene expression in search of patterns which might allow prediction of the mean and maximal lifespan for a cohort. Microarray data for all analyses were obtained from the public repository, "GEO." Genes with expression levels near the minimum or maximum sensitivity of the assays were excluded, and the remaining data normalized to reduce inter-assay technical variation. The underlying hypothesis was that inter-individual variability in gene expression would increase with age either programmatically or in response to environmentally induced, randomly occurring physiological decrements, and that said variability would be proportional to the cohort's expected lifespan. Contrary to this hypothesis, inter-individual variability in gene expression seems to remain relatively stable or to actually decrease with age, depending on the model system. The discussion presented here will include a detailed description of the methods used to exclude technical variation and hypotheses regarding the surprising outcome.

73. A Multi-Organism Approach to Selecting Strong Candidates for Mammalian Longevity Genes

George L. Sutphin¹ (P,G), Shannon Bean², Matt Kaeberlein¹, Ron Korstanje²

¹*University of Washington;* ²*The Jackson Laboratory*

The search for genetic factors involved aging has identified hundreds of genes for which altered expression is capable of increasing life span in one or more model organisms. As the first pharmacological agents targeting these genes begin to be translated into clinical trials for treatment of age-associated disease, it will be useful to prioritize potential clinical targets from the growing list of candidate aging factors that are likely to influence longevity in mammals. We have devised a candidate-gene approach to combine recent genomic methods in mammals with the powerful genetic tools available in invertebrates to identify evolutionarily conserved longevity genes with a high likelihood of impacting mammalian aging. An initial list of longevity-associated genes was selected based on a meta-analysis of human and mouse genome-wide association studies. Orthologs of each gene were then selected in both *Caenorhabditis elegans* and *Saccharomyces cerevisiae*. A screen is currently underway to determine whether RNAi knockdown or deletion of

each ortholog increases life span in worms or replicative life span in yeast. In cases where life span extension is observed, knockdown of the ortholog will be combined with knockdown of genes in commonly studied aging pathways to look for epistatic interaction. Interesting candidates will be carried forward for longevity studies in mice. Here we provide a detailed description of our screening strategy and report preliminary results.

74. Pcsk2 may Co-Regulate Female Sexual Maturation and Longevity Through the Regulation of Circulating IGF1

Dan Gatti¹, Rebecca Krier², Luanne Peters¹, David E. Harrison¹, Beverly Paigen¹, Gary A. Churchill¹, Rong Yuan³ (P)

¹The Jackson Laboratory; ²Loyola University Chicago Stritch School of Medicine; ³Southern Illinois University

Our previous study found that, across mouse inbred strains, lower IGF1 level associated with delayed female sexual maturation and extended longevity. This suggests that female sexual maturation and longevity may be genetically co-regulated. To identify the underlying genetic mechanisms, we generated 307 F2 female mice by crossing strains KK/HiJ and PL/J, which differ significantly in circulating IGF1 level and age of female sexual maturation. Correlation analyses confirmed that females with lower IGF1 have delayed sexual maturation (P = 0.0002) and longer longevity (P = 0.024). Using quantitative trait loci (QTL) analyses, we identified one significant lifespan QTL in the distal region of chromosome 2. In the same region, we also identified significant QTL for age of female sexual maturation and circulating IGF1. At this locus, the PL/J allele is associated with lower IGF1, delayed female sexual maturation and increased lifespan. Interestingly, the human region syntenic with this locus has been reported to be associated with age at menarche in a human genome-wide association study. Bioinformatic analyses, including haplotype and gene function analyses, identified proprotein convertase subtilisin/kexin type 2 (Pcsk2) as a promising candidate gene for the QTL. Further studies found that Pcsk2 null females have significantly lower IGF1 and delayed sexual maturation. Reducing the expression of the homologue of Pcsk2 in worm has been reported to reduce reproduction and extend longevity. The lifespan of Pcsk2 null mice is under observation.

75. Deregulation of Alternative Splicing in Human Aging

Alice Holly¹ (P), David Melzer¹, Luke Pilling¹, Luigi Ferrucci², Lorna Harries¹

¹University of Exeter Medical School; ²National Institute on Aging

Human aging is associated with decreases in cellular plasticity and adaptability. Alternative splicing may be a factor influencing this; age-related differences in the ratio of alternatively spliced transcripts have been described in humans. These changes may be brought about by alterations to the expression of regulatory splicing factors during aging, but this has yet to be systematically analysed in man.

Messenger RNA (mRNA) splicing is a co-transcriptional process whereby the pre-mRNA molecule is modified to remove the non-protein coding regions (introns) whilst retaining the coding regions (exons) and the 5' and 3' untranslated regulatory sequences. Consensus sequences signalling exon/intron boundaries are essential, but often not sufficient, for splicing to occur. Splice site usage is regulated by additional splicing regulators (SRSF and hnRNP proteins) that bind auxiliary sequences such as exon and intron splicing enhancers and silencers. These factors are important in regulation of splicing patterns, particularly in relation to temporal or spatial expression of alternatively expressed isoforms.

Approximately one third of transcripts coding for splicing regulators demonstrated age-related changes in their expression levels in peripheral leukocyte-derived microarray data from two human populations; InCHIANTI (n=695) and SAFHS (n=1238). Furthermore, primary fibroblasts and endothelial cells demonstrated senescence-associated alterations in splicing factor expression, accompanied by changes in alternative splicing within these cells. Finally, up-regulation of some age-responsive SR transcripts as a result of targeted knockdown of Ataxia Telangiectasia Mutated (ATM) transcripts were seen in primary fibroblasts.

We conclude that senescence-related up-regulation of the ATM kinase in fibroblast cells in response to accumulated DNA damage may have an inhibitory role on the expression of some splicing factors. These findings represent an important new link between the DNA damage response and regulation of alternative splicing, which may contribute to the aging process, and to susceptibility of age-related disease.

76. A Tumor Suppressor Complex with GAP Activity for the Rag GTPases that Signal Amino Acid Sufficiency to mTORC1

Liron Bar-Peled¹ (P,N), Lynne Chantranupong¹, Andrew D. Cherniack², Walter Chen¹, Kathleen A. Ottina¹, Brian Grabiner¹, Eric A. Spear³, Scott Carter², Matthew Meyerson⁴, David M. Sabatini¹
¹Whitehead Institute for Biomedical Research; ²Broad Institute of Harvard and MIT; ³John Hopkins Medical School; ⁴Dana Farber

The mTOR Complex 1 (mTORC1) pathway promotes cell growth and reduction in its activity has been shown to increase lifespan in yeast, *C. elegans*, *Drosophila* and mice. mTORC1 activity is regulated in response to many cues, including amino acids, which act through the Rag GTPases to promote mTORC1 translocation to the lysosomal surface, its site of activation. Although progress has been made in identifying positive regulators of the Rags, it is unknown if negative factors also exist and whether they are mutated in cancer. Here, we identify GATOR as an octameric complex that interacts with the Rags. GATOR is composed of two subcomplexes we call GATOR1 and 2. Its GATOR1 subunits have been implicated as tumor suppressors and their inhibition makes mTORC1 signaling insensitive to amino acid deprivation. In contrast, inhibition of GATOR2 subunits suppresses mTORC1 signaling, and epistasis analysis reveals that GATOR2 is an upstream negative regulator of GATOR1. Furthermore, the GATOR1 subcomplex has GTPase activating protein (GAP) activity for RagA and RagB, consistent with its inhibitory role in mTORC1 signaling. In cancer cell lines containing GATOR1 inactivating mutations, mTORC1 is hyperactive and resistant to amino acid regulation, and these cells are hypersensitive to rapamycin, an FDA-approved mTORC1 inhibitor. Thus, we identify the GATOR complex as a critical regulator of the pathway that signals amino acid sufficiency to mTORC1 and reveal that, like other mTORC1 regulators, the Rags can be deregulated in cancer.

77. Thioredoxin 2 Overexpression and Thioredoxin 1 Down-Regulation Attenuate Aging Through Independent and Common Mechanisms

Sara Dube¹, Lisa C. Flores¹, Madeline Roman¹, Yiqiang Zhang¹, Adam Salmon¹, Shuko Lee², Holly Van Remmen¹, Arlan Richardson¹, Gene B. Hubbard¹, Yuji Ikeno¹ (P)
¹Barshop Institute/UTHSCSA; ²Audie Murphy VA Hospital

Our laboratory has conducted the first detailed study investigating the effect of overexpressing or down-regulating thioredoxin 1 (Trx1: found in the cytosol) or thioredoxin 2 (Trx2: found in the

mitochondria) on aging. Interestingly, we found that while Trx2Tg mice showed an extension of median lifespan compared to wild-type mice, we observed little increase in survival of Trx1Tg mice. The extension of lifespan in Trx2Tg mice was correlated with less production of reactive oxygen species (ROS) from mitochondria and less oxidative stress. These data show that overexpressing Trx in mitochondria may be more important than overexpression in cytosol because mitochondria are a major source of ROS. When we tested the effects of reduced levels of Trx in the cytosol or mitochondria on aging, surprisingly we observed the reversed effects, i.e., an increase in survival of the Trx1KO mice compared to wild-type mice, while Trx2KO mice showed little effects on lifespan. The extension of lifespan of the Trx1 KO mice was associated with less cancer compared to wild-type mice at 22-24 months of age. These results indicate that reduced cancer development in the Trx1KO mice could be a contributing factor to the extended lifespan.

Our results are exciting in that we show 1) overexpressing Trx in the mitochondria increases lifespan, but overexpressing Trx in the cytosol has little effect on lifespan, which is similar to the results of mCAT mice; and 2) down-regulating Trx in the cytosol increases lifespan and reduces cancer, but down-regulating Trx in mitochondria has no effect on lifespan or cancer. These paradoxical but intriguing results could indicate that Trx2Tg and Trx1KO mice attenuate aging through different mechanisms, e.g., protection of mitochondria against oxidative stress and reduced age-related pathology, e.g., cancer.

Supported by grants from the VA Merit Review, the American Federation for Aging Research, and the Glenn Foundation.

78. Mechanisms that Extend Lifespan in Sprague-Dawley Rats by Cu/ZnSOD Overexpression

Madeline Roman¹, Lisa Flores¹, Adam Salmon¹, Sara Dube¹, Nicolas Musi², Shuko Lee³, Gene B. Hubbard¹, Holly Van Remmen¹, James Kirkland⁴, Tamar Pirtskhalava⁴, Tamar Tchkonja⁴, Arlan Richardson¹, Yuji Ikeno¹ (P)
¹Barshop Institute, University of Texas Health Science Center at San Antonio; ²UTHSCSA; ³Audie Murphy VA Hospital; ⁴Mayo Clinic

Recently, our laboratory made the surprising observation that overexpressing Cu/ZnSOD [Tg(SOD1-SD)+/0] in Sprague Dawley (SD) rats resulted in a significant increase in lifespan and a reduction in age-related pathologies. The purpose

of this study is to determine why overexpressing Cu/ZnSOD increases lifespan in SD rats. The Tg(SOD1-SD)+/0 rats showed lower levels of oxidative damage to DNA and lipids in vivo and higher resistance to oxidative stress in vitro. Both Tg(SOD1-SD)+/0 and wild-type rats showed an age-related increase in body fat, and Cu/ZnSOD overexpression did not attenuate adiposity. Interestingly, Tg(SOD1-SD)+/0 rats showed a significant increase in insulin sensitivity at a young age and lower plasma glucose levels at an old age, which were associated with an enhanced insulin signaling pathway.

To further investigate the role of Cu/ZnSOD overexpression on aging, we generated transgenic F344 rats overexpressing Cu/ZnSOD. Tg(SOD1-F344)+/0 rats showed similar levels of Cu/ZnSOD overexpression compared to Tg(SOD1-SD)+/0 rats. The Tg(SOD1-F344)+/0 rats showed lower levels of oxidative damage to lipids in vivo, however, neither Tg(SOD1-F344)+/0 nor wild-type rats showed age-related changes in body fat, insulin insensitivity, or plasma glucose levels. Furthermore, Tg(SOD1-F344)+/0 rats showed little increase in lifespan compared to wild-type rats.

Our results are very exciting because these data indicate that the overexpression of Cu/ZnSOD could provide more protection against oxidative stress, enhance insulin sensitivity, retard aging, and reduce age-related diseases under obese conditions in mammals.

Supported by grant from the VA Merit Review, American Federation for Aging Research, and Glenn Foundation.

79. Effects of Short-Term Phytoestrogen Supplementation on Cognitive Function in Male and Female Mice

Akram Sidhu (P,N), Michael J. Forster, Nathalie Sumien
UNT Health Science Center, Department of Pharmacology & Neuroscience, IAADR, Fort Worth TX

Plant-derived, non-steroidal compounds called phytoestrogens have been widely used as substitutes for estrogen in anticipation of estrogen-like therapeutic effects without producing the side effects associated with estrogen therapy. Human and animal data are still controversial regarding the beneficial effects of such compounds and whether they are differential based on the gender/sex of the subjects. Furthermore, the window of opportunity for successful interventions remains elusive. This study investigated the effects of short-term phytoestrogen intake on the cognitive function of young, middle and old mice of both sexes. Separate groups of young (6 months), middle (12 months)

and old (24 months) male and female C57BL/6J mice were placed on either a phytoestrogen-free (PF) diet (N=15-17) or a phytoestrogen-rich (PR) diet containing (350-650 mg/kg phytoestrogens (N=16-19)) for a period of 16 weeks. After 7 weeks on their respective diets, the mice were tested on a Morris water maze task including a visible platform phase, and an active avoidance task. In the Morris water maze, learning index of the female mice was greater than the one of the PF mice regardless of age (P=0.085). There was no effect of the diet in the visible platform phase of water maze. In the acquisition phase of the active avoidance task, a trend for the old PR males to perform worse than the old PF males was observed. In the reversal phase, middle age PR males performed worse than the PF males, whereas a similar trend was observed in the old females. Even though females were adversely affected in a spatial task and the cognitive flexibility of middle-aged males was diminished, the overall effects of phytoestrogens were relatively marginal.

80. Systemic Effects of Decreased Neuronal mTOR Signaling

Stacy A. Hussong (P,G), Jonathan J. Halloran, Raquel R. Burbank, Ai-Ling Lin, Vanessa Y. Soto, Veronica Galvan
University of Texas Health Science Center at San Antonio

Reduction of target of rapamycin (TOR) signaling has been shown to extend lifespan in invertebrates as well as in adult mice. In other genetic models of longevity in invertebrates, specific manipulations in the nervous system are sufficient to extend lifespan.

To determine whether the reduction of mammalian TOR (mTOR) signaling in mature neurons of adult mice is sufficient to extend lifespan and improve healthspan we inducibly knocked out the mTOR complex 1 specific protein, Raptor, in adult mouse neurons after brain development was complete (2.5 months). Cre-mediated recombination of genomic DNA was detected in brain, but not in liver, and Raptor protein levels were significantly reduced after induction of Cre expression. To determine whether decreasing Raptor in neurons of adult mice affected healthspan, we measured body mass composition, metabolism, motor coordination, muscle strength, brain metabolite concentrations, and cognitive function.

While no significant differences in motor coordination, strength or body weight were observed among experimental groups, genetic

reduction of Raptor in neurons of adult mice induced significant changes in body composition, with neuronal Raptor knock-out males becoming significantly leaner than non-transgenic controls. Adult neuronal Raptor conditional knock-outs also showed increased levels of neuronal N-acetylaspartate, a marker of neuronal health and function. Ninety-percent decrease of adult neuronal Raptor expression did not affect spatial learning but resulted in deficits in reversal learning, suggesting a role of mTORC1 in behavioral flexibility. In contrast, animals in which Raptor was decreased by 40% showed intact reversal learning and enhanced spatial memory. Future experiments will determine if decreased mTOR complex I signaling in adult mouse neurons is sufficient to extend lifespan and improve healthspan. Included in the evaluation of healthspan will be measures of neurological function as determined by electrophysiological and behavioral experiments.

81. Identifying and Quantifying Mitochondrial DNA Damage with the Progression of Age-Related Macular Degeneration

Deirdre Manion-Fischer¹ (P), Rebecca Kapphahn², Deborah Ferrington², Edgar Arriaga³

¹University of Minnesota; ²University of Minnesota, Department of Ophthalmology; ³University of Minnesota, Department of Chemistry

Age-related macular degeneration is a disease that causes deterioration of the central vision in elderly individuals. Mitochondrial DNA damage increases with the progression of macular degeneration, more so than with age-matched controls. Determining how mitochondrial DNA is damaged is crucial to understand how the disease progresses and the functional consequences that result. This depends on what regions of the mitochondrial genome are damaged and whether this damage is specifically associated with the disease. To answer these questions, it is necessary to identify the type and amount of damage that occurs with the progression of the disease and compare that to the extent of damage that occurs in age-matched controls. These patterns in mitochondrial DNA damage will be identified by a combination of quantitative PCR (qPCR), capillary gel electrophoresis (CGE), and DNA sequencing in retinal pigment epithelial cells isolated from the macula of human donor eyes. First, the amount of mitochondrial damage is determined by a qPCR assay utilizing nine primer sets that cover the entire mitochondrial genome. Next, the unamplified fragments resulting from damage will be separated from full length undamaged PCR products by CGE. Fractions

containing damaged PCR products will be collected and sequenced by next-generation sequencing to determine their location in the mitochondrial genome. The completion of this work will result in a better understanding of how specific mitochondrial DNA damage is correlated to the progression of age-related macular degeneration.

82. Human Aging System Diagram - A New Stage of the Analysis of Complex Problems

Anna Vladimirovna Kremensova¹ (P), Danila A. Medvedev², Alex A. Moskalev³, Boris A. Kaurov⁴, Elena V. Tereshina⁴, Valery B. Mamaev¹, Igor V. Artyuhov⁵, Elena G. Pasyukova⁶

¹Emanuel Institute of Biochemical Physics of Russian Academy of Science; ²International Research Centre for Advanced Technologies; ³Institute of Biology, Komi Science Center of Russian Academy of Science; ⁴Russian Gerontological Scientific Clinical Medical; ⁵Institute of Biology of Aging; ⁶Institute of Molecular Genetics of Russian Academy of Sciences

For today gerontology and interdisciplinary sciences have accumulated vast knowledge about ageing processes, there are hundreds hypotheses about the nature and mechanisms of aging and ways to overcome it. Therefore now presence of the synthesising project bridging knowledge together is natural continuation of development of a science about ageing. At the same time the scientific thought in all areas uses visual languages for solving problems more and more frequently, as text representation of the information already limits scientific search. The purpose of the project is creation of the general diagram of human ageing, including all mechanisms of ageing known to the present moment, beginning from molecular level and to the level of an organism. Creation of Human Aging System Diagram not only helps address the issue of aging in general, identify blind spots and promising points of intervention in the aging process, but also to assess the possible side-effects of such impacts, as in the diagram, we have tried to show all currently known main processes in aging, not just some of them. For more information and the latest version of the diagram can be found on the project website: www.sciencevsaging.org

83. Regulation of PGC-1 α Levels by GSK-3 β as a Mediator of Aging-Related Disease

Karl Miller (P), Albert Budhipramono, Porsha Howell, Michael Polewski, Monica Chou, Rozalyn Anderson
Department of Medicine, University of Wisconsin-Madison

Defects in energy metabolism are associated with various aging-related diseases, including cancer,

diabetes, and cardiovascular disease. The transcriptional coactivator PGC-1 α is a master regulator of energy metabolism that programs cellular metabolism through transcriptional control of gene targets involved in mitochondrial biogenesis and oxidative phosphorylation. PGC-1 α is regulated through extensive post-translational modification. We have previously shown that under conditions of oxidative stress, GSK-3 β phosphorylates PGC-1 α , targeting it for proteasomal degradation. However, it is not known whether GSK-3 β regulates PGC-1 α in the absence of stress. It has been established in the literature that the half-life of recombinant, tagged PGC-1 α is less than one hour. We show that endogenous PGC-1 α is stable in NIH 3T3 fibroblasts even up to 8 hours in the presence of cycloheximide inhibition of translation. However, PGC-1 α levels do decrease under conditions of constitutively active GSK-3 β . Constitutively active GSK-3 β was also associated with changes in sub-cellular localization of PGC-1 α . We next used an alternative method to inhibit translation by treating cells with rapamycin, an inhibitor of mTOR signaling. Interestingly, rapamycin treatment increased PGC-1 α levels and deactivated GSK-3 β by inhibitory phosphorylation. Coincident with increased levels of PGC-1 α , mitochondrial membrane potential was increased, a functional consequence of rapamycin treatment. These data put the metabolic regulator PGC-1 α downstream of mTOR, a kinase associated with longevity. This interaction is mediated by GSK-3 β , a kinase implicated in diabetes and Alzheimer's disease. This work connects and suggests a central role for three important mediators of metabolism, aging, and aging-related disease.

84. Habitual Physical Activity Improves Neutrophil Function in the Elderly: The Physical Activity and Healthy Ageing Study (PAHA)

David B. Bartlett¹ (P,N), Clare L. McNulty², Oliver Fox¹, Laura Murphy¹, Elizabeth Sapey¹, Anton J.M. Wagenmakers³, Janet M Lord¹

¹ MRC-ARUK Centre for Musculoskeletal Research, University of Birmingham; ² Sport & Exercise Sciences, University of Birmingham; ³ RISES, Liverpool John Moores University, Liverpool, UK

Increased bacterial infection is prevalent in the elderly, especially those moving towards a frail condition, and is accompanied by reduced immune function. Physical activity (PA) has many health benefits including slowing progression towards frailty. Here we investigate the hypotheses that regular PA improves immune function in the

elderly. The PAHA study assesses the impact of PA as a determinant of health in a cross-sectional cohort of the over 60's and includes an assessment of PA in relation to immune function. We report here for the first time a comprehensive analysis of neutrophil function in healthy aged physically active and inactive individuals.

211 elders (66.9 \pm 4.9yrs) were assessed for PA levels using accelerometry and the 20 highest (HA) and 20 lowest activity (LA) individuals evaluated. Controls of 10 healthy young (23 \pm 3.8yrs) individuals were also assessed. Immune function tests: Neutrophil phagocytosis of opsonized E.Coli and superoxide production in response to E.Coli Neutrophil surface expression of CD16, CXCR1, CXCR2, MAC-1, TLR2 and TLR4 were analysed by flow cytometry. Isolated blood neutrophil migration towards IL-8 was assessed using an Insall Chamber and time-lapse video-microscopy and migratory dynamics analysed using Image-J.

Neutrophil superoxide production was elevated (P<.05) in the LA group with no difference in the ability to phagocytose bacteria, suggesting a dysregulated and potentially damaging inflammatory response to infection. Compared to younger individuals neutrophils of the elders had a reduced velocity (P<.05) and directional accuracy (P<.05). Data analysed for the two activity level groups revealed the LA group had lower velocity and accuracy than the HA group (P<.05). No differences were observed for receptor expression on neutrophils.

Taken together these data suggest that habitual physical activity can maintain neutrophil migration towards infection and improve inflammatory responses. Maintaining PA in a frail elderly population may therefore reduce the susceptibility to bacterial infectious episodes.

Funded: BBSRC(BB/G018049/1)

85. Inflammation and Human Aging: Transcriptome-Wide Mediators in Blood Leukocytes

David Melzer¹ (P), Luke Pilling¹, Lorna Harries¹, William Henley¹, Dena Hernandez², Andrew Singleton², Luigi Ferrucci³

¹University of Exeter Medical School, UK; ²Laboratory of Neurogenetics, National Institute on Aging; ³National Institute on Aging, Baltimore, Maryland, USA

Introduction

Chronic inflammation is common in aging, but the pathways involved are unclear. We aimed to identify gene expression most closely associated with serum Interleukin 6 concentrations and age in humans.

Methods

Peripheral blood derived in-vivo RNA was from 694 respondents to the InCHIANTI aging study (ages 30-104 yrs). Expression data were from Illumina HT-12 arrays.

Using regression-based mediation analyses we identified gene transcripts robustly explaining part of the age-serum IL6 association, adjusted for confounders.

Results

942 genes mediated the age-IL6 association - mostly as positive mediators. The majority of associations (83%) were statistically attributable to differences in proportions of major leukocyte cell sub-types. The top independent expression probes (n=156) were related to lymphocyte, T and NK cell, monocyte and neutrophil markers. Mediator genes included those coding for extracellular matrix proteins, lysis of target cells, interferon response, MAP Kinase signalling plus novel genes. There was relatively little change in cytokine expression.

Conclusions

This first large-scale study of in-vivo gene expression in 'inflammaging' suggests that raised circulating inflammatory markers in older persons are mainly produced by non-blood compartments. Several leukocyte cell types are mediators. Further work is needed to characterize the specific cell subtypes and mechanisms by which the novel genes contribute to inflammation in older persons.

86. Skeletal Muscle Power Generation with Aging and Inactivity

Jong-Hee Kim, Ted G. Graber, and LaDora V. Thompson

University of Minnesota Medical School, Minneapolis Minnesota

Dept. of Physical Medicine and Rehabilitation

Muscle power generation is important for mobility and reductions in this contractile parameter significantly impair the quality of life of an individual. Because older individuals experience periods of imposed bed rest or inactivity and their muscles show molecular and cellular changes (sarcopenia), we are interested in determining if these age-related changes influence the capacity of muscles to adapt to inactivity. Therefore, the purpose of study was to evaluate the effect of aging on power generation in myosin heavy chain (MHC) type I fibers from the soleus and MHC type II fibers from the plantaris muscles in response to inactivity. We hypothesized that power generation by MHC type I fibers would be more detrimentally

affected by inactivity than MHC type II fibers and the adaptation to inactivity would differentiate with age. In order to test our hypothesis, young and old Fisher-344 rats were randomly assigned to one of four groups: weight bearing control (CON), hindlimb unloading (HU) for 1, 2, and 3 weeks. Single muscle fiber power generation was determined from force-velocity curves and MHC isoforms were identified by SDS-PAGE (total 403 single fibers - MHC type I: 225, type IIX: 93, type IIXB: 85). We found peak power generation of MHC type I fibers from the soleus and MHC type IIXB fibers from the plantaris was reduced by an average 59% (young 51-70%; old 46-60%) and 49% (young 46-60%; old 38-50%) with inactivity, respectively. This reduction in peak power generation was independent of age. In contrast, peak power generation of MHC type IIX fibers from the plantaris with inactivity was dependent on the age of the rats (age \times HU, $p=.02$). Peak power generation was reduced by an average of 49% and 27% in young and old rats, respectively. Collectively, the results show the detrimental effects of inactivity on single muscle fiber power generation and the fiber-type and muscle-type specific impact of aging during a period of inactivity. These results become very important when designing therapeutic approaches to attenuate aging and inactivity-induced contractile dysfunction.

87. The Effect of Visceral Fat Removal on Insulin Signaling in Ames Dwarf Mice

Vinal Menon (P), Xu Zhi, Michal Masternak
University of Central Florida

Obesity is a serious medical condition that is particularly prevalent in developed countries. This state of excess fat accumulation is the underlying cause of a number of diseases including type 2 diabetes. Ames dwarf (df/df) mice are homozygous for a spontaneous mutation in the prop1 gene due to which there is no pituitary development of somatotrophs, lactotrophs and thyrotrophs. These mutants are thus deficient in growth hormone, prolactin and thyrotropin. Ames dwarf mice tend to become obese as they age. However, in spite of this accumulation of excess visceral fat (VF) – normally considered as “bad fat” – they live longer and healthier lives compared to their normal controls (N). This leads us to believe that the VF in these mutant dwarfs may be functionally different from the same fat depots in N mice and may be beneficial, rather than detrimental, to the overall health of the animal. We performed surgeries involving removal of the VF depots (epididymal

and perirenal fat) in both groups of mice and found that VF removal improved insulin signaling only in N mice but not in the df/df mice. This intervention lead to an up regulation of certain players of the insulin signaling pathway including insulin receptor (IR) and insulin receptor substrate-2 (IRS-2), in the skeletal muscle of N mice only with no alteration in df/df mice. Understanding the mechanisms responsible for VF having positive effects on insulin signaling in df/df mice would be important for future treatment of obese diabetic patients.

88. Altered Gene Expression in the Brain of Senescence-Accelerated Mouse During Postnatal Development

Ryoya Takahashi (P) and Keiko Odera
Department Biochem., Fac. Pharmaceut. Sci., Toho University

The senescence-accelerated mouse (SAM) is an accelerated aging model that was established through phenotypic selection from a common genetic pool of AKR/J strain of mice. SAMP8/Toho mice have much shorter life-span (approx. 50% of control strain, accelerated senescence resistant strain SAMR1/ Toho). We previously found that the age-related change of various gene expressions accelerated from weaning in the brain of SAMP8 mice. We further investigated how such accelerated gene expression affects the postnatal expression of genes, such as myelin basic protein (MBP) gene, in the brain of SAMP8. MBP mRNA level increased sharply from about day 8 and peak at about day 15 in all brain regions of both strains. In the cerebellum of SAMP8, however, the MBP mRNA level declined suddenly at day 20, even though the level in SAMR1 was constantly high. We next conducted RT-PCR to see if the decrease of total MBP mRNA is due to decline by a certain variants of MBP mRNA. However, no significant difference was found in the population of MBP mRNA variants, suggesting that the temporary decrease of MBP mRNA level in SAMP8 may be due to decreased transcriptional activity and/or decreased mRNA stability. In rodent, cerebellum is continuously developed during 3 weeks after birth. It has been reported that expression of many genes related to development and maturation of the cerebellum is up and down-regulated. The decline of MBP mRNA level in the cerebellum of SAMP8 might be due to indirect effects of disordinated gene expression during weaning.

89. Withdrawn

90. Degenerative Changes in Neurons and Interstitial Cells of Cajal in Mouse Internal Anal Sphincter During Aging

M. Jill Saffrey¹ (P), Prasanna P.K.M. Gamage², Heather A. Davies², Frances M. Colyer², Bhavik A. Patel³, Mark S. Yeoman³, Richard N. Ranson⁴
¹*The Open University*; ²*Dept. Life, Health & Chemical Sciences, The Open University*; ³*School of Pharmacy & Biomolecular Sciences, University of Brighton*; ⁴*Faculty of Health & Life Sciences, Northumbria University*

Disorders of the gastrointestinal system, such as chronic constipation, fecal impaction and incontinence, are a major cause of morbidity in the ageing population. Changes in the cells that regulate intestinal motility and defecation during ageing are likely to contribute to the etiology of these conditions. Two cell types that play an essential role in the regulation of smooth muscle contractility in the terminal bowel are intrinsic (enteric) neurons of the myenteric plexus and Interstitial cells of Cajal (ICC) that form networks around the myenteric ganglia and also in the smooth muscle layers of the gut. We are therefore characterising the changes that occur in these cells in the mouse internal anal sphincter (IAS) during aging using immunofluorescence labelling, confocal microscopy and also by electron microscopy. Here we describe the results of immunolabelling of c-Kit positive ICC and ultrastructural analysis of ICC and enteric neurons and glia in myenteric ganglia of the IAS of C57BL/6 mice at 3-4, 24-25 and 26-18 months of age. 3D volume analysis of confocal stacks of c-Kit immunolabelled ICC in wholemounts of the IAS showed a significant reduction in the volume of these cells in both the longitudinal muscle and the circular muscle of the IAS in ageing animals. Ultrastructural analysis showed increased inclusions and autophagic vesicles in myenteric neurons and ICCs of old animals. These changes suggest that there may be age-related degeneration of both neurons and ICCs in the IAS, which could result in impaired signalling to the smooth muscle of the IAS, thus disrupting normal defecation.

Supported by BBSRC 'Ageing bladder and bowel' funding: BBSRC grant BB/G015988/1 to MJS & RR and BB/G015147/1 to MY.

91. Insulin-like Growth Factor (IGF-1), Neurogenesis and Synaptogenesis

Lalida Rojanathammanee (P,G), Sharlene Rakoczy, Holly Brown-Borg
Univeristy of North Dakota

Insulin-like growth factor-1 (IGF-1) is an important neurotrophic hormone. It plays a complex role in brain function including cognitive and synaptic functions. The decline in cognitive function with age has been shown to be associated with decreases in the growth hormone (GH)/IGF-1 axis and increased oxidative stress. Ames dwarf mice are GH-deficient with decreased plasma IGF-1. However, the levels of plasma and brain IGF-1 in dwarf mice differ and the affect on brain function remains unclear. In this study, we examined the relationship between hippocampal IGF-1 level, neurogenesis and synaptogenesis. We investigated the expression of doublecortin, a protein that indicates neurogenesis. The neurogenesis in 3 and 24 month-old dwarf mice was significantly higher than wild type mice at the same age. Immunohistochemistry also showed that the density of doublecortin in 3 and 24 month-old dwarf mice was significantly higher than wild mice at the same age. The presynaptic density in 3 month-old dwarf mice was significantly higher than wild type mice. Both pre- and postsynaptic density was significantly greater in 12 month-old dwarf mice compared to wild type mice. However, there was no significant difference in behavioral performance as assessed by the number of alternations on the T-maze between wild type and dwarf mice at each age. These data suggest that neurogenesis and synaptogenesis differ between Ames dwarf and wild type mice and that the expression of growth factors may be involved.

92. Stress Test and Redox Interventions to Determine the Relative Importance of GSH and NAD(P)H in Aging and AD-Like Neurons

Debolina Ghosh (P,N), Kelsey R. LeVault, Gregory J. Brewer
SIU School of Medicine, Springfield, IL

Aging, a major risk factor in Alzheimer's disease (AD), is associated with an oxidative redox shift, decreased redox buffer protection and increased free radical (ROS) generation. While NADH is the ultimate electron donor for many redox reactions, glutathione (GSH) is the major ROS detoxifying redox buffer in the cells. Culturing non-transgenic (non-Tg) and 3xTg-AD hippocampal neurons, we recently observed an early age 3xTg-AD redox deficit preceding ROS elevation and an overall decline in NADH regenerating capacity and GSH levels after middle age. Additionally, titrating GSH levels by inhibiting glutathione cysteine ligase in neurons, we observed that GSH depletion and not ROS elevation is likely to be the primary cause for increased neurodegeneration in aging and AD. We

further explored the relative importance to neurodegeneration of NADH and GSH in aging and AD neurons by inhibiting their synthesis and whether NADH can compensate for the GSH loss to maintain redox balance. Stressing neurons either by depleting NAD(P)H or GSH, we observed that NADH redox control is upstream of GSH levels and depleting NAD(P)H correlates better with higher neurodegeneration, especially in old age. Moreover, in young non-Tg neurons, a compensatory increase in NAD(P)H was observed with GSH depletion indicating that neuron maintenance of NAD(P)H is adequate to maintain a more physiologically reductive redox state. However, 3xTg-AD neurodegeneration was sensitive to both NAD(P)H and GSH depletion from the earliest age. We also determined an age-dependent loss of gene expression of key biosynthetic enzymes, NAMPT (nicotinamide phosphoribosyl transferase) and NNT (nicotinamide nucleotide transhydrogenase). Our data suggests that in aging, NAD(P)H redox control is upstream of a GSH oxidative redox shift and neurodegeneration while AD neurons behave more like old age non-Tg neurons in the relationship of NAD(P)H to GSH causing an overall oxidative redox shift and neurodegeneration.

93. Impaired Protein Homeostasis in ALS Mice: A Role for Mutant SOD1 in Peripheral Myelin Protein 22 Aggregation

Ryan T. Hamilton (P,G), Rochelle Wei, Amanda L. Jernigan, Arunabh Bhattacharya, Asish R. Chaudhuri, Holly Van Remmen
University of Texas Health Science Center at San Antonio

Amyotrophic lateral sclerosis (ALS) is a debilitating motor neuron degenerative disease that leads to the muscle weakness and death. Protein oxidation, misfolding and aggregation are considered causal in the pathology of ALS superoxide dismutase (SOD) 1 mutants. It was hypothesized that toxic gain of function SOD1 protein impairs protein homeostasis leading to aggregation of key myelin protein, peripheral myelin protein (PMP22) as is observed in multiple demyelinating neuropathies. To test this hypothesis, we isolated cytosolic and detergent-soluble proteins from the sciatic nerves of pre- and post-symptomatic G93A mice. In pre-symptomatic mice, we detected a 1.13 ± 0.04 fold increase in cytosolic protein carbonyls with no difference in detergent-soluble carbonyls which was elevated in post-symptomatic stage (135-140 days) cytosolic (1.55 ± 0.03 fold) and detergent-soluble fractions

(1.89 ± 0.14 fold) with no change in hSOD1 mice. We also observed a 19 ± 6% reduction in bisANS fluorescence in post-symptomatic mice which was reduced in one protein of pre-symptomatic mice with no change in hSOD1 mice. Post-symptomatic mice also exhibited a 53 ± 5% reduction in expression of HSP-70 which was unchanged in pre-symptomatic and hSOD1 mice. This observation was associated with a 1.7 ± 0.3 and 1.4 ± 0.1 fold increase in PMP22 protein oligomers in pre- and post-symptomatic mice and a 1.51 ± 0.13 fold increase in upper molecular mass PMP22 aggregates in post-symptomatic mice which was unaffected in hSOD1 mice. Immunoprecipitation of SOD1 or PMP22 and Western for PMP22 or SOD1 respectively demonstrated an interaction between G93A and PMP22 that was confirmed by in vitro treatment of WT sciatic nerve cytosolic homogenates with G93A protein yielding elevated G93A-dependent PMP22 aggregates. Together these data suggest that toxic gain of function G93A protein alters protein homeostasis in sciatic nerves and aggregation of PMP22 associated with demyelination at post-symptomatic ALS mice.

94. TOR And NO As Regulators of Brain Vascular Function in a Mouse Model of AD

Veronica Galvan (P), Ai-Ling Lin, Wei Zheng, Jonathan Halloran, Raquel Burbank, Stacy Hussong, Matthew J. Hart, Martin Javors, Eric Muir, James D. Lechleiter, Peter T. Fox
University of Texas Health Science Center at San Antonio

Vascular pathology is a major feature of Alzheimer's disease (AD) and other dementias. We recently showed that chronic administration of the target-of-rapamycin (TOR) inhibitor rapamycin, which extends lifespan and delays aging, halts the progression of AD-like disease and reduces amyloid-beta accumulation in (h)APP transgenic mice modeling AD. To investigate the effects of reduction of mTOR activity by rapamycin on hemodynamic, vascular and metabolic functions in brains of hAPP mice we used multi-metric imaging systems (MRI and PET). Our results demonstrate that hAPP mice have significantly reduced cerebral blood flow (CBF) and vascular density that is not related to metabolic changes, especially in areas that have a prominent role in learning and memory. Chronic rapamycin restored vascular density and CBF, reduced vascular amyloidosis and microhemorrhages, decreased amyloid burden, and relieved AD-like cognitive deficits in hAPP mice. Reduction of TOR activity also restored CBF in aged rats and in a model of atherosclerosis, suggesting that the mechanisms by which

attenuation of TOR activity restores CBF are common to different models of vascular disease, and to brain aging. In vivo multiphoton imaging revealed that rapamycin induced release of nitric oxide (NO) in vascular endothelium followed by vasodilation. Both rapamycin- and acetylcholine-induced NO release and vasodilation could be blocked by L-NAME, an inhibitor of NO synthases. Administration of L-NAME reversed the protective effects of rapamycin on brain blood flow and vascular density, indicating that rapamycin preserves vascular integrity and CBF in AD mouse brains through NO signaling. Our data suggest that the preservation of vascular density and brain blood flow may be key to the maintenance of cognitive function in the hAPP mouse model of AD. Rapamycin, an FDA-approved drug that is already used in the clinic, may have promise as a therapy for AD and possibly for age-associated brain diseases beyond AD alone.

95. Associations between Physical Activity, Inflammation and Cardiovascular Function in an Elderly Cohort

Clare L. McNulty¹ (P), David B. Bartlett², Nicola Crabtree², Janet M. Lord², James P. Fisher², Anton J. Wagenmakers³
¹*University of Birmingham*; ²*MRC-ARUK Centre for Musculoskeletal Ageing, University of Birmingham*; ³*RISES, Liverpool John Moores University, Liverpool, L3 3AF, UK*

Ageing is accompanied with physiological changes, including cardiovascular dysfunction and increased systemic levels of inflammatory cytokines. Elderly individuals who participate in regular physical activity better maintain cardiovascular function compared with their sedentary counterparts. This cross-sectional study aims to investigate the associations between age, physical activity, cardiovascular function, visceral fat mass (as source of inflammation) and neutrophil counts in a cohort of elderly individuals.

Method: 211 individuals (age 67±5) were assessed for physical activity level (PAL) using 7 day accelerometry (Actigraph GT3X). Complete white blood cell differentiation counts were assessed as markers of inflammation. Resting heart rate (RHR) and mean arterial blood pressure (MAP) were measured. Arterial stiffness was assessed as a representation of vascular function, whereby peripheral and central pulse wave velocities, and augmentation index (AI) were measured via applanation tonometry. Visceral fat mass was estimated via Dual-energy X-ray Absorptiometry (DXA). Statistical analyses were performed using

hierarchical regression analysis, controlling for sex, age and body mass index (BMI).

Results: A low PAL was associated with an elevated visceral fat mass ($\beta = -.179$, $P < 0.05$) and a trend towards elevated neutrophil counts ($\beta = -.13$, $P = 0.079$). Both a low PAL ($\beta = -.18$, $P < 0.05$) and elevated neutrophils ($\beta = 6.2$, $P < 0.05$) are associated with elevated central arterial stiffness, and higher visceral fat mass is associated with elevated peripheral arterial stiffness ($\beta = .392$, $P < 0.05$). Physical activity was not significantly associated with peripheral arterial stiffness, AI, RHR or MAP.

Conclusion: Our findings suggest that a low PAL and high visceral fat mass are both associated with declines in vascular function with ageing. Further investigations are required to elucidate the physiological mechanisms behind these associations.

We thank the BBSRC for support of the research with a doctoral training grant (BB/G018049/1).

96. Cardiac Aging in the Extremely Long-Lived Naked Mole-Rat

Kelly Grimes (P,N) and Rochelle Buffenstein
University of Texas Health Science Center San Antonio

Naked mole-rats (NMRs; *Heterocephalus glaber*) are extraordinarily long-lived mouse-sized rodents with a maximum lifespan of >31 years. These rodents maintain good health and reproductive potential even at ages equivalent to >90 year old humans. As such, NMRs provide a unique opportunity to explore mechanisms enabling prolonged maintenance of cardiac function. Like humans, NMRs have a lower than predicted heart rate for their body size (35 g). Interestingly, unlike in mice, and in keeping with their pronounced resistance to many stressors, isoflurane anesthesia has little depressive effect on NMR heart rates. Fractional shortening determined using echocardiography is much lower in NMRs than in physiologically age-matched mice. However, it is unchanged with age in NMRs, suggesting maintenance of cardiac contractile function. Low fractional shortening contributes to significantly lower NMR cardiac output under basal conditions. Dobutamine stress was used to simulate exercise-like conditions. This elicited a significantly greater increase in fractional shortening in NMRs than in mice, suggesting that NMRs have greater cardiac reserve than do mice. However, even under stress conditions, cardiac contractility in the NMR only just approached mouse baseline fractional shortening values. Surprisingly, young NMRs display enlarged cardiomyocytes and increased

collagen deposition in their ventricles when compared to physiologically age-matched mice. These histomorphometric data coupled with low fractional shortening commonly would be indicators of cardiac pathology if measured in mice or humans. However, it is unlikely that the young NMR cardiac phenotype is indicative of a pathological state and may instead reflect its phylogenetic history. Despite low levels of cardiac function, the NMR is able to achieve a lifespan longer than any other rodent. Thus it may have protective mechanisms allowing it to maintain cardiac function, and these will be the focus of future studies.

97. Ovariectomy and Vitellogenin-RNAi Extend Lifespan via Overlapping but Distinct Physiologies in Grasshoppers

John D. Hatle (P), Alicia G. Linquist, Jacob Burnett, Katherine A. Veleta, Derek R. Tokar, Joseph Canzano
University of North Florida

The mechanisms underlying longevity via reduced reproduction are not well understood (in comparison to dietary restriction). Here, we compare two means of directly reducing reproduction as a way of identifying the conserved physiological characteristics. The precursor to egg yolk protein, vitellogenin, is produced by the fat body, accumulates in the hemolymph, and is sequestered in the ovary. We have previously shown that ovariectomy increases lifespan 16%, reduces feeding 36%, doubles fat body mass, and increases levels of vitellogenin ~5-fold. Here, we compare ovariectomy to RNAi against vitellogenin. As a control for vitellogenin-RNAi, we injected RNAi against hexamerin90, an abundant storage protein in the hemolymph. Vitellogenin-RNAi reduced mRNA levels ~40-fold and doubled fat body mass. Further, vitellogenin-RNAi reduced ovarian mass ~4-fold, increased hemolymph vitellogenin ~10-fold, resulting in ~10-fold lower total reproductive proteins.

We next tested whether life-extension via ovariectomy and vitellogenin-RNAi was additive, using: 1) sham-operated & buffer-injected, 2) ovariectomized & buffer-injected, 3) sham-operated & hexamerin90-RNAi, 4) ovariectomized & hexamerin90-RNAi, 5) sham-operated & vitellogenin-RNAi, and 6) ovariectomized & vitellogenin-RNAi. All four treatments that reduced reproduction had decreased feeding. Ovariectomy increased lifespan 20% ($P = 0.016$), and vitellogenin-RNAi increased lifespan 18% ($P = 0.016$). Ovariectomy & vitellogenin-RNAi were not additive ($P = 0.002$), suggesting they act

through overlapping mechanisms. Despite this, ovariectomy and vitellogenin-RNAi are physiologically distinct, as patterns of hemolymph proteins differed. Ovariectomy increased levels of hexamerin270 (P=0.007) and hexamerin500 (P=0.002; two hemolymph storage proteins) yet decreased total anti-oxidant activity in the hemolymph (P=0.013), in comparison to sham-operated controls. In contrast, vitellogenin-RNAi increased levels of hexamerin90 (P=0.016) and decreased total anti-oxidant activity (P=0.038) in the hemolymph, in comparison to hexamerin90-RNAi controls. These results suggest that: 1) decreased feeding may be a consistent response to reduced reproduction, and 2) fat storage may be more important than protein storage, even for phytophagous animals.

Funded by NIH 2R15AG028512-02A1.

98. Protection of Protein Structure and Function in the Longest Lived Animal

Stephen Treaster¹ (P,N), Asish Chaudhuri², Steven Austad²

¹*Molecular Medicine, UTHSCSA;* ²*Barshop Institute for Longevity and Aging Studies, UTHSCSA*

Traditional aging models are short-lived, a useful trait for tracking changes over the course of their lifespan. However, it is within the exceptional long-lived models that we can expect to find the mechanisms necessary to resist aging, as evolution has provided them. To this end, we are utilizing a range of marine bivalve mollusk species, with lifespans ranging from under a decade to over five hundred years, in a comparative study to investigate the hypothesis that long life requires superior proteome stability. These ages can be individually determined by counting growth rings in the shell. This experimental system provides a unique opportunity to study closely related organisms with vastly disparate longevities, including the longest lived animal.

We are testing the long-lived bivalve's ability to maintain protein structure and function under various stressors, and identifying the macromolecules responsible for this protection. As protein homeostasis has been implicated in the aging process and age related diseases, these macromolecules could have dramatic medical value.

Preservation of protein function is measured by representative enzyme activity, such as GAPDH, when stressed in-vitro. Stressors include both oxidative and unfolding agents. Preservation of protein structure is measured by aggregation resistance as well as incorporation of

BisANS, a fluorescent probe that binds to hydrophobic pockets exposed as proteins unfold. Stress induced aggregation of endogenous proteins, as well as exogenous bait proteins is isolated by ultracentrifugation at 100,000g. The bait proteins used include medically relevant amyloid beta, super oxide dismutase, and GAPDH. To date, we have found that long-lived bivalves maintain protein function and prevent aggregation of the baits. Demonstrating the protection of these proteins and identifying the macromolecules facilitating enhanced proteostasis in the longest lived animal species could have dramatic importance to various age-related protein diseases.

99. Enhanced Protein Homeostasis Mechanisms in Naked Mole Rats Cells

Harrison Pride¹, Yiqiang Zhang², Rochelle Buffenstein², Peter Hornsby², Arlan Richardson², Viviana I. Perez¹ (P)

¹*Dept. Biochemistry & Biophysics; Linus Pauling Institute, OSU;* ²*Barshop Institute, UTHSCSA*

Phylogenic studies suggest that cells from long-lived species are more resistant to a variety of stressors than short-lived species. However, there is little information on the cellular mechanisms that give rise to increased resistance to stress. Our previous studies have shown that liver proteins from a long-lived species have lower levels of protein ubiquitination which is associated with increased proteasome activity, suggesting that mechanisms of protein quality control could play a critical role in assuring longevity of long-lived species. In this study, we evaluated whether autophagy and heat shock chaperones proteins (HSPs) are associated with longevity in rodents using skin fibroblasts isolated from mice and naked mole rats (NMR); two species that are similar in body size but differ almost 10 fold in longevity. Our results indicate that macroautophagy induced by serum-starvation is significantly enhanced in NMR compared to mouse which correlates with an inhibition of the mTOR pathway and increased LC3 conversion. We also found that several HSPs (e.g., Hsp90, Hsp70, Hsp40, Hsp 27) were significantly higher at both basal and after heat shock conditions. These observations suggest that NMR, a long-lived species, has increased mechanisms to ensure protein quality (autophagy and HSPs) and support the idea that protein homeostasis could play an important role in promoting longevity.

Financial support was provided by The Ellison Medical foundation.

100. Cytoprotection, Longevity, and Cancer Resistance in the Naked Mole-Rat

Kaitlyn N. Lewis (P,N) and Rochelle Buffenstein
UTHSCSA/Barshop Institute

Resistance to cytotoxins is a shared characteristic of many animal models of extended longevity. The longest-lived rodent, the naked mole-rat (~31y), is also extremely resistant to a wide array of xenobiotics in vitro, and exhibits no physiological or molecular declines during this extraordinarily long lifespan. Notably, no incidence of spontaneously occurring cancer has ever been reported in this species. We hypothesized that this profound broad-based toxin resistance was due to the nuclear factor-erythroid 2-related factor-2 [Nrf2] signaling cytoprotective pathway. Nrf2 is a transcription factor ubiquitously expressed in all tissues and is conserved from worms to humans. Nrf2 levels and half-life is regulated by kelch-like ECH-associated protein 1 [Keap1], which targets Nrf2 for ubiquitination and subsequent degradation via the proteasome. After a stressful insult (i.e. toxins, ROS), interactions between Nrf2 and Keap1 are inhibited and Nrf2 is able translocate into the nucleus, bind to the antioxidant response element [ARE] and thereby activate the transcription of >600 cytoprotective molecules, including those involved in detoxification, glutathione metabolism, and proteasome subunits. Largely studied with regards to cancer, Nrf2 has also been shown to interact with p53 and p21, playing a role in modulation of the cell cycle and cancer progression. We found that Nrf2-signaling activity showed a positive correlation with maximum lifespan in rodents with varying longevity. Interestingly, this was largely due to an inverse correlation with Keap1, the negative regulator of Nrf2. Unlike mice, both in vitro and in vivo studies reveal that naked mole-rats surprisingly show a decline in Nrf2-signaling activity after xenobiotic exposure, highlighting a potential disparate stress response that may be a critical component of extended healthspan and longevity.

101. C57BL/6 Lifespan Study: Age-Related Changes in Muscle Power Production and Contractile Velocity

Ted G. Graber (P,N), Jong-Hee Kim, LaDora V. Thompson
University of Minnesota Medical School-Twin Cities

The quantification of key outcome measurements in animal aging models is an important step preceding intervention testing and eventual translation. One such measurement, skeletal muscle

power generation (critical for movement and lower in old animals), has not been investigated for changes over the lifespan or for what contribution velocity provides. Therefore, the main purpose of this study was to calculate power output (force*velocity) over the male C57BL/6 mouse lifespan (2-32 months) and to determine the roles of force and velocity. We hypothesized force and velocity decreased with age; contributing to declining power. To test this hypothesis, we determined the force-velocity relationship (to derive power curves) of the EDL muscle (n=63) using in vitro contractile physiology to measure peak tetanic force (P0) and contractile velocity. We found an age-related change in the force-velocity relationship, with contractile velocity being significantly lower in old mice under heavily loaded conditions (60 - 90% of P0). In older mice, the power curves shifted down and to the left, indicating that the lower peak power generation was attained at lower P0%. Over the lifespan, peak power (pmax) declined more rapidly with a stronger correlation to age than did P0 (linear regression with age: pmax slope=-9.1, R=-0.66; P0 slope=-4.0, R=-0.56). Maximum unloaded velocity and P0 explained only part of the variability in pmax (multiple regression with power, r²=0.61). In contrast, velocity under heavy load (at 60, 80 and 90% of P0), age and P0 showed a much stronger correlation with pmax (from multiple regression: R=0.90). Our results indicate further investigation is needed to discover what other mechanisms contribute to power decline. The results also strengthen the concept that training interventions intended to improve power in the elderly should focus on activities designed to increase velocity of movement at higher percentages of maximum force.

102. A Novel Approach for the Quantification of Olfactory Acuity in a Murine Model

Keith Maslin (P,N), Samantha Rendon, Steven Austad
University of Texas Health Science Center San Antonio

Mouse urinary proteins (MUPs) contain unique genetic information relaying species, sex, and individual identity to other mice. These MUPs also carry metabolic information regarding reproductive and health status as well as territorial ownership. While a keen sense of smell is useful for determining if food is poisonous or spoiled, the detection of these specific proteins allow them to find kin as well as respond to mates, competitors and predators.

It is hypothesized that this ability to detect the presence of MUPs declines with age. To explore this hypothesis we chose a non-invasive behavioral method that tests the ability to discriminate between urine from wild derived mice and water. To identify the lowest dilution factor an animal can detect, scents are presented from lowest to highest concentration. Urine and water soaked pads were placed above the animal and time spent sniffing each pad was recorded manually. Results from 4, 20, 28, and 32 month old mice demonstrate that as animal's age they need an increasing concentration of urine to discern a difference.

Our current research utilizes a larger, custom built system to increase the separation between water and urine samples. These cages will be fitted with custom made lids which include two sample chambers and remove the distraction of food and water. Movement of the animal will be recorded by an infra-red beam grid system that can record time in each zone down to a fraction of a second, providing much more accurate data. This will also eliminate the need for human presence during testing allowing for the experiments to be blinded. A non-invasive method of characterizing such a critical sensory biomarker of aging will lead to a better understanding of current mouse models, as well as further characterization of commonly used frailty models.

103. Regulation of Mitochondrial Proteostasis by the Protein Oxidation Repair Enzyme MsrA

JennaLynn Styskal, Daniel Pulliam, Holly Van Remmen, Arlan Richardson, Adam Salmon (P)
Barshop Institute, UTHSCSA

Progressive decline in mitochondrial function is a hallmark of the aging process, though the causative mechanisms remain unclear. However, it is clear that maintenance of the mitochondrial proteome is essential to preserving mitochondrial respiration. A common challenge to protein quality control is oxidative stress; oxidation of proteins reduces their function and promotes unfolding and aggregation. The protein oxidation repair enzyme methionine sulfoxide reductase A (MsrA) plays a central role in preventing the accumulation of proteome oxidation. MsrA specifically repairs oxidized proteins by catalyzing oxidized methionine residues in proteins to the reduced form. The redox interaction between methionine and MsrA has been shown to act as a free radical sink that protects other amino acids in proteins from oxidation. Thus, altering MsrA expression broadly affects multiple forms of oxidative modifications but specifically modulates only protein oxidative modification. In

this study, we use novel MsrA transgenic mice to test whether overexpression of MsrA either specifically in mitochondria (mMsrA) or the cytosol (cMsrA) alters proteostasis or function of mitochondria. Mitochondria isolated from young mMsrA mice show increased ATP production in vivo suggesting improved respiratory function. Further, electron transport chain complex I and V activities are increased in mMsrA mice without concomitant increase in total protein levels. In contrast, mitochondria from cMsrA show no alterations in respiration or complex activities. We also find reduced levels of two common proteins oxidation markers (carbonyls and disulfides) in tissues from mMsrA mice and increased resistance to stress in mMsrA cells. These data show that reducing oxidative damage to the mitochondrial proteome can significantly improve mitochondrial function. We are currently testing whether overexpression of mMsrA slows age-related mitochondrial dysfunction as a possible means to prevent age-related disease.

104. Mitochondrial Overexpression of the Protein Oxidation Repair Enzyme MsrA Prevents Insulin Resistance

JennaLynn Styskal Hunnicutt (P,G)
University of Texas Health Science Center at San Antonio

Diabetes is currently one of the most prevalent diseases among the elderly. While aging is an independent risk factor for developing insulin resistance, the primary etiology of type 2 diabetes, the mechanisms by which this occurs aren't clear. Oxidative stress increases with aging and is also associated with insulin resistance and diabetes. A significant source of oxidative stress is adipose tissue expansion. Oxidative stress damages all molecules, but protein oxidation is particularly detrimental because oxidation can alter protein conformation and function. We previously showed that lack of the protein repair enzyme methionine sulfoxide reductase A (MsrA) in mice exacerbates insulin resistance caused by high fat feeding. MsrA repairs methionine sulfoxide residues to non-oxidized methionine, specifically regulating oxidation of proteins. This suggests that increasing protein oxidation repair may prevent insulin resistance. In this study, we use novel transgenic mouse models that overexpress MsrA either exclusively in mitochondria (MsrAmTG) or in cytosol (MsrAcTG) to test whether increased protein oxidation repair in either cellular compartment prevents insulin resistance. Chronic H₂O₂ treatment of primary mouse myotubes

reduces insulin-stimulated phosphorylation of insulin signaling proteins (insulin receptor and Akt). Using this model, we show MsrAmTG myotubes prevent the reduction in insulin signaling that occurs with oxidative stress. In contrast, myotubes from MsrAcTG mice are not protected from H₂O₂-induced insulin resistance. We also tested whether MsrAmTG prevents insulin resistance in vivo by feeding mice high fat (45%) diets. Overexpression of MsrA in mitochondria almost completely prevented insulin resistance (insulin tolerance tests) and preserved insulin signaling in tissues. Again, MsrAcTG showed no beneficial effect. These data suggest that improving protein oxidation repair specifically in mitochondria can prevent insulin resistance development with obesity. Future studies will determine whether MsrA directly regulates mitochondrial function and whether this could be a specific target to prevent insulin resistance with aging.

105. Heat Therapy Preserves Muscular Endurance in Aged Mice

Kylie Kavanagh (P), Marnie Silverstein, Ashley T. Wylie, Daniel C. Files, Carol E. Milligan, Stephen B. Kritchevsky
Wake Forest University School of Medicine

Age-associated sarcopenia has few therapeutic options. Heat shock proteins (HSPs) are molecular chaperones with roles in longevity and muscular preservation. Mechanisms purported include HSP70 mediated insulin sensitization, and HSP90 mediated nitric oxide synthase augmentation, together facilitating insulin-stimulated protein synthesis and increased muscle perfusion. We aimed to show elevating HSPs mitigates age-related sarcopenia. Aged C57/BL6 mice acclimated to a western diet were randomized into: geranylgeranylacetone (GGA;100mg/kg/d,n=9) to specifically induce HSP70, twice weekly dry-heat therapy for 20-30 minutes (HT,n=8) to non-specifically induce HSPs (including HSP70 and 90), or control mice (CTL,n=10). Assessments followed acclimation and at 8 weeks and included: treadmill performance, grip-strength, 2- and 4-limb hang times, body composition, glucose tolerance, muscle contractility, and muscle perfusion. No differences were seen in bodyweight, tissue weights, or body temperature. HT mice had significantly better glycemic control (p=0.008) and superior treadmill performance (p=0.03). Compared to baseline, heat treated mice ran for 23% longer, as compared only 9% longer in CTL and 4% less time in the GGA group. A trend

towards preserved hanging ability (muscular endurance) was seen in both GGA and HT mice (p=0.10 for 2-limb, p=0.12 for 4-limb). The change in hanging durations and treadmill work performed were significantly correlated (R=0.39, and R=0.42 for 2- and 4-limb tests respectively both p<0.05). Muscle power as assessed by grip strength decreased in all groups, and muscular force and fatigue induced by in situ peroneal nerve stimulation were not different between groups at study end. Heat treatment has a clear benefit on muscular endurance and metabolic state, but not power. Forthcoming results include measures of muscle innervation and fiber typing, body composition by computed tomography, muscle perfusion by microsphere dispersion, and HSP profiling. Initial results indicate that HT, with likely increases in both HSP70 and 90, are promising approaches for sarcopenia therapy in the aged.

106. Growth Hormone Receptor Knockout Mice Display Differences in DNA Methyltransferases and Interspersed Repeats

Armstrong, V.A. (P,N), Rakoczy, S., Brown-Borg, H.M.
University of North Dakota School of Medicine and Health Sciences

Methylation reactions are important for the establishment and maintenance of epigenetic methylation tags on DNA and histone molecules that are critical for the development and life-long function of an organism. Our previous work has shown the DNA methyltransferases (Dnmt1, Dnmt3a, Dnmt3b) are differentially expressed in the Ames dwarf and growth hormone transgenic (GHTg) murine liver compared to their wild-type counterparts suggesting that GH status may be involved. Differences in the hypomethylation of interspersed repeats in Ames dwarf and GHTg mice were also observed. Growth hormone binding protein knockout (GHRKO/BP) mice lack IGF1, contributing to their small size and increased longevity. We postulated that Dnmt transcription, hypomethylation, and interspersed repeat transcription differ in GHRKO/BP mice and wild type controls. Using McrPCR techniques and RT-PCR, we studied the hypomethylation and transcription of well-known interspersed repeats (LINE1, SINE B1, SINE B2, and IAP-LTR) at three age groups (3, 6 and 12 months). GHRKO/BP mice displayed age related differences in hypomethylation of SINE B2, LINE1, and IAP-LTR (p=0.0012, p<0.0001, and p=0.0691 respectively). Genotype was a factor only for the hypomethylation of LINE1 (p=0.0026). In

GHRKO/BP and GHtg mice, genotype transcriptional differences were observed in IAP-LTR and LINE1 (GHRKO: $p=0.0273, p=0.0059$, GHtg: $p=0.0672, p=0.0113$ respectively). In addition, transcriptional expression of all three catalytically active Dnmts (1,3a, and 3b) was studied in the GHRKO/BP mouse at 3, 12 and 24 months of age. Age was a factor in the expression of Dnmt1 ($p=0.003$), Dnmt3a ($p=0.0001$), and Dnmt3b ($p<0.0001$). Genotype was a major factor in the expression of Dnmt1 and Dnmt3a ($p=0.0079$ and $p=0.0085$ respectively). Dnmt1 expression exhibited a significant interaction between the two factors ($p=0.0473$.) These studies contribute to growing evidence of the importance of growth hormone on DNA methylation which we hypothesize may play an important role in the longer life span of growth hormone deficient mice.

107. The Age-Related Decline in Hemoglobin Concentration in Mice is Primarily Determined by Genetic Regulation of RBC Count

Kevin Flurkey¹ (P), Rong Yuan², Gary A. Churchill¹, Luanne L. Peters¹

¹The Jackson Laboratory Nathan Shock Center;

²Southern Illinois University School of Medicine

Circulating hemoglobin (Hgb) concentration is a valid biomarker of aging, age-related impairment, and mortality risk in mice. It has not been studied extensively. We determined Hgb concentration and related hematological parameters in 30 inbred mouse strains at 6, 12, and 18 months (4–8 mice per strain per sex, 60 genomes total). Hgb declined significantly from 6–12 months for 50% of the genomes (range, +7% to –12%; mean, –4.2%). This widespread reduction in mature adults reflects a normal — not pathologic — aging process. By 18 months Hgb had decreased significantly in 65% of the genomes (mean of all strains = –7.2%). We tested 23 of the genomes that were still healthy at 24 months; Hgb had significantly decreased in 78%, demonstrating that, over time, aging affects Hgb in a progressively broader range of genomes. Even at 24 months, however, Hgb had not decreased for 4 genomes (129, BLKS, WSB females; LP males), suggesting that certain genes may protect against Hgb aging.

Of the 30 genomes with diminished Hgb at 12 months, 26 expressed significant declines of either red blood cell (RBC) count or mean corpuscular hemoglobin (MCH) content; declines of both, however, occurred in only 4 of those 26 genomes, indicating that Hgb aging may be governed by 2 separate processes. After 12 months, continued reductions of Hgb were due primarily to

diminished RBC. Reticulocyte (RBC precursor) counts did not change from 6–12 months across strains, but it decreased by 4.6% from 12–18 months, about the same magnitude as RBC counts. Thus, Hgb aging in mice results from a progressively diminished RBC count that can be detected in mature adulthood in many strains and that affects an increasing number of genomes with age. From 12 months on, diminished Hgb concentration may result from limitations in RBC precursor production.

108. Role of Mitochondrial Matrix Protease ClpP in Mitochondrial Homeostasis, Metabolism and Aging

Deepa Sathyaseelan (P), Daniel Pulliam, Shauna Hill, JennaLynn Styskal, Michael Walsh, Yun Shi, Holly Van Remmen

Barshop Institute for Longevity and Aging Studies, San Antonio, TX

Mitochondrial dysfunction is an important contributor to aging and age-related diseases. Studies have shown that maintenance of mitochondrial homeostasis through the mitochondrial unfolded protein response (mtUPR), extends lifespan in *C.elegans*.¹ The mtUPR is a stress response pathway that activates transcription of nuclear-encoded mitochondrial chaperone genes to promote protein homeostasis in the mitochondria.² One key component of the mtUPR response is the mitochondrial matrix protease ClpP.² Importantly, inhibition of ClpP using RNAi attenuates mtUPR-mediated lifespan extension in *C.elegans* mit mutants.¹ This suggests a critical role of ClpP in the maintenance of mitochondrial homeostasis and longevity. However, no information is available about the function of ClpP in mitochondria or its role in lifespan in mammals. In the present study, we found that ClpP levels are lower in old wild type mice and that caloric restriction, an intervention that is known to increase lifespan, reverses the age related decline in ClpP levels in old mice. Similarly, we also found that ClpP levels are elevated in a long-lived mouse model of electron transport chain complex IV deficiency, *Surf1*^{-/-} mice. Furthermore, silencing of ClpP, *in vitro*, resulted in 25% decrease in cell viability, 1.2-fold increase in reactive oxygen species (ROS) levels and decreased oxygen consumption (28% and 18% decrease in basal and maximum respiration, respectively). Silencing of ClpP also attenuated insulin-stimulated Akt phosphorylation as well as fatty acid oxidation. Together, our study demonstrates for the first time the critical role of mitochondrial protease ClpP in

the maintenance of mitochondrial function, cellular metabolism and aging.

This work is supported by the American Heart Association Beginning Grant-in-Aid to D. S. and the Ellison Medical Foundation Senior Scholar Award to H. V. R.

1. Durieux, J., Wolff, S. & Dillin, A. *Cell* 144, 79-91 (2011).

2. Haynes, C. M. & Ron, D. J. *Cell. Sci.* 123, 3849-3855 (2010).

109. QTL Analysis of Lifespan in a Mouse

Model

Gary A. Churchill (P), Dan Gatti, Luanne Peters, Rong Yuan

The Jackson Laboratory Nathan Shock Center of Excellence in the Basic Biology of Aging

A four way reciprocal cross between mouse strains BTBR T+ t/J, C57L/J, MRL/MpJ and WSB/EiJ was created to study the effect of genetics on lifespan and health related parameters. 574 females were retained for this study. The mice were phenotyped at 6, 12 and 18 months for a variety of parameters, including complete blood counts, body weight, glucose and IGF1, and were allowed to age naturally. Mice from the WMCB cross direction were consistently larger, reached sexual maturity earlier, had higher levels of IGF1 and shorter lifespans than mice from the CBWM direction. WMCB mice also had lower white blood cell counts throughout life. We performed quantitative trait locus (QTL) mapping on the phenotypes at each time point. The phenotypes showed largely consistent QTL across time points. Body weight had a strong QTL on Chr 6. Weight gain from 12 to 18 months had a QTL on Chr 12. IGF1 had a strong QTL on Chr 1 at all time points. Several red blood cell related traits, including hemoglobin and hematocrit, had QTL on Chr 11 at several time points. White blood cell count had a QTL on Chr 13. Tail length, used as a surrogate for body size had a narrow QTL on Chr 1 which contains several promising candidate genes, including *Igfbp2* and *Tnfr1*. We will discuss the results of lifespan analysis (pending) and its relationship to other traits.

110. Compensatory Responses to Mitochondrial Complex IV Dysfunction in the Long-Lived Surf1 Knockout Mouse

Daniel Alan Pulliam (P,N), Deepa Sathyaseelan, Yuhong Liu, Shauna Hill, Holly Van Remmen
UTHSCSA/Barshop Institute

Increased mitochondrial dysfunction has been long been implicated in aging and age-related diseases.

However, inhibition of the electron transport chain (ETC) through genetic manipulation has been shown to increase the lifespan of yeast, *C. elegans*, *Drosophila*, and mice. In *C. elegans* this lifespan extension is influenced by reactive oxygen species, the mitochondrial unfolded protein response (mtUPR), hypoxia inducible factor 1 (HIF1), AMP-activated protein kinase (AMPK), and mitochondrial biogenesis. Here we show mechanisms resulting in increased lifespan in *C. elegans* mit mutants are conserved in the long-lived *Surf1* knockout mouse (*Surf1*^{-/-}). Deletion of *SURF1*, an ETC complex IV assembly protein, results in a 50-80% decline in complex IV. However, decline in ATP production with age is attenuated in the *Surf1*^{-/-} brain suggesting that function may be maintained with age.

Knockout of *SURF1* protein is associated with an activation of the mtUPR, a retrograde signaling response resulting in an increase in mitochondrial specific chaperones and proteases aimed at refolding misfolded proteins and degrading damaged proteins. Specifically the mtUPR-associated proteins Hsp60, ClpP, Lon protease are increased from 34-55% in brain, skeletal muscle and liver. Furthermore, the mtUPR is also increased in primary fibroblasts isolated from *Surf1*^{-/-} and wild-type mice following treatment with paraquat, a superoxide radical generator. Interestingly, the increase in mtUPR activation corresponded to cell survival with paraquat treatment. In vivo administration of diquat resulted in an attenuated increase in the oxidative damage. Additionally, *Surf1*^{-/-} mice have tissue-specific increases in other pathways implicated with longevity in *C. elegans* mit mutants including mitochondrial biogenesis, HIF-1 α and AMPK activation. Our data suggest that mitochondrial alterations induce activation of compensatory cellular response pathways that could contribute to increased longevity.

111. Long-Term Administration of Losartan Ameliorates Several Pathologies Associated with Sarcopenia in Mice

Tyesha N. Burks¹ (P,G), Ruth Marx-Rattner¹, Christopher W. Ward², Peter M. Abadir¹, Jeremy D. Walston¹, Ronald D. Cohn³

¹*Johns Hopkins University School of Medicine;*
²*University of Maryland School of Nursing;* ³*The Hospital for Sick Children, University of Toronto*

Sarcopenia, the physiological process of aging characterized by a critical loss of muscle mass and function, significantly contributes to morbidity and mortality in older adults. Considering the ability of

losartan to ameliorate the muscle architecture and regenerative potential of congenital diseases; its ability to restore the impaired regeneration of sarcopenic muscles; and its ability to protect sarcopenic muscles from disuse atrophy upon immobilization, we hypothesize that it may be used chronically to combat the loss of muscle mass and function characteristic of sarcopenia. The molecular mechanisms underlying sarcopenia are poorly understood, but we demonstrate that chronic treatment of losartan ameliorated several pathologies associated with sarcopenia in mice. Losartan reduced protein degradation evident by a reduction in the levels of atrogin protein and mRNA and resulted in an increase in the size of the individual myocytes. Treatment with losartan reduced oxidative stress levels as measured by decreased nitrotyrosine levels and a decrease in the levels of the antioxidant, catalase. Furthermore, losartan treatment affected mitochondria number and localization. The control mice had less mitochondria and more subsarcolemmal location as compared to more mitochondria with a more intermyofibrillar localization with treatment. Losartan also resulted in a shift of fiber type composition toward slow type I fibers and a more resistant to fatigue phenotype. Thus, blockade of the AT1 receptor using losartan appears to have clinical benefits to combat sarcopenia by mediating multiple molecular mechanisms associated with the loss of muscle mass and function.

112. Simple Syntheses of Diverse Polyphenolic Compounds – Facilitating Dissection of Multiple Modes of Activity

Vishal Birar, Angela Sheerin, Richard G.A. Faragher, Lizzy Ostler (P)
University of Brighton, UK

There is growing evidence that many of the deleterious processes of aging may be modulatable by simple chemical compounds. The potential to develop orally available anti-degenerative medicines has consequently excited intense interest from researchers in recent years. A wide variety of polyphenolic natural products, often isolated from “super-foods”, have been identified as potential lead compounds for anti-aging therapeutics. Such compounds have included examples of flavonoids, lignans and stilbenes. A common motif in such compounds is a central (trans-substituted) double bond positioned between two phenolic groups. It has been suggested that such compounds may exert positive effects via antioxidant activity. However, it should not be forgotten that many of these have multiple other

activities, including oestrogenic effects, and some can even interrupt DNA synthesis and repair via intercalation. Consequently, there is a need to dissect the diverse bioactivities of potential therapeutic compounds via detailed structure-activity relationship (SAR) studies. Accordingly we have established simple, robust and high-yielding syntheses to facilitate access to a broad range of structural variants of compounds containing this motif. Our syntheses place an emphasis on simple and rapid (<24h) reactions without the need for air sensitive reagents or complex purification strategies. Characterisation of the *in vitro* activity of the compounds synthesised to date is ongoing. Available compounds, synthetic methods and quantified activities will be presented.

113. Development of a Frailty Index in Aging Mice

Haiming Liu (P,N), Ted G. Graber, Lisa Ferguson-Stegall, LaDora V. Thompson
University of Minnesota

Frailty is a clinical syndrome observed during aging, which often predicts imminent mortality and poor prognosis. A standardized set of five relevant clinical indicators for human frailty has previously been defined: large unintentional weight loss, grip weakness, decreased walking speed, low activity level, and self-reported exhaustion with physical activity. However, a noninvasive mouse frailty index has not yet been developed. Therefore, the purpose of our study was to establish frailty criteria and develop a frailty index in mice that mimics clinical frailty indicators: weakness, walking speed, activity level and endurance. Each criterion, respectively, was measured using: inverted-cling grip test time, rotarod running speed, weekly voluntary wheel running distance, and a derived endurance score. First, we evaluated a cohort of eleven male C57BL/6 mice (27-28 months) using a cut-off point (1.5 standard deviations below the mean) for frailty within each measure. Second, we developed the frailty index. Frailty was defined if three or more of the criteria measures were below the cut-off. Whereas, mild frailty was designated if one or two fell below. Using this frailty index, one mouse of the cohort was designated as frail and one as intermediate frail. The frailty index detected a 9% incidence of frailty in our aging mouse cohort. This outcome is consistent with the prevalence of frailty in aging humans (6.7%), given the comparative human age of our mice (~80 years) was higher than the age in the human studies (65+). These results support our selection of frailty

criteria and the defined frailty index. Collectively, the results provide a potential standardized definition for frailty in mice that is consistent with the operational definition of frailty in humans. The frailty index thus has potential use in predicting mortality risk in mice and for testing interventions for frailty mitigation.

114. Functional Genomics of Stress Resistance and Longevity in Mice

Wallace S. Chick (P)

University of Colorado Denver

The link between stress resistance and extended life span was first developed in the nematode and has been confirmed in other species, including the mouse. In many cases, selecting for stress-resistance mutants concomitantly yields long-lived phenotype as well. Although this forward genetic is a very powerful genetic tool, it has largely been limited to lower organisms and invertebrates. Since one cannot effectively screen millions of mice for novel mutations, we have moved the selection into mouse embryonic stem (ES) cells, and have developed strategies allowing these cells to retain their ability to develop into an intact mouse. Mice developed from paraquat-resistant ES cells have retained the stress-resistant trait in fibroblasts. Using this ES cells screening strategy to derive long-lived mouse strains, we might be able to discover the mammal-specific causes of aging. We have gone well beyond our initial studies (Chick et al., 2009), and now use a transposon mutagenesis approach to easily identify the gene(s) mutated. Our initial screens have identified several genes not previously known to modulate stress resistance or aging in any species, as well as mutational hits previously reported to modulate aging in the nematode. The genes we have identified so far have roles in diverse physiological functions, such as nutrient transport, cell surface anchoring, tumor suppression, and inflammatory regulation. They could be immediate targets for therapeutic intervention. Overall, this is a highly efficient system to generate novel stress-resistant mouse mutants for functional genomic analysis of longevity and extended health span.

115. A Novel Role for the Immunoproteasome in Cellular Stress Response

Marcela Maldonado (P,G), Rebecca J. Kappahn, Neal Heuss, Dale S. Gregerson, Ching Yuan, Deborah A. Ferrington

University of Minnesota

Immunoproteasome is a multisubunit complex that is found in abundance in cells of the immune

system and to a lesser extent in non-immune tissues. A well-described role for immunoproteasome is in the generation of peptides for presentation on MHC class I molecules. However, immunoproteasome is upregulated in response to diseases or injury of retina and brain (Ethen C.M. et al 2007, Ferrington D.A. et al. 2008), suggesting its involvement in the cellular stress response. We have previously shown that cells deficient in immunoproteasome are more susceptible to oxidation-induced cell death, supporting a role for immunoproteasome in regulating NF- κ B response to stress (Hussong S.A. et al 2010). Our recent focus has been on defining the how the immunoproteasome is involved in regulating two key stress response pathways, NF- κ B and autophagy. The current study used retinal pigment epithelial (RPE) cells derived from wildtype and knock-out mice lacking either one (LMP2, *Imp2* $-/-$) or two (L7M1, *Imp7* $-/-$ /*mecl* $-/-$) catalytic subunits of the immunoproteasome. Our results show that cells deficient in the LMP2 subunit demonstrate substantial differences in the alternative pathway of NF- κ B signaling, as well as diminished response to autophagic stimuli. These results support a novel role for immunoproteasome in the cellular stress response.

116. Reproductive Mode Versus Environmental Temperature in the Senescence Switch of *H. oligactis*

oligactis

Samantha Rendón ^{1,2} (P,N), Vanessa Y. Soto¹, Natalia Podlutskaya¹, Kathleen E. Fischer ^{1,3}, and Steven N. Austad ^{1,2}

¹*Barshop Institute for Longevity and Aging Studies,*

²*Department of Cellular & Structural Biology,*

University of Texas Health Science Center San Antonio,

³*Department of Physiology, University of Texas Health Science Center San Antonio*

Hydra, a genus of freshwater polyps, is a simple cnidarian that has been studied for its remarkable regenerative abilities for more than two centuries. Long-term studies have suggested that hydra do not undergo senescence (Brien 1953; Martinez 1998). Their reputed immortality is thought to be attributable to their three distinct stem cell lineages: ectodermal epithelial stem cells, endodermal epithelial stem cells, and interstitial stem cells that allow for continual tissue renewal (Bosch 2008). *Hydra* species reproduce either by asexual budding or by the production of gametes. Typically, sexual reproduction occurs in times of environmental stress (Thorpe & Covich 2001). One species of hydra, *H. oligactis*, appears exceptionally promising for elucidating mechanisms of aging. There are several known

strains of this species. One strain (Japanese) has been reported not to age when reproducing through asexual budding at 18°C, but ages quickly when switches to sexual reproduction at 10°C (Yoshida et al 2006); other strains (European) do not reliably switch reproductive mode under this condition. Thus as an experimental system, this species can be used to determine the relative contributions of reproductive mode versus temperature in the switch from a non-aging to an aging phenotype. In order to determine the relative contributions of reproductive mode versus environmental temperature in the senescence switch of *H. oligactis*, we performed longitudinal studies on populations of both European and Japanese strains at normal rearing temperature (18°C) and at 10°C. Demographic, behavioral and physiological markers were used to assess senescence, operationally defined as an increase in mortality rate with age, and a decrease in budding (for animals still reproducing asexually), regeneration rate, contraction response, or prey capture ability. These measures in sum revealed that reproductive mode was the main contributor to the aging phenotype observed in the Japanese strain of *H. oligactis*.

117. Mice Harboring a Complex IV Mutation have a Distinct Metabolic Phenotype

Shauna Hill¹ (P,N), Daniel Pulliam², Deepa Sathyaseelan², Yuhong Liu², Holly Van Remmen²
¹UTHSCSA/Barshop Institute for Longevity and Aging Studies; ²Department of Cellular and Structural Biology, UTHSCSA

Preservation of mitochondrial function correlates with increased lifespan. However, studies in invertebrates and more recently in rodents have demonstrated that alterations in mitochondrial electron transport chain correlates with increased longevity. For example, inhibition of complex IV (cytochrome c oxidase, COX), an essential transmembrane protein complex in the mitochondrial respiratory electron chain, has been shown to extend lifespan in worms and flies. Similarly, mice lacking the COX assembly protein Surf1 show increased longevity associated with decreased adiposity and enhanced insulin sensitivity, despite 50-70% reduction in COX activity. Here we asked whether a mouse model of cytochrome c oxidase deficiency due to a mutation in the Sco2 gene, a copper chaperone that is required for the activity of COX would have similar metabolic phenotype as Surf1^{-/-} mice. A complete knockout of the Sco2 gene in mice is embryonic lethal, however mice harboring a Sco2 knock-out allele and a mutated Sco2 knock-in

(KI/KO) allele are viable, and have a 30-60% reduction in COX activity. We found that Sco2 KI/KO mice have increased fat mass (46%) and decreased lean mass (5%), compared to control littermates. Adipose tissue depot morphology and weights indicate that this increased fat mass phenotype is fat depot-specific. The Sco2 KI/KO mice have increased hepatosteatosis, elevated serum triglyceride (32%) and cholesterol levels (32%), and changes in circulating adipokine levels compared to wild-type controls. Interestingly, these alterations are associated with the development of insulin resistance in the Sco2 KI/KO mice. These findings counter to the metabolic phenotype of Surf1^{-/-} mice, illuminating the complex nature of mitochondrial dysfunction on physiology. Results from this study will further enhance our understanding of the role of complex IV in physiological outcomes due to mitochondrial dysfunction.

118. Short-Term Dietary Restriction Prevents Neurogenic Muscle Atrophy Through a Novel ROS/HDAC4 Mediated Mechanism

Michael E. Walsh¹ (P,N), Yuhong Liu², Holly Van Remmen¹

¹Department of Cellular and Structural Biology, UTHSCSA; ²Barshop Institute, UTHSCSA

Skeletal muscle atrophy can occur as a result of aging, disuse, neuromuscular disease, cachexia and muscular dystrophy. Age-related muscle loss, or sarcopenia, is the consequence of dysfunction along the entire motor unit, and several factors contribute to sarcopenia, including oxidative stress, neuromuscular junction defects and loss of muscle stem cells. Our laboratory has demonstrated a strong relationship between oxidative stress and muscle atrophy in mouse models of neuromuscular disease, including Sod1(G93A), Sod1^{-/-}, surgical models of neuromuscular disease as well as normal aging. However, it is not known how reactive oxygen species modulate the muscle atrophy machinery. One important mediator of neurogenic muscle atrophy is histone deacetylase 4 (HDAC4). HDAC4 is increased in neurogenic, but not myogenic, models of muscle dysfunction, and mice lacking HDAC4 in skeletal muscle are protected from muscle atrophy as a result of surgical denervation, suggesting that HDAC4 is a key mediator of neurogenic muscle atrophy.

Here we show that dietary restriction protects against muscle atrophy in a surgical model of denervation even when initiated after surgery. While the control-fed mice lost 18% of their gastrocnemius mass one week after surgery, the

dietary restricted mice lost only 9% (n=18-19, p<0.01). Consistent with this observation, dietary restriction protects against the loss of muscle fiber cross sectional area one week after surgery. Interestingly, dietary restriction prevented the increase in mitochondrial reactive oxygen species production after denervation and prevented the upregulation of HDAC4. Although the Erk1/2 signaling pathway has been implicated in regulating HDAC4 expression, we found increased phosphorylation of Erk1/2 in injured muscle from dietary restricted animals, suggesting dietary restriction potentially affects other Erk1/2 targets involved in muscle atrophy, including protein synthesis. Our data suggest that ROS-induced neurogenic muscle atrophy is mediated by HDAC4. Future experiments will determine whether a direct relationship exists between oxidative stress and HDAC4.

119. 2013 Wild Blueberry Health Study Report: Web Measurements are able to Detect 0.2%

Annual Memory Changes at 95% Confidence

H.A. Raphaelson¹, D.J. Burns¹, R.J. Coppings², D.L. Doiron¹, K.E. Gerstmann³, K. Hull⁴, A.C. Kokesh⁵, B.S. Kristal⁶, A. Pruchnicki⁷, B. Sachs⁸, R. Schnoll⁹, J.H. Vogelman¹⁰, A. Wetherell¹¹, R.J. Martin¹² (P)
¹Mansfield Senior Center, Mansfield, CT; ²Lane College, Jackson, TN; ³New York, NY; ⁴New Fairfield Senior Center, New Fairfield, CT; ⁵Raleigh, NC; ⁶Weymouth, MA; ⁷St. Luke's Roosevelt Hospital, New York, NY; ⁸HR Herbs, Teas and Gifts, Sherman, CT; ⁹Brooklyn College, Brooklyn, NY; ¹⁰Orentreich Foundation for the Advancement of Science, Inc., Cold Spring-on-Hudson, NY; ¹¹Defence Science & Technology Laboratory (Retired), UK; ¹²MMT Corporation, Sherman, CT

BACKGROUND: In 1979 Sir Alex Comfort described methods to measure age-associated change with a battery of 62 measurements. He never reached his goal of "leapfrogging dog or primate studies and testing non-hazardous [diets/nutrients] directly on man" partly because of costs. In 2004 and 2010 at this conference we presented simulated data to compare our measurement power with Comfort's battery and concluded both had similar power. In this report we present actual (rather than simulated) memory data with sufficient power for two-year studies if intervention effect-size is 0.2% or 1/5th of the 1% annual change seen in many biological functions.

METHODS: Ability to recognize nouns, verbs and proper names has been measured at BlueberryStudy.com since 2007 (nouns since 2002). Participants set their own measurement schedules and have conducted up to 216

measurements/year (average=62.1/year). 3,714 measurements from 60 annual data sets were subjected to non-parametric Kolmogorov-Smirnov (KS) and Mann-Whitney (MW) tests to determine if 0.2% year-to-year changes can be detected at 95% confidence.

RESULTS: Annual score increases averaged 0.701 percent (paired t-test p=0.0007) for a six-year cumulative error reduction of 33.0% during this period and an average score improvement of 4.22%. At 0.2% change, KS for 33 two-year data sets yielded p=0.001. MW required 920 data sets for p=0.0424. Average within-person, year-to-year, standard deviation was 4.31%. Within-person standard error was 0.9%. For data sets with over 50 measurements/year, median standard deviation was 2.6% (far below 5% used for simulated data in 2010) and standard error was 0.27% indicating that most participants can detect 0.5% changes in their own scores at 95% confidence if they conduct 50 measurements/year.

CONCLUSIONS: Two-year online Comfort-style memory intervention studies are feasible at less cost than expected. Similar power can be achieved in less time if different measurements are combined and/or pre-set data cleaning methods are applied.

120. 2013-2014 Study Protocol to Determine if High-Polyphenol, Wild Maine Blueberries can Postpone Frailty and Aging

D.J. Burns¹, B.S. Kristal², A. Pruchnicki³, A. Raphaelson⁴, B. Sachs⁵, R. Schnoll⁶, J.H. Vogelman⁷, A. Wetherell⁸, R.J. Martin⁹ (P),
¹Mansfield Senior Center, Mansfield, CT; ²Weymouth, MA; ³St. Luke's Roosevelt Hospital, New York, NY; ⁴Mansfield Senior Center, Mansfield, CT; ⁵HR Herbs, Teas and Gifts, Sherman, CT; ⁶Brooklyn College, Brooklyn, NY; ⁷Orentreich Foundation for the Advancement of Science, Inc., Cold Spring-on-Hudson, NY; ⁸Defence Science & Technology Laboratory (Retired), UK; ⁹MMT Corporation, Sherman, CT

National Institute on Aging-Interventions Testing Program successes and other studies involving blueberries, different polyphenols, losartan, melatonin and other interventions have increased longevity, reduced stroke and heart damage, inhibited cancer growth and provided diverse benefits for many tissues. These results suggest it is time to combine and optimize these benefits, coordinating step-by-step with participants and their physicians, to determine if progress toward frailty can be slowed or reversed on a large scale. To measure possible benefits, a consensus set of markers is needed to show that personal health

trajectories improve significantly during the intervention period. Since measured functions may change by 1% per year, markers should detect 0.2% annual changes at 95% confidence in order to document year-to-year aging-rate changes as small as 1/5th of 1%. Since CT-NY Wild Blueberry Study participants have measured annual changes as small as 0.2% since 2007 through repeated web measurements, these measures will be retained in our 2013-2014 protocol, along with new high-powered hearing and pattern matching measurements and more precise health/diet/activity diary analysis and voice analysis options. To include biochemical and other markers within the composite study end-point, the 1999-2010 CDC/NCHS Multiple Cause of Death (MCO) database will be our central reference data set since it provides 37,000,000 physician-assigned contributing causes of death which follow classic Gompertz-type kinetics and produce prediction-accuracy coefficients as high as 0.998. Within this MCO-framework, online measurements, regular checkup results, multi-level-OMICs data and online diary and voice analysis results will be merged using 300+ neural-machine-learning algorithms to quantify changes in each participant's health trajectory. This study will rely on a network of Connecticut/NY organizations including the Ice House of Danbury, HydroTechnologies [New Milford], Danbury C-Town, Sherman IGA and Cold Spring-on-Hudson [NY] Foodtown supermarkets, HR-Herbs, Teas and Gifts [Sherman], Citizen News [New Fairfield] and the Mansfield and New Fairfield Senior Centers.

121. Longevity Patterns of Four Long-Lived US Populations: Chinese-, Japanese-, Cuban- And Spanish-Americans

R.J. Martin¹ (P), H.A. Raphaelson², J.W. Ashford³
¹MMT Corporation, Sherman, CT; ²Mansfield Senior Center, Mansfield, CT; ³Stanford / VA Aging Clinical Research Center, Palo Alto, CA

BACKGROUND: Human health studies are often conducted without careful controls for divorce, ethnicity and other factors that can affect long-term health. To build a comparatively solid groundwork for longevity-intervention trials, we surveyed twenty five population groups represented within the Centers for Disease Control-National Center for Health Statistics (NCHS) Multiple Cause of Death data files for 2008-2010.

METHODS: Turbo Pascal software was developed to tally 2,600 possible three-character ICD10 codes used to describe underlying and contributing causes of mortality. Output includes

number of cases assigned each code and average longevity for each code in the presence and absence of divorce and other factors represented in the NCHS data files. To exclude or minimize effects of a variety of gender- and divorce-related factors, our primary endpoints were mortality and longevity of non-divorced women in each ethnic group. Results were validated by comparison with published NCHS totals for top ten causes of death.

RESULTS: Average 2008-2010 longevity for all twenty five groups was 79.87 years of age, not including those listed as divorced because divorce shortens survival by as much as eight years. Spanish-American women lived longest (83.46 years) followed by Cuban-Americans (82.34), Japanese-Americans (82.43), Chinese-Americans (81.25) and White-Americans (80.47). Mortality patterns in the four longest-lived groups showed relatively uniform longevity increases for all major ICD10 contributing causes of mortality compared to White-Americans (paired t-test $p < 0.02$; Wilcoxon signed-rank test $p < 0.002$). Graphs of average age for each major contributing cause of death, including infectious, endocrine/metabolic, mental, nervous system, renal, respiratory, circulatory and heart diseases, flu-pneumonia, diabetes, Alzheimer's, osteoporosis and neoplasms, generally show a one to three year advantage for the long-lived groups vs. all groups combined.

CONCLUSIONS: The relatively uniform longevity increase across ICD10 categories merits further study to determine if a common set of interventions can help prevent many different kinds of illness.

122. Systems Biology of Human Aging - Network Model 2013

John D. Furber (P)
Legendary Pharmaceuticals

This network diagram is presented to aid in conceptualizing the many processes of aging, the causal chains of events, and the interactions among them. Contemplation of this network suggests promising intervention points for therapy development. This diagram is maintained on the Web as a reference for researchers and students. Content is updated as new information comes to light.

www.LegendaryPharma.com/chartbg.html

At first glance the network looks like a complicated web. However, as a conceptual summary, in one view, we can see how most biogerontological processes relate to each other.

Importantly, examination of these relationships allows us to pick out reasonably plausible causal chains of events. Within these chains, we can see age-related changes or accumulations that appear to be promising targets for future therapy development.

The many observable signs of human senescence have been hypothesized by various researchers to result from several primary causes. Inspection of the biochemical and physiological pathways associated with age-related changes and with the hypothesized causes reveals several parallel cascades of events that involve several important interactions and feedback loops. This network model includes both intracellular and extracellular processes. It ranges in scale from the molecular to the whole-body level. Effects due to externalities, lifestyle, environment, and proposed interventions are highlighted around the margins of the network.

123. Effect of Dietary Restriction from Old on the Age-Related Changes of Skeletal Muscle

Keiko Odera (P) and Ryoya Takahashi

Dept. Biochem., Fac. Pharmaceut. Sci., Toho Univ

Dietary restriction (DR) extends lifespan in rodents and also slows the onset of age-related diseases. However, the effects of DR when performed at middle age or later have not been well investigated. Our previous studies in rats demonstrated DR initiated later in life reduces the content of oxidatively modified proteins, measured as protein carbonyls, in mitochondria from old rats. Thus, our findings suggest that DR initiated even relatively late in life can restore animal's youthful conditions, reducing the accumulation of altered proteins. Dietary restriction, however, may increase the risk of loss of muscle mass with age, especially in old age. We therefore investigated the effects of DR from old on the change of muscle weight and fiber size. DR was performed by every-other-day (EOD) feeding on weekdays. The regimen was started at 28 months of age and continued for about 3 months. The body weight of the old rats was reduced by about 35% at the end of the experiment. Although the weights of soleus (SOL) and gastrocnemius (GC) muscles in control rats were decreased during the three-month DR, no effect of DR was observed in the weights of these muscles. The number and area of type II fibers of SOL and GC muscles were also decreased with age but again DR did not affect these changes. Thus, DR from old have no apparent negative effect on the degenerative loss of skeletal muscle mass of rats with age.

124. A Mitochondrial ATP Syntase Interacts with Macronutrients to Modulate Lifespan in *Drosophila*

Xiaoping Sun (P,G), Yolitz Jason, Yaning Sun and Sige Zou

Functional Genomics Unit, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD 21224

Aging is modulated by genetic and environmental factors and accompanied by expression changes in numerous age-related genes. Nutrient balance has profound effect on healthspan and lifespan. Diet composition is a critical determinant of lifespan. However, the relationship between nutrient imbalance and age-related changes and its impact on aging remain elusive. Here we investigated how age-related genes are involved in lifespan response to diet composition in *Drosophila*. We found that mitochondrial ATP synthase subunit d (ATPsyn-d) is post-transcriptionally regulated by age and diet. ATPsyn-d knockdown by RNAi extended lifespan in flies fed low carbohydrate-to-protein (C:P) diets, but not in flies fed high C:P ratio diets. This lifespan extension was associated with broad transcriptional changes in genes involved in metabolism, proteostasis and innate immune response. ATPsyn-d knockdown reduced phosphorylation of S6 kinase, a component of Target-of-rapamycin (TOR) signaling. Consistent with the biochemical data, ATPsyn-d knockdown did not further extend lifespan in flies fed rapamycin, a drug suppressing TOR signaling and promoting longevity. Our findings suggest that ATPsyn-d modulates lifespan and antagonizes detrimental effects of nutrient imbalance through regulating TOR signaling. This study demonstrates a role of age-related post-transcriptional regulation of mitochondrial genes in animals' response to diet composition. Our findings reveal the contribution of age-related changes to nutrient imbalance and a novel link between post-transcriptional regulation of a mitochondrial gene and TOR signaling.

125. Flipping the Switch: How Hormetic Stress Resistance Proteins Influence Metabolism

Sophia Rose Levan (P,N), Evi Mercken, Jess Curtis, Michel Bernier, Rafael de Cabo

Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, USA.

Caloric restriction (CR) has been shown to increase lifespan and improve health in animal models. NQO1 and Nrf2 are oxidative stress response proteins that are upregulated under CR. It has been hypothesized that Nrf2 contributes to the anti-

cancer effects of CR, while NQO1 may be responsible for improved insulin sensitivity. However, the effects of NQO1 and Nrf2 on metabolism remain unknown. The purpose of this study was to determine whether NQO1 and/or Nrf2 are responsible for the positive effects of CR on metabolism. Here, we show that Nrf2-KO cells and mice exhibited an increase in mitochondrial respiration and fatty acid metabolism and that these changes in metabolism may be due to regulation of the Sirt1 pathway. We found that NQO1-KO cells had improved aerobic glycolysis, while Nrf2-KO cells exhibited more efficient mitochondrial respiration and increased expression and activation of proteins in the Sirt1 pathway. These changes in metabolism extended to animal models. Nrf2-KO mice had significantly lower body weights and increased fat metabolism. Microarray data demonstrated that changes in metabolism in Nrf2-KO and NQO1-KO mice were due to significant changes in gene expression. Our results demonstrate that NQO1 has a positive effect on metabolism, increasing mitochondrial respiration and fatty acid metabolism through possible upregulation of the Sirt1 pathway. We anticipate our study to be a starting point for a more detailed examination on the influence of NQO1 on metabolism and the Sirt1 pathway.

126. The Stress Response Gene “Fit” for Lifespan Regulation in *Drosophila*

Jinhwan Lim (P,G), Xiaoping Sun and Sigge Zou
Functional Genomics Unit, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD 21224

Oxidative stress has been implicated in various aspects of aging, but intrinsic protective pathways against cellular stress that affect lifespan remain unclear. The goal of this study is to investigate the role of stress response genes in modulating lifespan. The *Drosophila* gene called female-specific independent of transformer (fit) is known to be involved in the cold stress and the innate immune response. However, molecular function of fit is largely unknown. Here we investigated the role of fit in modulating lifespan in *Drosophila*. We found that knocking-down fit by RNA interference significantly extended the lifespan of male flies. This lifespan extension was associated with increased resistance to paraquat-induced acute oxidative stress. Consistent with stress resistance data, fit knockdown up-regulated the expression of various oxidative stress response genes, including dFOXO and Jafrac1, a *Drosophila* homologue of human peroxiredoxin 2, relative to age-matched controls. We also found that fit knockdown

increased both mitochondrial protein content and citrate synthase activity when compared to age-matched controls. Taken together, these findings suggest that fit is involved in modulating lifespan by influencing oxidative stress response pathways and mitochondrial biogenesis.

127. Cranberry Interacts with Dietary Macronutrients to Modulate Lifespan in *Drosophila*

Yaning Sun (P,G), Cecilia Wang, Jason Yolitz, Xiaoping Sun, Thomas Alberico, Mara Laslo and Sigge Zou
Functional Genomics Unit, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD 21224

Cranberry (*Vaccinium macrocarpon*) contains rich amount of bioactive phytochemicals and has been shown to provide numerous health benefits to humans. However, the effect of cranberry as a dietary supplement on lifespan has not been extensively evaluated. Here we investigated the effect of a cranberry-containing botanical on lifespan and healthspan in *Drosophila*. Specifically we fed flies with the cranberry extract under three sugar-yeast based dietary conditions, standard, high sugar-low protein (HS-LP) and low sugar-high protein (LS-HP). We found that 2% cranberry could extend the lifespan of female flies on the standard diet and more prominently on the HS-LP diet but not the LS-HP diet. Lifespan extension induced by cranberry was associated with increased expression of oxidative stress and heat shock response genes, including *Fer1HCH* involved in iron homeostasis, and *Peroxiredoxin 5*, a redox gene. Moreover, cranberry improved survival of *sod1* knockdown flies but did not increase flies' resistance to paraquat-induced acute oxidative stress. Cranberry also improved survival of dfoxo null flies on the HS-LP diet and slightly extended lifespan of flies fed a high fat diet. These findings suggest that cranberry can promote healthy aging likely by increasing stress response in *Drosophila*. Our results also stress the importance of considering diet composition in designing interventions for promoting healthy aging in humans.

128. Metformin Improves Healthspan and Lifespan in Mice

Hector H. Palacios (P,N), Alejandro Martin-Montalvo, Evi M. Mercken, Sarah J. Mitchell, Michel Bernier and Rafael de Cabo
Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, USA.

Metformin is a drug commonly prescribed to treat type 2 diabetes. Here, we show that long-term treatment with metformin (0.1% w/w in diet) starting at middle age extends healthspan and lifespan in male mice, while a higher dose (1% w/w) was toxic. Treatment with metformin mimicked some of the benefits of calorie restriction, such as improved physical performance, increased insulin sensitivity, and reduced LDL and cholesterol levels without a decrease in caloric intake. At a molecular level, metformin increased AMP-activated protein kinase activity and increased antioxidant protection, resulting in reductions in both oxidative damage accumulation and chronic inflammation. Our results indicate that these actions may contribute to the beneficial effects of metformin on healthspan and lifespan. These findings are in agreement with current epidemiological data and raise the possibility of metformin-based interventions to promote healthy aging.

129. Cytochrome B5 Reductase 3 Increases Lifespan Through the Poly-unsaturation of Fatty Acids and Improvement of Mitochondrial Performance

Vincent Gutierrez (P,N), Alejandro Martin-Montalvo, Hector H. Palacios, Michel Bernier and Rafael de Cabo
Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, USA.

Understanding the mechanisms by which metabolism is controlled is critical in order to achieve therapeutic strategies for the treatment of metabolic diseases and aging. Cytochrome B5 reductase 3 (CYB5R3) is a major reductase that required for the elongation and unsaturation of fatty acids and cholesterol synthesis that has been associated with a protective effect against metabolic disorders. We generated CYB5R3 transgenic mice to investigate the function of CYB5R3 in mice metabolism. When overexpressed, CYB5R3 improved several metabolic parameters resulting in lifespan extension. CYB5R3 transgenic mice accumulate of highly poly-unsaturated fatty acids which is associated with an overall improvement of mitochondrial function and decreased oxidative damage that promote the health benefits. These findings indicate that CYB5R3 plays a critical role mice metabolism and represent a new target in the study of genes that control the lifespan.

130. Improved Glucose Homeostasis by NQO1, A New Insulin Receptor Target

Alejandro Martin-Montalvo (P,G), Hector H. Palacios, Vincent Gutierrez, Jessica M. Curtis, Sophie Levan, Michel Bernier and Rafael de Cabo
Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, USA.

Understanding the mechanisms by which obesity leads to impaired insulin action is critical in order to achieve therapeutic strategies for the treatment of chronic metabolic diseases. NAD(P)H: Quinone oxidoreductase 1 (NQO1) is an antioxidant protein that detoxifies pro-oxidant molecules associated with the development of cancer and diabetes, but its role in metabolism remains unknown. We generated NQO1 transgenic mice to investigate the physiological function of NQO1 and we unveiled a novel role for NQO1 in glucose homeostasis. Overexpression of NQO1 conferred increased insulin sensitivity and protection from diet-induced morbidities. Insulin administration led to a rapid increase in NQO1 Tyr-43 and Tyr-76 phosphorylation promoted by the insulin receptor, followed by its translocation from the plasma membrane to the cytosol. Our findings identify a metabolic role of NQO1 in the insulin signaling cascade and support the notion that targeting NQO1 is an attainable strategy for the treatment and prevention of metabolic disorders.

131. Are Healthspan and Longevity Necessarily Coupled in Rodent Studies?

Sarah Mitchell(P,G) and Rafael de Cabo
Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, 251 Bayview Blvd., Suite 100, 9th Floor, Baltimore, MD 21224

Aging results in a progressive decline in all organ systems having a negative impact on reproductive, cognitive, physical, metabolic function and survival. Understanding the mechanisms underlying these processes has become one of the primary focuses in the field of gerontology. For decades the goal of rodent studies was to identify interventions that lead to increases in both mean and maximal lifespan paying little attention to the impact of that particular intervention on overall health and wellbeing of the organism. The aim of all these studies was to ultimately translate these findings to humans. However, whether healthspan and lifespan are necessarily coupled in rodent studies is the question that this talk will address. Here we will present an overview of various rodent studies conducted in our laboratory using different dietary manipulations that had a positive impact on

healthspan, lifespan and both. Results include responses to oral glucose tolerance tests, locomotor activity in behavioral testing and the effects of the interventions on longevity.

132. The SIRT1 Activator SRT1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet

Michel Bernier¹ (P), Sarah Mitchell¹, Alejandro Martin-Montalvo¹, Evi M. Mercken¹, James Ellis², George Vlasuk², Rafael de Cabo¹

¹*Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD and* ²*Sirtis, a GSK company, Cambridge, MA*

The prevention or delay of the onset of age-related diseases prolongs survival and improves quality of life while reducing the burden on the health care system. Activation of sirtuin 1 (SIRT1), a NAD⁺ deacetylase, improves metabolism and confers protection against physiological and cognitive disturbances in old age. SRT1720 is a specific SIRT1 activator that has health and lifespan benefits in adult mice fed a high-fat diet. Here, we show that SRT1720 extends lifespan, delays the onset of age-related metabolic diseases, and improves general health in mice fed a standard diet (SD). A reduction in body weight and fat mass without changes in food consumption and fat-to-lean ratio was observed in SRT1720-treated mice fed a SD. There was improvement in muscle function and motor coordination over the life of SD-fed animals maintained on SRT1720. Cataract formation and glucose disposal after an oral glucose tolerance test were significantly reduced following SRT1720 supplementation. SRT1720 improved insulin sensitivity while lowering circulating total cholesterol and LDL levels. Gene expression analysis was performed in liver and muscle cDNAs and revealed potent suppression of inflammatory responses by SRT1720. Western blotting and phosphoantibody arrays were carried out in wild-type and *Sirt1* gene knockout MEFs incubated with SRT1720. The results showed that SRT1720 induced alteration in the phosphorylation status of key proteins implicated in NF- κ B activation in a SIRT1-dependent manner. Combined with our previous work, the current study further supports the beneficial effects of SRT1720 on health across the lifespan in mice.

This work was supported by the NIA Intramural Research Program and conducted under a CRADA agreement with GSK

133. Resveratrol Improves Adipose Insulin Signaling And Reduces The Inflammatory

Response In Adipose Tissue Of Rhesus Monkeys On A High-Fat, High-Sugar Diet

Irene Alfaras¹ (P,G), Yolanda Jimenez-Gomez¹, Julie A. Mattison¹, Kevin J. Pearson^{1,2}, Alejandro Martin-Montalvo¹, Hector H. Palacios¹, Joseph A. Baur³, Jonathan S. Bogan⁴, Michel Bernier¹, and Rafael de Cabo¹

¹*Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD,* ²*Graduate Center for Nutritional Sciences, University of Kentucky, Lexington, KY,* ³*Department of Physiology, Institute for Diabetes, Obesity, and Metabolism, University of Pennsylvania, School of Medicine, Philadelphia, PA,* ⁴*Section of Endocrinology, Department of Internal Medicine, and Department of Cell Biology, Yale University School of Medicine, New Haven, CT*

Obesity is associated with a chronic, low-grade, systemic inflammation that may contribute to the development of insulin resistance and type 2 diabetes. Resveratrol, a natural compound with anti-inflammatory properties, is shown to improve glucose tolerance and insulin sensitivity in obese mice and humans. Here we tested the effect of a 2-year resveratrol administration on the pro-inflammatory profile and insulin resistance caused by a high-fat, high-sugar (HFS) diet in white adipose tissue (WAT) from rhesus monkeys. Eighty mg/day of resveratrol for 12-month followed by 480 mg/day for the second year decreased adipocyte size, increased sirtuin 1 expression, decreased NF- κ B activation and improved insulin sensitivity in visceral but not subcutaneous WAT from HFS-fed animals. These effects were reproduced in 3T3-L1 adipocytes cultured in media supplemented with serum from monkeys fed HFS +/- resveratrol diets. In conclusion, chronic administration of resveratrol exerts beneficial metabolic and inflammatory adaptations in visceral WAT from diet-induced obese monkeys.

This work was funded by the NIA Intramural Research Program, the Office of Dietary Supplements, NIH, and by the NIH R01 DK075772 (to J.S.B.).

134. Resveratrol Supplementation Offers Neuroprotection in Rhesus Macaques Fed a High-Fat, High-Sugar Diet

Shakeela J. Faulkner¹ (P,N), Joanne S. Allard², Julie A. Mattison¹, Kevin J. Pearson³, Jessica Curtis¹, Michel Bernier¹, Rafael de Cabo¹

¹*Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, MD,* ²*Department of Physiology and Biophysics, Howard University College of Medicine, Washington, DC, and* ³*Graduate Center for Nutritional Sciences, University of Kentucky College of Medicine, Lexington, KY*

Diets rich in saturated fat and refined sugar are largely responsible for the increased incidence of obesity seen today. In addition to its deleterious effects on peripheral systems, obesity has adverse effects on brain health and function, and growing evidence substantiates it as a risk factor for cognitive impairment. Inclusion of the plant-derived polyphenol resveratrol into the diet has been shown to have a myriad of beneficial biological effects, including cardioprotection as well as anti-carcinogenic and anti-inflammatory actions in several animal models. Studies in rodent models also show that resveratrol improves amyloid beta (A β) clearance and reduces plaque pathology, supporting a role for resveratrol as a neuroprotectant. Using rhesus macaques, a nonhuman primate model, we show that resveratrol supplementation added to a high-fat, high-sugar diet (HFS) alters gene expression pathways related to amyloid biogenesis and degradation, synaptic transmission, axon injury, and oxidation-reduction processes in the brain temporal neocortex. Validation of the gene microarray was performed with select target genes by quantitative PCR analysis. The study on the effect of resveratrol supplementation on *ex vivo* insulin stimulation using brain slices from HFS-fed monkeys is currently underway. Our results demonstrate that resveratrol confers protection against central neuroinflammation and related adverse effects associated with consumption of a high-fat, high-sugar diet in a nonhuman primate model.

This work was supported by the NIA Intramural Research Program and the Office of Dietary Supplements.

135. Regulation Of Skeletal Muscle Regeneration By Diet And Age

Jessica Curtis¹(P,G), Shakeela Faulker¹, Vincent Gutierrez¹, Cuong Nguyen¹, Robert Wersto¹, Amy Wagers², Luigi Ferrucci¹, and Rafael de Cabo¹

¹*Translational Gerontology Branch, National Institute on Aging, National Institute of Health, Baltimore, MD*

²*Harvard Stem Cell Institute, Harvard Medical School, Cambridge, MA*

Maintenance of skeletal muscle regenerative capacity is crucial for preservation of muscle mass and function with age. Skeletal muscle precursor (SMP) cells are myogenic stem cells that play a predominant role in muscle regeneration. These cells are located beneath the basal lamina of the myofiber and respond to tissue injury with activation, differentiation and fusion into an existing myofiber. The current study assessed the

impact of age and diet on SMP content and function. By analyzing male C57Bl/6 mice aged 18-100 weeks on a standard ad libitum diet, it was found that the SMP population decreases by 20-60% with age, depending on the muscle group. The greatest decline was found in the triceps brachii, which is composed predominantly of Type IIb fibers. Furthermore, the regenerative capacity of isolated cells was impaired in older mice, as measured by proliferation and differentiation of SMP cells into myofibers.

Diet composition is a major determinant of metabolic health. Reduced caloric intake prevents weight gain, insulin resistance, atherosclerosis, cardiovascular disease, and even extends lifespan. To specifically investigate the role of diet on skeletal muscle health, male C57Bl/6 mice were fed ad libitum, 40% calorie restricted (CR), or high fat diets. After 20 weeks on these diets, stem cell abundance was assessed by flow cytometry. Surprisingly, diet composition had profound effects. The total abundance of stem cells in the muscle of high fat diet fed animals was markedly reduced compared to ad libitum animals. Conversely, calorie restricted mice showed substantial increases in the total population of skeletal muscle stem cells. Changes of *in vivo* abundance were matched by *in vitro* proliferative capacity. These findings suggest that diet composition plays a large role in maintenance of skeletal muscle mass and regenerative potential, and calorie restriction or pharmacological CR mimetics may be a feasible intervention to boost regenerative potential in the elderly or sarcopenic humans.

136. No Longer Limber: A Sarcopenic Tale in Mammals

Jordan J Licata (P,N), Evi M Mercken, Julie A Mattison and Rafael de Cabo

Translational Gerontology Branch, National Institute on Aging/NIH, 251 Bayview Blvd., Suite 100, 9th Floor, Baltimore, MD 21224

Aging is associated with a loss of muscle mass, strength, and function, a condition known as sarcopenia. Sarcopenia is conserved across species, from rodents to humans, yet the impact of aging on muscle wasting may differ. Due to this, models of sarcopenia and any effective therapy gained from understanding these models may not be translatable to humans. There are benefits to using either rodent or nonhuman primate models to investigate age-associated muscle loss, yet the question still remains as to which will most closely mimic the changes observed in human muscle atrophy. For

these reasons, furthering our understanding of the molecular mechanisms leading to sarcopenia in humans and across species will provide new insight for more effective interventions and new therapies. Thus, the goal of this study is to examine the transcriptional response to aging in skeletal muscle of different species. For this, we employed oligonucleotide-based arrays. We found common key regulatory pathways of the mitochondria to be altered with age across different species.

American Aging Association Membership Directory* - 2013

Rozalyn Anderson, PhD
University of Wisconsin-Madison
Email: rmanderson5@wisc.edu

Robert M. Anson, PhD
Community College of Baltimore County
Email: anson@jhu.edu

James Appleby, BS, MPH
Gerontological Society of America
Email: jappleby@geron.org

Arthur K. Balin, MD, PhD, FACP, FAAA
Chesley Office Campus
Email: akbalin@balin.com

Andrzej Bartke, PhD, FAAA
Southern Illinois University, School of Medicine
Email: abartke@siumed.edu

David Bartlett
University of Birmingham
Email: dbb984@bham.ac.uk

Arsun Bektas
National Institute on Aging/NIH
Email: bektasar@mail.nih.gov

Elliot Bergman, PhD
ChemLife Sciences
Email: ebergman2@earthlink.net

Benjamin Best, President
Email: contact2@benbest.net

Paula Bickford, PhD, FAAA
University of South Florida
Email: pbickfor@health.usf.edu

Jeffrey B. Blumberg, PhD, FAAA
Tufts University
Email: jeffrey.blumberg@tufts.edu

Gregory J. Brewer, PhD
Southern Illinois University School of Medicine
Email: gbrewer@siumed.edu

Holly Brown-Borg, PhD
University of North Dakota
Email: holly.brown.borg@med.und.edu

Tyesha Burks, PhD
Johns Hopkins University School of Medicine
Email: tburks1@jhmi.edu

Christy S. Carter, PhD
University of Florida
Email: ccarter@aging.ufl.edu

Kiran Chaudhari
UNT Health Science Center
Email: kchaudha@live.unthsc.edu

Ying Chen, PhD
Avon Products
Email: ying.chen@avon.com

Wallace Chick
University of Colorado Denver
Email: wallace.chick@ucdenver.edu

Mark R. Collins
Glenn Foundation for Medical Research
Email: mrc@glennfoundation.org

Aubrey de Grey, PhD, FAAA
SENS Research Foundation
Email: aubrey@sens.org

Maria De Luca, PhD
University of Alabama at Birmingham
Email: mdeluca2@uab.edu

Ward Dean
Email: warddeanmd@gmail.com

Varsha Desai, PhD
NCTR
Email: varsha.desai@fda.hhs.gov

Yuqing Dong, PhD
Clemson University
Email: ydong@clemson.edu

Jeffrey Dudycha, PhD
University of South Carolina
Email: dudycha@biol.sc.edu

Gregory M. Fahy, PhD, FAAA
Intervene Biomedical
Email: nooshinfahy@sbcglobal.net

Yimin Fang
Southern Illinois University
Email: yfang@siu.edu

Deborah A. Ferrington, PhD
University of Minnesota
Email: ferri013@umn.edu

Kathleen Fischer, PhD
UTHSCSA, Barshop Institute
Email: fischerke@uthscsa.edu

Michael J. Forster, PhD
University North Texas Health Sci. Ctr.
Email: michael.forster@unthsc.edu

Andrew Froehle, PhD
Wright State University
Email: andrew.froehle@wright.edu

John D. Furber,
Legendary Pharmaceuticals
Email: johnfurber@legendarypharma.com

Kelly Grimes, BS
UTHSCSA
Email: grimeskm@uthscsa.edu

Tory M. Hagen, PhD
Oregon State University
Email: tory.hagen@oregonstate.edu

Ryan T. Hamilton, PhD
University of Texas Health Science Center San Antonio
Email: hamiltonrt@uthscsa.edu

Linda Harootyan
The Gerontological Society of America
Email: harootya@geron.org

Peggy Harris
Case Western Reserve University
Email: Peggy.Harris@case.edu

John D. Hatle, PhD
University of North Florida
Email: jhatle@unf.edu

Kevin High
Wake Forest University Health Sciences
Email: khigh@wfubmc.edu

John O. Holloszy, MD, FAAA
Washington University School of Med.
Email: jhollosz@wustl.edu

Donna J. Holmes, PhD
Washington State University
Email: djholmes@wsu.edu

Peter J. Hornsby, PhD
University of Texas Health Science Center
Email: hornsby@uthscsa.edu

Stacy Hussong, PhD
University of Texas Health Science Center
Email: hussong@uthscsa.edu

Yuji Ikeno, MD, PhD
University of Texas Health Science Center
Email: ikeno@uthscsa.edu

Donald K. Ingram, PhD, FAAA
Pennington Biomedical Research Center
Email: Donald.Ingram@pbrc.edu

Matt Kaeberlein, PhD
University of Washington
Email: kaeber@u.washington.edu

Yasushi Kasahara, PhD
Showa University School of Medicine
Email: yashikasahara@aol.com

Kylie Kavanagh, DVM, MS, MPH
Wake Forest University
Email: kkavanag@wfubmc.edu

David Kekich
Maximum Life Foundation
Email: kekich@maxlife.org

Jae-Sung Kim, PhD
University of Florida
Email: jae.kim@surgery.ufl.edu

Gwendalyn King,
University of Alabama at Birmingham
Email: gdking@uab.edu

Steve Kohama, PhD
ONPRC/OHSU
Email: kohamas@ohsu.edu

Mina Konigsberg, PhD
Universidad Autonoma Metropolitana
Email: mkf@xanum.uam.mx

Christiaan Leeuwenburgh, PhD
University of Florida
Email: cleeuwen@aging.ufl.edu

George M. Martin, MD
University of Washington
Email: gmmartin@uw.edu

Julie Mattison, PhD, FAAA
NIA
Email: mattisonj@mail.nih.gov

David Melzer
University of Exeter Medical School
Email: david.melzer@pms.ac.uk

Simin Nikbin Meydani, DVM, PhD, FAAA
Tufts University
Email: simin.meydani@tufts.edu

Karl Miller, Research Assistant
University of Wisconsin-Madison
Email: knmiller2@wisc.edu

Mark Moss, PhD
Boston University School of Medicine
Email: markmoss@bu.edu

Keiko Odera, PhD
Toho University
Email: k-odera@phar.toho_u.ac.jp

Alfred (Roc) Ordman, PhD
Beloit College, Biochemistry Program
Email: ordman@beloit.edu

Elizabeth Ostler, PhD
University of Brighton
Email: e.ostler@bton.ac.uk

Mary Ann Ottinger, PhD
University of Maryland
Email: maotting@umd.edu

Daniel Paredes
National Institute of Health/NINDS
Email: paredesd@ninds.nih.gov

Kevin Pearson
University of Kentucky
Email: kevin.pearson@uky.edu

Viviana Perez
Oregon State University
Email: viviana.perez@oregonstate.edu

Kevin Perrott
SENS Foundation
Email: kevin.perrott@kevsplace.net

George Perry, PhD
University of Texas at San Antonio
Email: george.perry@utsa.edu

Bernard Rabin, PhD
UMBC
Email: rabin@umbc.edu

Peter Rabinovitch, MD, PhD
University of Washington
Email: PeterR@medicine.washington.edu

Michael Rae
SENS Foundation
Email: mikalra@lycos.com

Guru Ramanathan, PhD
General Nutrition
Email: guru-ramanathan@gnc-hq.com

Barry Reisberg, MD, FAAA
NYU Medical Center
Email: barry.reisberg@med.nyu.edu

Rose M. Reynolds
William Jewell College
Email: reynoldsr@william.jewell.edu

Karl Rodriguez, PhD
University of Texas Health Science Center
Email: rodriguezrk@uthscsa.edu

Lalida Rojanathammanee, PhD
University of North Dakota
Email: lrojanat@med.und.edu

Mark Romanick, PhD
Univ. of North Dakota School of Med
Email: mark.romanick@med.und.edu

Douglas L. Rosene, PhD
Boston University School of Medicine
Email: drosene@bu.edu

M. Jill Saffrey, PhD
Open University
Email: j.saffrey@open.ac.uk

Minna Scholl
Email: mescholl@gwmail.gwu.edu

Shepherd Schurman
NIH
Email: schurmansh@mail.nih.gov

Christian Sell, PhD
Drexel College of Medicine
Email: christian.sell@drexelmed.edu

Edward H. Sharman, PhD
University of California - Irvine
Email: esharman@uci.edu

Kaizhi G. Sharman, PhD
University of California - Irvine
Email: kguo@uci.edu

Toshiro Shigemitsu, MD, PhD
Shigemitsu Eye Clinic and Research Foundation
Email: eyeshige@blue.ocn.ne.jp

Pooja Shivshankar
University of Texas Health Science Center
Email: shivshankar@uthscsa.edu

Barbara Shukitt-Hale, PhD, FAAA
USDA/HNRCA
Email: barbara.hale@tufts.edu

Akram Sidhu
University of North Texas Health Science Center
Email: akram.sidhu@live.unthsc.edu

Megan J. Smithey, PhD
University of Arizona
Email: smithey@email.arizona.edu

Shinichi Someya, PhD
University of Florida
Email: shinsomeya@gmail.com

Paul M. Spiegel, JD, PhD
Email: pms314@aya.yale.edu

Brian Stoveken
University of Texas Health Science Center
Email: stoveken@livemail.uthscsa.edu

Thomas J. Sullivan
The Sullivan Company
Email: tjsullivan@thesullivancompany.com

Nathalie Sumien, PhD
University of North Texas Health Science Center
Email: nsumien@hsc.unt.edu

George Sutphin
The Jackson Laboratory
Email: lothos@u.washington.edu

Ryoya Takahashi, PhD
Toho University
Email: takahasi@phar.toho-u.ac.jp

Nopporn Thangthaeng, PhD
University of North Texas HSC
Email: nthangthaeng@gmail.com

LaDora Thompson, PhD, BSPT
University of Minnesota
Email: thomp067@umn.edu

Claudio Torres
Drexel University
Email: Claudioi.Torres@drexelMed.edu

Kazuo Tsubota, MD
Keio University School of Medicine
Email: tsubota@z3.keio.jp

Holly Van Remmen, PhD, FAAA
University of Texas HSC- San Antonio
Email: vanremmen@uthscsa.edu

Mary Lou Voytko, PhD, FAAA
Wake Forest University School of Medicine
Email: mlvoytko@wfubmc.edu

David Mark Welch,
Marine Biological Laboratory
Email: dmarkwelch@mbl.edu

Ying Xu
West Virginia University
Email: yingxufl@yahoo.com

Amna Yaqoob
St. Joseph Hospital Phoenix
Email: amna.yaqoob@dignityhealth.org

Daniel Zamzow
Oregon State University
Email: drzamzow@hotmail.com

Xu Zhi, MD, PhD
University of Central Florida
Email: xu.zhi@ucf.edu

*Directory contains only those members in good standing at time of print.