INFLAMMATION AND AGING: CAUSES AND CONSEQUENCES

39th Annual Meeting of the
American Aging Association

Pre-Conference

BIOLOGY OF AGING:
A MEETING OF MINDS TO CELEBRATE
AWARD WINNING SCIENCE
June 4, 2010

THE NINES HOTEL
PORTLAND, OREGON
JUNE 4-7, 2010

SCHEDULE AT A GLANCE

FRIDAY JUNE 4, 2010 PRE-PROGRAM THE BIOLOGY OF AGING	***GALLERY*** **8:30 AM – 10:30 AM** THE BIOLOGY OF AGING **10:30 AM – 11:00 AM** BREAK **11:00 AM – 12:30 PM** THE BIOLOGY OF AGING CONTINUED **12:30 PM – 1:30 PM** LUNCH ON YOUR OWN **1:30 PM – 3:00 PM** THE BIOLOGY OF AGING CONTINUED **3:00 PM – 3:30 PM** BREAK **3:30 PM – 5:30 PM** THE BIOLOGY OF AGING CONTINUED
SATURDAY JUNE 5, 2010 INFLAMMATION AND AGING: CAUSES AND CONSEQUENCES	***THE NINES BALLROOM*** **8:15 AM – 10:30 AM** PLENARY SESSION I: MICROBES, IMMUNITY & INFLAMMATION **10:30 AM – 10:50 AM** BREAK **10:50 AM – 12:30 PM** ***FASHION BALLROOM*** MICROBES, IMMUNITY & INFLAMMATION ***CULTURE BALLROOM*** MUSCLE & INFLAMMATION **12:30 PM – 2:00 PM** ***GALLARY BALLROOM*** ***VINCENT CRISTOFALO AWARD LUNCHEON*** ***VINCENT CRISTOFALO AWARD LECTURE*** **2:00 PM – 3:30 PM** **THE NINES BALLROOM** PLENARY SESSION III:FAT STREET – THE ROUTE TO AGE-RELATED INFLAMMATION **3:30 PM – 3:50 PM** BREAK **3:50 PM – 5:20 PM** ***FASHION BALLROOM*** FAT ORGAN AS THE SOURCE OF INFLAMMATION IN AGING ***CULTURE BALLROOM*** TRANSATLANTIC SYMPOSIUM **5:30 PM – 7:00 PM** **DESIGN BALLROOM** COCKTAIL RECEPTION AND POSTER SESSION I

SUNDAY *JUNE 6, 2010* *INFLAMMATION AND AGING: CAUSES AND CONSEQUENCES*	***THE NINES BALLROOM*** **8:30 AM – 10:30 AM** PLENARY SESSION IV: NEURAL INFLAMMATION **10:25 AM – 10:50 AM** BREAK **10:50 AM – 12:20 PM** ***FASHION BALLROOM*** NEURAL INFLAMMATION ***CULTURE BALLROOM*** BONES, JOINTS, & INFLAMMATION **12:30 PM – 1:30 PM** LUNCH ON YOUR OWN **1:30 PM – 3:30 PM** **THE NINES BALLROOM** PLENARY SESSION V: FRAILTY & INFLAMMATION **3:30 PM – 4:00 PM** BREAK **4:00 PM – 6:00 PM** **THE NINES BALLROOM** PLENARY SESSION VI: HORMONES & INFLAMATION **6:00 PM – 6:30 PM** AGE BUSINESS MEETING **5:30 PM – 7:00 PM** **DESIGN BALLROOM** COCKTAIL RECEPTION AND POSTER SESSION II I
MONDAY *JUNE 7, 2010* *INFLAMMATION AND AGING: CAUSES AND CONSEQUENCES*	***THE NINES BALLROOM*** **9:00 AM – 10:40 AM** ***FASHION BALLROOM*** PLENARY SESSION VII: ENGINEERING NEGLIGIBLE SENESCENCE ***CULTURE BALLROOM*** PLENARY SESSION VIII NATHAN SHOCK CENTER SYMPOSIUM **10:40 AM – 11:00 AM** BREAK **11:00 AM – 12:20 PM** ***FASHION BALLROOM*** PLENARY SESSION VII: ENGINEERING NEGLIGIBLE SENESCENCE ***CULTURE BALLROOM*** PLENARY SESSION VIII NATHAN SHOCK CENTER SYMPOSIUM **GALLARY BALLROOM** 12:30 PM – 2:00 PM AWARDS LUNCHEON PLENARY SESSION VIII DENHAM HARMAN AWARD LECTURE

Table of Contents

A C K N O W L E D G E M E N T S

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

British Society for Research on Ageing

Glenn Foundation for Medical Research

The Ellison Medical Foundation

American Federation for Aging Research

The Gerontological Society of America

The SESN Foundation

Wild Blueberry Association of North America

Springer Science & Business Media

IOS Press

Aging Research Network

National Institute on Aging
National Institutes of Health

NATIONAL INSTITUTES OF HEALTH / NATIONAL INSTITUTE ON AGING

Overview

The National Institute on Aging (NIA), one of the 25 institutes and centers of the National Institutes of Health, leads a broad scientific effort to understand the nature of aging and to extend the healthy, active years of life. In 1974, Congress granted authority to form the National Institute on Aging 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 the NIA as the primary federal agency on Alzheimer's disease research.

Mission

The NIA's mission is to improve the health and well-being of older Americans through research, and specifically to:
Support and conduct high quality research on:
-aging processes
-age-related diseases
-special problems and needs of the aged
Train and develop highly skilled research scientists from all population groups
Develop and maintain state-of-the-art resources to accelerate research progress
Disseminate information and communicate with the public and interested groups on health and research advances and on new directions for research.

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

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

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

PLATINUM SPONSOR

The Ellison Medical Foundation

The Ellison Medical Foundation supports basic biomedical research on aging relevant to understanding lifespan development processes and age-related diseases and disabilities.

The Foundation particularly wishes to stimulate new, creative, research that might not be funded by traditional sources or that is often under-funded in the U.S

www.ellisonfoundation.org

GOLD SPONSOR

American Federation for Aging Research

For 26 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

SENS Foundation
human regenerative engineering

http://www.methuselahfoundation.org

The Methuselah Foundation is a non-profit 501(c)(3) charity dedicated to hastening the development of science-based aging interventions using modern technologies. The Foundation believes that the combined use of directed research funding and competitive financial awards will capture the interest of researchers and the public, drawing attention to the very real possibility that the aging process and the consequent occurrence of age-related disease may be slowed, reversed and possibly avoided altogether. The ultimate goal of the Foundation is nothing less than the defeat of age-related disease and the extension of the healthy human lifespan. Through the private donations of individuals and organizations who share this common vision, the Foundation is an agent of change in turning the attitude of grudging acceptance of age-related decline to one of defiance. The Foundation is helping give voice to the desire for the longer healthier life spans that, as science is making increasingly clear, will be available if we work together to use the tools of the present day against an ancient problem.

GOLD SPONSOR

THE GERONTOLOGICAL SOCIETY OF AMERICA

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.

SILVER SPONSOR

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

EXHIBITOR

Commencing its publishing activities in 1987, IOS Press serves the information needs of scientific and medical communities worldwide. IOS Press now publishes 72 international journals about 130 book titles and each year on subjects ranging from computer sciences and mathematics to medicine and the natural sciences. Headquartered in Amsterdam with satellite offices in the USA, Germany, India and China, IOS Press has established several strategic co-publishing initiatives. Notable acquisitions included Delft University Press in 2005 and Millpress Science Publishers in 2008.

EXHIBITOR

STUDENT TRAVEL AWARD DONATION

MEMBERSHIP DONATIONS

STUDENT TRAVEL AWARD DONATIONS

Thomas Johnson
Janko Nikolich-Zugich

RESEARCH FUND DONATIONS

Elliot Bergman
Eberhard Bleicher
Denham Harman
Donna Holmes

GOLD DONATIONS

Gregory Brewer
Mark A. Smith

SILVER DONATIONS

Andrzej Bartke
Donald Ingram

GENERAL DONATIONS

Holly Brown-Borg
Donna Cini
Gregory Fahy
Garrick Lee
Julie Mattison
Paul M. Spiegel
Delia Tamasan
Paul Wakfer
Kelvin Yen

Friday, June 4, 2010
Pre-Meeting: The Biology of Aging

Biology of Aging:
A Meeting of Minds to Celebrate Award Winning Science

A Special Symposium Co-Sponsored by:
The American Aging Association (AGE)
The American Federation for Aging Research (AFAR)
And
The Gerontological Society of America (GSA)

Featuring past awardees for the Denham Harman Research Award (AGE), the Irving S. Wright and Vincent Cristofalo Awards (AFAR) and the Robert W. Kleemeier Award (GSA)

7:30 am - 8:30 am	**Registration and Continental Breakfast**
8:30 am – 9:00 am	**Welcome and Opening Remarks** *Donald K. Ingram, PhD (Harman Awardee)* *Janko Nikolich-Zugich, MD, PhD (AGE President)* *Mark A. Smith, PhD (AGE Executive Director)* *Stephanie Lederman, Ed.M (AFAR Executive Director)* *James Appleby, RPh, MPH (GSA Executive Director)*
9:00 am – 10:30 am	**Session One** *Chairs: Donald K. Ingram,PhD, Pennington Biomedical Research Center, Baton Rouge, LA Janko Nikolich-Zugich, MD, PhD, University of Arizona, Tucson, AZ*
9:00 am – 9:30 am	I. Steven N. Austad, PhD (Kleemeier Awardee) *University of Texas Health Science Center, San Antonio TX* **Evolutionary Keys to Longevity and Negligible Senescence**
9:30am – 10:00 am	II. Andrzej Bartke, PhD, (Harman Awardee) *Southern Illinois University, Springfield, IL* **Regulation of Aging by Growth Hormone and Related Molecules**
10:00 am – 10:30 am	III. Tom Johnson, PhD (Kleemeier Awardee) *University of Colorado, Boulder CO* **Stochastic Processes of Aging**
10:30 am – 11:00 am	*Break*
11:00 am – 12:30 pm	**Session Two** *Chair:* St*ephanie Lederman, Ed.M, AFAR*
11:00 am – 11:30 am	IV. Brian Kennedy, PhD (Cristofalo Awardee) *University of Washington, Seattle, WA* **Genetic Dissection of Aging and Longevity**

11:30 am – 12:00 pm	V. Mark A. Smith, PhD (Harman Awardee) *Case Western Reserve University, Cleveland, OH* **Factors Driving the Pathogenesis of Alzheimer's Disease**
12:00 pm – 12:30 pm	VI. Donald K. Ingram, PhD, (Harman Awardee) *Pennington Biomedical Research Center, Baton Rouge, LA* **Evolution of Calorie Restriction Mimetics as a Research Paradigm**
12:30 pm – 1:30 pm	*Lunch Break (on your own)*
1:30 pm – 3:00 pm	**Session Three** *Chair: Mark A. Smith, PhD, Case Western Reserve University, Cleveland, OH*
1:30 pm – 2:00 pm	VII. Rita B. Effros, PhD, (Kleemeier Awardee) *University of California, Los Angeles, CA* **Immune Senescence: Causes, Consequences and Cures**
2:00 pm – 2:30 pm	VIII. Simin Meydani, DVM, PhD *Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA* **Nutritional Modulation of T Cell Function in the Aged**
2:30 pm – 3:00 pm	IV. Arlan Richardson, PhD (Harman, Wright and Kleemeier Awardee) *University of Texas Health Science Center, San Antonio, TX* **Current Status of the Free Radical Theory of Aging**
3:00 pm – 3:30 pm	*Break*
3:30 pm – 5:30 pm	**Session Four** *Chair: James Appleby, RPh, MPH, GSA Executive Director*
3:30 pm - 4:00 pm	X. Richard A. Miller, MD, PhD (Wright and Kleemeier Awardee) *University of Michigan, Ann Arbor, MI* **NIA Interventions Testing Program: Progress and Potential**
3:30 pm - 4:00 pm	XI. Caleb Finch, PhD (Harman and Kleemeier Awardee) *Andrus Gerontology Research Center, University of California, Los Angeles, CA* **Complexities in the Future of Human Longevity**

Friday, June 4, 2010
Pre-Meeting: The Biology of Aging

4:30 pm – 5:30 pm **Panel Discussion: The Biology of Aging – Successes and Challenges**
Discussants:
Caleb Finch, PhD (Harman and Kleemeier Awardee) University of California, Los Angeles, CA
George M. Martin, MD (Harman, Wright and Kleemeier Awardee), University of Washington, Seattle, WA
Robert A. Floyd, PhD, FAAA (Harman Awardee), Oklahoma Medical Research Foundation, Tulsa, OK
Donald K. Ingram, PhD, FAAA (Harman Awardee), Pennington Biomedical Research Center, Baton Rouge, LA

PRE- CONFERENCE ADJOURNS

6:30 pm – 8:00 pm **AGE Conference Registration**

6:30 pm – 8:00 pm **AGE Welcome Reception**

Inflammation and Aging: Causes and Consequences
Chair: Janko Nikolich-Zugich, MD, PhD
University of Arizona, Tucson, AZ

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

8:15 am – 8:30 am **Welcome and Opening Remarks**
Janko Nikolich-Zugich, MD, PhD, President American Aging Association

8:30 am – 10:30 am **Plenary Session I: Microbes, Immunity and Inflammation**
Chairs: Janko Nikolich-Zugich, MD, PhD, University of Arizona, Tucson, AZ; Magdalene So, PhD, University of Arizona, Tucson, AZ

Sponsored by The Ellison Medical Foundation

8:30 am – 9:00 am 1. Richard Flavell, PhD Yale, New Haven, CT
The Inflammasome in Health and Disease

9:00 am – 9:30 am 2. Grace Y. Chen, MD, PhD, University of Michigan, Ann Arbor, MI
Nod-Like Receptors: Role in Intestinal Homeostasis and Disease

9:30 am – 10:00 am 3. Howard Petrie, PhD, Scripps Florida, Jupiter FL
Understanding the Molecular Mechanisms of Thymic Atrophy and Regeneration

10:00 am – 10:30 am 4. Magdalene So, PhD, University of Arizona, Tucson, AZ
Commensal Neisseria: Genomic Clues to Pathogenesis and Inflammation

10:30 am – 10:50 am ***Break***

Session 1A and Session 1B are Concurrent Sessions

10:50 am – 12:30 pm **Session 1A: Microbes, Immunity and Inflammation (Continuation)**
Chairs: Janko Nikolich-Zugich, MD, PhD, and Magdalene So, PhD, University of Arizona, Tucson, AZ

10:50 am – 11:10 am 5. Felicia Goodrum, PhD, University of Arizona, Tucson, AZ
Human Cytomegalovirus Latency and the ULb' Region

11:10 am – 11:30 am 6. Graham Pawelec, PhD, University of Tuebingen, Germany
Human Immunosenescence?

11:30 am – 11:50 am 7. Rosanna Vescovini, PhD and Paolo Sansoni, MD, PhD, University of Parma, Italy
HCMV Infection, Inflammation and Age-Related Diseases: A Dangerous Association

Saturday, June 5, 2010
Inflammation and Aging: Causes and Consequences

11:50 am – 12:10 pm 8. Afam Okoye, PhD, Oregon Health & Science University, Beaverton, OR
The Role of IL-7 in T Cell Rejuvenation in the Non-Human Primate Model of Aging

12:10 am – 12:25 pm 9. Elizabeth Sapey, MD, University of Birmingham,
British Society for Research on Ageing Prize Presentation
Aberrant Peripheral Neurtophil Migration in the Healthy Elderly

10:50 am – 12:30 pm Session 1B: Muscle and Inflammation
Chairs: LaDora Thompson, PhD, University of Minnesota, Minneapolis, MN
Holly VanRemmen, PhD, FAAA, Barshop Institute, San Antonio, TX

10:50 am – 11:10 am 10. Emanuele Marzetti, MD, PhD, University of Florida, Gainesville, FL
Chronic Inflammation and Myocyte Apoptosis in Sarcopenia of Aging

11:10 am – 11:30 am 11. Deborah A. Ferrington, PhD, University of Minnesota, Minneapolis, MN
Non-Immune Roles for Immunoproteasome in Muscle

11:30 am – 11:50 am 12. Charlotte A. Peterson, PhD, University of Kentucky, Lexington, KY
Predictors of Skeletal Muscle Response to Exercise Training in Elderly Adults

11:50 am – 12:05 am 13. Anne McArdle, PhD, University of Liverpool, Great Britian
Heat Shock Proteins as Modulators of Cytokine Production by Skeletal Muscle

12:05 pm – 12:20 pm 14. Arunabh Bhattacharya, University of Texas Health Science Center at San Antonio, San Antonio, TX
Role of 12/15-Lipoxygenase Pathway in Muscle Atrophy

12:30 pm – 2:00 pm Plenary Session II – Special Luncheon

VINCENT CRISTOFALO MEMORIAL RISING STAR AWARD AND LECTURE

Using Aging Research to Inform Biology
Andrew Dillin, PhD
Salk Institute for Biological Studies, La Jolla, CA

Sponsored by:
The American Federation for Aging Research (AFAR)
In Collaboration with
The Glenn Foundation for Medical Research
Margaret F. Cristofalo
The Gerontological Society of America

2:00 pm – 3:30 pm **Plenary Session III: Fat Street – The Route to Age-Related Inflammation**
Chairs: Donald K. Ingram, PhD, FAAA, and Vishwa Deep Dixit, DVM, PhD, Pennington Biomedical Research Center, Baton Rouge, LA

2:00 pm – 2:30 pm 15. Jeremy Walston, PhD, Johns Hopkins University, Baltimore, MD
Fatness and Proinflammatory State in Older Persons

2:30 pm – 3:00 pm 16. Philipp Scherer, University Texas Southwestern Medical Center, Dallas, TX
Adipose Tissue Dysfunction: All Roads Lead to Inflammation

3:00 pm – 3:30 pm 17. Vishwa Deep Dixit, DMV, PhD, Pennington Biomedical Research Center, Baton Rouge, LA
Inflammasome Signaling and the Origin of Adipose Tissue Inflammation

3:30 pm – 3:50 pm *Break*

Sessions 2A and 2B are Concurrent Session

3:50 pm – 5:20 pm **Session 2A: Fat Organ as the Source of Inflammation in Aging**
Chairs: Donald K. Ingram, PhD, FAAA, and Vishwa Deep Dixit, DVM, PhD, Pennington Biomedical Research Center, Baton Rouge, LA

3:50 pm – 4:10 pm 18. Martin Obin, PhD, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
A Tail of Life and Death: How Dietary Blueberry Attenuates Obesity-Associated Adipose Tissue Inflammation and Insulin Resistance

4:10 pm – 4:30 pm 19. Carey Lumeng, MD, PhD, University of Michigan, Ann Arbor, MI
Adipose Tissue Macrophage Diversity over Space and Time

4:30 pm – 4:50 pm 20. Simin Meydani, DVM, PhD, FAAA, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA
A**ging and Adipose Tissue Inflammation: Role of Nutrition**

4:50 pm – 5:05 pm 21. Chen-Yu Liao, University of Texas Health Science Center at San Antonio, San Antonio, TX
Dietary Restriction and Adiposity: Reduction of Fat is Inversely Related to Longevity in Mice

5:05 pm – 5:20 pm 22. Michal M. Masternak, Southern Illinois University, Springfield, IL
The Role of Visceral Fat on Insulin Signaling in Long-Living Mice

Saturday, June 5, 2010
Inflammation and Aging: Causes and Consequences

3:50 pm – 5:20 pm	**Session 2B: Transatlantic Symposium** *Chair: Richard Faragher, PhD, University of Brighton, United Kingdom and Anna McCormick, PhD, NIA*
3:50 pm – 4:10 pm	23. Nancy Manley, PhD, University of Georgia, Athens, GA and Claire Blackburn, PhD, University of Edinburgh , United Kingdom **Transcriptional Control of Thymic Rebound**
4:10 pm – 4:30 pm	24. Brian Kennedy, PhD, Washington University, Seattle, WA **S6 Kinase, Aging and Age-Related Disease**
4:30 pm – 4:50 pm	25. Quee Lin Ch'ng, PhD, King's College London, United Kingdom and Hang Lu, PhD, Georgia Institute of Technology, Atlanta, GA **Sources, Transmission and Effects of Transcriptional Noise in C. Elegans Aging**
4:50 pm – 5:10 pm	26. Arnie Akbar, PhD, University College London, United Kingdom and Janko Nikolich-Zugich, MD, PhD, University of Arizona, Tucson, AZ **Mechanisms of Reduced T Cell Immunity in Older Adults**
5:10 pm – 5:30 pm	27. John Sedivy, PhD, Brown University, Providence, RI and Peter Adams, MD, Beatson Institute for Cancer Research, Glasgow **The WNT-Chromatin Axis in Aging**
5:30 pm – 5:50 pm	28. Iain Ridgeway, MD, University of Bangor and Steven Austad, PhD, University of Texas Health Science Center, San Antonio, TX **Mechanisms of Exceptional Longevity in the World's Longest Lived Animal**
5:30 pm – 7:30 pm	**Poster Session 1**
5:30 pm – 7:30 pm	**Cocktail Reception**
7:00 pm – 10:00 pm	**AGE Board of Directors Dinner Meeting (Invitation Only)**

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

8:30 am – 10:30 am **Plenary Session IV: Neural Inflammation**
Chairs: Carol A. Barnes, PhD, University of Arizona, Tucson, AZ and Susanna Rosi, PhD, University of California, San Francisco, CA

8:30 am – 8:40 am Carol A. Barnes, PhD, University of Arizona, Tucson, AZ
Introduction and Overview

8:40 am – 9:15 am 29. Susanna Rosi, PhD, University of California, San Francisco, CA
Neuro-inflammation and Gene Expression Involved in Synaptic Plasticity and Memory: Pharmacological Approaches to Restore Neuronal-Microglia Communication

9:15 am – 9:50 am 30. Paula Bickford, PhD, FAAA, University of South Florida, Tampa, FL
Nutritional Support for Aging Stem Cells

9:50 am – 10:25 am 31. Donald K. Ingram, PhD, FAAA, Pennington Biomedical Research Center, Baton Rouge, LA
Brain Aging: Influence of Inflammation and Obesity

10:25 am – 10:50 am ***Break***

Session 3A and 3B are Concurrent Sessions

10:50 am – 12:20 pm **Session 3A: Neural Inflammation (Continuation)**
Chairs: Carol A. Barnes, PhD, University of Arizona, Tucson, AZ and Susanna Rosi, PhD, University of California, San Francisco, CA

10:50 am – 11:30 am 32. Fulton T. Crews, PhD, University of North Carolina, Chapel Hill, NC
Persistent Oxidative Stress Through NFkB Induction of Proinflammatory Genes and Oxidases That Lead to Age Related Brain Degeneration

11:30 am – 12:05 pm 33. Caleb Finch, PhD, University of California, Los Angeles, CA
Inflammatory Processes Begin Before Birth and Extend Throughout the Lifespan

12:05 pm – 12:20 pm 34. M. Hasan Mohajeri, DSM Nutritional Products, Basel, Switzerland
Resveratrol Supplementation Supports Mitochondrial Function and Improves Associative and Spatial Learning and Memory Performance in Aged Mice

Sunday, June 6, 2010
Inflammation and Aging: Causes and Consequences

10:50 am – 12:20 pm	**Session 3B: Bones, Joints, Other Organs and Inflammation in Aging** *Chair: Nicholas Ziats, PhD, Case Western Reserve University, Cleveland, OH*
10:50 am – 11:10 am	35. Julie Glowacki, PhD, Brigham & Woman's Hospital, Boston MA **Human Marrow-Derived Bone Stem/Progenitor Cells: Effects of Age and Inflammation**
11:10 am – 11:30 am	36. Charles J. Malemud, PhD, Case Western Reserve University, Cleveland, OH **Prevention of Inflamation-Induced Bone Destruction in Arthritis**
11:30 am – 11:50 am	37. Kurt Kasper, PhD, Rice University, Houston, TX **Harnessing Inflammation in Strategies for Bone Tissue Engineering**
11:50 am – 12:05 pm	38. Jennifer P Chou, David Geffen School of Medicine at UCLA, Los Angeles **Modulatory Effects of Inflammatory Isoprostanes and Vitamin D on Telomerase in Human T Lymphocytes: Impact on Bone Loss During Aging**
12:05 pm – 12:20 pm	39. Norman S. Wolf, The University of Washington, Seattle, WA **The Aging Eye, Mechanisms Related to Cataract**
12:30 pm – 1:30 pm	*Lunch On Your Own*
1:30 pm – 3:30 pm	**Arthur Balin Plenary Session V: Frailty and Inflammation** *Chairs: Mindy J. Fain, MD, University of Arizona, Tucson AZ and James Kirkland, MD, PhD, Mayo Clinic, Rochester, MN*
1:30 pm – 2:00 pm	40. Mindy J. Fain, MD, University of Arizona, Tucson AZ **Frailty: A Clinical Perspective**
2:00 pm – 2:30 pm	41. Jeremy Walston, PhD, Johns Hopkins University, Baltimore, MD **Models of Frailty**
2:30 pm – 3:00 pm	42. Kevin P. High, MD, Wake Forest University, Winston-Salem, NC **Infectious Diseases and Inflammation: A Clinical Perspective**
3:00 pm – 3:30 pm	43. James Kirkland, MD, PhD, Mayo Clinic, Rochester, MN **Scientists and Doctors: Lost in Translation (Roundtable)**
3:30 pm – 4:00 pm	*Break*

4:00 pm – 6:00 pm **Plenary Session VI: Hormones and Inflammation**
Chairs: S. Mitch Harman, MD, PhD, FAAA, Kronos Longevity Research Institute, Phoenix, AZ and Holly Brown-Borg, PhD, University of North Dakota, Grand Forks, ND

4:00 pm – 4:25 pm 44. Vishwa Deep Dixit, DVM, PhD, Pennington Biomedical Research Center, Baton Rouge, LA
Regulation of Inflammation and Immunosenescence by Ghrelin

4:25 pm – 4:50 pm 45. Steve Bondy, PhD, University of California, Irvine, CA
Melatonin, Brain Aging and Neuroinflammation

4:50 pm – 5:15 pm 46. Subhadeep Chakrabarti, MBBS, PhD, University of Alberta, Alberta, Canada
Estrogen Effect on Endothelial Inflammation: Pro-Inflammatory, Anti-Inflammatory or Immunomodulator?

5:15 pm – 5:40 pm 47. E. J. Giltay, MD, PhD, Leiden University Medical Center, Leiden, Netherlands
Testosterone, Mental Well-Being, and Inflammation

5:40 pm – 5:55 pm 48. Maarit Ahtiainen, University of Jyväskylä, Findland
Age and Hormone Replacement Therapy Affect Systemic and Local IL-6 and IFG-1 Pathways in Women

6:00 pm – 6:30 pm **AGE Business Meeting – Open to all AGE Members**

6:30 pm – 7:30 pm **Poster Session II**

6:30 pm – 7:30 pm **Cocktail Reception**

7:30 pm – 9:00 pm **Special Student Session/Data Blitz followed by Student Social**
Sponsored by The Gerontological Society of America
and
The American Aging Association

Monday, June 7, 2010
Inflammation and Aging: Causes and Consequences

8:00 am – 9:00 am	**Continental Breakfast**
9:00 am – 12:30 pm	**Plenary Session VII: Engineering Negligible Senescence** *Chair: Aubrey de Grey, PhD, FAAA, SENS Foundation, Cambridge, United Kingdom*
9:00 am – 9:25 am	49. Aubrey de Grey, PhD, FAAA, SENS Foundation, Cambridge, United Kingdom **Regenerative Medicine against Aging: Can it be Comprehensive Enough?**
9:25 am – 9:50 am	50. Barbara Shukitt-Hale, PhD, FAAA, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA **Nutritional Interventions in Brain Aging**
9:50 am – 10:15 am	51. Irina Conboy, PhD, University of California Berkeley, Berkeley CA **Do Organ Stem Cells Age?**
10:15 am – 10:40 am	52. Ashley Bush, MD, PhD, Massachusetts General Hospital, Boston, MA **PBT2 for Cognitive Aging and Alzheimer's Disease: Advances in the Metals Theory**
10:40 am – 11:00 am	***Break***
11:00 am – 11:25 am	53. David Gardiner, PhD, University of California Irvine, Irvine, CA **Understanding Mechanisms of Regeneration in the Salamander: Strategies to Repair and Reverse the Accumulation of Chronic Damage**
11:25 am – 11:50 am	54. Buddy Ratner, PhD, University of Washington, Seattle, WA **Rebuilding Bone, Sclera, Heart, Skin and Other Tissues and Organs with a Unique, Sphere-Templated Porous Scaffold**
11:50 am – 12:05 pm	55. Dana L. Miller, Fred Hutchinson Cancer Research Center, Seattle, WA **Adaptation to Hydrogen Sulfide Improves Protein Homeostasis in C. Elegans**
12:05 pm – 12:20 pm	56. Andrei Seluanov, University of Rochester, Rochester, NY **Anticancer Mechanisms in a Long-Lived Rodent, the Naked Mole-Rat**
9:00 am – 12:30 pm	**Plenary Session VIII: Nathan Shock Center Symposium on the Biology of Aging** *Chair: Peter S. Rabinovitch, MD, PhD, University of Washington, Seattle WA*

9:00 am – 9:10 am 57. Felipe Sierra, PhD. Director, Division of Aging Biology, NIA
Introduction

9:10 am – 9:50 am 58. Dao-Fu Dai, MD, PhD, University of Washington, Seattle WA
Mitochondrial ROS Plays a Central Role in Cardiac Aging, Hypertrophy and Failure

9:50 am - 10:40 am 59. Arlan Richardson, PhD, University of Texas Health Science Center, San Antonio TX
Do Rapamycin and Caloric Restriction Increase Lifespan Through a Similar Mechanism(s)?

10:40 am – 11:00 am *Break*

11:00 am - 11:40 am 60. Richard A. Miller, MD, PhD, University of Michigan, Ann Arbor MI
Stress Resistance: From Culture to Critters All-Sorts

11:40 am - 12:20 pm 61. Rong Yuan, MD, PhD, the Jackson Laboratory, Bar Harbor ME
Genetic Regulation of Female Sexual Maturation

12:30 pm – 1:00 pm **American Aging Association Awards Luncheon**
(All Attendees are Invited to Attend)

Awards Presentations:
Distinguished Achievement Award
Denham Harman Award
Poster Awards: Paul E. Glenn Award and Walter R. Nicolai Award

1:00 pm – 2:00 pm **Plenary Session VIII: Denham Harman Award Lecture**

The Discovery of Longevity Mutants
Tom Johnson, PhD
University of Colorado, Boulder CO

Meeting Adjourns

Poster Session I

Saturday, June 5, 2010

62	**B7-H1 Immune Co-Signaling Regulates Age-Related Inflammation in a Sex-Dependent Manner** *T. J. Curiel(P), V. Hurez, P. Lin, S. Thibodeaux, A. Richardson, P. Hornsby, Z. D. Sharp*
63	**Role of Regulatory T-Cells in Age-Related Susceptibility to West Nile Virus** *Jennifer L. Uhrlaub (P) and Janko Nikolich-Zugich*
64	**Antigen Related Changes in DC Priming Function in response to Listeria Infection** *Gang Li (P, G), Brien Rudd, Megan Smithey, Ty Lebsack, Sarah Foster, Janko Nikolich-Zugich*
65	**Aging Alters Inflammation – and Coagulation – Related Gene Expression in White Adipose Tissue During Inflammatory Stress** *Marlene E Starr (P, N), B Mark Evers and Hiroshi Saito*
66	**Peripheral Inflammation and Cerebral Metabolism: A Magnetic Resonance Spectroscopy Study** *Danielle E. Eagan (P) Mitzi M. Gonzales, Takashi Tarumi, Steve C. Miles, Hirofumi Tanaka, Andreana P. Haley*
67	**A Molecular Mechanism for TNF-α-Mediated Down-Regulation of B Cell Responses** *Bonnie B Blomberg (P), Maria Romero, Alain Diaz, Ana Marie Landin, Richard L Riley, Daniela Frasca*
68	**Immunoproteasome Upregulation Activates NFkB Activity in Cultured Retinal Pigment Epithelial Cells** *Marcela Maldonado(P,G), Rebecca J. Kapphahn, Neal*
69	**Examining the Correlation Between T Cell Diversity and Susceptibility to West Nile Virus Infection in the Elderly** *Michael S. Bennett (P, G), Anne M. Wertheimer, Janko Nikolich-Zugich*
70	**Age-Related Alterations to the Antigen-Specific CD8+ TCR Repertoire** *Brian D. Rudd (P, G), Vanessa Venturi, Miles P. Davenport, and Janko Nikolich-Zugich*
71	**Infection of Aged Rhesus Macaques with SVV: A New NHP Model to Study Herpes Zoster** *K.Haberthur (P,N), A.Barron, F.Engelmann, A.Legasse, S.Planer , I.Messaoudi*
72	**Diet Restriction that Improves Longevity and Health Span also Modifies Gut Microbiology** *Roy J Martin (P), Reshani N Senevirathne, Don Ingram, Marlene Janes, Vishwa Dixit, Michael J Keenan*
73	**Evaluating Safe (But Weak) Vaccines in Old Mice by Analyzing CD8 T Cell Effector Status and Transcriptional Profile** *Kristin R. Renkema, Megan J. Smithey (P), Brian D. Rudd, Sarah Foster, and Janko Nikolich-Zugich*
74	**May Autoimmune Inflammation Protect Against Cancer? New Evidence on Cancer and Rheumatoid Arthritis** *Svetlana V. Ukraintseva (P) , Konstantin Arbeev, Liubov Arbeeva, Alexander Kulminski, Igor Akushevich, Irina Culminskaya, Anatoli I. Yashin*
75	**The Dendritic Cell Response to Influenza Virus is Impaired in Aged and Calorie Restricted C57BL6J Mice** *David M. Duriancik (P) and Elizabeth M. Gardner*

76	**Kaposi's Sarcoma in HIV+ Subjects: A Model of Accelerated Immunological Aging and Altered Tumor Surveillance** *Jeffrey Dock (P, N), Patrick Unemori, Toby Mauer, Kieron S Leslie, Steve Deeks, Peter Martin, Peter Hunt, Rita B Effros*
77	**Inflammatory Proteins and Depression in Older Adults** *R.S.Newson PhD (P), N.Direk MD, A.Hofman MD PhD, J.Wittemann PhD & H.Tiemeier, MD PhD*
78	**Cellular Senescence in the Lungs Increases Susceptibility to Pneumococcal Infection in Aged Mice** *P. Shivshankar(P), A. R. Boyd, I-T. Yeh and C. J. Orihuela*
79	**Oxidative Stress and Apoptosis in Ischemia/Reperfusion Injury of Young and Old Skeletal Muscle** *David W. Hammers (P, N), Martin L. Adamo, Holly Van Remmen, Thomas J. Walters, and Roger P. Farrar*
80	**Increased Reactivity of Dendritic Cells from Aged Subjects to Self-Antigen, the Human DNA** *Anshu Agrawal (P), Jia Tay, Steven Ton, Sudhanshu Agrawal, Sudhir Gupta*
81	**Does Cytomegalovirus Deserve the Bad Rap?** *Ann B. Hill, Carrie Nielson, Priya Srikanth, Amanda Simanek, Jennifer Dowd and Allison Aiello*
82	**Negative Feedback Effects of Chronic 17ß-Estradiol on Hypothalamic KiSS-1 And NkB in the Aging Female Rhesus Macaque** *Dominique H. Eghlidi (P, N), Steve G. Kohama , and Henryk F. Urbanski*
83	**The Effect of Age on Steroidogenesis in Skeletal Muscle of Women** *E Pöllänen (P), P Ronkainen, S Sipilä, H Suominen ,M Alen, Y Konttinen ja V Kovanen*
84	**Age-Related Expression of Steroidogenic Enzymes in the Rhesus Macaque Hippocampus** *Krystina G. Sorwell (P), Steven G. Kohama, Henryk F. Urbanski*
85	**Untargeted Metabolomics Implicates Phosphocholine Dysregulation in Muscle Aging** *Gary J. Patti (P, G), Leah Shriver, Ralf Tautenhahn, Jens Bruening, Ewa Kalisiak, Sunia Trauger, Eric Ravussin, Andrew Dillin, and Gary Siuzdak*
86	**Seeking Possible Mechanisms by Which combined Postmenopausal Hormone Replacement Therapy (HRT) Preserves Muscle Properties** *P.H.A. Ronkainen (P, N), E. Pöllänen, M. Horttanainen, V. Kovanen*
87	**Healthspan Assessment in Ames Dwarf Mice** *Lauren B. Sloane (P, G), Steven N. Austad*
88	**A Role for Fibroblast Growth Factor 21 (FGF21) as a Putative Longevity Factor** *Ravneet K Boparai (P, G), Oge Arum, Michal M Masternak, Romesh Khardori, Andrzej Bartke*
89	**Leukocyte Mitochondrial DNA Content is Associated With Depression in Older Women** *Moo-Young, Kim(P),Byung-Jin, Park Yu-Na, Son A-Rhm, Han Duk-Chul, Lee Duc Chul*
90	**The Relationship Between Visfatin and Metabolic Syndrome in Postmenopausal Women** *Jung-Ha Kim, Sang-Hwan Kim, Jee-Aee Im, Duk Chul Lee (P)*

Poster Session I Continued:

Saturday, June 5, 2010

91	**Association Between Serum Adiponectin and Ferritin Level in Apparently Healthy Women** *Ji-Won Lee (P, N), Moo Young Kim, Duk-Chul Lee*
92	**Chemical Analysis of Aging: Testing Predictions From Green Theory** *Elizabeth L. Ostler,(P) Aamira Iqbal, Declan Naughton, Matthew D. Piper and Linda Partridge*
93	**Effects of Dietary Restriction on Short-Lived Saccharomyces Cerevisiae Mutants** *Jennifer Schleit (P), Brian K. Kennedy, and Matt Kaeberlein*
94	**Age-Dependent Increases in 5'-Adenosine Monophosphate-Activated Protein Kinase, C-JUN-N-Terminal Kinase, and Glycogen Synthase Kinase-3 Beta and Role for Caloric Restriction: Implication for Mitochondrial Energy Substrate Control** *Ryan T. Hamilton (P, G), Fei Yin, Enrique Cadenas*
95	**Global Analysis of the Liver Mitochondrial Proteome Half-Lives Demonstrates Increase Turnover Rate with Ageing** *Dao-Fu Dai(P, G), Nick Schulman, Edward Hsieh, Michael MacCoss, Peter Rabinovitch*
96	**Mouse Models of Muscle Remodeling** *Ted G. Graber (P,N), CN (Joyce) Chen*, Kelsey H.H. Mosser, Wendy M. Bratten, Deborah A. Ferrington, LaDora V. Thompson*
97	**Do the Lifestyle Factors that Minimise Inflammation and Optimise Healthy Aging Change Throughout Life?** *Judith H Ford (P)*
98	**Caspase-2 Acts as an Initiator Caspase in Oxidative Stress Induced Apoptosis in Primary Neurons** *Meenakshi Tiwari (P, G), Marisa Lopez-Cruzan, William W. Morgan and Brian Herman*
99	**Methionine Sulfoxide Reductase A (MsrA) Does not Affect Lifespan, but Protects From Metabolic Disease** *Adam Salmon (P, G), Jennalynn Styskal, Florence Nwagwu, Yvonne Watkins, Viviana Pérez, Nicholas Musi, Arlan Richardson*
100	**Re-Evaluation of the Free Radical Theory of Aging: Short, Normal and Even Long Lifespan in a SOD Mutant In C. Elegans** *Shin Murakami (P), Hana Murakami, Angela Veh, Kelly Cabana, and Danielle Anderson*
101	**Resveratrol Depends on Red Wine Polyphenols for Antioxidant Activity** *Ettore Bergamini (P), Gabriella Cavallini, Alessio Donati, Sara Straniero*
102	**A Novel Physiological Strategy of Intervention on Aging and Age-Associated Diseases: The DANI Protocol** *Ettore Bergamini (P), Gabriella Cavallini, Alessio Donati, Zina Gori*
103	**Is the Attenuation of Insoluble Carbonylated Proteins a Marker of Longevity in Long-Lived Species? A Comparative Approach.** *Viviana Perez, Shanique Leonard, Arlan Richardson, Steve Austad, Rochelle Buffenstein, and Asish Chaudhuri*
104	**Calorie Restriction (CR) Protects Against Oxidative Stress-Induced Muscle Atrophy by Preserving Mitochondrial Function and Muscle Integrity Even in the Absence of Antioxidant Enzyme CuZnSOD** *Young C. Jang (P, G), Michael S. Lustgarten, Florian Muller, Chris Hayworth, Yuhong Liu, Arlan Richardson , and Holly Van Remmen*

105	**Do Thioredoxin 2 Transgenic and 1 Knockout Mice Extend the Lifespan Through Different Mechanisms?** *Ikeno, Y (P)., Cortez, L.A., Webb, C.R., Guerra, J., Mahlke, M., Bhattacharya, A., Zhang, Y., Qi, W., Tominaga, K., Liu, Y., Lee, S., Van Remmen, H., and Richardson, A.*
106	**Does the Nitration of NGF Trigger Neuronal Damage in Aging and Alzheimer's Disease?** *Kristine M. Robinson (P, G), Randall L. Woltjer, Joseph F. Quinn*
107	**The Proteasome System in Oxidative Stress and Aging: Are There Common Traits?** *Karl A. Rodriguez (P, N), Maria E. Gaczynska, Pawel A. Osmulski*
108	**MLC_{3f} Gene Transfer with a Recombinant Adenovirus into Hindlimb Unloaded Fischer-344 Rat Semimembranosus: The Effect of MLC_{3f} on a Single Fiber Size, Force Generation, and Cell Damage** *Jong-Hee Kim (P, G), Windy S. Torgerud, Kelsey H. Mosser, Shuichi Watanabe, Hiroyuki Hirai, Atsushi Asakura, LaDora V. Thompson*
109	**SIRT6 Promotes DNA Repair Under Stress by Mono-ADP-Ribosylating PARP1** *Vera Gorbunova (P), Zhiyong Mao, Chris Hine, Amita Vaidya, Marina Feigenson, Andrei Seluanov*
110	**Inhibition of mTOR Signaling Promotes Mammalian Longevity** *Dudley W. Lamming(P), Nada Kalaany, Pekka Katajisto, Maki Saitoh, Deanna Stevens, David A Guertin and David M. Sabatini*
111	**Free Radicals in Aging: Studies of Antioxidants in Models of Diseases of Aging** *Robert A. Floyd (P)*

Poster Session II

Sunday, June 6, 2010

112	**The Physiological and Molecular Effects of Rapamycin on Heterogeneous Mice** *Qingying Meng (P), Kevin Flurkey, Robin Ertl, Mike Astle, David Harrison, Rong Yuan*
113	**A Point Mutation in the Oxidation Sensitive DNA Repair Gene XRCC1 Suppresses Tumor Progression** *C Pettan-Brewer (P), J Goh, L Enns, R Coil, J Morton and W Ladiges*
114	**Anti-Oxidation and Lifespan-Prolongation Activities of CordyMax in Oxidative Stress and Aging Models** *Jia-Shi Zhu (P), Yan Zhang, Jieying Yang, Ninzhi Tan, and Chunsheng Zhao*
115	**Diseases that Favor Longevity: Case of Goiter** *Svetlana V. Ukraintseva (P), Konstantin Arbeev, Liubov Arbeeva, Alexander Kulminski, Igor Akushevich Anatoli I. Yashin*
116	**Caenorhabditis Remanei as the Perfect "Aging" Organism: Genetic Variation for Lifespan and Heat, UV and Oxidative Stress Response, and in a Conserved Aging Pathway** *Rose M. Reynolds (P), Richard Jovelin, Patrick C. Phillips*
117	**Acetaminophen Improves Protein Translational Signaling in Aged Skeletal Muscle** *Miaozong Wu (P), Hua Liu, Jacqueline Fannin, Anjaiah Katta, Yeling Wang, Ravi Kumar Arvapalli, Satyanarayana Paturi, Sunil K. Karkala, Kevin M. Rice, and Eric R. Blough*
118	**Aging-Induced Change in Neurotransmitter Levels in Rat Brain: HPLC Study** *Mahendra Bishnoi (P, N)*
119	**Dysregulation of the Hippocampal Synaptoproteome with Age-Related Cognitive Decline** *H. VanGuilder (P, G), C. Van Kirk, J. Farley, H. Yan, W. Sonntag, W. Freeman*
120	**Disruption of Protein Kinase A Protects Against Age-Induced Cardiac Dysfunction** *Linda C Enns (P,G), Kenneth L Bible, Warren C Ladiges*
121	**SSeCKS/AKAP12 Prevents Polyploidy/Multinucleation and Rb-Dependent Cellular Senescence by Attenuating PKC Activation** *Shin Akakura (P), Peter Nochajski, Lingqiu Gao, Paula Sotomayor, Sei-ichi Matsui and Irwin H. Gelman*
122	**The Impact of Aging on the Mouse Bone Marrow Microenvironment** *Stephanie N. Zimmer (P), Holly VanRemmen, Vivienne I. Rebel (S. Zimmer)*
123	**A Quantitative Assessment of the Role of Oxidative Stress During Aging** *Nicolas Brandes, Heather L. Tienson (P), and Ursula Jakob*
124	**Monitoring Oxidative Stress in Aging C. elegans** *Maike Thamsen *, Daniela Knoefler * (P, N), Ursula Jakob*
125	**An Intervention That Extends Lifespan Abolishes Cognitive Deficits in a Mouse Model of AD** *Veronica Galvan (P), Patricia Spilman, Natalia Podlutskaya, Matthew J. Hart, Jayanta Debnath, Olivia Gorostiza, Dale Bredesen, Arlan Richardson, Randy Strong*
126	**Altered Levels and Localization of pCaMKII and pCREB in Alzheimer Hippocampi** *Lindsay C. Reese (P,N), Wen-Ru Zhang, Giulio Taglialatela*
127	**Naked Mole-Rats as a Model for Alzheimer's Disease** *Yael H Edrey (P,N), James Mele, Asish R Chaudhuri, Rochelle Buffenstein*

128	**Blueberry Extracts Sequester Toxic Proteins in the Brain Through Induction of Autophagy** *Shibu M. Poulose (P, G), Donna Bielinski, Derek Fisher, Barbara Shukitt-Hale, James A. Joseph*
129	**Hippocampal M1 Receptor Function Associated with Spatial Learning and Memory in Aged Female Rhesus Macaques** *Gwendolen E. Haley (P, G), Chris Kroenke, Daniel Schwartz, Steven Kohama, Henryk Urbanski, Jacob Raber*
130	**Hippocampal Synaptosomal miRNAs are Alternatively Regulated with Aging and Cognitive Decline** *C. Van Kirk(P, N), H. VanGuilder, R. Brucklacher, W. Sonntag, W. Freeman*
131	**Mechanisms of Telomere Maintenance and Aging** *Saumitri Bhattacharyya (P), Dwitiya Sawant and Joanna Groden*
132	**A Test of Artificially Selected, Long-Lived Flies as a Prospective Model for Further Life Extension in Drosophila Melanogaster** *Robin J. Mockett (P), Jordan L. Ciza, Shruti Puri, Mye Nguyen, Mehran Nisa and Manami Hatanaka*
133	**DFOXO Modulates the Effects of Dietary Composition and Restriction on Lifespan in Drosophila Melanogaster** *Xiaoping Sun (P, G), Luc Poirier, Chunxu Wang, Toshimitsu Komatsu and Tom Alberico and Sige Zou*
134	**Increased Expression of the GluN2B (NR2B) Subunit of the NMDA Receptor in the Frontal Cortex Improves Memory in Aged Mice** *B. L. Brim (P, N), R. Haskell, R. Awedikian, M. Ellinwood, L. Jin, K. Magnusson*
135	**Dietary Natural compounds Improve High Glucose-Induced Neuronal Death and Modulate Oxidative Stress and Apoptosis Markers** *Maria-Grazia Martinoli (P), Julie Bournival, Marc-André Francoeur, Fanny Longpré*
136	**Distinct Nutrient Biomarker Patterns are Associated with Brain Volume and White Matter Hyperintensities in the Oldest Old** *Gene L. Bowman (P), Jackilen Shannon, Lisa Silbert, Jeffrey A. Kaye, Joseph F. Quinn*
137	**Changes in Growth Factors, Matrix Proteins and Signaling in the Aged Kidney** *K Sataranatarajan (P, G), MJ Lee, D Feliers, G Ghosh Choudhury, JL Barnes, H Van Remmen, A Richardson and BS Kasinath*
138	**Sirt1 is Required for the Pathogenesis of Age-Related Hearing Loss in Mice** *Shinichi Someya (P, G) and Tomas A. Prolla*
139	**Age Related Changes in Human Tear Lipid** *Douglas Borchman (P), Gary N. Foulks, Marta C. Yappert*
140	**Ghrelin Receptor Null Mice Have Reduced Visceral Fat and Improved Insulin Sensitivi during Aging** *Ligen Lin (P), Pradip K. Saha, Iyabo Osifeso, Longjiang Shao, Alexander G. A. Smith, Owen P. McGuinness, Lawrence Chan and Roy G. Smith, Yuxiang Sun*
141	**Insulin Resistance in Rapamycin-Fed Mice: Lifespan and Insulin Signaling may not be Directly Linked** *JennaLynn Styskal (P, N), Adam Salmon, Elizabeth Fernandez, Vivian Diaz, Randy Strong, Dave Sharp, Arlan Richardson*

Poster Session II Continued:

Sunday, June 6, 2010

142	**FAT10 (UBD): A Novel Regulator of Adipose Mass, Inflammation and Aging** *Allon Canaan (P), Jason Defuria, Hui-Young Lee, Varman T. Samuel, Martin S. Obin, Sherman M. Weissman*
143	**Antagonistic Pleiotropy with Yeast Longevity: Slow and Delayed Living** *Joe R Delaney (P, N), Chris J Murakami, Brian K Kennedy, Matt R Kaeberlein*
144	**Replicative Life Span Extension by Dietary Restriction in Yeast Requires the Golgi Calcium/Manganese ATPase PMR1** *George L. Sutphin (P, N), and Matt Kaeberlein*
145	**Testing the Somatic Theory of Aging: Relevance of KEAP1-NRF2 Pathway and Cell-Cycle Arrest Among the Mice and the Long-Lived Naked Mole-Rat** *James Mele (P, G) and Rochelle Buffenstein*
146	**The GLUN1$_{0XX}$ (NR1-A) Splice Variant of the NMDA Receptor is Involved in Spatial Reference but not Working Memory** *Siba Das (P, N), Brenna Brim and Kathy Magnusson*
147	**Upregulation of the NRF2 Cytoprotective Pathway contributes to Species Longevity** *Kaitlyn N. Lewis (P,N), James Mele, Yael Edrey, Sung-A Kim, John D.Hayes and Rochelle Buffenstein*
148	**Mice Hypomorphic for the Igf1 Allele are Resistant to Weight Gain Induced by High Fat Diet** *Adam B. Salmon, Yuji Ikeno, Roger McCarter, Christian Sell (P)*
149	**Testing the Oxidative Stress Hypothesis of Aging in Primate Fibroblast Cell Lines: Inverse Correlation Between Species Longevity and Cellular ROS Production** *Zoltan Ungvari, Andrej Podlutsky, Natalia Podlutskaya, William E. Sonntag, Steven Merlin, Eva E. R. Philipp, Kristian Doyle, Antonio Davila, Steven N. Austad, Anna Csiszar (P)*
150	**Computational Aids for Systems Biology of Aging** *Pat Langley (P)*
151	**Systems Biology of Human Aging – Network Model 2010** *John D. Furber (P)*
152	**Absence of Dietary Carotenoids and N-3 Fatty Acids Promotes Age-Related Macular Degeneration in Rhesus Monkeys** *Martha Neuringer (P), Peter J. Francis, Laurie Renner, Alison Weiss, Brett G. Jeffrey*
153	**The Effect of Visceral Fat Removal on Metabolism in GHRKO and Normal Mice** *Reyhan Westbrook (P), Michal Masternak, April D. Strader, Andrzej Bartke*
154	**Multi-Platform Radial-Arm Water Maze Deficits Following High-Energy Particle Irradiation, A Model of Accelerated Aging** *Marshall G. Miller (P), Barbara Shukitt-Hale, Bernard M. Rabin, Kirsty Carrihill-Knoll, James A. Joseph*
155	**Damage Assays Rather Than Biomarkers of Aging** *Benjamin P. Best (P)*
156	**Pilot Studies to Find Measurable Effects of Meditation** *Alfred B. Ordman (P)*
157	**Body Height is Associated with Cognitive Function in community Dwelling Old Women** *Moo Young Kim, M.D., Ji-Won Lee, M.D., Duk Chul Lee, M.D., Ph.D*

158	**Disease Dissection and Dietogenesis of Paradoxical Protective Pathophysiologies (3DP)** *Narayan deVera, M.D (P)*
159	**2002-2010 Blueberry Health Study Report: Memory Data Analysis Suggests that 100 Participants Conducting 100 Measurements Each Year Can Document a 0.2% Annual Change During a Two-Year Study at 95% Confidence** *Diana J. Burns, David L. Doiron, Howard A. Raphaelson, Kathy Hull, James A. Joseph, Amy C. Kokesh, Bruce S. Kristal, Alec Pruchnicki, Barrie S. Sachs, Roseanne Schnoll, Joseph Vogelman, Anthony Wetherell, Rolf J. Martin (P)*
160	**The Kronos Science Laboratory-Blueberry Study-Memtrax Cognitive Assessment Reliability Study** *Susan Kaib, S. Mitchell Harman, J. Wesson Ashford, Anthony Wetherell, Michael Klvana, Rolf J. Martin(P)*
161	**Towards a Systems Theory of Aging** *Vincent E. Giuliano (P, G)*
162	**Effects of Cranial Irradiation and the Antioxidant Alpha-Lipoic Acid on Hippocampal-Dependent Learning and Memory of Mice in the Water Maze** *Laura E. Villasana (P) and Jacob Raber*
163	**Immune Effects of Short or Long-Term Rapamycin Feeding in Bl6 Mice** *T. J. Curiel(P), V. Hurez, L. Sun, S. Thibodeaux, H. van Remmen, P. Hornsby, A. Richardson, Z. D. Sharp*
164	**Age-Dependent Increase in Cholesterol Efflux, Clearance, and Catabolism in the Aging Intact Female 3xtg Mouse Model Of Alzheimer's Disease** *Ryan T. Hamilton (P, G), Amanda J. Compadre , Julian Lemus , Esosa Agbonwaneten , Jia Yao , Ronald W. Irwin , Roberta Diaz Brinton*
165	**Healthspan Promotion by SRT1720 in C57Bl/6J Mice** *Robin K. Minor (P), Theresa Ward, Andrew Levette, James Ellis, David Sinclair and Rafael de Cabo*

VINCENT CRISTOFALO MEMORIAL RISING STAR AWARD AND LECTURE

Using Aging Research to Inform Biology

Andrew Dillin, PhD
Salk Institute for Biological Studies, La Jolla, CA

Mitochondria have been the cornerstone of longevity research in yeast, worms, flies and rodents to connect rates of metabolism with longevity. The initial finding that mitochondrial reduction during a specific time in the worm's life cycle could be uncoupled from mitochondrial metabolic activity suggested that mitochondria might establish the rate of aging in a manner that is independent of previously anticipated modes, such as generation of reactive oxygen species. In our search for this signaling mechanism we report that key tissues are essential for establishing and maintaining the prolongevity cue from altered mitochondria. Additionally, we find that the mitochondrial unfolded protein response is essential and specific for the ETC longevity pathway. Finally, we find that mitochondrial perturbation in one tissue can be perceived and acted upon in distal tissues that have not undergone mitochondrial perturbation. This last finding indicates that mitochondrial stress in one cell can be communicated to unaffected cells in a multicellular organism.

DENHAM HARMAN AWARD LECTURE

The Discovery of Longevity Mutants

Tom Johnson, PhD
University of Colorado, Boulder CO

The idea that a mutation in a single gene could lengthen life was unthinkable 30 years ago when I began the use of genetic alterations to identify mechanisms of aging in *C. elegans.* Indeed, my own skepticism led me to critically test mutants generated by my fellow postdoc at Boulder: Michael Klass-to convince myself, and the rest of the world's aging research community, that it was possible. Our discovery of such Age mutants has revolutionized the way we think and approach the basic biology of aging. Several hundred genetic changes have been shown to lengthen life and slow aging in *C. elegans* and several other species. Moreover, numerous environmental manipulations, including reduced feeding (dietary restriction) and hormesis, can prolong life and these processes are also being genetically dissected.

In addition to these gene/protein-based processes rooted in the physiology of the organism, there are variations in aging and function that are not genetically specified. These processes are stochastic in nature and like other stochastic processes can be described mathematically, but cannot be predicted with certainty. Individuals vary in their trajectories of frailty and the probability of death increases with age, environment and genotype. When an animal falls outside of its homeostenotic boundary, wherein physiological parameters necessary for life are sustainable, one function after another ceases and the organism dies. There is no "aging program". Instead, there are a series of events, processes, and interactions, perhaps thousands, or even millions of them - often acting independently. It is the collective ensemble of these multiple processes that we call "aging".
(Acknowledgments: I wish to thank all the members of my laboratory over the years for their faithful, accurate and discerning work, especially Pat Tedesco who has persevered and maintained our laboratory environment throughout. I wish to thank the many NIH Institutes (NIAAA, NICHD, NIDA, NIGMS, NIMH), and especially the NIA; also the NSF, the Glenn Foundation, the Ellison Foundation, the Politz Foundation, the University of Colorado, the AFAR and numerous "angels", private donors, clients, and investors.)

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

Pre-Meeting Abstracts:

I. Evolutionary Keys to Longevity and Negligible Senescence

Steven N. Austad (P)
University of Texas Health Science Center, San Antonio TX

Exceptional longevity, here provisionally defined as living in the wild for more than 100 years, has evolved again and again in animals. Such species can yield clues as to cellular and physiological design features required for long life. An evolutionary question of interest is whether there are definable ecological conditions that favor the evolution of long life? A mechanistic question of interest is whether long life is achieved by similar mechanisms across species or whether there are many ways nature can design an organism for exceptional survival? This talk will address the evolutionary diversity of exceptional longevity and provide at least partial answers to these latter two questions.

II. Regulation of Aging by Growth Hormone and Related Molecules

Andrzej Bartke (P)
Southern Illinois University, Springfield IL

Mutations leading to GH deficiency or resistance in laboratory mice produce a robust extension of longevity in both sexes, along with numerous indications of delayed aging and longer "healthspan." It remains to be demonstrated whether equally pronounced alterations in aging can be produced by altering IGF-1 or insulin signaling in mammals. Suspected mechanisms linking reduced GH signaling with delayed aging include alterations in stress resistance, target of rapamycin (TOR) axis, mitochondrial functions, genome maintenance, apoptosis, insulin sensitivity and adipokines levels. In Ghr-/- and Prop1df mice, enhanced insulin sensitivity combined with reduced insulin levels and reduced circulating IGF-1 coexisting with preservation of some of the local IGF-1 actions appear to be particularly important.

In contrast to the remarkable extension of longevity in GH-deficient and GH-resistant mice, the relationship of GH to normal aging and the potential utility of modifying GH signaling in anti-aging and geriatric medicine are poorly understood and highly controversial. The inverse relationship of growth as assessed by adult body size and life expectancy clearly applies to species other than mice, but existence of a similar relationship in the human continues to be debated. While reduced somatotropic signaling in women has been associated with reduced old-age mortality and attainment of exceptional longevity, reduced GH and IGF-1 levels are often viewed as important etiological factors in age-related functional decline.

Supported by NIA, Ellison Medical Foundation and Glenn Foundation for Medical Research.

III. Stochastic Processes of Aging

Thomas E. Johnson[1,2](P), Alexander R. Mendenhall[1], James R. Cypser[1], Alexander K. Seewald[3], Patricia M. Tedesco[1], Oskar Alexanderson[1], Larry Taylor[1] ,Chris Link [1,2]
[1]Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado
[2]Department of Integrative Physiology; [3]Seewald Solutions, Vienna, Austria

The central premise of modern aging research is that aging is a stochastic process that is modulated by both environment and genetics. Thirty years ago we instituted a study of the genetics underlying modulation of the aging processes in *Caenorhabditis elegans.* In this nematode, development is spatially and temporally deterministic and adult cell number and anatomy are nearly invariant. Nevertheless, even isogenic cohorts cultured in homogenous, liquid environments show 20-fold range of variation in individual lifespan. Five years ago, we found (Rea et al., 2005) that the level of expression of a heat-shock promoter-GFP fusion construct (*Phsp-16.2::GFP*), when stimulated by a mild heat stress, predicts subsequent lifespan in isogenic populations. Thus, *Phsp-16.2* reporter expression is a physiological variable (or "biomarker") predictive of lifespan; these results essentially stand alone in their ability to predict subsequent longevity.

We have begun a systematic dissection of the expression of this construct into different components, which are then individually tractable to genetic and other analyses. To do so, we measure expression of different fluorescent reporter proteins, under the control of identical and of different promoters, quantify components of the variation based on simple mathematical models, and use the results to guide subsequent hypothesis-directed experiments. Here we show that this variation in longevity is associated with variation in rate of aging. It is possible that individuals expressing higher *Phsp-16.2::GFP* live longer because of an increase in the amount of native HSP-16.2 protein; alternatively, lifespan may be determined by other factors that independently determine expression of the *Phsp-16.2::GFP* biomarker. We are beginning a systematic study of sources of noise. We have created multiple strains of *C. elegans* in which we have independently integrated the same *Phsp-16.2::gfp* reporter gene construct. Not surprisingly, each strain exhibits a unique level of mean expression and we have characterized the positional effects of these constructs that inform as to the nature of the genomic regions into which the constructs have been inserted. We are also asking if there is a relationship between expression level and transgene copy number. In individual strains, we again see considerable variation in the level of GFP expression between individual worms; but we also see variation across tissues and among cells within the same tissue (the intestine), indicating that there are factors responsible for gene expression, even within a tissue.

Furthermore, we have constructed strains expressing red and green fluorescent reporter genes both under *Phsp-16.2* control in two distinct loci (TJ2734 animals). These strains allow us to understand how different loci containing the same sequence information are, nonetheless, regulated differently, both among individual worms and within an individual. When analyzing whole worms, the brightest red animals are also the brightest green animals, indicating a significant co-specification of overall expression levels, which we interpret to say that there are common elements (transcription factors, etc.) within individual worms that have an intrinsic effect on level of expression. However, when animals are analyzed in detail under the microscope, some individuals exhibit striking differences in which reporter is activated both within and between tissues. We are currently working to understand how promoter sequence, transgene copy number, flanking DNA sequence, genetic background, chromatin structure, and other variables contribute. We are also determining the predictive capabilities of each of the *Phsp-16.2* reporter gene strains with regard to frailty and longevity. (Supported by the NIA and the Glenn Foundation).

See Rea *et al.,* 2005 A stress-sensitive reporter predicts longevity in isogenic populations of *Caenorhabditis elegans*? *Nat. Genet.* **37**: 894-898.

IV. Genetic Dissection of Aging and Longevity

Brian Kennedy (P)
Department of Biochemistry, University of Washington, Seattle, WA 98195; Aging Research Institute, Guangdong Medical College, Dongguan 523808, Guangdong, P.R. China

Invertebrate model organisms have proven invaluable for aging research, leading to the identification of hundreds of aging genes. We have recently identified a set of genes which modulate the aging process in multiple invertebrate organisms. Deletion of the gene in yeast (*S. cerevisiae*) extends replicative lifespan and reduced expression of the orthologous gene in *C. elegans* also extends lifespan. In a few cases that have been tested, reduced expression or activity of the mouse ortholog also results in lifespan extension. Interestingly, these conserved aging genes appear to cluster in pathways linked to nutrient sensing and some have been linked to dietary restriction. The major focus of current research in the lab centers on understanding at the mechanistic level why these pathways, particularly the TOR pathway, modulate longevity.

Genetic approaches to longevity have been informative, with epistasis being a fundamental approach to mapping longevity mutants to specific pathways. We have been collecting epistasis data for yeast replicative aging on an unprecedented scale and new insights are emerging. Foremost among these is that one epistasis experiment can be very misleading if interpreted in the context of linear pathways. Our current goal is to establish an epistatic longevity network that will provide a more holistic image of the genes modulating longevity and their complex interplay. Progress will be discussed.

V. Factors Driving the Pathogenesis of Alzheimer's Disease

Mark A. Smith[1], Xinglong Wang[1], Hyoung-gon Lee[1], George Perry[1,2], Xiongwei Zhu[1], Gemma Casadesus[3]
[1]Department of Pathology, Case Western Reserve University, Cleveland, OH, USA; [2]UTSA Neurosciences Institute and Department of Biology, University of Texas at San Antonio, San Antonio, TX, USA; [3]Department of Neurosciences, Case Western Reserve University, Cleveland, OH, USA

Cell bodies of neurons at risk of death in Alzheimer disease (AD) have increased lipid peroxidation, nitration, free carbonyls, and nucleic acid oxidation. Such oxidative changes are one of the earliest events in disease pathogenesis. Our work is focused on investigating key abnormalities that may initiate and promote neuronal oxidative damage. First, mitochondrial abnormalities are a major source of reactive oxygen species yielding perikaryal oxidative damage. An altered mitochondria dynamic tipped towards fission in AD neurons appears to cause more reactive oxygen species production. Also, the common 5kb-deletion mtDNA subtype is also greatly increased in AD, but only in neurons at risk. The importance of such mitochondrial abnormalities to oxidative stress is indicated by a high correlation coefficient between the extent of the mtDNA increase and RNA oxidative damage (r^2 = 0.87). Nonetheless, since mitochondria in AD do not show striking oxidative damage, as one would expect if they were the direct producer of free radical species, we suspected and directly demonstrated that abnormal mitochondria supply a key reactant that, once in the cytoplasm, releases radicals. One such reactant, H_2O_2, abundant in mitochondria, can react with iron via the Fenton reaction to produce •OH. Finally, we are investigating the proximal cause(s) of mitochondrial abnormalities. One interesting mechanism involves alterations in metabolic hormones such as leptin. Supporting this, we have considerable *in vivo* and *in vitro* evidence for leptin disturbances in AD and its relationship with the pathogenesis of AD.

VI. Evolution of Calorie Restriction Mimetics as a Research Paradigm

Donald K. Ingram (P)
Pennington Biomedical Research Center, Baton Rouge, LA

By reducing intake of a nutritious diet by 20-50%, many health benefits can be observed, including increased lifespan, reduced incidence and retarded onset of chronic diseases, enhanced stress protection, and maintenance of youthful function. This paradigm, known as calorie restriction (CR), has proven to be the most robust means to retard aging as demonstrated in numerous species, but its application to human aging represents a challenge. Reports of persons who practice DR and from controlled clinical studies also indicate such regimens can positively impact indices of health and risk factors for disease. Nonetheless, despite evidence that CR produces beneficial effects in humans, therapeutic application would be problematic due to difficulties of compliance and other quality of life issues. To address this challenge, the concept of CR "mimetics" (CRM) has been introduced as a method to obtain "anti-aging" and health-

promoting benefits of DR without reducing food intake. Several candidate CRM compounds have been proposed including the sirtuin activator, resveratrol, and the insulin sensitizer, metformin, but neither candidate has shown reliable and consistent prolongevity effects. A recent report from the Intervention Testing Program demonstrating prolongevity of mice treated with rapamycin indicates that compounds inhibiting the mTOR pathway are candidate CRMs. Following previous work with 2-deoxyglucose which was eventually found to have toxicity issues, we have been examining the anti-aging benefits of glycolytic inhibition produced by mannoheptulose (MH), a seven carbon sugar that inhibits hexokinase. Preliminary results in several animal models indicate that a diet supplemented with an avocado extract enriched with MH, has potential as a CRM. From very early observations, the field of CRM has evolved to commercial applications. Scientifically, research in CRM has progressed to a point whereby questions can now be addressed regarding the effectiveness of strategies focused on "downstream" vs "upstream" targets and whether targeting a single pathway will yield the robust effects of CR.

VII. Immune Senescence: Causes, Consequences and Cures

Rita B. Effros (P)
Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA

Aging of the immune system is believed to be the main factor responsible for the increased severity of infections, reduced responses to vaccines, and higher cancer incidence in the elderly. In humans, a major category of stressors that putatively contribute to the alterations within the T cell compartment is the family of herpesviruses. These viruses, usually acquired early in life, persist for many decades and drive certain T cells to the end stage of replicative senescence, which is characterized by a variety of phenotypic and functional changes, including altered cytokine profile, resistance to apoptosis, shortened telomeres, and loss of telomerase activity. Large clonal populations of senescent CD8 T cells are associated with latent cytomegalovirus (CMV) infection in the elderly, and are part of a cluster of immune biomarkers that are associated with early mortality. Senescent CD8 T cells also accumulate at younger ages in persons chronically infected with HIV-1, and in certain types of cancer, underscoring the role of chronic antigenic stimulation in driving T cells to senescence *in vivo*. Moreover, high proportions of senescent CD8 T cells correlate with a variety of deleterious health consequences, such as poor vaccine responses, osteoporotic fractures, and more rapid progression to AIDS. Cell culture studies are addressing possible strategies to prevent or delay the process of senescence as possible approaches to enhance immune function in older persons. This presentation will highlight the importance of investigating immunosenescence in humans, since other model systems are not subject to the particular factors that cause the striking age-related reconfiguration of the human immune system.

(Supported by NIA, NIAID, Geron Corp. and TA Therapeutics)

VIII. Nutritional Modulation of T Cell Function in the Aged

Simin Nikbin Meydani, DVM, PhD (P)
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Aging is associated with impairment of T cell function, which predisposes the aged to a higher incidence of infectious and other immune-related diseases. *In vitro* and *in vivo* vitamin E (E) supplementation has been shown to improve the immune response of old mice and humans and to increase resistance to respiratory infections. We recently showed that genetic polymorphisms in cytokine genes could influence immune response to E in elderly. Further, we showed that E improves T cell mediated function in aged mice by enabling their T cells to produce more IL-2 and to progress through cell cycle division. To investigate the underlying mechanisms of E-induced enhancement of T cell function in aged mice, we first demonstrated (as reported by others) that age-associated declines in T cell signaling were due to their inability to form effective immune synapses (IS) at the site of T cell receptor and antigen interaction, resulting in reduced phosphorylation of key signaling molecules including LAT and Vav. Subsequent experiments showed that the lipid domains associated with T cell receptor in aged mice are enriched in sphingolipid ceramide and certain of its specific fatty acid subspecies. Given that ceramide has been shown to regulate activation of key signaling molecules through up-regulation of phosphatase activity, the observed changes in ceramide could contribute to impaired T cell signaling defects in aged T cells. Next, we showed that *in vitro* and *in vivo* E supplementation increased the percent of old $CD4^+$ T cells capable of forming functional IS, particularly in naïve cells, which are associated with enhanced LAT phosphorylation in T cells from old mice, but not those of young mice. We conclude that aging hinders the phosphorylation of early signaling proteins, impairing effective IS formation, IL-2 production, and T cell proliferation. E supplementation restores phosphorylation of key early signaling proteins and effective IS formation, leading to improved IL-2 production and T cell function in aged mice. Further studies are underway to determine if the E-induced improvement in phosphorylation of proteins involved in T cell activation is mediated through modification in sphingolipid ceramide.

Supported by NIA #R01AG13975, NIA #R01AG009140-10A1, NIH #AG030931-01, and USDA agreement # 58-1950-7-707.

IX. Current Status of the Free Radical Theory of Aging

Arlan Richardson (P)
Barshop Institute for Longevity and Aging Studies, the University of Texas Health Science Center at San Antonio, and the Audie Murphy VA Center, San Antonio.

Currently, the Oxidative Stress (or Free Radical) Theory of Aging is the most popular explanation of how aging occurs at the molecular level. The oxidative stress theory of aging predicts that manipulations that alter oxidative stress/damage will alter aging. Because the

gold standard for determining whether aging is altered is lifespan, investigators have studied the effect of altering oxidative stress/damage on lifespan. While data from studies in invertebrates (e.g., *C. elegans* and *Drosophila*) and rodents show a correlation between increased lifespan and resistance to oxidative stress (and in some cases reduced oxidative damage to macromolecules), direct evidence showing that alterations in oxidative damage/stress play a role in aging are limited to a few studies with transgenic *Drosophila* that overexpress antioxidant enzymes. Over the past eight years, our laboratory has conducted an exhaustive study on the effect of under- or overexpressing a large number and wide variety of genes coding for antioxidant enzymes. Because only one (the deletion of the *Sod1* gene) of the 18 genetic manipulations we studied had an effect on lifespan, our data calls into serious question the hypothesis that alterations in oxidative damage/stress play a role in the longevity of mice. However, when these transgenic/knockout mice are tested using models that develop various types of age-related pathology, they show alteration in progression/severity of pathology as predicted by the oxidative stress theory; increased oxidative stress accelerates pathology and reduced oxidative stress retards pathology. These contradictory observations suggest that (1) oxidative stress plays a very limited, if any, role in aging but a major role in healthspan or (2) the role oxidative stress plays in aging depends on the environment. In environments with minimal stress, as expected under optimal husbandry, oxidative damage plays little role in aging. However, under chronic stress, including pathological phenotypes that diminish optimal health, oxidative stress/damage plays a major role in aging. Under these conditions, enhanced antioxidant defenses exert an "anti-aging" action, leading to changes in lifespan, age-related pathology, and physiological function as predicted by the oxidative stress theory of aging.

X. NIA Interventions Testing Program: Progress and Potential

Richard A. Miller (P)
University of Michigan, Ann Arbor, MI

The NIA-sponsored Interventions Testing Program (ITP) does lifespan analyses of mice exposed to agents thought to have promise as anti-aging medicines. The protocol uses genetically heterogeneous mice to avoid the complications of strain-specific idiosyncrasies, and tests each agents in both male and female mice, at each of three sites, each of which adheres to a standard operating protocol. Interventions can be proposed by anyone, and selected for inclusion in the study through a two-stage review process. To date, three compounds have produced a significant positive effect on lifespan in one or both sexes: aspirin (males only), nordihydroguaiaretic acid (NDGA, males only) and rapamycin (both sexes). The rapamycin effect was strongest, and was significant at each test site, whether initiated at 9 months or at 20 months of age. The most recently completed data set, using mice born in 2006, found no beneficial effects of either simvastatin (at 12 or 120 mg per kg food) or resveratrol (at 300 or 1200 mg/kg food, initiated at 12 months). Rapamycin (14 mg/kg food, started at 9 months) led to a 10% increase in median lifespan in males (averaged across sites) and an 18% increase in females; age at 90th percentile was increased by 16% in males and 13% in females. Rapamycin led to a small effect on weight: treated males were as much as 10% lighter than controls, and treated females up to 6% lighter than controls. Mice in Cohort 2007, now well past the median age, are being treated with green tea extract, oxaloacetic acid, curcumin, a mixture of medium chain length triglycerides, or resveratrol (initiated at 4 months). None of these agents showed a significant beneficial effect at the interim analysis point, although there is a trend ($p = 0.02$, prior to correction for multiple comparisons) for improved early life survival in females exposed to green tea extract. Mice in the most recent cohort are being exposed to □-estradiol, methylene blue, or acarbose, or to rapamycin at doses of 4, 14, or 42 ppm. In addition, new groups of rapamycin-treated mice are being evaluated for multiple age-sensitive traits, to see if the beneficial effects of this agent on longevity reflect merely a broad-spectrum anti-cancer activity, or an authentic anti-aging action which includes anti-neoplastic protection as an important side effect.

Key collaborators: David Harrison, Nancy Nadon, Randy Strong
Support: U01-AG022303

XI. Complexities in the Future of Human Longevity

Caleb Finch (P)
Andrus Gerontology Center and Dept Biological Sciences, University of Southern California, Los Angeles CA

Since 1800, human life expectancy (LE) has doubled, whether measured at birth or at advanced ages. These advances which preceeded modern medicine, reflect major improvements of environment and nutrition. Those, in turn, reduced the inflammatory burden that interacts with many chronic diseases of aging (Finch and Crimmins, 2004; Finch 2007). Although further increases in LE may come from new drugs and technology, there are global trends for environmental deterioration of air, water, and rapidly spreading infections that could more than offset anticipated expansion of LE. Understanding these complex interactions is at the very core of the evolution of human aging from shorter-lived primates, which manifest very different patterns of pathology with aging than seen in modern humans (Finch 2010).

Finch CE, Crimmins EM (2004) Inflammatory exposure and historical changes in human life spans. Science 305: 1736-1739.
Finch CE (2007) The Biology of Human Longevity: Nutrition, Inflammation, and Aging in the Evolution of Lifespans, Academic Press: San Diego.
Finch CE (2010) Evolution of the human lifespan and diseases of aging: roles of infection, nutrition, and nutrition. PNAS, 107 (suppl. 1) 1718-1724

Session Abstracts:

1. The Inflammasome in Heatlh and Disease

Stephanie Eisenbarth [1,3], Fayyaz Sutterwala, [1,4], Richard Flavell, [1,2] (P)
[1]Department of Immunobiology and [2]Howard Hughes Medical Institute; [3]Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT, USA; [4]Present address: Inflammation Program, Department of Medicine, University of Iowa, Iowa City, IA, USA

The NLR (NOD-like receptor) family of proteins is involved in the regulation of innate immune responses and cell death pathways. Some NLR family members promote the activation of pro-inflammatory caspases within multiprotein complexes called inflammasomes. In addition to the clear role of inflammasome activation in host defense from microbes, we have recently discovered three unique agonists of the Nlrp3 (also called Nalp3 or Cryopyrin) inflammasome that implicate this pathway in both acute and chronic inflammatory conditions. Inhalation of silica and asbestos particles both cause chronic pulmonary inflammation ultimately leading to fibrosis and impaired respiration. Although alveolar macrophages are believed to initiate these inflammatory responses, the mechanism by which this occurs has been unclear. We found that stimulation of LPS-primed macrophages with silica or asbestos results in dramatic IL-1beta and IL-18 production in a caspase-1 and Nlrp3-dependent manner. Furthermore, silica-induced pulmonary fibrosis was reduced in Nalp3- and ASC-deficient mice. Finally, we found a critical role for Nlrp3 inflammasome activation in the immunostimulatory properties of the most widely used vaccine adjuvant, aluminum hydroxide ("alum"). Alum, like the large insoluble crystals of silica and asbestos, are phagocytosed by macrophages and induce the production of the potent pro-inflammatory cytokines, IL-1beta and IL-18. Like many of the pathogen-derived Nlrp3 inflammasome agonists, alum, silica and asbestos all require potassium efflux from the activated phagocyte to activate this NLR pathway. In the absence of Nlrp3 inflammasome activation, alum-induced T cell and humoral immune responses in mice were severely reduced indicating that crystal-induced Nlrp3 stimulation plays a central role in the activation of the adaptive immune system.

Inflammatory responses to liver toxicity are also mediated through the inflammasome. We found that APAP toxicity leads to liver damage through the activation of TLR9, providing signal-1 and the inflammasome through an as yet unidentified signal-2. Mice lacking either of these components were protected against this toxicity. Moreover, inflammation has been connected directly with the development of a variety of different cancers. We have used a model of inflammation induced cancer, DSS Colitis to show that the inflammasome is directly involved. Specifically, expression of caspase-1 leads to protection from tumors. Deletion of the inflammasome, for example by loss of caspase-1 leads to the enhanced susceptibility to colon cancers. Mice lacking caspase-1 have more tumors with a greater overall tumor mass. We suggest therefore that the inflammasome functions as a form of tumor suppressor which protects under normal circumstances for the development of colon cancer, currently, at least in the animal models.

2. Nod-Like Receptors: Role in Intestinal Homeostasis and Disease

Grace Y. Chen (P)
University of Michigan, Ann Arbor, MI

There are two major classes of receptors involved in the initial host defense against pathogenic bacteria: 1) the Toll-like receptors that localize to the cell surface or within endosomes and, 2) the Nod-like receptors (NLRs) that are intracellularly-located. These pathogen recognition receptors, or PRRs, recognize conserved microbial structures, which are also referred to as pathogen-associated molecular patterns (PAMPs). Although primarily involved in mounting inflammatory responses against invasive pathogens, these receptors are also capable of 'sensing' and interacting with commensal bacteria. This is especially true within the intestine where at least 10^{14} bacteria reside and provide important functions to the host. It has been demonstrated that innate immune receptor signaling, in particular by the TLR receptors, are important for intestinal homeostasis and its dysregulation can result in gut pathology such as inflammation and cancer. A role for NLRs in the regulation of both intestinal inflammation and carcinogenesis has also emerged, which will be reviewed.

3. Understanding the Molecular Mechanisms of Thymic Atrophy and Regeneration.

Howard T Petrie (P)
The Scripps Research Institute, Jupiter FL.

The thymus is the most rapidly deteriorating tissue in the body, and by mid-life exhibits less than ten percent of its peak (prepubescent) size and function. The hematopoietic component of the thymus (bone marrow-derived lymphoid cells) does not display obvious age-related changes until quite late in life. Thus, this early aging phenotype appears to be related to degeneration of the relatively longer-lived stromal cells that constitute the thymic microenvironment. The cause of thymic stromal aging remains almost completely obscure. A major obstacle to understanding thymic stromal biology is their diversity, which represents multiple different types of epithelial, mesenchymal, and non-lymphoid hematopoietic cells. Further, thymic stromal cells are very difficult to isolate, and are known to be substantially changed by the isolation process. To address these issues, we have developed a computational method for identifying stromal gene expression in situ. In this approach, stromal gene expression in histologically or functionally distinct tissue compartments is revealed by comparing gene expression in the intact (microdissected) tissue to that of the corresponding lymphoid components. Global assessment of cortical versus medullary stromal gene expression in young mice revealed the unexpected finding that cortical stromal cells are mainly characterized by metabolic (rather than signaling) functions, such as glutamate and ketone synthesis. Analysis of the corresponding lymphoid cells, many of which are rapidly dividing lymphoblasts, revealed a

decreased representation of metabolic functions that primarily provide ATP, and an increased representation of metabolic functions that result in the production of biomass. While advantageous for rapid cell division, some products of these pathways can overload the TCA cycle, resulting in elevated levels of reactive oxygen species; predictably, both lymphoid and stromal cells in the cortex exhibit high levels of genes associated with exposure to oxygen radicals. However, while cortical lymphoid cells also express genes responsible for protection from or repair oxidative damage, cortical stromal cells appear to lack expression of most such genes. Our findings suggest that the metabolic environment required to support rapid proliferative expansion of thymic lymphoblasts also results in constant exposure of stromal cells to oxygen radicals that, coupled with an inability to protect/repair themselves, leads to an accumulation of genetic lesions and accelerated atrophy.

4. Commensal Neisseria: Genomic Clues to Pathogenesis and Inflammation

Magdalene So (P)
University of Arizona, Tucson, AZ

Commensal bacteria comprise a large part of the microbial world, playing important roles in human development, health and disease. Yet, little is known about their genome content, their relatedness to their pathogenic cousins, and their interactions with their host. The genus *Neisseria*, containing both commensal and pathogenic species, provided an excellent opportunity to examine these issues. We undertook a comprehensive genomic analysis of the genus *Neisseria*. We sequenced the genomes of 8 species of commensal *Neisseria* that commonly inhabit the mucosa, and compared them to the published genomes of 11 clinical isolates of *N. gonorrhoeae* and *N. meningitidis*, the two pathogens in this genus. Commensals are ancestral members of the genus; the pathogens evolved most recently. Surprisingly, commensals are reservoirs of virulence alleles, containing nearly all the genes known or hypothesized to function in virulence. Moreover, they are able to exchange DNA with other *Neisseria* species, *in vivo* and *in vitro*. Our results suggest that *Neisseria* can quickly alter their pathogenetic potential through DNA uptake. They have important implications for the rapid evolution of pathogens with high frequency horizontal gene transfer systems. Based on these and other findings, we present a model to explain in mechanistic terms why commensals are nonpathogenic, and why they do not elicit an inflammatory response in the human host. We are currently testing this model, especially with regard to inflammation and aging.

5. Human Cytomegalovirus Latency and the ULb' Region

M. Umashankar, Alex Petrucelli, Lora Grainger, Louis Cicchini, Mike Rak, Peter Knepler, and Felicia Goodrum (P)
University of Arizona, Tucson, AZ

The ability of herpesviruses to maintain a lifelong relationship with their host through a latent infection is a remarkable adaptation requiring complex and coordinated interactions between multiple viral and cellular determinants. The molecular mechanisms underlying latency and persistence of a beta herpesvirus, human cytomegalovirus (HCMV), is poorly understood. While reactivation of the life long latent infection is associated with life-threatening pathology in immunocompromised individuals, co-existence of HCMV in healthy individuals is associated with increase risk of chronic diseases, including atherosclerosis and age-related immune senescence. We have previously characterized *UL138* as a viral determinant necessary, but not sufficient, for HCMV latency in CD34+ hematopoietic progenitor cells infected *in vitro*. *UL138* is a previously uncharacterized ORF encoded in the ULb' region of the genome unique to clinical or low-passage virus strains. *UL138* encodes a 21-kDa protein, pUL138, which localizes on the cytosolic face of Golgi membranes. Interestingly, pUL138 is encoded at the 3' end of three long 3' co-terminal transcripts. We have determined that these transcripts are polycistronic. pUL138 is translated by alternative IRES-mediated mechanisms and the sequences 5' of UL138 encode three novel proteins, pUL133, pUL135, and pUL136, in addition to pUL136. Each of these proteins localizes on the cytosolic face of Golgi membranes similarly to pUL138. Importantly, pUL133 and pUL135 physically associate with pUL138 in vector-based expression systems. This finding suggests that these proteins may impact the function of pUL138 and, therefore, the outcome of infection. Our work demonstrates that multiple mechanisms exist to ensure the expression of pUL138 infected cells and may represent a strategy to coordinate the expression of viral proteins required for latency and persistence.

6. Infectious Immunosenescence?

Graham Pawelec (P)
University of Tübingen, Germany

The umbrella term "immunosenescence" is applied to describe age-associated failing systemic immunity, believed to contribute to the increased incidence and severity of infectious disease in old animals and people. Very limited longitudinal studies in humans have begun to reveal biomarkers of immune ageing ("immune signatures") increasingly recognized as an "immune risk profile", or IRP, predicting mortality in the elderly. Studies in animals seem consistent with idea that most or all other mammals may also show an IRP. It is of practical and scientific interest to more accurately determine the IRP and to devise interventions to modulate immune ageing. In humans, usually asymptomatic infection with the persistent β-herpesvirus HHV5 (Cytomegalovirus, CMV) has an enormous impact on biomarkers associated with immunosenescence; a significant fraction of the human immune system is committed to controlling CMV. This commitment increases with age and may itself cause pathology as a result of maintaining higher systemic levels of inflammatory mediators and decreasing the "immunological space" available for immune cells with other specificities. On the other hand, and perhaps due to this enhanced inflammatory state, CMV infection may carry an early-life benefit in environments with a high pathogen load (ie. "natural" environments), which becomes deleterious for the majority of the population only in later (post-reproductive) life or under

pathological conditions. Moreover, recent research is beginning to suggest that certain individuals from families with multiple generations of exceptionally long-lived siblings are resistant to CMV infection and to the effects of CMV on immune signatures. Thus, the manner in which the immune system confronts persistent CMV infection may materially affect longevity of the host in protected environments. In this sense, immunosenescence may be said to be infectious.

7. HCMV Infection, Inflammation and Age-Related Diseases: A Dangerous Association

Rosanna Vescovini (P) and Paolo Sansoni (P)
Department of Internal Medicine and Biomedical Sciences, University of Parma, Italy.

The increase of cytomegalovirus (HCMV) seroprevalence with age and the age-related inflation of anti-HCMV T-cell responses are well-described phenomena in human aging, but questions about their origins, immunological relevance and consequences for health and diseases still remain unresolved. We conducted an observational cross-sectional study to evaluate both humoral and CD4+ and CD8+ T-cell responses against HCMV in groups of elderly subjects of variable health status. We found that both humoral and CD4+ T-cell anti-HCMV responses were specifically intensified in advanced aging associated with comorbidity, cognitive and functional impairments. This pattern of adaptive immunity indicates that immune responses targeting the extracellular phase of HCMV increase in the oldest subjects in poor health with physical and mental impairment, and could represent an indirect effect of localized and undetectable HCMV reactivation. We suggest that these subjects may be at risk for both direct pathogenic effects due to HCMV reactivation and indirect pathogenic effects linked to pro-inflammatory anti-HCMV effector responses.

8. Role of IL-7 in T cell Rejuvenation in the Nonhuman Primate Model of Aging

Afam Okoye[1](P), Mukta Rohankher[1], Christopher Pexton[1], Chike Abana[1], Audrie Pattenn[1], Janko Nikolich-Zugich[2], Louis J. Picker[1].
[1]Vaccine and Gene Therapy Institute, and the Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR 97006, [2]Dept of Immunology and the Arizona Center on Aging, University of Arizona College of Medicine, Tucson, AZ 85724.

Aging of the immune system in humans is characterized by diminished T cell production in the thymus and a loss of naïve and accumulation of effector memory T cells leading to dysregulated maintenance of peripheral T cell homeostasis. These changes lead to weakening of the immune defense against a wide spectrum of pathogens particularly those that have not been previously encountered by the host. Therapeutic approach to restore naïve T cell production and homeostatic maintenance of peripheral T cells has been a goal in combating immunological aging. Interleukin 7 (IL-7) is a pivotal cytokine in the support of thymocyte development and the maintenance of peripheral T cell homeostasis, and we therefore sought to use the aging rhesus macaque model to determine whether therapeutic use of this cytokine is efficacious in reversing the homeostatic dysreglation of aged immune systems. We demonstrate that exogenous rhesus IL-7 induces peripheral T cell proliferation and increases the numbers of circulating T cells in both adult and aged rhesus macaques with no measureable contribution from the thymus. Both CD4+ and CD8+, naïve and central memory T cells were expanded with therapy, but the increase in naïve T cell numbers was transient, whereas that of central memory T cell was prolonged. Although thymic rejuvenation has long been the primary goal of immunotherapy of senescent immune systems, the ability to expand central memory populations may also provide clinical benefit, an hypothesis we are currently pursing in the rhesus macaque model.

9. Aberrant Peripheral Neutrophil Migration in the Healthy Elderly

Elizabeth Sapey (P), Hannah Greenwood, James Stockley, Hema Chahal, Alex Love, Natasha Aaronson, Robert .H. Insall, Robert A Stockley, Janet M Lord.
School of Clinical and Experimental Medicine and MRC Centre for Immune Regulation, University of Birmingham, Birmingham, UK

Neutrophil function declines with age, with reduced phagocytosis and superoxide production. There have been conflicting data as to whether neutrophil migration is altered during ageing. Importantly, aberrant migration of neutrophils to a site of infection may reduce pathogen clearance and cause an increase in "by-stander" tissue damage, as neutrophils use proteases to aid migration through tissue. The aim of this study was to assess whether migratory dynamics of circulating neutrophils were different in the healthy aged.

Migratory parameters, (including chemotaxis and chemokinesis, directional changes and accuracy) were measured in neutrophils isolated from 20 healthy elderly and 20 young subjects. Interleukin 8 (IL-8), Growth related oncogene alpha (GROα), fMLP, Leukotriene B4 (LTB4) and C5a were used as chemoattractants. Surface expression of receptors for all ligands was measured by immunostaining. Neutrophils were then incubated with receptor antagonists in order to assess the effect on migration.

Neutrophils from older subjects migrated with the same speed (chemokinesis) but with reduced velocity (chemotaxis), directional persistence and accuracy towards all the chemoattractants, (e.g. IL-8: Chemotaxis, 1.4μm/min Vs. 0.6 m/min, $p < 0.0001$: Accuracy, 0.3 Vs. 0.05, $p<0.005$). There were no differences in surface expression for any receptor studied (for example: CXCR2: young MFI 28 (17 – 48), older MFI 36 (29 – 53), $p=0.09$). However, there was evidence of impairment of downstream signalling, as pre-incubating neutrophils from young subjects with receptor antagonists (for example, a CXCR2 antagonist) reduced their velocity, persistence and accuracy to levels comparable with those from older subjects.

We conclude that neutrophils from old subjects demonstrate reduced chemotactic efficiency when migrating towards a number of physiologically important chemoattractants. There are no differences in receptor surface expression. That inhibition of downstream signalling in young neutrophils produced an "old migration phenotype" suggests that altered chemokine

receptor signalling is likely to underlie reduced chemotaxis in neutrophils with age.

10. Chronic Inflammation and Myocyte Apoptosis in Sarcopenia of Aging

Emanuele Marzetti (P)
University of Florida, Gainesville, FL

Myonuclear apoptosis, a muscle-specific process of programmed nuclear death, is increasingly recognized as a possible mechanism underlying the pathogenesis of sarcopenia of aging. Chronic low-grade systemic inflammation, a common feature of aging, may contributeto the development of sarcopenia by promoting the execution of myocyte apoptosis. This hypothesis is supported by studies in animal models showing that the death-receptor pathway of apoptosis, triggered by tumor necrosis factor-α (TNF-α), is activated in the aged skeletal muscle, in conjunction with declines in muscle mass and strength. Furthermore, interventions such as exercise training and calorie restriction have shown to attenuate the extent of TNF-α-mediated myonuclear apoptosis, while preserving muscle mass and strength into old age. Recent experimental evidence suggests that interleukin 15 (IL-15), a muscle-derived anabolic cytokine, might mediate the anti-apoptotic actions of calorie restriction in the skeletal muscle by mitigating the activation of the TNF-α-mediated pathway of apoptosis. However, further research is necessary to understand the complexity IL-15 activity in the aged skeletal muscle, as well as to test if manipulation of IL-15 signaling may serve as a novel strategy to restore muscle mass and function at old age.

11. Non-Immune Roles for Immunoproteasome in Muscle

Deborah A. Ferrington [1] (P), Wendy Bratten [1] , Rebecca J. Kapphahn [1] , Haiming Liu [2] ,LeAnn Snow [2] , LaDora Thompson [2]
Departments of Ophthalmology [1] and Physical Medicine and Rehabilitation [2], University of Minnesota, Minneapolis, MN

The proteasome is a proteolytic complex that plays a fundamental role in regulating processes essential for cell viability, such as cell cycle regulation, control of signal transduction and gene expression, and the degradation of oxidized and misfolded proteins. Two types of proteasomes, the standard and immunoproteasome, have been described. Immunoproteasome was first characterized in cells of the immune system, where its role in generating peptides for antigen presentation to CD8 T cells as part of the immune surveillance was clearly described. However, we and others have reported that it is present in non-immune tissues, such as neurons and glia of the central nervous system and in skeletal muscle, suggesting other non-immune functions are possible. The focus of our studies have been to elucidate immunoproteasome's function in skeletal muscle, using aging and hindlimb unweighting (HU) as model systems to monitor how proteasome structure and function is altered under conditions eliciting muscle atrophy and fiber remodeling.

We have previously reported that in aged rat skeletal muscle, immunoproteasome content increased three-fold compared with content in young muscle. A similar upregulation in immunoproteasome content was also observed in young skeletal muscle after 21 and 28 days of HU. Measures of soleus fiber cross-sectional during HU showed that maximum fiber atrophy occurred between 7 and 14 days. Assessment of myosin heavy chain (MHC) expression indicated a significant increase in soleus fibers co-expressing both fast and slow MHC isoforms by 21 days of HU, suggesting active remodeling at later times of HU. Comparison of serial sections stained for immunoproteasome, slow MHC, and fast MHC showed the antibody for immunoproteasome stained most intensely in fibers co-expressing both MHC isoforms. These results suggest that immunoproteasome is not involved in the active phase of atrophy, but rather may be involved in protein isoform transformation.

Supported by AG032391 (DAF), AG17768, AG21626 (LVT), and HD49459 (LAS).

12. Predictors of Skeletal Muscle Response to Exercise Training in Elderly Adults

Charlotte A Peterson (P), Haiyan Zhu, Patrick M Kortebein, Heather M Bush, Jonathan F Harvey, Dennis H Sullivan and Richard A Dennis
University of Kentucky, Lexington, KY 40536 and University of Arkansas for Medical Sciences, Little Rock, AR 72205

Resistance exercise training typically increases muscle size and strength, however, the magnitude of the response varies significantly between individuals, particularly in the elderly. We hypothesized that specific acute responses to resistance exercise may be predictive of training outcome in the elderly. To test this hypothesis, gene expression was quantified in vastus lateralis biopsies from healthy older adults (68±6yrs) at baseline, following a single bout of resistance exercise, and after 12 weeks of resistance exercise training, to determine if expression was correlated with the training induced changes in muscle size or strength. After training, average muscle size and leg extension strength increased, ranging from -1% to +18% for size and +8% to +65% for strength. Post-acute exercise changes in the expression of genes that function in tissue inflammation, growth, and remodeling were observed, but did not correlate with training outcomes. However, a strong correlation was observed between leg extension strength gain and expression of specific genes at baseline ($P \leq 0.003$ and $R \geq 0.89$). Change in expression of these genes after training was inversely correlated with training outcome. Thus, higher baseline expression of key genes in muscle may convey an adaptive advantage for older adults and strength gains can be predicted prior to training by quantifying specific mRNAs.

Supported by AG12411.

13. Heat Shock Proteins as Modulators of Cytokine Production by Skeletal Muscle.

Anne McArdle (P), Dawn Harrison, Adam Lightfoot, Richard Griffiths, Francis McArdle, and Malcolm Jackson
School of Clinical Sciences, University of Liverpool, UK.

Skeletal muscles of adult mice and humans adapt

rapidly to contractile activity. Many changes in gene expression in skeletal muscle following contractions are mediated by Reactive Oxygen Species (ROS) through the activation of redox-sensitive transcription factors (TFs). NFκB is one such factor, NFκB activation is associated with increased production of pro- and anti-inflammatory cytokines and chemokines by muscle cells, which can then exert both autocrine and paracrine effects. Among numerous cytoprotective proteins demonstrating adaptive responses to contraction are Heat Shock Proteins (HSPs).

Muscles of old mice and mice with an accelerated loss of muscle mass (Cu,Zn superoxide dismutase null mice) demonstrate chronic activation of redox-sensitive TFs and an inability to acutely activate NFκB following a non-damaging contraction protocol. The chronic activation of NFκB is associated with a chronic systemic increase in inflammatory cytokines. The inability to further activate redox responsive TFs in response to contractions is associated with severe attenuation of normal changes in gene expression. Thus, increases in HSP content evident following isometric contractions in muscles of adult rodents are abolished in old rodents. Studies using transgenic mice have shown that functional deficits in skeletal muscle with aging are associated with an inability to produce HSPs. The mechanisms by which HSPs provide protection is unclear but is associated with levels of NFκB activation at rest and following contractions similar to those in muscles of adult mice and there is evidence from other studies that HSPs can interact directly with IKβ kinase (IKK). In addition, HSPs are released from muscle cells and act as signalling molecules to adjacent cells where they are able to activate NFκB in a similar manner to myokines.

This presentation will focus on the role of skeletal muscle of adult and old mice in the production of cytokines (myokines), the interaction between HSPs, NFκB activation and myokine production and the effect of modulation of muscle content of HSPs, such as those that occur during aging, on myokine production.

This work is funded by Research into Ageing, Biotechnology and Biological Sciences Research Council, Medical Research Council and United States National Institute on Aging (Grant No: AG-20591).

14. Role of 12/15-Lipoxygenase Pathway in Muscle Atrophy

Arunabh Bhattacharya (P), Amanda L Jernigan, Marian Sabia, Holly Van Remmen
Sam and Ann Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, TX

Aging is associated with a progressive decline in muscle mass and function which leads to significant increase in morbidity and mortality in the elderly. We previously found that skeletal muscle atrophy during aging and sciatic nerve transection (denervation) is associated with elevated levels of cytosolic phospholipase A2 (cPLA2). cPLA2 cleaves arachidonic acid from the membrane phospholipids, which is oxygenated to the fatty acid hydroperoxides, 12-hydroperoxyeicosatetraenoic acid (12-HpETE) and 15-HpETE by the downstream 12/15-lipoxygenase (12/15-LO) pathway. In the presence of GPx4, 12- and 15-HpETE are converted to 12-hydroxyeicosatetranoic acid (12-HETE) and 15-HETE, respectively. 15-HETE has been previously shown to activate the NFkB/ubiquitin–proteasome proteolytic pathway in C2C12 myotubes and decrease the IGF-1/Akt pathway in carcinoma cells. Therefore, the present study was designed to examine the role of the 12/15-LO pathway in muscle atrophy and to determine whether the effects are mediated through the modulation of ubiquitin-proteasome and lysosomal autophagy pathways of protein degradation. We found that protein expression of 12/15-LO and 15-HETE levels were elevated ~2-3 fold during aging and denervation-induced muscle atrophy. In addition, genetic ablation of the pathway in 12/15-LO homozygous knockout mice significantly attenuated denervation-induced muscle atrophy (7 days post-surgery), when compared to wild-type mice (gastrocnemius muscle: wild-type ~30% vs 12/15-LO-/- ~20%; soleus muscle: wild-type ~45% vs 12/15-LO-/- ~10%). Our initial results suggest that the attenuation of denervation-induced muscle atrophy in 12/15-LO-/- may be associated with the modulation of the lysosomal autophagy pathway, as indicated by lower LC3-II/tubulin ratio in denervated muscles from 12/15-LO null mice, compared to denervated muscles from wild-type mice. Our ongoing studies are further examining the role of the 12/15-LO pathway during aging and denervation-induced muscle atrophy.

15. Fatness and Proinflammatory State in Older Persons

Luigi Ferrucci[1] and Jeremy Walston[2] (P)
1National Instutue of Aging, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD

Obesity and Inflammation

Studies of the effect of aging gene expression in different animal species and across different tissue have persistently demonstrated that over-expression of immune response/complement activation genes and under-expression of genes related to mitochondrial function. Consistently, a wide range of studies in animal species and human have shown that aging is often accompanied by a mild pro-inflammatory state, testimonied by high level of inflammatory markers such as IL-6, even in individuals who are healthy and free of cardiovascular risk factors and diseases. Studies of gene expression at rest and after stimulation with LPS suggest that adipose and vascular tissues are major sources of pro-inflammatory cytokines. Obesity is a major concern, strong risk factor for inflammation, given the obesity epidemic developed over the last few years in the US and other countries. There is evidence that adypocytes, especially those located in the visceral fat, can affect inflammation and metabolism though different pathways, including direct secretion of signaling molecules, infiltration of macrophages that secrete inflammatory mediators and others. Accordingly, global obesity and visceral obesity appear to be additive independent contributors to inflammation. The production of pro-inflammatory cytokines (TNF-alpha) by adypocytes causes obesity-related insulin resistance in mice and possibly also in humans. A number of studies have demonstrated that weight loss is followed by a significant reduction of serum leveld of pro-inflammatory markers, including but not limited to IL-6

and CRP. Long term exercise also contributes to reducing inflammation but weight loss appears to be more effective than exercise. Bariatric surgery is effective, while liposuction is not, possibly because it mostly reduces subcutaneous fat. The effect of weight loss on inflammation is possibly the mechanism by which losing weight is effective in primary prevention.

16. Adipose Tissue Dysfunction: All Roads Lead to Inflammation

Philipp E. Scherer (P)
Touchstone Diabetes Center, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas

During the progression from the lean to the obese state, adipose tissue undergoes **hyperplasia** as well as **hypertrophy** in an attempt to cope with the increased demand for triglyceride storage. This requires a high degree of plasticity at both the cellular and at the tissue level. Even though adipose tissue as a whole seems to be a relatively static tissue containing many adipocytes that turn over relatively slowly, these cells are embedded in an environment that can rapidly adapt to the needs of expanding and newly differentiating adipocytes. The extracellular matrix of adipose tissue faces unique challenges with respect to adjusting to the need for remodeling and expansion. In parallel, the vasculature has to adapt to altered requirements for nutrient and oxygen exchange. A decrease in the plasticity of these processes leads to metabolic dysfunction. To maintain a healthy, non-inflamed phenotype, complex regulatory mechanisms are in place to ensure adipocytes and stromal vascular cells efficiently crosstalk to allow adipose tissue to expand upon increased demand for storage of triglycerides. Therefore, we propose a model of stepwise adipose tissue dysfunction that is initiated by **rapid expansion of existing adipocytes** to accommodate triglycerides during excess caloric intake. This leads very quickly to an acute, and eventually chronic, state of **hypoxia** in adipose tissue. As a result, HIF1α (hypoxia-induced factor α) is induced in adipocytes. However, rather than inducing a pro-angiogenic response like in many other tissues, HIF1α induces a **pro-fibrotic program**. This causes a generalized upregulation of many collagens, which eventually contributes to a significant **increase in the rigidity** of the extracellular matrix (ECM). This reduced flexibility of the ECM causes a reduction in expansion potential of the existing fat cells and eventually leads to significant **mechanical cellular stress**. Increased rates of **necrosis** of adipocytes are observed under those conditions. Residual lipid droplets require infiltrating **macrophages** to dispose of the excess lipids. These macrophages, exposed to high levels of triglycerides, interact with surrounding adipocytes and mutually enhance local secretion of pro-inflammatory factors. This local adipose tissue **inflammation** eventually results in systemic elevation of pro-inflammatory cytokines and mediates directly **insulin resistance** in a number of additional tissues. **Thiazolidinediones** (TZDs) enhance local adipose tissue **angiogenesis**, enhance **adipogenesis** and are potently **anti-fibrotic** and also effectively **suppress adipocyte and macrophage inflammation**. TZDs therefore exert positive effects at multiple levels, thereby enhancing overall health of adipose tissue and, as a consequence, reducing systemic insulin resistance. Fat pads differ a great deal with respect to how well they cope with the expansion process, and some of this expansion occurs in a **sexually dimorphic and age-dependent fashion**.

17. Inflammasome Signaling and the Origin of Adipose Tissue Inflammation

Vishwa Deep Dixit (P)
Pennington Biomedical Research Center, Baton Rouge, LA

Although a direct role for adipose tissue in immune-surveillance is not defined, the adipose depots in obesity harbour several innate and adaptive immune cells which contribute towards inflammation. The development of age-related adiposity is associated with increased inflammation which leads to type 2 diabetes, atherosclerosis, cancers, CNS dysfunction and dementia. However, the emergence of chronic 'sterile' inflammation and immune cell activation in adipose tissue in absence of overt infections or autoimmune process is a puzzling phenomenon. The Nod Like Receptor (NLR) family of innate immune cell sensors like the Nalp3/Cryopyrin inflammasome are implicated in recognizing several non-microbial origin 'danger-signals' leading to caspase1 activation and release of pro-inflammatory cytokines such as IL-1β and IL-18. Our data from mice and humans indicate that adipose tissue Nalp3 expression is correlated with chronic caloric-excess and insulin-resistance. Conversely, chronic caloric restriction and weight-loss induced improvements in insulin-sensitivity is associated with reduction in adipose tissue expression of Nalp3 and IL1β. Ablation of Nalp3 in mice prevented the obesity-induced inflammation, caspase-1 activation and enhanced the P13K-AKT mediated insulin signaling. Overall, our data establish that Nalp3 inflammasome is one of the important sensor of obesity-associated 'danger signals' that trigger activation of inflammation by processing and secretion of IL-1β and IL-18. Our data highlights the potential of targeting molecular pathways regulating caspase-1 activation in obesity and aging for management chronic inflammation induced co-morbidities.

18. A Tail of Life and Death: How Dietary Blueberry Attenuates Obesity-Associated Adipose Tissue Inflammation and Insulin Resistance

Martin Obin (P)
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Increased adiposity (and visceral adiposity in particular) promotes the metabolic syndrome, age-related disease and aging *per se.* These obesity comorbidities are associated with- and hypothesized to reflect- increased adipose tissue (AT) inflammation, a pathologic hallmark of both obesity and aging. AT inflammation is 'fueled' by adipocyte death, which, coincident with oxidative stress (OS) increases commensurate with AT expansion. Importantly, dying adipocytes recruit pro-inflammatory CD11c+ AT macrophages (ATMΦs) to scavenge the copious amouints of remnant lipid, and these ATMΦs are directly implicated in the inflammatory and

metabolic sequelae of obesity in both rodents and humans. Thus we hypothesized that preventing / delaying adipocyte death would attenuate the AT inflammation and metabolic dysregulation of obesity. We selected whole blueberry (BB) as a dietary supplement to prevent obesity-associated adipocyte death, because BB anthocyanins have been shown to 1) protect against OS, 2) alter MAPK and NFκB signaling pathways that regulate cell fate and inflammatory gene expression, 3) retard age-related functional declines, and 4) extend lifespan in *C. elegans*.

Accordingly, male C57Bl/6j mice were maintained for 8 wk on one of three diets: low (10% of energy) fat diet (LFD), high (60% of energy) fat diet (HFD) or HFD containing 4% (w:w) whole BB powder (HFD+BB). BB supplementation (constituting 2.7% of total energy) had no effect on HFD-associated alterations in energy intake, metabolic rate, body weight or adiposity. As expected we observed increased adipocyte death and an emerging pattern of gene expression in intra-abdominal AT of HFD mice indicating a shift towards global up-regulation of inflammatory genes (TNFα, IL-6, MCP-1, iNOS), increased CD11c+ ATMΦ recruitment, and increased oxidative stress (reduced GPx3). Notably, adipocyte death was dramatically reduced in mice fed HFD+BB, and this reduction was associated with globally attenuated inflammation, CD11c+ ATMΦ infiltration and OS. In keeping with these salutary effects, mice fed HFD+BB were significantly protected from IR and fasting hyperglycemia-i.e., obesity complications that promote accelerated aging. These results suggest that the cytoprotective and anti-inflammatory actions of BB and other dietary components can provide metabolic benefits that may delay age related disease and extend the "healthspan."

19. Adipose Tissue Macrophage Diversity Over Space and Time

Carey Lumeng (P)
University of Michigan Medical School, Ann Arbor, MI

The alterations in adipose tissue biology over the life of an organism is related to more than just what happens to the fat cells. It is now clear that stromal cells (non-adipocyte cells) in fat play a critical role in regulating fat function. Adipose tissue macrophages (ATMs) are the predominant leukocyte in fat and while there is much interest in these cells in obesity, the function of these cells in normal adipose tissue homeostasis is poorly understood. We will present our work detailing the diversity of adipose tissue macrophage phenotypes and outlining the properties of Type 1 and Type 2 ATMs in neonates as well as adults. Evidence will be presented that show that ATM subtypes differ in their location, recruitment kinetics, inflammatory capacity, and their ability interact with other leukocytes in adipose tissue. Newly defined chemokine receptors such as MGL1 that regulate the appearance of ATM subtypes in fat will be discussed in the context of lean and obese states and the regulation of nutrient metabolism.

20. Aging and Adipose Tissue Inflammation: Role of Nutrition

Simin Nikbin Meydani (P) and Dayong Wu
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Inflammation has been indicated in pathogenesis of many age-associated diseases including cancer, infection, cardiovascular diseases, diabetes, Alzheimer's and osteoporosis. Pro-inflammatory cytokines and cyclooxygenase products such as prostaglandin (PG)E_2 have been shown to contribute to age-associated inflammation. We previously showed that macrophages (Mϕ) and adipose tissue from old mice have up-regulated prostaglandin (PG) E_2, as well as inflammatory cytokines IL-6, IL-1 β, and TNFα production compared to young mice. We further showed that the increase in Mϕ PGE_2 production is an important contributor to the age-related decline in T cell function. Furthermore, up-regulation of adipose tissue PGE_2 and inflammatory cytokines has been indicated in the higher incidence of insulin resistance and diabetes in the elderly. Investigation into the mechanism of age-associated increase in PGE_2 and inflammatory cytokines showed that similar mechanisms might be involved in Mϕ and adipose tissue. In Mϕ, we showed that the age-related increase in PGE_2 production is due to increased COX-2 mRNA and protein levels leading to higher COX enzyme activity. The higher COX-2 mRNA expression was shown to be due to ceramide-induced inhibition of Ik-βdegradation leading to up-regulation of NF-κB activation, a key transcription factor in regulation of Cox-2 and inflammatory cytokine genes. Similar to Mϕ, adipocytes from old mice have higher expression of COX-2 as well as inflammatory cytokines IL-1β, IL-6, and TNF-α compared to young mice, which was also shown to be, at least in part, due to elevated levels of ceramide and NF-κB activation. Data will be presented on efficacy of calorie restriction and other nutrients/dietary interventions such as plant and fish-derived n-3 PUFA, and antioxidants to reduce age-related increase in inflammatory products as well as their implications for age-related diseases.

Supported by NIA grant RO1-AG009140-09, NIH # R21 AG030931-01, and US Department of Agriculture agreement #58-1950-7-707.

21. Dietary Restriction and Adiposity: Reduction of Fat is Inversely Related to Longevity in Mice

Chen-Yu Liao[1, 2] (P), Brad A. Rikke [3], Thomas E. Johnson [3, 4], Vivian Diaz[2], James F. Nelson[1, 2]
[1]Department of Physiology, University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, San Antonio, TX; [3]Institute for Behavioral Genetics, University of Colorado, Boulder, CO; [4]Department of Integrative Physiology, University of Colorado, Boulder, CO

Dietary restriction (DR), one of the most robust life-extending manipulations in rodents, is usually associated with reduced adiposity. Because excess adiposity is associated with metabolic disease, reduced adiposity has been hypothesized to play a role in the life-extending effect of DR. There is, however, little direct evidence to support this hypothesis. Previously, we described marked variation in the lifespan response of 41 recombinant inbred (RI) strains of mice to DR (60% of ad libitum (AL) food intake), ranging from life extension

to life shortening. Here, we used this strain variation to examine the relationship between lifespan modulation by DR and fat reduction. Lean mass was also measured to determine the specificity of any relationship found between lifespan and fat. Fat reduction, which averaged 35%, varied markedly across strains. Surprisingly, a number of strains under DR had no reduction of fat; others had reductions as great as 80%. The strain variation in the reduction of lean mass was less, ranging from none to > 30%. Across strains, longevity was inversely correlated with the extent of fat reduction after DR (males, $r = -0.41$, $P < 0.05$; females, $r = -0.63$, $P < 0.001$). Thus, strains with the least reduction of fat were most likely to show life extension and those with the greatest reduction of fat were most likely to have shortened lifespan under DR. This relationship was specific to fat; reduction of lean mass and lifespan were not correlated in DR mice. Absolute fat mass was also positively correlated with lifespan in DR mice, as well as in AL mice. In summary, these data do not support the idea that fat reduction plays an important role in life extension by DR. They suggest instead that factors associated with the maintenance of adiposity under DR are important to its life extending effect.

22. The Role of Visceral Fat on Insulin Signaling in Long-Living Mice

Michal M. Masternak(P), Andrzej Bartke, Feiya Wang, Adam Spong, Adam Gesing, Adam Salmon, Larry F. Hughes, Teresa Liberati, Ravneet Boparai, Yimin Fang, John J. Kopchick, Reyhan Westbrook
Departments of Internal Medicine, Geriatrics Research, Southern Illinois University School of Medicine, Springfield, IL

Longevity is positively correlated with enhanced insulin sensitivity and glucose metabolism. In the human that a decline in glucose tolerance begins in the third decade and continues throughout one's entire adult life. Obesity is also strongly associated with insulin resistance and glucose intolerance. Visceral fat (VF) depots are considered pro-diabetic, while subcutaneous fat is "good" body fat, and fat infiltration into tissues such as skeletal muscle or liver is considered as a critical pathology, causing insulin resistance. Our data indicate that concomitant with higher overall fat accumulation, growth hormone receptor knockout (GHRKO) mice have more VF than their normal counterparts and that the infiltration of fat into skeletal muscle and liver appears to be increased in GHRKO mice when compared to normal (N) animals, yet these knockouts are still very insulin sensitive. Interestingly, surgical VF removal (VFR) decreased insulin sensitivity and glucose tolerance in GHRKO mice in comparison to sham controls, while the same intervention improved insulin sensitivity and glucose tolerance in N mice. Additionally, VFR enhanced responses of insulin receptor to insulin in skeletal muscle ($P<0.0047$) and suppressed the inhibitory IRS1 phosphorylation at IRS1307ser in normal mice only ($P<0.04$) without any alterations in GHRKOs. GHRKOs have increased level of plasma adiponectin ($P<0.0001$), the adipokine which enhances insulin sensitivity and positively correlates with longevity. Analysis of subcutaneous and epididymal fat pads indicated that epididymal fat from GHRKO mice has an elevated level of adiponectin in comparison to the same fat tissue from N mice and to subcutaneous fat pads from both GHRKO and N mice. These findings show that the same endocrine organ plays different role on insulin sensitivity in GHRKO and N mice. We hypothesize that this divergent role of VF is due to different secretory pattern-mainly enhanced production of adiponectin in epididymal fat in GHRKOs.

Supported by NIA

23. Transcriptional Control of Thymic Rebound

Claire Blackburn [1] (P) and Nancy Manley [2] (P)
[1]Center for Stem Cell Research, University of Edinburgh, Scotland, UK
[2]Dept of Genetics, University of Georgia, Athens, GA, USA

Immunosenescence, or the decrease in immune system function with aging, is a major contributor to the general decrease in the quality of human health associated with aging. A primary cause of aging-related immunodeficiency is the postnatal involution of the thymus with age, which results in decreased production of naïve T cells. The postnatal thymus is the primary source of T cells in vertebrates, and many if not all stages of thymocyte development require interactions with thymic epithelial cells (TECs). The central importance of thymic involution in the development of immunosenescence is well established; however, the cellular and molecular mechanisms by which this process occurs are less clear. Identification of these mechanisms is of clear clinical relevance, as they represent potential therapeutic targets for inducing thymic rebound and immune system regeneration, and also have significance for cell replacement strategies. Identification of the molecular mechanisms underlying postnatal thymic epithelial homeostasis and involution is crucial to understanding and controlling these processes. The transcription factor Foxn1 is required for fetal TEC differentiation and proliferation, and is widely expressed in postnatal TECs; however, its role in the postnatal thymus is unknown. The Blackburn and Manley labs have generated several alleles of Foxn1, including hypomorphic alleles and an allele with decreased postnatal expression. Phenotypes for all of these alleles are sensitive to Foxn1 gene dosage, and are more severe in combination with the null allele, nude. Through analysis of these alleles, we have established that Foxn1 is required at multiple checkpoints for normal development and function of both fetal and postnatal TEC. The Manley lab has further shown that down-regulation of this epithelial-specific transcription factor is sufficient to trigger a premature involution phenotype. Based on these and other data, we propose that Foxn1 is required to maintain postnatal thymic homeostasis, and that changes in Foxn1 expression in TECs during aging contribute to the mechanism of aging-associated thymic involution.

24. S6 Kinase, Aging and Age-related Disease

Dominic Withers[1] and Brian Kennedy[2]
[1]Medical Research Council Clinical Sciences Centre, Imperial College, London W12 0NN
[2]Department of Biochemistry, University of Washington, Seattle, WA 98195; Aging Research Institute,

Guangdong Medical College, Dongguan 523808, Guangdong, P.R. China

Recent findings in invertebrates and mammals have demonstrated that reduced TOR kinase signaling leads delays aging. Moreover, rapamycin, a drug that inhibits TOR was recently reported to lead to robust lifespan extension even when administered relatively late in the lifespan of a mouse. These findings collectively point to the importance of understanding links between TOR signaling and aging at a mechanistic level. TOR activity regulates several processes that have been linked to aging including protein translation, autophagy and mitochondrial biogenesis. Two important substrates of TOR linked to translation are S6 kinase and 4E-BP1. Recent findings from the Withers lab indicate that mice lacking S6K1, one of two S6 kinases in mammals, have extended longevity. The goal of our collaborative project is to address two key questions: in which tissue or tissues does reduce S6 kinase activity slow aging and what are the specific translational changes accompanying reduced S6 kinase activity that are linked to aging.

We have made progress toward these goals, establishing conditional S6K1 knockout mice that can be crossed to tissue-specific Cre expressing mice for generation of tissue-specific knockouts. We have also performed translational studies on mice lacking S6K1. Progress toward these goals will be discussed and potential results will be placed into a broader context of TOR signaling, protein translation and aging.

25. Sources, Trasmission and Effects of Transcriptional Noise in C. Elegans Aging

Quee Lin Ch'ng[1] and Hang Lu[2]
[1]King's College London, United Kingdom; [2]Georgia Institute of Technology, Atlanta, GA

Aging is a complex process affected by genetic, environmental and stochastic factors. How these factors interact is not fully understood. Our long term goal is to define the relationships between genetic pathways, environmental inputs and stochastic factors that contribute to aging, and build models that predict the aging outcomes of individuals based on their genetic makeup, past experiences, and readouts from biomarkers. Our approach exploits the key advantages of the C. elegans model by integrating analysis of gene expression, signaling, behavior and physiology in the intact animal. The aims of this collaborative project are to determine how transcriptional noises in environmental responses translate to heterogeneity in lifespan and aging in C. elegans, and to define environmental and genetic factors that contribute to these sources of noise. To achieve these aims, we have been developing new microfluidic and automated microscopy systems capable of collecting large scale data necessary for our analysis, as well as generating a molecular genetic pipeline for single copy insertions of transcription markers. These new technologies greatly accelerate the experimental process and allow us to quantify for the first time at single cell resolution, the large number of samples needed to uncover mechanisms related to transcriptional noise contributing to aging.

26. Mechanisms of Reduced T Cell Immunity in Older Adults

Arnie Akbar[1] and Janko Nikolich-Zugich[2]
[1]University College London, United Kingdom; [2]University of Arizona, Tucson, AZ

Aging correlates with a marked susceptibility to infectious diseases. The progressive decline with age of the immune system – immunosenescence - is the primary underlying cause of this increased susceptibility. Important gaps remain in our understanding of the fundamental nature of immunosenescence, as well as in our practical ability to protect older adults against infectious diseases. Some of these result from the insufficient integration of the available models in which to research immunosenescence, and incomplete validation of the relevance of obtained data to the human aging.

This proposal seeks to reduce this gap by a concerted effort to integrate human and mouse models and study memory T cell response in the skin of healthy young and old donors. In a novel human model, we have identified a significant defect in older adults in delayed-type hypersensitivity (DTH) responses to tuberculin antigens (Ag) by cutaneous CD4 memory T-cells. This has led to our **central hypothesis: that one of the main age-related defects in immunity is the inability to efficiently direct Ag-specific memory responses to the sites of initial microbial challenge (**skin, mucosa). We are testing this hypothesis using a combination of complementary mechanistic mouse and human studies, designed to cross-inform each other, and always ultimately verifying the mechanisms in humans.

27. The WNT-Chromatin Axis in Aging

John Sedivy[1] and Peter Adams[2]
Brown University, Providence, RI; 2Beatson Institute for Cancer Research, Glasgow

The survival of populations in developed nations into extreme old age is a remarkable phenomenon in human history. This change has come about largely through improved public hygiene, decreased child mortality and a decrease in infectious diseases. However, the steady increases in the average age of the population have resulted in an ever increasing burden of the degenerative diseases of aging, such as osteoporosis, Alzheimer's disease, diabetes and cancer. Currently, there are several mutually non-exclusive models to explain the mechanisms behind these degenerative aging processes. One theory is centered on the idea that replicative senescence of cells limits their proliferative capacity and hence tissue renewal. Other models suggest that accumulation of genetic and/or epigenetic (chromatin) damage with age eventually impairs cell and tissue function. In this application, we test a hypothesis that links two of these ideas – cellular senescence and epigenetics – to a pathway that has not previously been considered to be a major regulator of aging, namely, Wnt signaling. Although not widely viewed as a regulator of aging, the Wnt signaling pathway is well documented to be an evolutionarily conserved determinant of tissue and organismal development, and later in life, adult tissue homeostasis. The research proposed here is based on recent and exciting discoveries in the two collaborating laboratories. First, the work of Peter D. Adams has

implicated Wnt signaling in the regulation of cellular senescence by showing that *in vitro* – human fibroblast cell culture – repression of Wnt signaling triggers extensive heterochromatinization and cellular senescence. Second, the *in vivo* studies of John M. Sedivy have found that a marked expansion of facultative heterochromatin occurs in association with cellular senescence and aging in mouse and primate tissues. Based on these results we propose that a Wnt–Chromatin–Senescence signaling axis is an important determinant of organismal aging. We propose here a series of experiments to initiate the investigation of this novel signaling axis, the mechanisms of its operation, and its role in organismal aging. Aim 1 will perform high resolution, genome-wide mapping of senescence-associated changes in chromatin structure that are triggered by reduced Wnt signaling *in vitro*. Aim 2 will investigate the links between Wnt signaling, heterochromatinization, cellular senescence and aging *in vivo*, using mouse, primate and human models. Aim 3 will assess cellular senescence and genomewide chromatin changes in mice harboring hypomorphic Wnt pathway mutations. Our goal is to use a discovery-based approach to reveal epigenome-wide characteristics of aging processes, functionally connect these with Wnt signaling pathways, and ultimately open the road to new pharmaceutical targets.

28. Mechanisms of Exceptional Longevity in the World's Longest lived Animal

Iain Ridgeway[1] and Steven Austad[2]
[1]University of Bangor, Bangor, Wales; [2]University of Texas Health Science Center, San Antonio, TX

We are investigating mechanisms of aging in bivalve mollusks, including the ocean quahog (*Arctica islandica*) which is the longest-lived animal known. Many species of biivalve molluscs can be aged precisely from their shell morphology, can be collected in large numbers and transported alive to research laboratories. Within this group of animals longevities in natural populations range from about 1 year to more than 400 years. These traits in sum make the bivalve mollusks a potentially informative group in which to discover novel mechanisms modulating resistance to life's damaging processes. Our project utilizes 7 bivalve species encompassing the full range of longevities noted above to evaluate the hypothesis that longevity is modulated by mitochondrial efficiency in producing ATP while minimizing reactive oxygen species production. We will also evaluate hypotheses that proteome stability is a critical longevity determinant and that the ability to resist stress is a critical determinant of longevity.

29. Neuroinflammation and Gene Expression Involved in Synaptic Plasticity and Memory: Pharmacological Approaches to Restore Neuronal-Microglia Communication

Susanna Rosi (P)
University of California San Francisco, San Francisco, CA

Chronic neuroinflammation is present in the early stages of many neurodegenerative diseases and is reliably detected by the presence of activated microglia. Activated microglia and their products are key mediators of the neuroinflammatory process, and may contribute to cognitive dysfunctions associated with these disorders. Neuroinflammation can be induced by chronic lipopolysaccharide (LPS) infusion into the fourth ventricle of rodents and results in: 1) impaired hippocampal-dependent memory; 2) region selective microglia activation; 3) astrocytosis; and 4) elevated levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). TNF-α is one of the primary cytokines synthesized and released by activated microglia. Once TNF-α is released, it initiates a cascade of self propagating cellular events including a blockade of glutamate uptake by glia, enhanced released of glutamate by astrocytes and disruption of normal physiological activity that could alter the hippocampal functioning. Further support for the role of microglia in altered hippocampal function comes from our previous studies that show that chronic neuroinflammation alters the expression of the plasticity related behaviorally-induced immediate early gene (IEG) *Arc* (activity-regulated cytoskeleton-associated protein) in the dentate gyrus and CA3 regions. Both of these hippocampal regions are characterized by a pronounced increase in activated microglia, which result in altered coupling of neuronal activity with macromolecular synthesis (transcription and translation) implicated in learning and memory. LPS is known to activate microglia directly, leading to increase of glutamate release and in enhanced NMDA signaling and TNF-α synthesis. We investigated whether treatment with 1) a low affinity NMDAR antagonist (memantine); or 2) with selective inhibitor of TNF-α protein synthesis (TNF-α SI) could prevent the consequences of neuroinflammation and restore information processing in the hippocampus. Both memantine and TNF-α SI significantly lowered the number of activated microglial cells, normalized the expression of the immediate early gene *Arc*. Combined these findings suggest that pharmacological intervention to interrupt the cycle of events initiated by activated microglia may confer neural and cognitive protection and may be of significant benefit in the setting of neuroinflammation-associated diseases.

30. Nutritional Support for Aging Stem Cells

Paula C. Bickford (P)
James A Haley VAMC and Center of Excellence for Aging and Brain Repair, USFHealth, Tampa, FL

Aging is associated with a decline in many forms of synaptic plasticity, one of which is a decline in neurogenesis in the tow primary stem cell niches of the brain the subgranular layer of the dentate gyrus and the subventricular zone. There are several possible alteration that may underlie this age-related alteration neurogenesis including intrinsic alteration in gene expression as well as extrinsic influences of the environment on the stem cell niche. We have examined the role of microglia as one of the extrinsic influences on the stem cell niche. Microglia under "resting" conditions are in a surveillance mode that entails constant interactions and sensing for signals that would require a response, either a classical activation or an alternative activation. There are several key signals from neurons that are used to keep microglia from progressing towards an activation state. One of these that we have studied is fractalkine, a chemokine that we have shown is reduced

in aging and thus loss of this signal may be one reason that microglia in a normal aged brain are more activated. This has long reaching implications for neural plasticity in the form of LTP and neurogenesis. We have also demonstrated that nutritional supplementation with spirulina or a proprietary supplement called NT-020 can reduce classical activation of microglia and increase neural plasticity as measured by neurogenesis both in vivo and in vitro.

31. Brain Aging: Influence of Inflammation and Obesity

Donald K. Ingram, PhD, Paul J. Pistell, PhD, Christopher D. Morrison, PhD, Annadora J. Bruce-Keller PhD, Jeffrey N. Keller, PhD
Pennington Biomedical Research Center, LSU System, Baton Rouge, LA

Current estimates of the number of obese persons over 65 years of age are close to 30%. For those aged 45-64, estimates are near 40% with incidence having more than doubled over the last 35 years. This obesity epidemic will have major negative impact upon the health and quality of lives of older persons as well as create incredible challenges to the health care system and its financing. Given the relationship of caloric intake to risk of Alzheimer's disease, the impact of this epidemic on neurodegenerative diseases is of great concern. To address a critical research need, we have been developing rodent models to evaluate the effects of long-term dietary-induced obesity on brain aging. We have focused on oxidative stress and inflammation as major drivers of accelerated brain aging with functional consequences assessed as performance in a complex T-maze. Comparing responses of young and aged mice (C57BL/6) to high fat diets of different compositions (Western diet: 40% butterfat and 29% sucrose vs a High Fat Lard diet: 60% animal fat), we have noted that both regimens induce the pathophysiology of the metabolic syndrome (increased adiposity, blood glucose, insulin, leptin). Despite these diet-induced changes, measures in brain of oxidative stress (protein carbonyls; Nrf2 activity), inflammation (NADPH oxidase, levels of TNFα, IL-6, MCP-1, Iba-1) and neurotrophic activity (BDNF) revealed differential effects across diet and age. Mice on the High Fat Lard diet were more greatly affected as were aged mice. These changes associated with this diet were related to impaired memory performance in the complex T-maze. Although these findings remain to be expanded, our initial insight appears to be that diet composition rather than the induction of obesity and metabolic changes appears to be the driving force behind elevated markers of oxidative stress and inflammation in brain that are associated with cognitive impairment.

32. Persistent Oxidative Stress Through NFkB Induction of Proinflammatory Genes and Oxidases That Lead to Age Related Brain Degeneration

Fulton T. Crews (P)
John Andrews Distinguished Professor, Dept. of Pharmacology and Psychiatry, School of Medicine at the University of North Carolina at Chapel Hill.

Our studies suggest that induction of brain innate immune genes, including proinflammatory cytokines, proteases and oxidases form a pathological loop of activation of NFkappaB (NFkB) a transcription factor that increases expression of cytokines, NADPH oxidase (NOX), iNOS, COX2 and other genes increasing reactive oxygen species (ROS). Reactive oxygen species (ROS), cytokines, and proteases act to sustain NFkappaB innate immune gene induction for long periods. In C57BL/6 mice systemic TLR immune agonists TLR4 (LPS), TLR3 [polyI:C], TNFα, and ethanol all induce brain innate immune genes. Aging leads to increased innate immune gene activation. TLR agonists, LPS and PolyI:C, as well as ethanol treatment activate oxidative enzyme induction accelerating and leading to persistent increases in brain mRNA and protein levels of MCP-1, IL-1beta and $gp91^{phox}$, the catalytic subunit of NOX (real-time PCR and ELISA). These changes in gene expression coincide with increased ROS, loss of hippocampal neurogenesis and markers of neuronal death. Agents that block NFkB or NOX protect the brain. Environmental factors, e.g. exercise or drugs that increase CREB transcription can blunt NFkB transcription reducing neuronal death, increasing neurogenesis and increasing trophic factor expression factor. In a senescent model Parkinson's disease we studied dopamine neurons (TH+IR) for long periods after a single LPS injection. Innate immune genes were persistently induced in brain although no marked change in TH neurons occurred for 5 months. However, at 7-months a 23% decrease was found that progressed to 47% by 10 months. L-DOPA reversed motor deficits in senescent LPS treated animals. NOX-deficient (PHOX-$KO^{-/-}$) mice do not show LPS-induced senescent loss of TH neurons. Markers of neuroinflammation including activated microglial morphology, TNFα levels and other factors were reduced in LPS treated PHOX-$KO^{-/-}$). These results suggest induction of innate immune genes, particularly NOX leads to: production of ROS and amplification of proinflammatory innate immune genes, associated microglial activation, loss of neurogenesis and neurodegeneration underlie senescent neurodegenerative diseases. (Supported by NIH-NIAAA).

33. Inflammatory Processes Begin Before Birth and Extend Throughout the Lifespan

Caleb Finch (P)
Andrus Gerontology Center and Dept Biological Sciences, University of Southern California, Los Angeles CA

Inflammatory processes interact with virtually all chronic conditions of aging and are manifested in many tissues independently of specific pathology (Finch 2007). Vascular degeneration, which is a major source of morbidity and mortality, can be traced prenatally in late trimester human arteries which show microscopic foci of inflammatory cells and oxidative damage. Prenatal evironmental influences on atherosclerosis are iindicated by the 1919 birth cohort, which was exposed during gestation to the peak of 1918 Influenza pandemic: 60 years later, those born in the 1st quarter of 1911 showed 25% excess of heart disease (Mazumder et al 2010). These environmental influences on aging, together with recent findings that cell senescence leads to increased focal inflammatory expression, support the theory that inflammation is a core process of human aging (Finch and Crimmins, 2004; Finch 2010).

Finch CE, Crimmins EM (2004) Inflammatory exposure and historical changes in human life spans. Science 305: 1736-1739.
Finch CE (2007) The Biology of Human Longevity: Nutrition, Inflammation, and Aging in the Evolution of Lifespans, Academic Press: San Diego.
Finch CE (2010) Evolution of the human lifespan and diseases of aging: roles of infection, nutrition, and nutrition. PNAS, 107 (suppl. 1) 1718-1724
Mazumder B, Almond D, Park K, Crimmins EM, Finch CE (2010) Lingering prenatal effects of the 1918 Influenza Pandemic on cardiovascular disease. J Devel Origins Health Dis 1:26-34.

34. Resveratrol Supplementation Supports Mitochondrial Function and Improves Associative and Spatial Learning and Memory Performance in Aged Mice

M. Hasan Mohajeri (P), Annis O. mechan, Nicole Seifert, Hnery Rieger, Jenny Piussi, Adrian Wyss
R&D Human Nutrition and Health, DSM Nutritional Products, Basel, Switzerland

Resveratrol (trans-3,5,4'-trihydroxystilbene) is a natural polyphenol found in several food sources including grapes, peanuts and red wine. Due to changes in demographic structure, the decline of cognitive abilities with age is among the largest socio-economic problems of modern societies. Therefore, it is desirable to search for safe nutritional compounds to delay or prevent age-associated reductions in learning and memory. Beneficial effects of resveratrol on brain functions have been studied in several paradigms including animal models of neurodegenerative disorders, such as Alzheimer's disease, and particularly in behavioral tests examining spatial memory only. Here we have tested aged animals, after chronic dietary supplementation with 100 mg/kg/d b.w. resVida® (a nature-identical 99% pure trans-resveratrol) for at least 4 weeks, in four different behavioral paradigms examining exploratory-, associative-, stress-related- and spatial- learning and memory. Animals did not differ in their general health status or body weight. Our data show that resveratrol supports neuronal survival by supporting mitochondrial function, through protection against oxidative stress, and that resveratrol significantly promotes associative- and spatial- learning and memory but is ineffective in supporting other learning paradigms tested in this study. These data suggest that supplementation with resVida may be helpful in improving specific aspects of learning and memory in daily life situations and further may help to prevent the normally occurring age-associated deterioration of cognitive performance.

35. Human Marrow-Derived Bone Stem/Progenitor Cells: Effects of Age and Inflammation

Julie Glowacki (P)
Department of Orthopedic Surgery, Brigham & Woman's Hospital, Harvard Medical School and Harvard School of Dental Medicine, Boston, MA

Adult bone marrow includes stem/progenitor cells of the lineage of bone-resorbing osteoclasts and the lineage of bone-forming osteoblasts. Adult marrow is an available source of cells for tissue engineering and for studying mechanisms of skeletal aging. We use marrow discarded during the course of orthopedic surgery as a source of osteoclast and osteoblast progenitors. Low-density cell preparations are enriched in the stem/progenitor cells. Their *in vitro* behaviors are correlated with the age and clinical status of the subject from whom they were obtained.

Freshly isolated low-density bone marrow cells include non-adherent stem/progenitors of osteoclasts and the adherent cells that provide factors that regulate osteoclast differentiation. There was an age-related increase in *in vitro* differentiation of osteoclasts (Spearman r=0.89, p=0.007). Osteoclast progenitor cells possess two receptors whose activation promotes osteoclastogenesis; there was an age-related increase in expression of both *c-fms* (r=0.61, p=0.006) and RANK (r=0.59, p=0.008). In addition, there was an age-related increase in the activating ligand for RANK (RANKL, r=0.41, p=0.049). Osteoprotegerin (OPG) is a decoy factor than blocks RANKL binding with its receptor RANK; the expression of OPG was inversely correlated with age (r=-0.43, p=0.049). Thus, the age-related increase in bone-resorbing osteoclasts can be attributed to intrinsic changes in the factors and receptors that regulate their differentiation.

In a pilot study, marrow cells were isolated from matched subjects with/without inflammatory rheumatoid arthritis (RA). Production of the pro-osteoclastogenic cytokine Interleukin-6 (IL-6) was 18-fold higher in cells from RA than from matched controls. Constitutive IL-6 production by cells from an RA subject receiving *in vivo* glucocorticoid treatment, however, was equal to controls. Thus, *in vivo* status of inflammatory disease and anti-inflammatory therapy influenced the *in vitro* behavior of marrow cells.

Adherent stromal cells from adult marrow include progenitors of the osteoblast lineage, among others. Those marrow stromal cells (MSCs) showed intrinsic age-related decreases in proliferation (p=0.005) and in osteoblast differentiation (p<0.001). Further, their *in vitro* functions are influenced by estrogen status, vitamin D status, co-morbidities, and medications being taken by the subject.

In sum, studies with human marrow-derived cells indicate profound effects of age and clinical status that are retained when the cells are studied *in vitro*. There are intrinsic changes in the marrow that increase bone resorption and decrease bone formation; these changes explain the mechanisms of skeletal aging. This approach reveals mechanisms of skeletal aging and pathophysiology and allows for testing approaches for rejuvenation and for tissue engineering for elders.

36. Prevention of Inflammation-Induced Bone Destruction in Arthritis

Charles J. Malemud, (P)
Department of Medicine, Division of Rheumatic Diseases, Case Western Reserve University, School of Medicine, Cleveland, Ohio

Inflammation-induced destruction of subchondral bone is one of the hallmarks of the pathology of rheumatoid arthritis (RA). Experimental studies in the mouse showed that osteoclast development from bone marrow-derived osteoprogenitor cells correlated with the administration of tumor necrosis factor-α (TNF-α). Therefore, RA

patients administered anti-TNF-α therapy in combination with methotrexate (i.e. combination therapy) would be expected to show dampened development of osteoclasts from monocyte precursor cells *ex vivo*. This proposed mechanism could account for the finding that combination therapy reduced the progression of RA bone destruction as measured by digital X-ray radiogrammetry. Bone erosion is also mediated by the *R*eceptor *A*ctivator for *N*uclear Factor *κ*B *L*igand (RANKL)/RANK signaling pathway which in RA is activated, in part, by elevated levels of circulating interleukin-6 (IL-6). Thus, IL-6 receptor (IL-6R) neutralization by the anti-IL-6R monoclonal antibody, tocilizumab, might also be expected to suppress RANKL/RANK-mediated bone destruction in RA. Indeed, IL-6 blockade in experimental arthritis in transgenic mice expressing human TNF-α inhibited osteoclast development and bone erosions but did not suppress other biomarkers of inflammation. Finally, IL-1β and TNF-α were shown to be strong stimulators of IL-7 production. Further, IL-7 was a critical inducer of osteoclastogenic cytokines in T-cells which required RANKL, but was independent of TNF-α. Importantly, high levels of IL-7 receptor-α (IL-7Rα) were found in human RA synovial fluid and experimental *ex vivo* studies using monocytes collected from RA patients showed that recombinant human soluble IL-7Rα inhibited IL-7-induced T-cell proliferation and interferon-γ production. Thus, in RA, neutralization of IL-7Rα activation may also be useful for dampening T-cell responses as well as erosive bone destruction.

37. Harnessing Inflammation in Strategies for Bone Tissue Engineering

F.K. Kasper (P), P.M. Mountziaris, S.N. Tzouanas and A.G. Mikos
Department of Bioengineering, Rice University, Houston, Texas

Inflammation plays an immediate and crucial role in the process of healing after fracture or injury to bone. However, in certain clinical contexts, such as in inflammatory diseases or in response to the implantation of a biomedical device, the inflammatory response may become chronic and result in destructive catabolic effects on the bone tissue. Indeed, tremendous effort has been invested in the development and application of pharmacologic approaches to mitigate uncontrolled inflammation following bone fracture. Nevertheless, incorporation of approaches for the rational control of inflammation in reparative therapies may facilitate bone fracture healing. This talk will present tissue engineering strategies to harness inflammation for the purpose of promoting bone regeneration in large bone defects.

38. Modulatory Effects of Inflammatory Isoprostanes and Vitamin D on Telomerase in Human T Lymphocytes: Impact on Bone Loss During Aging

JP Chou (P), ST Parish, RB Effros
Department of Pathology & Lab Medicine, David Geffen School of Medicine at UCLA, Los Angeles

Osteoporosis and reduced bone mass, which are associated with increased morbidity and mortality in the elderly, are mediated by a variety of immunological factors. Two major influences on bone homeostasis are Receptor Activator of NFkB Ligand (RANKL), which stimulates the maturation of bone-resorbing osteoclasts, and vitamin D, which is essential for bone integrity and bone mineralization. Previous studies have shown that exposure of human T lymphocytes to oxidized lipids results in increased RANKL production, and that binding of vitamin D to its receptor (VDR) augments T cell receptor signaling and activation. We hypothesized that both of these observations may relate to the process of replicative senescence and telomerase dynamics of T cells, in part based on clinical associations between osteoporotic fractures and the presence of high proportions of senescent T cells. Purified T lymphocytes from healthy donors were activated in the presence of diluent or iso-PGE2, an inflammatory isoprostane produced by lipid peroxidation, and telomerase activity was measured by the telomere repeat amplification protocol. Exposure to iso-PGE2 was associated with an approximately 50% and 70% reduction in telomerase activity on day 3 and day 50, respectively. The iso-PGE2-treated cells also exhibited reduced proliferative potential as compared to control-treated cells. The effects of 1,25-hydroxyvitamin D, the active form of vitamin D in the body, were also investigated. Treatment of CD8+ T lymphocytes with vitamin D was associated with 30% greater telomerase activity following primary stimulation and 60% greater activity following secondary stimulation. Since reduced telomerase activity in T cells is associated with progression to replicative senescence and production of multiple pro-inflammatory cytokines that can stimulate bone resorption, our findings have important implications in understanding how to maximize nutritional benefits of a low-fat and high vitamin D diet in order to maintain bone integrity during aging.

Supported by NIH AG023720.

39. The Aging Eye, Mechanisms Related to Cataract

Norman S. Wolf (P), William R. Pendergrass, Galynn D. Zitnik, Silvan R. Urfer
The University of Washington, Department of Pathology, Seattle, WA

Age-related cataract (ARC) is the leading cause of human blindness in the world, even today. It occurs with high incidence in all mammals and birds that survive to old age. In order to prevent this pathology, it is necessary to understand the events in the lens that precede ARC. These changes occur gradually and with increasing severity. We have followed in the mouse and rat lens the accumulating age-related alterations in cell differentiation, cell function, and cell damage. These aging changes include a reduced replication rate and numerical reduction of lens surface epithelial cells (LEC), the presence in the lens cortex of reactive oxygen species (ROS), the presence of 8-oxo-guanine (8-oxo-G) adducts in the DNA of the LEC and lens fiber cells, and a failure to remove LEC nuclei fragments during the differentiation phase of surface LEC changing to lens fiber cells. Possibly related to this last item is the age-related loss of lysosomal activity in the lens. These events can be shown by IHC and confocal/fluorescent dye studies. They lead to obstruction of the ocular light path and concur with the development of age-related cataract, as will be presented. We suggest that a major

cause of these events is oxidative damage and show anti-oxidant means to delay ARC occurrence.

40. Frailty: A Clinical Perspective

Mindy J. Fain (P)
University of Arizona, Tucson AZ

Frailty is a new and emerging syndrome in geriatrics associated with functional decline, hospitalization and death. It affects ~ 7% of people over the age of 65, and ~ 20% of community dwelling older adults over the age of 80. Frailty, as distinguished from normal aging, represents a state of enhanced vulnerability to stress due to decreased physiological reserves in multiple organ systems. Contrary to popular belief, not all elderly are frail – and frailty frequently occurs in elders without other acute or chronic conditions. Frailty is manifested as a loss of skeletal muscle mass (sarcopenia), abnormal function in inflammatory and neuroendrocrine system, and poor energy regulation. A commonly used phenotypic definition of frailty is the Frailty Index (Fried and colleagues), where frailty is defined as meeting 3 or more criteria for weight loss, grip strength, endurance, walking speed, and physical activity. Of great interest, selected proinflammatory cytokines and coagulation factors are elevated in frail adults when compared with age-matched controls. Current research attempts to elucidate the physiological causes of frailty, and the etiologies of the presumed global dysregulation.

Selected References:

Fried LP, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-M156

Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: towards a better understanding of physiology and etiology: summary from the American Geriatrics Society National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54:991-1001

Ahmed N, Mandel R, Fain M. Frailty: An Emerging Geriatric Syndrome. Am J Med. 2007;120:748-753

Kanapuru B, Ershler W. Inflammation, Coagulation and the Pathway to Frailty. Am J Med. 2009;122:605-613

41. Models of Frailty

Jeremy Walston (P)
Johns Hopkins University, Baltimore, MD

Clinicians and Investigators working with older adults have long recognized a subset of older patients who are weak, fatigued, less responsive to treatments, and more likely to develop iatrogenic complications. Many investigators have operationalized frailty models that attempt to capture the vulnerability to adverse health outcomes observed in vulnerable populations. Some have utilized disability, others medical illnesses, and some muscle weakness or mobility measures. A research group at Johns Hopkins University has developed and validated a frailty screening tool that includes measures of muscle strength, walking speed, weight loss, physical activity levels, and fatigue as its major components. These who meet the frailty threshold are up to 6 times more likely to die over a 3 year period when compared to age-matched non-frail individuals. Those who meet these criteria are much more likely to have increased serum levels of inflammatory mediators and salivary cortisol and decreased levels of IGF-1 and DHEAS. This altered physiology is hypothesized to provide a 'platform of vulnerability' from which adverse health outcomes and chronic disease states are more likely to develop. In order to more carefully study this physiology and the molecular biology that underlies frailty, a mouse model of frailty that replicates the frailty phenotype late in life has also been developed and validated. This mouse lacks the anti-inflammatory cytokine IL-10 and develops chronic inflammation and muscle weakness later in mid-late life. This mouse model has afforded an opportunity to study age-related biological changes in many tissues and physiological systems that may be influencing late life decline and vulnerability to adverse outcomes and chronic illness in humans.

42. Infectious Diseases and Inflammation a Clinical Perspective

Kevin P. High (P)
Wake Forest University, Winston-Salem, NC

The inflammatory response presumably began as something "good" - a major player in host defense. In a world in which childhood immunization, sanitation, and antibiotics have greatly decreased the risk of death due to infection, inflammation is now seen by many in the field of aging as an "evil." Interestingly, the "evil" of inflammation triggered by occult or overt inflammation in the aged is associated with a reduced capacity to shut-down the inflammatory response when compared with young adults. Further, frailty and co-morbidity further exacerbate the inability of older adults to turn off inflammation after it is triggered. Interestingly, chronic infections, particularly CMV, but also HIV, hepatitis C, and others may contribute to immune senescence and underlying inflammation by clonal expansion of pro-inflammatory cells (particularly CD8+ T cells). Thus infection may be a cause of inflammation that can accelerate the aging process in many organ systems. Finally, there is a reciprocal relationship between inflammation and infection in that reducing baseline inflammation back to levels seen in young adults results in enhanced immune responses and may reduce infection risk.

43. Scientists and Doctors: Lost in Translation

James L. Kirkland (P)
Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, MN

The aging biology field has moved from a descriptive phase through definition of mechanisms and recently into development of interventions that increase longevity. Whether these interventions not only increase survival, but also enhance function and healthspan and delay frailty and onset of age-related disease, needs to be determined. They need to be translated into clinical therapies. Translation of interventions from animals into humans is a difficult, expensive process for which the field is not fully prepared. In clinical research, outcomes are carefully defined to allow comparison across studies by different research groups, much as analysis of survival curves has been standardized. To allow comparisons among experimental animal studies and

between animal and human studies, standardized outcomes that are relevant, reproducible, inexpensive, and reliably capture age-related changes across major physiological and functional domains need to be devised for use in each experimental animal model. It could be helpful to involve clinicians in developing appropriate outcome measures. Successful translation is an iterative process between basic and clinical studies. It ideally involves a partnership on an equal footing between basic and clinical groups, both with clear expertise. It also requires an understanding of scientific and regulatory steps required for clinical translation and intellectual property protection, which is necessary for commercialization. A cadre of clinicians in geriatrics needs to be trained who will be interested in and conversant with the basic biology of aging. Of the 7,200 geriatricians in the US, less than a half dozen have R01s from the Division of Aging Biology of the National Institute on Aging, a situation that needs to be addressed now, so well-trained clinical collaborators with sufficient credibility to attract grants become available within the next 5 to 10 years. Training and career-long funding mechanisms for geriatricians in basic science research and for basic scientists in geriatric issues are needed, as are translationally capable review and funding mechanisms. With respect to treatments, lifestyle interventions, especially nutritional interventions, are particularly challenging. For example, it is unlikely that an intervention like lifelong caloric restriction will be generally accepted and implemented, particularly in the face of an obesity epidemic that is proving difficult to control. For pharmaceutical agents to be acceptable to regulatory agencies and for realistic timeframes for clinical trials, treatments to increase healthspan should be effective in subjects who are already elderly and who are either at immediate, high risk or are already affected by frailty or multiple age-related conditions. We are reaching the time to consider multi-center, collaborative efforts in translating basic biological advances into clinical interventions that could transform health care by attacking age-related diseases as a group. We need to take the scientific, training, outcome definition and standardization, and organizational steps to orchestrate these efforts.

44. Regulation of Inflammation and Immunosenescence by Ghrelin

Vishwa Deep Dixit (P)
Pennington Biomedical Research Center, Baton Rouge, LA

The endocrine-immune interactions are mediated via a complex array of hormones, cytokines and neuropeptides to regulate diverse physiological functions. Ghrelin is an acylated endocrine peptide that is predominantly secreted from the gut in response to negative energy balance and caloric restriction. Ghrelin binds to 7 transmembrane G-protein coupled, growth hormone secretagogue receptor (GHSR) and induces GH production and also increase food intake. Several studies over the past few years have demonstrated that apart from pituitary and hypothalamus, the GHSR is also expressed in several lymphoid organs and immune cell subsets. Ghrelin binds to GHSR receptors on human T cells and monocytes and inhibits the production of pro-inflammatory cytokines such as TNFα, IL-6 and IL-1β. Despite the short half-life, the treatment with native ghrelin peptide confers partial protection from LPS induced sepsis and cytokine storm. Consistent with these data many recent studies have demonstrated anti-inflammatory effects of ghrelin in several disease models including Crohns Disease, Multiple Sclerosis, arthritis, pancreatitis and hepatic fibrosis. Furthermore, 2 week ghrelin infusion via osmotic pumps can partially reverse the age-related inflammation in mice by inhibiting NFkB activation. In addition, ghrelin infusion augments the naïve T cell production from thymus and protects against age-related loss of T cell receptor repertoire diversity. Ablation of ghrelin signaling accelerates the age-related involution of thymus by increasing the generation of local tissue fibroblasts through the process of epithelia-mesenchymal transition (EMT). Interestingly, small molecule ghrelin-mimetic compounds have been shown to be safe in humans and effective in reducing frailty in the elderly. As new data emerge and future therapeutic approaches for age-related diseases are developed, investigation of long-acting ghrelin mimetics merits further clinical evaluation.

45. Melatonin, Brain Aging and Neuroinflammation

Stephen C. Bondy[1] (P), and Edward H. Sharman[2]
Departments of Medicine[1] and Neurology[2], University of California, Irvine School of Medicine, Irvine, CA

The aging brain is characterized by evidence of elevated levels of inflammation. Such elevation appears to be intrinsic in that it is present in the absence of any exogenous stimulus such as infection or trauma. It may be that it represents failure of the immune system to reset to low basal levels after the cessation of a provocative stimulus. In time, this could lead to a gradual accumulation of persistent responses to prior insults.

In experimental animals, most of those genes whose expression increases markedly with age, are related to inflammation and immune function. These include several inflammatory cytokines, such as IL-6 and TNF□. The expression levels of these genes can be reduced by chronic exposure of aged animals to low levels of dietary melatonin. This is accompanied by a corresponding reduction in levels of cerebral proteins associated with cerebral inflammatory events such as glio-fibrillary acid protein (GFAP), nitric oxide synthetase (NOS) and amyloid peptides 1-40 and 1-42.

In addition, following melatonin treatment, the genetic response within the brains of aged animals to an inflammatory stimulus (an i.p. injection of lipolysaccharide, LPS), is altered so that it becomes similar to that of the younger animal. Thus, the overall effect of melatonin is to cause the immune system of aged animals to more closely resemble that of younger animals, both in the resting state and in the response to activation.

The changes following dietary melatonin to aged mice, also include improved overall appearance, a lower incidence of cancer incidence and a limited restoration of behavioral function.

Since melatonin is non-toxic, inexpensive and readily available, this offers a potential means of slowing some aspects of brain aging. Slowing the rate of brain aging could have significant effects on the incidence of neurodegenerative disorders such as Alzheimer's and

Parkinson's diseases which require a degree of senescence before they can be manifested.

46. Estrogen Effect on Endothelial Inflammation: Pro-Inflammatory, Anti-Inflammatory or Immunomodulator?

Subhadeep Chakrabarti (P)
University of Alberta, Alberta, Canada

Cardiovascular diseases such as heart attacks and stroke are the leading cause of morbidity and mortality in developed nations. The endothelial cells lining the blood vessels are key sites of inflammatory changes that lead to these diseases. Epidemiological studies in premenopausal women suggest a beneficial role for estrogen in preventing vascular inflammation and its complications. However, the beneficial effects of estrogen are absent or even reversed in older postmenopausal subjects. The modulation of inflammation by estrogen under different conditions might explain this discrepancy. Estrogen exerts its anti-inflammatory effects on the vasculature through different mechanisms such as direct antioxidant effect, generation of nitric oxide, prevention of apoptosis in vascular cells and suppression of cytokines and the renin-angiotensin system. On the other hand, estrogen also elicits pro-inflammatory changes under certain conditions, which are less completely understood. Some of the mechanisms underlying a possible pro-inflammatory role for estrogen include increased expression of the pro-inflammatory receptor for advanced glycation end products, increased tyrosine nitration of cellular proteins and generation of reactive oxygen species through an uncoupled eNOS. In addition, recent evidence from our group suggests estrogen may act as a modulator of immunological and inflammatory signaling pathways. Aging is associated with a loss of circulating estrogen levels (menopause) as well as increased oxidative stress, both of which can further alter the estrogen effects on the endothelial responses.

47. Testosterone, Mental Well-Being, and Inflammation

Erik J. Giltay(P)
Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands;

Many studies suggests a causal relationship between low testosterone levels with depression, low vitality and sexual dysfunction, as many randomized placebo-controlled trials on testosterone did find beneficial effects of testosterone on end/points of general well-being. The mechanism through which testosterone exerts these beneficial effects, however, remains largely unknown.

Depression is associated with low-grade inflammation, as revealed by elevated levels of C-reactive protein (CRP), interleukin-6, interleukin-1 and tumour necrosis factor (TNF)-alpha, and an elevated white blood cell count. There is evidence for a bidirectional regulation between mental well-being and inflammation, as depression may induce an enhanced immune response and, in turn, proinflammatory cytokines may induce depressive symptoms. The latter is supported by the observation (in animal and human studies) that some behavioural characteristics of depression (i.e., sickness behaviour) appear to be a consequence of the enhanced immune system. On the opposite, inhibition of TNF-alpha by etanercept is used in the treatment of autoimmune disease, and did reduce depressive symptoms in a trial with patients with psoriasis. Studies in depressed patients have found that inflammation and depression both change concurrent with antidepressant treatment.

Moreover, data from trials suggests that testosterone administration reduces levels of CRP, interleukin-6, and TNF-alpha in hypogonadal men. Moreover, testosterone administration to hypogonadal men did reduce fat mass and increased lean body mass, especially in case of comorbid obesity, diabetes mellitus or the metabolic syndrome. Adipose tissue not only functions to store energy, but also secretes a large number of factors, that directly and indirectly affects inflammatory factors, such as IL-6 and TNF-alpha. We found that part of the beneficial effects of testosterone on mental well-being and sexual well-being might have been mediated through weight reduction and a change in the distribution of body fat. In conclusion, hypogonadism generates an important opportunity for treatment of poor mental well-being. The beneficial effects may be mediated through visceral fat mass reduction, that subsequently lowers inflammation.

48. Age and Hormone Replacement Therapy Affect Systemic and Local Il-6 and Igf-1 Pathways in Women

Maarit Ahtiainen[1](P), Eija Pöllänen[1], Paula Ronkainen[1], Markku Alen[1,2], Jukka Puolakka[3], Jaakko Kaprio[4], Sarianna Sipilä[1], Vuokko Kovanen[1]
[1]Department of Health Sciences, University of Jyväskylä, Finland ; [2]Department of Medical Rehabilitation, Oulu University Hospital and Institute of Health Sciences, University of Oulu, Finland; [3]Central Finland Central Hospital, Jyväskylä, Finland; [4]Department of Public health, University of Helsinki, Finland.

Our recent study with postmenopausal monozygotic (MZ) twin sisters discordant for hormone replacement therapy (HRT) associated HRT with better mobility, greater muscle power and favorable body and muscle composition, suggesting HRT's potential to prevent muscle weakness. Currently, the importance of the balance between the catabolic effects of cytokines and the anabolic effects of IGF-1 on the state of skeletal muscle has been underlined. In the present study, we analyzed systemic and local levels of IL-6 and IGF-1related factors in fertile 30-35-yrs-old (n=14) women without hormonal contraceptives and in 54-62-yrs-old monozygotic female twin pairs discordant for HRT (n= 11 pairs, duration of HRT 7.3±3.7years). Muscle biopsies were taken from vastus lateralis muscle and needle aspiration biopsies from abdominal adipose tissue. Serum levels were measured by specific ELISAs and transcript levels by quantitative PCR. The serum levels of soluble IL-6 receptors, gp130 and IL-6R (sgp130 and sIL-6R), were higher and serum IGF-1 levels lower in postmenopausal women compared to their fertile counterparts. HRT decreased the serum levels of sgp130 and sIL-6R, but did not have any remarkable effect either on IGF-1 or IGFBP3 levels. A strong negative correlation between serum IGF-1 and sIL-6R was found in HRT users. The transcript analyses

emphasize the impact of adipose tissue on systemic levels of IL-6, sgp130 and sIL6R, both at fertile and postmenopausal age. In muscle, the most remarkable changes were significantly decreased expression of mechano-growth factor (MGF) with age and the increased expression of IGF1-receptor in HRT users. The observed long-term effects of HRT on IL-6 and IGF-1 pathways are suggested at least partly account for the effects of HRT on muscle composition and power. Further studies are needed to clarify, whether the HRT has an effect on these pathways separately or if the soluble receptors of IL-6 function as mediators for HRT.

49. Regenerative Medicine Against Aging: Can it be Comprehensive Enough?

Aubrey D.N.J. de Grey (P)
SENS Foundation, Sunnyvale, CA

Historically, biogerontologists speculating on how we might eventually postpone aging have focused on understanding its mechanisms in sufficient detail to be able to "clean up metabolism" - to slow the rate at which metabolism creates the accumulating molecular and cellular side-effects that eventually cause age-related ill-health. In principle, a clearly superior alternative would be to repair those side-effects after they had occurred, since this would allow us to restore the health of the elderly and pre-empt the ill-health of the middle-aged, rather than providing the greatest benefits only to the young. However, it has traditionally been presumed that various key aspects of aging are intrinsically impossible to repair. I will argue that regenerative medicine, defined broadly to include intra- and extracellular restoration as well as cell therapies, has in recent years progressed to the point where this presumption must be revisited.

50. Nutritional Interventions in Brain Aging

B. Shukitt-Hale (P) and J.A. Joseph
USDA, HNRC on Aging Tufts University, Boston, MA

The onset of age-related neurodegenerative diseases such as Alzheimer's or Parkinson's Disease, superimposed on a declining nervous system, could exacerbate the motor and cognitive behavioral deficits that normally occur in senescence. In cases of severe deficits in memory or motor function, hospitalization and/or custodial care would be a likely outcome. This means that unless some way is found to reduce these age-related decrements in neuronal function, health care costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse age-related neuronal deficits, as well as their subsequent, behavioral manifestations, in order to increase healthy aging. In this regard, consumption of diets rich in antioxidants and anti-inflammatory polyphenolics, such as those found in fruits and vegetables, may lower the risk of developing age-related neurodegenerative diseases. Fruits and vegetables high in antioxidant and anti-inflammatory activity, such as blueberries, blackberries, and strawberries, can prevent and even reverse the occurrence of the neurochemical and behavioral changes that occur in aging. Previously, we have shown that whole, crude berry extracts are able to reverse several parameters of brain aging as well as age-related motor and cognitive deficits when fed to rats from 19-21 months of age. Our results suggest that the polyphenolic compounds found in berry fruits, such as blueberries and strawberries, may exert their beneficial effects either through their ability to lower oxidative stress and inflammation, or directly by altering the signaling involved in neuronal communication, calcium buffering ability, neuroprotective stress shock proteins, plasticity, and stress signaling pathways. We have found that several blueberry anthocyanins and flavonols were able to cross the blood brain barrier and localize in various brain regions important for learning and memory (e.g., cerebellum, striatum, and hippocampus), suggesting that polyphenolic compounds may deliver their antioxidant and signaling modifying capabilities centrally. These interventions, in turn, may exert protection against age-related deficits in cognitive and motor function.

51. Do Organ Stem Cells Age?

Irina Conboy (P)
University of California, Berkeley, CA

The Conboy lab investigates the decline of tissue repair seen with aging, using muscle as the model tissue and focusing on the cellular and molecular regulation of the resident adult stem cells, called satellite cells. In recent years, it has become clear that to combat age-related disorders (either in situ or with the help of cell and tissue transplantation) we must better understand why the stem cells dedicated to organ maintenance and repair fail in the old in the first place. We have found that muscle stem cells residing in aged tissue retain their intrinsic ability to regenerate and that aged, differentiated muscle actually inhibits the responses of these endogenous stem cells dedicated to the repair and maintenance. Old satellite cells still maintain telomeres and repair DNA, and when moved to a young environment exhibit hallmarks of young stem cells: activation, proliferation and ultimately muscle regeneration. Our recent work determined that old myofibers inhibit their own maintenance and repair by shifting the balance from active Notch to over-pronounced TGF-beta/pSmad3 in satellite cells, leading to an induction of CDK inhibitors and thwarting satellite cell regenerative capacity, which explains the rescue of old muscle repair either by activation of Notch or by RNA-interference of Smad3. We had previously found that a young systemic milieu rejuvenated the responses of aged satellite cells in heterochronic parabiosis; however, the nature of the age-specific circulatory inhibitor was not determined. Our current work identifies TGF-beta-1 as the possible inhibitory culprit of the aged circulation, in both mouse and human, and shows that biologically active TGF-beta-1 is elevated in old blood and is reduced through heterochronic parabiosis. An organism-wide systemic delivery of a small molecule inhibitor of TGF-beta/pSmad rejuvenates muscle regeneration, enabling new opportunities for the rescue of stem cell responses in aged tissues. This introduces an interesting idea that the up-regulation of TGF-beta/pSmad3 locally in old muscle and perhaps other aged tissues, and the elevation of TGF-beta-1 systemically in aged circulation, might be connected to provide feed-back for each other, thus reinforcing the lack of organ stem cell responses throughout the old body.

52. PBT2 for Cognitive Aging and Alzheimer's Disease: Advances in the Metals Theory

Ashley I. Bush[1,2](P)
1. Mental Health Research Institute, University of Melbourne, Parkville, Victoria, Australia; 2. Harvard Medical School, MA, USA

Background:
PBT2 is a zinc ionophore that restores cognitive performance and decreases interstitial brain Aβ in APP transgenic mice within days (*1*). A Phase IIa study for mild Alzheimer's Disease (AD) demonstrated a reduction in CSF Aβ42 with improved Executive Function performance within 12 weeks (*2*). The speed of these improvements suggested that PBT2 may also be correcting other aspects of synaptic dysfunction in early stage disease, such as the trans-synaptic movement of zinc. Presynaptic zinc is concentrated by ZnT3 and released with glutamate, and ZnT3-/- x Tg2576 progeny fail to develop amyloid pathology. The therapeutic relevance of zinc/copper ionophores such as PBT2 to prevent Aβ oligomers being attracted to zinc at glutamatergic synapses has been demonstrated with clioquinol (*3*). ZnT3 levels fall with aging in humans and mice, which could inhibit the trans-synaptic movement of zinc, preventing it from reaching post-synaptic targets that mediate cognition such as TrkB, NMDAR, ZnR and p75(NTR) receptors. Recently we showed that ZnT3-/- mice exhibits marked cognitive and memory deficits by 6 months of age, concomitant with decreased expression of these zinc targets, and are therefore a phenocopy for AD (*4*).

Objective:
To understand the mechanism of age-dependent cognitive loss, and investigate ionophores PBT2 and clioquinol as potential treatment approaches.

Methods & Results:
LTP in acute hippocampal slices from ZnT3-/- mice is markedly suppressed compared to wild-type controls, but is partially rescued by exogenous zinc and completely rescued by zinc + clioquinol. ZnT3-/- mice expressing the cognitive aging phenotype were treated with clioquinol orally, which restored these deficits within 6 weeks. Levels of NR2A, NR2B and AMPA, which were decreased in the ZnT3-/- brain, were normalized with the treatment. We tested PBT2 on aged and cognitively impaired wildtype mice (C57Bl/6) with no amyloid burden. Oral PBT2 treatment caused an almost complete normalization of Morris water maze performance within 11 days (ANOVA $p < 0.001$). Young mice were unaffected.

Conclusion:
Decreased turnover of zinc in the glutamatergic synapse may underlie age-dependent cognitive decline, and lead to amyloid deposition. Amyloid may exacerbate cognitive impairment by trapping zinc. These findings indicate that PBT2 can both decrease amyloid load, and restores zinc homeostasis leading to improved synaptic function. These data support the treatment of age-related cognitive decline with ionophores.

References:
1. Adlard et al., Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with decreased interstitial Abeta. Neuron 59, 43–55, 2008. **2.** Lannfelt et al., Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurology 7, 779-86, 2008. **3.** Deshpande et al., A Role for Synaptic Zinc in Activity-Dependent AβOligomer Formation and Accumulation at Excitatory Synapses. J. Neuroscience 29, 4004-15, 2008. **4.** Adlard et al., Cognitive Loss in Zinc Transporter-3 Knock-Out Mice: A Phenocopy for the Synaptic and Memory Deficits of Alzheimer's Disease? Journal of Neuroscience 30, 1631-6, 2010

Disclosure: Dr Bush is a shareholder in Prana Biotechnology Ltd.

53. Understanding Mechanisms of Regeneration in the Salamander: Strategies to Repair and Reverse the Accumulation of Chronic Damage

David M. Gardiner (P)
Department of Developmental and Cell Biology, University of California Irvine, Irvine, CA

Throughout most of our lives, damage to our tissues is balanced by regenerative mechanisms that maintain a more or less homeostatic balance. However, at some point in life, there is a shift in this balance such that our bodies accumulate damage progressively and persistently. Assuming that the rate of damage remains relatively constant, this overall decline from vitality to frailty must be a result of either a decline in regenerative abilities and/or an accumulation of damage that is not normally repaired by our unaided, intrinsic regenerative abilities. Regardless, understanding our regenerative potential and developing strategies to activate and/or enhance this potential are essential to maintaining or restoring a more youthful balance. The remarkable regenerative abilities of salamanders demonstrate what we reasonably can expect in terms of the basic biological potential for regeneration. Although the ability of these animals to regenerate entire organs seems extraordinary, the mechanisms of regeneration involve basic biological processes regulated by conserved signaling pathways. To date much has been learned about the response to acute injury, e.g. amputation; however, this model has not yet been exploited to investigate the regenerative responses to chronic damage that accumulates as the animal ages. It presumably would be feasible to repair chronic damage by surgically removing the damaged tissue(s) and triggering an acute regenerative response. Alternatively it may be the case that many of the signals that regulate an acute regenerative response would also function to repair damage continuously *in situ*. This possibility has yet to be tested experimentally and is a challenge for investigations using the salamander regeneration model.

54. Rebuilding Bone, Sclera, Heart, Skin and Other Tissues and Organs with a Unique, Sphere-Templated Porous Scaffold

Buddy D. Ratner (P)
University of Washington Engineered Biomaterials (UWEB21), Department of Bioengineering, Seattle, WA

Tissue engineering has demonstrated the potential in humans to repair and replace damaged tissues and organs. This is in contrast to the fibrotic, avascular repair usually seen with synthetic biomaterials or many surgical approaches. Scaffolds for tissue engineering serve to

guide anatomical shape, generate sites for cell attachment, direct cell growth and differentiation and provide an environment for tissue formation. Ultimately, these scaffolds must biodegrade leaving behind only functional tissue. However, they cannot degrade before they have fulfilled their tissue-organizational function. Scaffolds can be pre-seeded with cells prior to implantation, or can be implanted without cells. Most synthetic scaffolds, without cellular pre-conditioning, will lead to a fibrotic, avascular outcome after implantation. In this talk, a novel scaffold technology will be addressed that permits implantation without cells, but leads to implant site reconstruction and organized tissue.

Specific technologies for creating tissue engineering scaffolds include salt leaching, gas foaming, sintering, templating, solvent precipitation, freeze-induced phase separation, aphrons foams, rapid prototyping and decellularization of tissue. A central question in engineering scaffolds is what pore sizes, pore shape, pore orientation and interconnectivity are best for tissue engineering. The focus of this talk will be on a precision porous material made by sphere templating that rapidly induces angiogenesis and minimizes fibrotic outcomes. Successful outcomes from implantation in skin (subcutaneous and percutaneous), bone, sclera, vaginal wall and heart will be summarized. A "sweet spot" in spherical, interconnected pore size is found in a pore size range from 30-40 microns. Templates with pores of this size heal in a relatively afibrotic, vascularized manner. Staining of histological sections by Masson's trichrome, picro-sirius red, vascular endothelial markers and biotinylated lectins (to demonstrate perfusion of newly formed vasculature) will be shown. It is interesting that these sphere-templated implanted porous structures become rapidly and heavily infused with macrophages. Stains for cell surface markers suggest these macrophages show an M1/M2 mixed phenotype, in contrast to fibrotic reactions where predominate M1 phenotype is seen. Directing macrophages to this mixed phenotype may suggest new approaches to healing and regeneration that could have impact on aging and quality of life.

55. Adaptation to Hydrogen Sulfide Improves Protein Homeostasis in C. Elegans

Dana L. Miller (P) and Mark B. Roth
Fred Hutchinson Cancer Research Center, Division of Basic Sciences, Seattle, WA

With age, the ability to maintain protein homeostasis declines. The resulting deficiencies in protein quality control can have devastating physiological consequences, including neurodegenerative diseases. We have shown previously that low levels of hydrogen sulfide increases lifespan and thermotolerance in the nematode C. elegans (Miller and Roth, 2007). Here we show that sulfide also improves the ability to maintain protein homeostasis, as judged by the aggregation of polyglutamine (polyQ) containing proteins. Our data suggest that adaptation to sulfide impinges on protein homeostasis through a mechanism that is distinct from the effects of sulfide on lifespan. Remarkably, we have found that sulfide also improves the ability to maintain protein homeostasis in stressful environmental conditions. We demonstrate that polyQ proteins aggregate in vivo when animals are exposed to specific hypoxic environments. The range of oxygen concentrations that induce protein aggregation is modulated by genetic factors, including hif-1. Adaptation to sulfide protects against hypoxia-induced protein aggregation, as animals pre-treated with sulfide develop fewer protein aggregates when exposed to hypoxia. Moreover, we have also observed that treatment with sulfide after the hypoxic insult retards subsequent polyQ protein aggregation. These experiments show that polyglutamine-protein aggregation is induced both during and after exposure to hypoxia, which may have important clinical implications. Recently, it has been demonstrated that HIF-1 protein is stabilized and activated by sulfide (Budde and Roth, 2010), suggesting the possibility that sulfide acts through HIF-1 to modulate protein quality control mechanisms. Together, our studies show that sulfide can have remarkably long-lasting physiological effects that can improve homeostatic mechanisms required to appropriately respond to subsequent environmental perturbations.

56. Anticancer Mechanisms in a Long-Lived Rodent, The Naked Mole-Rat

Andrei Seluanov (P), Christopher Hine, Jorge Azpurua, Marina Feigenson, Zhiyong Mao, and Vera Gorbunova
Department of Biology, University of Rochester, Rochester, NY, USA

The naked mole-rat is the longest living rodent with a maximum lifespan exceeding 28 years. In addition to its longevity, naked mole-rats have an extraordinary resistance to cancer as tumors have never been observed in these rodents. Furthermore, we demonstrated that naked mole-rat fibroblasts require more "hits" for malignant transformation than the mouse cells. Interestingly, naked mole-rat cells constitutively express telomerase and do not become senescent in culture. Replicative senescence is an important anticancer mechanisms that limits cell proliferation. The presence of active telomerase may provide an advantage by allowing for better cell renewal in the naked mole-rat tissues, but on the other hand, active telomerase is often associated with tumorigenesis. These observations make the cancer resistance of naked mole-rats even more intriguing, and suggest that naked mole-rats evolved alternative telomere-independent tumor-suppressor mechanisms. We identified one such mechanism, termed early contact inhibition (ECI). Contact inhibition is a key anticancer mechanism that arrests cell division when cells reach a high density. In cell culture, naked mole-rat fibroblasts arrest at a much lower density than those from a mouse. We demonstrate that early contact inhibition requires the activity of p53 and pRb tumor suppressor pathways. ECI is triggered by a recently identified extra-cellular signal, which then leads to accumulation of a cyclin dependent kinase inhibitor p16INK4A. INK4 locus is an important tumor suppressor, and regulator of stem cell aging. Our preliminary data suggests that naked mole-rat INK4 locus has a highly unusual structure, which is divergent from both human and mouse.

Cancer-prone mouse models are valuable for development of cancer treatments. However, to find ways to prevent cancer before it occurs it would be extremely useful to study cancer-resistant models such as

the naked mole-rat. We anticipate that these unusual rodents have evolved multiple novel anticancer adaptations, which would pave the way for development of novel therapies for cancer treatment and prevention.

57. Introduction to the Nathan Shock Center Symposium on the Biology of Aging

Felipe Sierra, PhD (P)
Division of Aging Biology, NIA/NIH

The Nathan Shock Centers of Excellence were created in 1995 to serve as cores for research on basic biology of aging at institutions that already had a significant activity in the field. The Centers facilitate research in aging by Faculty not currently funded by the NIA, both at their institutions and their geographical vicinity. They do so by supporting cores, providing seed money and organizing courses and symposia.
In addition, the Centers serve as beacons to the larger community of aging biology researchers, and within their capability, they provide collaborative services in areas of specific expertise. The Centers were competitively renewed in 2010, and the presentation will highlight the unique capabilities of each of the current five Centers, with an emphasis on collaborations with investigators from other institutions.

58. Protection from Mitochondrial ROS Confers Resistance to Cardiac Aging, Pressure-Overload Induced Cardiac Hypertrophy and Failure

Dao-Fu Dai (P, G), Hazel H. Szeto*, George M. Martin, Peter S. Rabinovitch
University of Washington, Seattle WA and *Weill Cornell Medical College, New York, NY.

We have previously shown that overexpression of catalase targeted to mitochondria (mCAT) prolongs murine median lifespan by ~20%. Using echocardiography to study cardiac function in aging cohorts of wild-type and mCAT mice, we found age-dependent increases in left ventricular mass index and left atrial dimension, worsening of the myocardial performance index, and a decline in diastolic function. All of these changes were significantly attenuated in aging mCAT mice. Cardiac aging in mice is accompanied by accumulation of mitochondrial (mt) protein oxidation, increased mitochondrial DNA mutations and deletions and mt biogenesis, increased ventricular fibrosis, enlarged myocardial fiber size, decreased cardiac SERCA2 protein, and activation of the calcineurin–NFAT pathway. All of these changes were also significantly attenuated in mCAT mice. Echocardiographic cardiac aging at middle age was shown to be an independent predictor of murine survival. As aging is accompanied by elevated levels of intracardiac angiotensin II (AngII), we hypothesized that mt reactive oxygen species (mt ROS) might mediate effects of AngII. Indeed, AngII increases mt ROS in cardiomyocytes and induces cardiac mt damage and mt DNA deletions, concomitant with increased autophagy and signaling for mt biogenesis. The causal role of mt ROS was shown by the observation that mCAT mice, but not mice that overexpress wild-type peroxisomal catalase, are resistant to cardiac hypertrophy, fibrosis and mt damage induced by AngII, as well as heart failure induced by overexpression of Gαq or transverse aortic constriction. Treatment of mice with the mt antioxidant peptide SS-31 provided cardioprotection from AngII infusion and Gαq overexpression that was similar to that conferred by mCAT. Conversely, primary damage to mt DNA produced by AZT or polymerase gamma mutation (Polga $^{D257A/D257A}$) was also shown to contribute directly to the development of cardiac hypertrophy and failure, concomitant with age-dependent increase in mt protein oxidative damage, mt DNA deletions, apoptosis, and expression of senescence marker p16INK4a. All of the above changes were also attenuated by mCAT. These data indicate that mt ROS and DNA damage play a critical role in cardiac hypertrophy and failure, as found in aging and hypertensive cardiomyopathy, and support the potential use of mitochondrial-targeted antioxidants for prevention and treatment of these age-related cardiovascular diseases.

59. Do Rapamycinmycin and Caloric Restriction Increase Lifespan Through a Similar Mechanism(s)?

Arlan Richardson (P), Adam Salmon, Holly Van Remmen, and Viviana Pérez,
San Antonio Nathan Shock Aging Center and Barshop Institute for Longevity and Aging Studies.

A major challenge in aging is to determine whether different manipulations that increase lifespan involve common or different mechanisms. Because rapamycin is a specific inhibitor of the target of rapamycin (TOR), which acts as a key regulatory nexus in the responses of eukaryote cells to nutrients, growth factors, and cellular energy status, it has been hypothesized that rapamycin is a caloric restriction (CR) mimetic and that rapamycin and CR act through a similar mechanism(s). Using an epistasis approach, five studies in invertebrates show that life-extension by CR is not increased by mutations in the TOR (target of rapamycin) pathway, suggesting that CR and reduced TOR signaling increase lifespan through the same mechanism(s). However, a recent study shows that feeding rapamycin increases the lifespan of *Drosophila* fed a CR diet. We have compared the effect of rapamycin and CR on various physiological and biochemical processes. First, we observed that rapamycin and CR had different effects on mouse models of accelerated muscle mass loss. We also compared various parameters in mice fed *ad libitum* with and without rapamycin and mice fed CR with and without rapamycin for 6 months, starting at 2 months of age. Both CR and rapamycin increased liver autophagy, however, the effects of CR and rapamycin on GSH levels and redox signaling in liver was different in the mice fed CR and rapamycin. In addition, CR and rapamycin had different effects on the glucose and insulin tolerance. Thus, our preliminary experiments suggest that while CR and rapamycin may affect some processes similarly, many processes are affected differently.

60. Stress Resistance: From Culture to Critters All-Sorts

Richard Miller, MD, PhD (P),
University of Michigan, Ann Arbor, MI

Justice Potter Stewart, in Jacobellis v Ohio (1964), admitted that he could not produce an intelligible definition of the term "hard-core pornography," but that he knew it when he saw it. "Stress resistance" is like

that: a term that biogerontologists use to cover a wide range of cellular sins whose relationship to one another, and to aging, is too often left unparsed. It is now common knowledge, and perhaps even true, that long lifespan and slow aging are frequently accompanied by, or maybe even caused by, "stress resistance," but we are still far from a clear and comprehensive understanding of which cellular responses, to which stimuli, under which conditions of hormonal and metabolic milieu, are good for long-term survival and resistance to age-related diseases. Published studies have shown that early passage fibroblasts, derived from skin biopsies of young adult mice carrying anti-aging mutations, are resistant to a wide range of oxidative and non-oxidative poisons, and also resistant to metabolic changes triggered by inhibition of the plasma membrane redox system (PMRS). This talk will present recent data on two related topics: (1) To what extent do liver and kidney cells of pituitary dwarf mice show the same patterns of stress resistance exhibited by cultured fibroblasts from these mutant mice? (2) To what extent do fibroblasts from long-lived species (of rodents, birds, and primates) show the same pattern of stress resistance characteristic of cells from Ames and Snell dwarf mice? Early results suggest that changes in expression of Nrf2- and ERK-dependent genes, and changes in responses to ER stress, may be particularly important in modifying cellular properties of fibroblasts of long-lived mice and long-lived species.

Key collaborators: Andrzej Bartke, Alex Bokov, Jim Harper, Scott Leiser, Michal Masternak, Arlan Richardson, Amir Sadighi Akha, Mike Steinbaugh, Liou Sun, Joe Williams

Support: UM Nathan Shock Center (AG013283), P01-AG031736, P30-AG024824, and Ann Arbor VA Medical Center GRECC.

61. Genetic regulation of female sexual maturation

Rong Yuan, MD, PhD, (P)
The Jackson Laboratory, Bar Harbor ME

The timing of female sexual maturity in mammals is a life history trait that has broad clinical, commercial and scientific relevance, yet little is known about its genetics. To investigate the genetic regulation of female sexual maturity, we measured the age of sexual maturation in 31 inbred strains by observing vaginal patency. The ages of vaginal patency varied among strains from 24.9 to 42.9 days, with wild-derived strains having delayed sexual maturation compared to domesticated inbred strains. In correlation analysis, the age of vaginal patency showed a significant negative correlation with body weight at 38 days (R^2 = 0.48, P < 0.0001). Haplotype association mapping identified three loci — *Vpq1, 2, 3* — on chromosomes 4 and 16 that significantly associated with the variation of ages of vaginal patency. After the effects of body weight were removed, the haplotypes of *Vpq1, 2, 3* explained 44.2% of the remaining variation in the age of vaginal patency. At the three loci, wild-derived strains — WSB/EiJ, CAST/EiJ, PWD/PhJ, MOLF/EiJ — which represent different sub-species of the mouse family, have unique haplotypes that differ from those in domesticated inbred strains. A consomic strain, which carries chromosome 16 of PWD/PhJ on the C57BL/6J background, had significantly delayed age of vaginal patency. This confirms that chromosome 16 of wild-derived strains carries allele(s) that delay sexual maturation. Bioinformatic analysis suggested that nuclear-receptor-interacting protein 1 (*Nrip1*), also known as *Rip140*, is one of the candidate genes. Age of vaginal patency was delayed in the *Rip140* knock out mice compared to heterozygous and wild-type controls, supporting the idea that RIP140 is involved in regulating the age of sexual maturation.

Poster Presentations:

62. B7-H1 Immune Co-Signaling Regulates Age-Related Inflammation in a Sex-Dependent Manner

T. J. Curiel(P, G), V. Hurez, P. Lin, S. Thibodeaux, A. Richardson, P. Hornsby, Z. D. Sharp
University of Texas Health Science Center, San Antonio, TX, USA

Age-related inflammation contributes to age-related debilities, but its origins are obscure. The immune co-signaling molecule B7-H1 has pleiotropic immune regulatory effects, including inhibiting or activating T lymphocytes. In young (<6 months) BL6 mice, B7-H1 maintained function of $CD4^{+}CD25^{hi}$ regulatory T cells (Treg) in females, but not males in an estrogen-dependent manner. Effects did not depend on known B7-H1 ligands. Female B7-$H1^{-/-}$ Tregs exhibited significantly elevated mammalian target of rapamycin (mTOR) signaling versus B7-$H1^{-/-}$ males and wild type (WT) of either sex. Rapamycin restored female B7-$H1^{-/-}$ Treg function *in vivo*. Dendritic cell B7-H1 restored WT-level Treg function and normalized mTOR signaling in young B7-$H1^{-/-}$ female Tregs *in vitro* and *in vivo*. Anti-cytotoxic T lymphocyte antigen-4 antibody provoked inflammation in young B7-$H1^{-/-}$ females but not males. Aged (18-26 month) B7-$H1^{-/-}$ females, but not males developed spontaneous inflammation (elevated interleukin-2, interferon-γ and granulocyte-macrophage colony stimulating factor and increased activated T cells). Strikingly, Treg function in aged male and female B7-$H1^{-/-}$ and WT mice was comparable, equal to sex-matched young mice, suggesting failure of a distinct regulatory system in age. Aged (18-30 months) syngeneic mitogen activated protein kinase kinase $6^{-/-}$ mice and type I interferon $receptor^{-/-}$ mice of neither sex developed spontaneous elevations of inflammation over WT. These data establish B7-H1 signals, possibly delivered by dendritic cells, as defending against age-related inflammation in a sex-dependent fashion. Because B7-H1 regulates mTOR signaling, and mTOR blockade prolongs life in mice, we tested B7-H1 effects in mice fed long-term rapamycin. Rapamycin feeding of 3-6 month old BL6 mice reduced B7-H1 expression on dendritic cells and other myeloid cells over 9-12 months, the functional significance of which is under investigation. Work to identify pro-inflammatory cytokine producing cells in B7-$H1^{-/-}$ mice, and defects in regulatory cell allowing increased inflammation in females is also ongoing.

63. Role of Regulatory T-Cells in Age-Related Susceptibility to West Nile Virus

Jennifer L. Uhrlaub (P) and Janko Nikolich-Zugich
Department of Immunobiology and Arizona Center on Aging, University of Arizona College of Medicine, Tucson, AZ

Aging is associated with an increased accumulation of regulatory T cells (Tregs) in both humans and mice. Under steady-state conditions, Tregs preserve immune system homeostasis, help maintain tolerance to self-antigens and limit potential pathology caused by over activation of effector T cells in response to microbial pathogens. We hypothesize that in aged hosts already harboring an expanded number of Tregs, this increased regulatory population may limit the expansion and/or effector differentiation/function of adaptive immune responses required to control pathogens. As West Nile Virus (WNV) infection causes life-threatening meningoencephalitis predominantly in the elderly population for reasons that are not fully understood, we have used a mouse model of age-related vulnerability to WNV to address these questions. Specifically, we confirmed that aged mice have a greater frequency of Tregs that correlates with a reduced anti-WNV T cell response. T-cell responses could be improved in old mice by in vivo Treg depletion. However, this intervention did not result in improved resistance of old mice to WNV infection. Currently, we are studying the response of old animals to vaccination in the presence or the absence of Tregs, with an idea of manipulating this arm of the immune system to improve protection of the elderly to WNV and other infections.

64. Antigen Related Changes in DC Priming Function in response to Listeria Infection

Gang Li (P, G), Brien Rudd, Megan Smithey, Ty Lebsack, Sarah Foster, Janko Nikolich-Zugich
Department of Immunobiology, University of Arizona, AZ

Listeria monocytogenes (Lm) is a Gram-positive bacterium which causes Listeriosis, a leading cause of death among foodborne bacterial pathogens. We have observed that the protective capacity of CD8+ T cells responding to Lm infection in old mice is impaired; however the underlying basis for these defects remains unclear. Dendritic cells (DC) are a heterogeneous cell population that bridges the innate and adaptive immune system, and are the most important antigen presenting cells involved in CD8+ T cells priming. Therefore, a defect in CD8 T cells could belie problems in DC activation and function. In this study we found that the number and composition of CD11c+ DCs in the spleen does not change following Lm infection. We further investigated whether old mice have a defect in their DC compartment by comparing the ability of adult and old DCs to stimulate naïve OTI $CD8^{+}$ T cells after Lm-OVA infection. Purified CFSE-labeled naïve Ly5.2 OTI $CD8^{+}$ T cells were adoptively transferred into adult and old C57BL/6 mice at various times after i.v. infection with Lm-OVA. Proliferation of transferred Ly5.2 OTI $CD8^{+}$ T cells was assessed in the spleen 48h after transfer by evaluating loss of CFSE fluorescence. Positive priming, indicated by T cell proliferation, began on day 3 and continued until day 10 post-infection. Interestingly, our studies indicate the adult mice are capable of priming a significantly higher number of OT1 CD8+ T cell compared to old mice. To confirm that DCs are the predominant cell type involved in CD8+ T cell priming in LM-infected mice, we also compared the ability of isolated DCs, macrophages, and B cells to prime OT-1 CD8+ T cells ex vivo. From these studies, we were able to conclude; 1) that DCs are the most potent APC involved in the activation of CD8+ T cells in LM-infected mice; 2) diminished CD8+ T cell responses observed in old mice may be at least partially attributed to impaired DC priming. By focusing on age-related differences in DC biology, we hope to understand how aging impacts CD8+ T cell priming to better guide the rational design of T cells vaccination in elderly populations.

65. Aging Alters Inflammation – and Coagulation – Related Gene Expression in White Adipose Tissue During Inflammatory Stress

Marlene E Starr (P, N), B Mark Evers and Hiroshi Saito
Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, TX ; Department of Surgery and Markey Cancer Center, University of Kentucky, Lexington, KY

Aging is associated with an altered stress response that often affects outcomes of late-life complications such as systemic inflammatory response syndrome and sepsis, serious medical conditions characterized by widespread inflammation and disseminated intravascular coagulation. Although adipose tissue is now recognized as an important organ for inflammatory and immune responses, little is known about age-associated changes in gene expression within this tissue upon inflammatory stress. We therefore performed a microarray analysis comparing the effects of aging on gene expression of white adipose tissue at rest and during inflammatory stress. Young and aged C57BL/6 mice were injected with bacterial endotoxin lipopolysaccharide, sacrificed 0, 6 and 12 hours later and the epididymal adipose tissues harvested for RNA analysis by Affymetrix cDNA expression arrays. Analysis revealed that approximately 32,000 transcripts were present in the adipose tissue of at least one treatment group; of these, 2,303 were differentially expressed by aging alone and 10,723 were differentially expressed upon inflammatory stress regardless of age. Most importantly, 1,855 genes showed significantly altered expression patterns by the combined effect of aging and inflammatory stress. Pathway analysis determined the group of genes whose expression was altered by aging alone to be associated with inflammatory response, ribosomal proteins, T-cell signaling and the complement/coagulation cascade. The pathways of immune/inflammatory response, cytokine signaling, apoptosis and adipogenesis included a number of genes whose expression was altered by both aging and inflammatory stress. Interestingly, the expression of several coagulation pathway genes, including tissue factor, TFPI, PAI-1 and -2, and factors X and XIII, were also altered by aging and/or inflammatory stress. qPCR was performed to confirm expression patterns of selected genes. In summary, the adipose tissue is highly involved in many biological processes.

66. Peripheral Inflammation and Cerebral Metabolism: A Magnetic Resonance Spectroscopy Study

Danielle E. Eagan (P) Mitzi M. Gonzales, Takashi Tarumi, Steve C. Miles, Hirofumi Tanaka, Andreana P. Haley
The University of Texas at Austin, Austin, TX

Introduction: Inflammation is a recognized risk factor for late-life cognitive impairment. Peripheral elevations in inflammatory markers such as C-reactive protein (CRP) are linked to the development and progression of Mild Cognitive Impairment (MCI), Vascular dementia, and Alzheimer's disease (AD). Since inflammation is detectable decades before cognitive dysfunction manifests, it represents an excellent treatment target for early intervention. However, the literature linking inflammation and dementing disorders remains controversial in part because the relationship between peripheral inflammation and physiological changes in the brain remains unclear. Methods: In an effort to address this gap the current study investigated the relationship between CRP and cerebral metabolism as measured by magnetic resonance spectroscopy (MRS). Thirty-nine healthy, cognitively intact middle-aged adults participated in the study. Results: The relationship between neurometabolite concentrations and peripheral CRP was modeled using multivariate multiple regression analysis. Higher plasma CRP was significantly related to higher cerebral myo-inositol (mI) concentrations ($F(5, 33)= 3.640$, $p= 0.010$), independent of age, sex, and education level. Conclusion: Elevated mI, an organic osmolyte and possible marker of myelin degeneration and gliosis, is an established signature of AD and amnestic MCI. The current findings suggest a relationship between peripheral inflammation and changes in brain metabolism associated with late-life dementia. Because these biomarkers are detectable in midlife they may serve as useful indicators of risk for cognitive decline during the preclinical period when successful intervention is still possible.

67. A Molecular Mechanism for TNF-α-Mediated Down-Regulation of B Cell Responses

Bonnie B Blomberg (P), Maria Romero, Alain Diaz, Ana Marie Landin, Richard L Riley, Daniela Frasca
Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami FL

Aging is characterized by a low-grade chronic pro-inflammatory status referred to as inflammaging. In the present study, we wanted to investigate whether B cells can contribute to inflammaging by secreting pro-inflammatory cytokines, such as TNF-α and whether the pro-inflammatory microenvironment seen in old mice can impair B cell function in responding to stimuli such as LPS. Our hypothesis is that in aging there is a feedback mechanism of inflammatory cytokines on B cells which lowers expression of activation-induced cytidine deaminase (AID), crucial for class switch recombination (CSR). Our results show that unstimulated (*ex vivo*) B cells from old (18-25 month old) mice make significantly more TNF-α mRNA and protein than B cells from young (3-5 month old) mice, but after stimulation the old make less than young, indicating that the old B cells show an intrinsic defect in immune response, as we have previously shown (for other stimuli, endpoints). Moreover, pre-incubation of B cells with TNF-α before stimulation with LPS decreases both young and old B cell responses (AID, CSR), the inhibiting effect of pre-incubation being more pronounced with longer TNF-α incubation times (e.g. 12h *versus* 1h). We also show that pre-incubation of B cells with TNF-α, before LPS stimulation, induces tristetraprolin, a physiological regulator of mRNA stability of the transcription factor E47, which is crucial for CSR and is down-regulated in old B cells. These results altogether clearly reveal new molecular mechanisms to generate reduced antibody responses in aging.

Keywords: Aging, B cells, Inflammation, Tristetraprolin

68. Immunoproteasome Upregulation Activates NFkB Activity in Cultured Retinal Pigment Epithelial Cells

Marcela Maldonado(P,G), Rebecca J. Kapphahn, Neal Heuss, Dale S. Gregerson, Deborah A. Ferrington
Department of Ophthalmology, University of Minnesota, Minneapolis, MN

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 1 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. Activation of the NF-kB pathway is the primary response to a myriad of stressors, including oxidative stress, and is necessary for cell survival. We have previously shown that cells deficient in immunoproteasome are more susceptible to oxidation-induced cell death, supporting a role for immunoproteasome in regulating NFkB response to stress (Hussong S.A. et al 2010). The current study used retinal pigment epithelial (RPE) cells that have immunoproteasome catalytic subunit content genetically manipulated by knock-out, overexpression, or shRNA knockdown. These cultured RPE cells maintain their phagocytic activity and epithelial morphology. RT-PCR and western blots showed that these cells express prototypic epithelial (pigment epithelium derived factor, PEDF) and RPE (RPE65) cell markers. Our genetically manipulated RPE cells provide a useful model system to compare how eliminating or overexpressing immunoproteasome catalytic subunits affect NFkB activation. Preliminary results showed that RPE cells overexpressing the LMP7 catalytic subunit of the immunoproteasome had a 50% increase in production of the proinflammatory cytokine, IL-6, following 24hrs of TNF-alpha exposure. These results suggest that upregulating immunoproteasome content increases NFkB activation and may play a key role in regulating NFkB signaling.

69. Examining the Correlation Between T Cell Diversity and Susceptibility to West Nile Virus Infection in the Elderly

Michael S. Bennett[1](P, G), Anne M. Wertheimer[1], Janko Nikolich-Zugich[1]
Department of Immunobiology and Arizona Center on Aging, College of Medicine, The University of Arizona, Tucson, AZ.

T cell diversity is believed to play a key role in susceptibility to infectious disease and the efficacy of vaccination in old animals, such as humans and mice. As individuals age, decreased thymic output and the appearance of large T cell clonal expansions (TCE) are frequently observed, and both of these factors may increase the risk of developing serious disease from previously unencountered pathogens. The recent appearance of West Nile Virus (WNV) in the western hemisphere provides the opportunity to study the primary immune response to an infectious disease in older individuals. The elderly have been shown to suffer disproportionately in WNV infection, displaying higher mortality and more sever symptoms than younger adults who contract the disease. In this study, we are examining the role of TCE in the development of severe WNV disease. We are currently examining a cohort of old and adult individuals who have contracted WNV for presence of TCE using a combination of CDR3 fragment length analysis and antibody staining for V beta TCRs. Cells have also been stained for CD4, CD8ß, CD95 and CD28, in order to assess the level of memory versus naïve T cell phenotypes. Using this analysis, we have observed a general trend in which older individuals posses a more skewed CDR3 length distribution, indicative of lowered T cell diversity as a result of expansion of specific T cell clones. Furthermore, in some individuals, V beta staining has revealed particular V betas as disproportionately expanded. Using these methods, we hope to determine if a correlation exists between lowered T cell diversity and greater susceptibility to primary viral infections such as WNV in older individuals. If such a correlation exists, therapeutic methods aimed at restoring T cell diversity in older individuals could hold promise in increasing their ability to ward off new infections.

70. Age-Related Alterations to the Antigen-Specific CD8+ TCR Repertoire

Brian D. Rudd (P, G), Vanessa Venturi, Miles P. Davenport, and Janko Nikolich-Zugich
Department of Immunobiology and, the Arizona Center on Aging, University of Arizona College of Medicine, Tucson, AZ and The BIO-5 Institute, University of Arizona, Tucson, AZ

Aging of the immune system results in a less diverse T cell compartment and impaired immunity. Maintaining a diverse repertoire of T cells has been shown to be a key determinant of immune protection, since TCR diversity is likely to enrich for T cells that detect microbial pathogens with high sensitivity and efficacy, to limit the emergence of viral escape mutants in acute and chronic infections and to promote heterologous immunity. Defining the specific impact that aging has on TCR usage and repertoire diversity is critical for the development of cellular based vaccines that could potentially cover a larger age-range of individuals. However, since most studies thus far have only described age-associated perturbations to the T cell repertoire with broad-based techniques (limiting dilution, spectratyping, etc.) in a limited number of individuals, it is still unclear how the clonal architecture of the epitope-specific CD8+ T cell response is precisely altered within and among individuals across the lifespan. More specifically, it is presently not known if the changes in T cell repertoire with age are entirely stochastic or whether there is a preferential selection of clonotypes with a certain CDR3 length, gene element usage or amino acid sequence. Resolving these important issues requires extensive sequencing of antigen-specific CD8+ TCRs in large groups of individuals at various ages. In this present study, we investigated the influence of age on the clonal composition of CD8+ T cells responding to an overwhelmingly dominant peptide derived from herpes simplex virus

glycoprotein B (HSV gB). Adult (2-3 month) and old (18 and 22 month) mice were infected with Vaccinia Virus expressing the dominant gB-8p peptide and TCR usage and repertoire diversity were evaluated. Our data describes exactly how the antigen-specific CD8+ TCR repertoire 'deconstructs' with age. Collectively, these findings have important implications for the development of vaccines designed to protect individuals across the entire lifespan.

71. Infection of Aged Rhesus Macaques with SVV: A New NHP Model to Study Herpes Zoster

K.Haberthur[1,2] (P,N), A.Barron[2,3], F.Engelmann[2,3], A.Legasse[2,3], S.Planer[2,3], I.Messaoudi[1,2,3]
[1]Vaccine and Gene Therapy Institute, Oregon Health and Science University; [2]Graduate Program in Molecular Microbiology and Immunology, Oregon Health and Science University; [3]Division of Pathobiology and Immunology, Oregon National Primate Research Center

The reactivation of latent varicella zoster virus (VZV) results in herpes zoster (HZ), or shingles, which causes significant morbidity and occasionally mortality in the elderly and immune compromised. Given that 17% of the United States population will be over the age of 65 by 2020, the incidence of HZ and its associated complications will certainly increase. Clinical studies show that the currently FDA-approved vaccine offers only a 51% reduction of HZ cases in vaccinated versus unvaccinated populations. Thus, it is necessary to continue investigations that will lead to the development of a more effective vaccine. Our laboratory has recently developed the first animal model that recapitulates hallmarks of human VZV infection. In this model young rhesus macaques that are inoculated with simian varicella virus (SVV), a homolog of VZV, develop a generalized varicella rash, as well as cellular and humoral responses, followed by the resolution of acute SVV viremia, and the establishment of latency in sensory ganglia. This novel model offers a unique opportunity to uncover the mechanisms by which immune senescence results in VZV reactivation. Indeed, we show that in contrast to young animals, aged animals experience increased peak SVV viral loads and persistent viremia. Interestingly, aged animals generate an IgG response that is comparable in kinetics and magnitude to that of young animals. On the other hand, T cell responses are delayed and reduced in aged animals. Thus, similar to clinical findings regarding VZV control in the elderly, the inability of aged rhesus macaques to control SVV infection is most likely due to defects in cellular and not humoral immunity. These results provide the framework for future studies in immune senescence and its role in VZV reactivation.

72. Diet Restriction that Improves Longevity and Health Span also Modifies Gut Microbiology

Roy J Martin (P)[1,2],Reshani N Senevirathne[1], Don Ingram[2], Marlene Janes[1], Vishwa Dixit[2], Michael J Keenan[1]
[1]LSU AgCenter, Baton Rouge, LA, [2]Pennington, Biomedical Research Center, Baton Rouge, LA

The importance of gut microbiota in gut health and health in general has received considerable attention. The elderly are known to have reduced diversity and decreased relative abundance of desirable microbiata. These age-related changes in gut microflora could diminish health span. For example, reductions in the relative abundance of important sub-populations such as Clostridium cluster IV and bifidobacteria might result in reduced formation of short chain fatty acids, altered epithelial cell maintenance, and altered barrier function of the gut epithelium in the elderly. Those changes in the GI microbiota have previously been linked to impaired immune function prevalent in older individuals and may result in a greater susceptibility to disease. It is well established that diet restriction leads to improved health and increased longevity in many species. In addition, resistant starch diets improve gut function and metabolic status. Does part of this increase in health involve an improvement in gut function and specifically in gut microbiota? The data from 2-year old C57BL/6 mice fed either resistant starch or were diet restricted show similar trends for the bacteria levels measured by qRT-PCR. Both treatments increase Bifidobacterium and total Clostridium IV. These data support our hypothesis that dietary fermentable fiber mimics many of the effects of diet restriction on health span and longevity.

Supported by National Starch and LSU AgCenter

73. Evaluating Safe (But Weak) Vaccines in Old Mice by Analyzing CD8 T Cell Effector Status and Transcriptional Profile

Kristin R. Renkema, Megan J. Smithey (P), Brian D. Rudd, Sarah Foster, and Janko Nikolich-Zugich
Department of Immunobiology, University of Arizona, Tucson, AZ

The population aged 65 and older has been steadily growing; by 2050, this population will reach 80 million in the United States. Infectious diseases remain amongst the leading causes for death in people over 65 years old. Alarmingly, current vaccines are not very effective in aged people, as their design did not take into account age-related immune defects. Widespread defects in the immune system have been found to increase with age, including qualitative and quantitative decline with adaptive immunity. Current strategy in vaccine development involves creating the "safest and weakest" vaccine without losing efficacy.

CD8 T cells have been found to decrease in both number and function in aged mice. We recently found that in response to systemic Listeria monocytogenes (Lm) infection, old mice mobilize fewer Lm-specific CD8 T cells. Moreover, these cells exhibited lower effector cytokine production, and are less polyfunctional. The purpose of this study was to evaluate different Lm-based vaccine strengths in adult and old mice by analyzing primary, memory, and recall responses. We found that old mice displayed a less functional immune response, both in magnitude and in quality, regardless of the vaccine strength. We were able to trace these functional defects to the expression and induction of master transcription factors which regulate T cell effector function, T-bet and eomesodermin, both in vivo and in vitro. These defects may constitute a common denominator underlying suboptimal function of old CD8 T cells in response to

primary infection. Experiments are in progress to correct these defects and improve function of aged CD8 T cells.

74. May Autoimmune Inflammation Protect Against Cancer? New Evidence on Cancer and Rheumatoid Arthritis

Svetlana V. Ukraintseva (P) , Konstantin Arbeev, Liubov Arbeeva, Alexander Kulminski, Igor Akushevich, Irina Culminskaya, Anatoli I. Yashin
Duke University, Center for Population Health and Aging, Trent Drive Hall, room 002, Durham, NC

Recent studies suggested that inflammation involved in autoimmune responses may be protective against cancer (Martin-Orozco et al. 2009). An autoimmune disorder, rheumatoid arthritis (RA), was previously associated with reduced risks of some hormone-related cancers and melanoma, while with increased risks of lymphomas (Parikh-Patel et al. 2009). However, there were few studies that addressed the net effect of being diagnosed with RA on cancer risk in the elderly, and vice versa, and how this effect changes over time. To address these questions, we evaluated the age-patterns of incidence rate and probability of staying free of cancer (all sites) in presence of RA, and vice versa, in the Framingham Heart Study (FHS) original cohort (5,209 individuals, 55% females, majority reached old age (65+) in 1970s), and in the National Long Term Care Survey (NLTCS) (38,214 individuals, 60% females, aged 65+ in 1990s). Results. In the FHS, being diagnosed with RA significantly decreased cancer risk in postmenopausal women (by about 10% for most ages), and vice versa. In the NLTC, however, RA diagnosis did not reduce the risk of cancer, while being diagnosed with cancer increased chances of RA (up to 20% in some ages). Conclusion. This study suggests that autoimmune conditions (such as RA) may be protective against cancer but this effect is modulated by factors specific for population and period of the study. E.g., the observations that RA was cancer-protective in 1970s, but not in 1990s, or that cancer diagnosis increased chances of RA in 1990s (i.e., in more recent years), but not in 1970s, suggest that changes in treatment of cancer and RA may play major role. To clarify this, we next are going to investigate the effects of specific cancer and RA treatments used in the different periods of time on respective disease risks.

75. The Dendritic Cell Response to Influenza Virus is Impaired in Aged and Calorie Restricted C57BL6J Mice

David M. Duriancik (P) and Elizabeth M. Gardner
Department of Food Science & Human Nutrition, Michigan State University, East Lansing, MI

Aged and calorie-restricted (CR) populations are more susceptible to influenza virus infection. Previously, we have shown that the natural killer (NK) response to influenza infection is impaired in aged and CR populations. Since NK activity can be enhanced by dendritic cells (DC), the objective of our study was to identify changes in the DC-NK cell interaction of aged and CR mice. In the mouse, one precursor DC can give rise to all mature DC populations. Mature $CD11b^+$ myeloid DC stimulate Th2 responses, while mature $CD8\alpha^+$ lymphoid DC stimulate Th1 responses. Mature plasmacytoid DC produce large amounts of type 1 interferons to augment antiviral responses. Mice at 6 months of age, 22 month of age, and 40% CR were purchased from the National Institute on Aging. We used multicolor flow cytometry to identify and quantify the DC populations of the spleen, lung and draining lymph nodes during the innate immune response to 100 hemagglutination units of mouse-adapted Puerto Rico 8 influenza. Aged and CR populations had altered DC responses compared to young, *ad libitum* fed control animals. Plasmacytoid DC were decreased in the lung of aged and CR compared to young, *ad libitum* fed animals. In addition, the precursor DC response was decreased as a percentage of total cells and delayed one day in aged and CR compared to young, *ad libitum* control mice. The altered DC response to influenza virus contributes evidence to impaired innate immunity of aged and CR populations. Future research should focus on improving the early innate immune response to infection, specifically improving DC and NK cell numbers and function.

76. Kaposi's Sarcoma in HIV+ Subjects: A Model of Accelerated Immunological Aging and Altered Tumor Surveillance

Jeffrey Dock (P, N), Patrick Unemori, Toby Mauer, Kieron S Leslie, Steve Deeks, Peter Martin, Peter Hunt, Rita B Effros
Department of Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, and Departments of Dermatology and Medicine, University of California, San Francisco.

Young adults with HIV disease experience deleterious changes in their adaptive immune system similar to those seen in advanced age, indicating chronic HIV disease may cause premature immune system aging and cellular senescence. Supporting this model are multiple epidemiological observations that HIV+ individuals have an increased risk of cancer, suggesting accelerated aging of immune cells involved in tumor surveillance, leading to loss of tumor control. Kaposi's sarcoma (KS) is the most common AIDS-defining malignancy. Similar to many human cancers, KS is associated with a viral infection, namely, human herpesvirus 8 (HHV8). However, as with many virally-induced cancers, not all persons with HIV who are HHV8+ actually develop KS. The goal of our research is to evaluate the potential role of the immune system in the development of KS. Cytotoxic (CD8+) T cells with markers of replicative senescence are found within the local environment of many human tumors, and, in the elderly, high proportions of senescent CD8+ T cells are associated with early mortality. We, therefore, sought to evaluate several features of replicative senescence in blood samples from HIV+HHV8+ persons Twenty subjects who were KS+ and 40 control subjects without KS were compared for biomarkers reflecting replicative senescence. We observed that ex vivo baseline telomerase activity of total peripheral blood mononuclear cells (PBMC) was significantly higher in the subjects who did not have KS. However, on day 7 following activation, both PBMC and purified CD8+ T cells from the KS+ subjects showed a

trend toward greater telomerase activity compared with that of the subjects without KS. The complex relationship between telomerase activity, telomere length, viral load and age will be presented to evaluate the effect of altered immune surveillance in this model of virally-induced cancer.

Support: NIH AI 045008, AG032422

77. Inflammatory Proteins and Depression in Older Adults

R.S.Newson PhD (P), N.Direk MD, A.Hofman MD PhD, J.Wittemann PhD & H.Tiemeier, MD PhD
Dept. Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

Inflammation has been proposed to play a role in depression in older adults, such that older adults with depression reportedly have higher levels of inflammatory markers. It has been suggested this may occur due to an altering of neurotransmitter metabolism or HPA axis functioning. However, the majority of evidence for this association is cross-sectional and therefore the direction of this association remains unclear. We sought to examine the causal nature of this association in a prospective cohort study of older adults. Set within the prospective population-based Rotterdam Study, approximately 3,500 healthy older adults (age 65+) were assessed on measures of inflammation at baseline and after six year follow-up and followed continuously for incident depressive events for a further six years. Inflammation was assessed in a fasting specimen with C-Reactive protein and α1-anti-chymotrypsin and in a random subset with Interleukin-6. Depression was assessed using multiple sources: doctor and mental health specialist reports, pharmacy records noting antidepressant usage, standardised questionnaires (Centre for Epidemiological Studies-Depression scale), clinical interviews, and self-report. Correlational analyses between inflammation markers and depression at baseline revealed a significant, although small, cross-sectional relationship (r ranging from .070 - .117, $p < .001$). Regression analyses indicated that in non-depressed older adults inflammation, particularly C-reactive protein, was predictive of depression over a six year period. Interestingly, regression analyses also demonstrated that depression was predictive of subsequent inflammation, even when controlling for prior inflammation levels. These significant, although small, findings suggest the possibility of a bi-directional relationship between inflammation and depression. Thus inflammation may result from and contribute to depression in older adults. As such inflammation has a potentially important role in the physical and mental health of older adults.

Key Words
Inflammation, depression, aging, bi-directional

78. Cellular Senescence in the Lungs Increases Susceptibility to Pneumococcal Infection in Aged Mice

P. Shivshankar (P) A. R. Boyd, I-T. Yeh and C. J. Orihuela
Department of Microbiology and Immunology, University of Texas Health Science Center at San Antonio, Texas-78229, USA

Community-acquired pneumonia (CAP) in the elderly is associated with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis; conditions that are linked to the presence of replicative senescent cells. Recently, we have shown that age-associated inflammation increases the pneumococcal ligands, polymeric immunoglobulin receptor (pIgR) and platelet activating factor receptor (PAFr) expression in mouse lungs cells; and identified keratin 10 (K10) as a ligand expressed on the lung cells for binding through pneumococcal adhesin, PsrP. We determined if K10 is over-expressed during aging. A 7-fold increase in K10 expression was observed in lung biopsies of aged humans (51-89 years) versus their young counterparts (43-50 years); and, a 10-fold high expression of K10 in aged mouse lungs (19-21 months) versus young controls. Correlating these analyses, we observed 100% mortality on day 4 in aged mice as compared to that of 33% in young mice, when challenged intranasally with 10^6 CFU of pneumococcal strain TIGR4. Infection was attenuated in mice challenged with PsrP-deficient TIGR4 strain. Given that K10 induces cell cycle arrest via retinoblastoma protein (pRb) in differentiated keratinocytes, we examined if age-related cellular senescence modulated pneumococcal ligands expression on lung cells. Aged mice, fibrosis- and oxidative stress-induced senescent mice showed elevated expression of pneumococcal ligands in the lungs; and showed significant increase in bacterial burden in their lungs and blood, 48h post-pneumococcal challenge. Cell cycle and BrdU-labeling analyses demonstrated increased presence of senescent cells in the lungs of aged, senescence-induced mice versus young/normal controls. Given that chronic inflammation increases pIgR and PAFr expression in aged mice, our results suggest that inflammatory mediators in senescent cells may enhance the expression of pneumococcal ligands. The paracrine effect of the proinflammatory cytokines secreted from these cells may contribute to total increase in the ligand expression resulting in increased pneumococcal binding to lungs cells.

79. Aging Oxidative Stress and Apoptosis in Ischemia/Reperfusion Injury of Young and Old Skeletal Muscle

David W. Hammers (P, N), Martin L. Adamo, Holly Van Remmen, Thomas J. Walters, and Roger P. Farrar
Department of Kinesiology, The University of Texas, Austin, TX ; Department of Biochemistry, Department of Cellular and Structural Biology, and the Sam and Ann Barshop Institute for Longevity and Aging Studies, The University of Texas Health-Science Center in San Antonio, San Antonio, TX; Regenerative Medicine, US Army Institute of Surgical Research, Fort Sam Houston, TX

Previous work in our laboratory demonstrated that aged skeletal muscle exhibits greatly diminished expression of the regenerative growth factor, IGF-I, and subsequent anabolic signaling following tourniquet (TK)-induced ischemia/reperfusion (I/R) injury. The focus of the present work is to identify age-related alterations in the I/R pathology that precede the regenerative effort. To accomplish this 6 mo and 24-27 mo C57BL mice were subjected to 2 hour TK-induced ischemia, followed by up to 21 days of reperfusion. To examine the I/R pathology,

we performed histological analyses, measured oxidative stress [F2-Isoprostane (Isp) levels], and Western blotted for markers of apoptosis (caspase-3 and PARP cleavage). The injured muscles from aged mice showed greater histological pathology and contained significantly higher levels of Isps than those of young. In addition, caspase-3 and PARP cleavage are strongly evident in both young and old I/R-injured muscles, suggesting apoptosis is contributing to the I/R pathology. These data indicate that increased susceptibility to oxidative stress is a major contributor to the age-related decrement of skeletal muscle following I/R.

80. Increased Reactivity of Dendritic Cells from Aged Subjects to Self-Antigen, the Human DNA

Anshu Agrawal (P), Jia Tay, Steven Ton, Sudhanshu Agrawal, Sudhir Gupta
University of California, Irvine

Diminished immune functions and chronic inflammation are hallmarks of aging. The underlying causes are not well understood. In this investigation, we show an increased reactivity of dendritic cells from aged subjects to self-antigens as one of the potential mechanism contributing to age-associated inflammation. Consistent with this, DCs from aged subjects display increased reactivity to intracellular human DNA, a self-antigen, by secreting enhanced quantities of type I interferon and Interleukin-6 compared to the DCs from young subjects. Furthermore, this is accompanied by an increased upregulation of costimulatory molecules CD80 and CD86. These DNA primed DCs from aged subjects enhanced T cell proliferation compared to the young subjects further substantiating our findings. Investigations of signaling mechanisms revealed that DNA-stimulated DCs from aged subjects displayed a significantly higher level of interferon regulatory factor-3 and NF-kappaB activity compared to their young counterparts. More importantly, DCs from aged subjects displayed a higher level of NF-kappaB activation at the basal level suggesting an increased state of activation. This activated state of DCs may be responsible for their increased reactivity to self-antigens such as DNA, which in turn contributes to the age-associated chronic inflammation.

81. Does Cytomegalovirus Deserve the Bad Rap?

Ann B. Hill, Carrie Nielson, Priya Srikanth, Amanda Simanek, Jennifer Dowd and Allison Aiello
Department of Molecular Microbiology and Department of Public Health and Preventative Medicine, Oregon Health and Science University, Portland, OR, and Department of Epidemiology, Center for Social Epidemiology and Population Health, University of Michigan-School of Public Health, Ann Arbor, MI

The size of CD8+ T cell response to CMV defines an immune risk phenotype (IRP) associated with all-cause mortality and poor vaccine response in the elderly. Associations have also been reported between the IRP and/or anti-CMV antibody titers with various diseases of "inflammaging". However, CMV not only causes inflammation, but is also reactivated in response to inflammation. Hence, these studies could reflect an association with an inflammatory diathesis that both triggers more CMV activity (hence increased antibodies and CD8+ T cells), and also causes the disease in question. If CMV is involved in pathogenesis, there should be an association with CMV seropositivity per se, and not just the size of the immune response. We analyzed data from the third National Health and Nutrition Examination Survey (NHANES III) for 6,543 individuals aged 50 and over for whom CMV serology data, mortality follow-up (median 7.8 years) and mortality risk-factor data was available. Proportional hazards regression was used to evaluate whether CMV seropositivity at baseline was associated with incident all-cause, cardiovascular, or cancer mortality. 88% of individuals were CMV seropositive at baseline, and, amongst the seropositives, antibody titer increased with age, suggesting a high level of ongoing viral activity. After age and sex adjustment, CMV positivity was associated with an increased risk of all-cause mortality (hazard ratio [HR]: 1.32, 95% confidence interval [CI]: 1.08-1.62) and cardiovascular mortality (HR: 1.47, CI: 1.11-1.94) but not cancer mortality. Additional adjustment for socioeconomic status markers, body mass index, smoking, blood lipids, hypertension, and diabetes attenuated the association, but a statistically significant association remained for cardiovascular mortality (HR: 1.34, CI: 1.00-1.79). We conclude that CMV's bad reputation is at least partially deserved.

82. Negative Feedback Effects of Chronic 17ß-Estradiol on Hypothalamic KiSS-1 And NkB in the Aging Female Rhesus Macaque

Dominique H. Eghlidi [1, 2] (P, N), Steve G. Kohama [1], and Henryk F. Urbanski [1, 2]
[1]Division of Neuroscience, Oregon National Primate Research Center, Beaverton, Oregon; [2]Department of Physiology and Pharmacology, and Behavioral Neuroscience, Oregon Health and Science University, Portland, Oregon

Kisspeptin, neurokinin B, and dynorphin A, [collectively KiND] are peptides co-expressed in neurons of the hypothalamic arcuate nucleus (ARC) and are encoded by KiSS-1, NKB, and PDYN, respectively. KiND neurons express estrogen receptors and are conduits for 17ß-estradiol (E2)-mediated regulation of steroid receptor deficient gonadotropin-releasing hormone neurons. In the current study we examined relationships between age, hormone replacement therapy (HRT), and reproductive (cyclicity) status by measuring hypothalamic mRNA expression of KiND and the corresponding receptor genes; G-protein coupled receptor 54 (GPR54), neurokinin receptor 3 (NK3), and kappa opioid receptor (KOR) – in young, middle-aged pre-menopausal and old-peri-menopausal rhesus macaques. Using real-time qPCR, we observed higher KiSS-1 and NKB expression in old peri-menopausal, compared to young or middle-aged pre-menopausal macaques. In old animals, KiSS-1 and NKB levels were higher in ovariectomized (OVX) compared to intact peri-menopausal animals or OVX animals undergoing long-term chronic (~4-year) E2 replacement where expression was suppressed to normally cycling

young macaques, while PDYN and KiND receptor gene expression was unchanged. In contrast, there was no difference in young animals in the level of gene expression between intact, OVX and OVX animals receiving short-term (1-month) E2 replacement. Moreover, in normally cycling young macaques, no KiND expression differences were noted in hypothalami collected during the early follicular, late follicular or mid-luteal phases. Taken together, these data provide evidence that duration of steroid treatment, rather than age per se, have a major effect on kisspeptin and neurokinin B gene expression in the primate ARC.

Grant Support: Supported by NIH grants AG-029612, HD-029186, and RR-000163

83. The Effect of Age on Steroidogenesis in Skeletal Muscle of Women

E Pöllänen[1, 2] (P), P Ronkainen[1, 2], S Sipilä[1], H Suominen[2] ,M Alen[3], Y Konttinen[4] ja V Kovanen[2]

[1]Gerontology Research Centre, University of Jyväskylä, Jyväskylä, Finland; [2]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; [3] Department of Medical Rehabilitation, Oulu University Hospital and Institute of Health Sciences, University of Oulu, Oulu, Finland;
[4]Department of Medicine, University of Helsinki, Helsinki, Finland

The purpose of this study was to examine the potential effects of age on steroidogenesis in skeletal muscle of women. Sex steroid hormones are important in regulation of muscle mass and composition. In fertile women they are mainly secreted from gonadal tissues. In postmenopausal women they are to a significant extent produced by peripheral conversion of prohormones to estrogens and androgens by a cascade of steroidogenetic enzymes, namely steroid sulfatase (STS), 17beta-dehydrogenases (HSD), 13beta-HSDs and aromatase; testosterone can be converted to estradiol by aromatase or to dihydrotestosterone by 5alpha-reductases (SRD5A1, SRD5A2). It is not known if age affects the expression of steroidogenesis-related enzymes. In this study we analyzed gene expression of STS, HSD17B5, HSD3B1, aromatase, SRD5A1 and SRD5A2 in muscle of 13 fertile women (35±3 yr) not using any contraceptives and 13 postmenopausal women (64±2 yr) who had never used any estrogen containing hormone replacement therapy. The young and older women did not differ in their physical activity levels or body composition. However, as defined from computed tomography scans from quadriceps muscle, postmenopausal women had 10% lower muscle mass ($p=0.07$) and 11% lower muscle density ($p<0.0001$) due to fat infiltrated within muscle tissue. The transcript levels of all studied enzymes were slightly higher in postmenopausal women but only aromatase and SRD5A2 were significantly more abundant (16%, $p<0.03$ and 33% $p<0.05$, respectively). The expression of STS, aromatase and SRD5A2 also negatively correlated with muscle density values ($r=-0.50$, $p=0.03$; $r=-0.58$, $p=0.01$; $r=-0.56$, $p=0.01$, respectively) indicating that the more these genes were expressed the less fat was present within muscle. No such correlation was seen for muscle mass. According to our results peripheral intracrine steroidogenesis occurs in skeletal muscle and is affected by age and/or the availability of circulating sex hormones. Furthermore, muscular hormone synthesis may participate in regulation of muscle quality.

84. Age-Related Expression of Steroidogenic Enzymes in the Rhesus Macaque Hippocampus

Krystina G. Sorwell[1,2](P), Steven G. Kohama[1], Henryk F. Urbanski[1,2]
[1]Division of Neuroscience, Oregon National Primate Research Center, Beaverton, OR 97005; [2]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR

Aging is associated with a significant decline in peripheral steroid production, including the adrenal hormone dehydroepiandrosterone (DHEA) and its sulfate, DHEAS. Rodent studies suggest a procognitive effect of DHEAS in aged animals; however, human studies of DHEAS supplementation have not shown similar results. We propose that the procognitive mechanism of DHEAS involves its conversion to estradiol (E_2), and that the lack of efficacy in aged humans is due to a decline in the brain's ability to perform this conversion. Additionally, reduced central neurosteroid production, together with markedly attenuated circulating levels of DHEAS and E_2, may contribute to cognitive decline in the elderly. To investigate these hypotheses, we sought to identify expression of the genes involved in the de novo production of DHEAS and its conversion to E_2 in the rhesus macaque (*Macaca mulatta*) hippocampus, and to quantify this expression through advanced aging using real-time PCR. The results clearly show that all of these genes are expressed in the rhesus hippocampus, suggesting that this cognitive brain center is a potential source of DHEAS and E2. We also identified an age-related decline in expression of cytochrome p450 17a1 (CYP17A1), steroid sulfatase (STS), and 3β-hydroxysteroid dehydrogenase type 2 (3BHSD2). Such declines are consistent with the hypothesis of a reduced potential for steroid synthesis in the aging brain. If these reductions in gene expression do in fact contribute to cognitive decline in the elderly, targeting the neurosteroidogenic pathway may be a potential treatment mechanism for mild cognitive impairment and Alzheimer's disease.

This work was supported by NIH grants: AG-023477, RR-000163, and AG-029612.

85. Untargeted Metabolomics Implicates Phosphocholine Dysregulation in Muscle Aging

Gary J. Patti (P, G), Leah Shriver, Ralf Tautenhahn, Jens Bruening, Ewa Kalisiak, Sunia Trauger, Eric Ravussin, Andrew Dillin, and Gary Siuzdak
The Scripps Research Institute and The Salk Institute, La Jolla CA

Sarcopenia, or the degenerative loss of skeletal muscle mass with age, leads to physical, psychological, and economic burdens in the elderly that contribute to age-related disease and decrease quality of life. The molecular

mechanisms governing skeletal muscle decline are incompletely understood, limiting effective therapeutic intervention. We describe the first global metabolomics study to identify metabolic pathways that are differentially regulated in human quadriceps with age. The screening platform used an untargeted, mass spectrometry-based approach beginning with HPLC/electrospray ionization and accurate-mass determination, followed by novel data alignment and database screening for metabolite identification. Despite the overall accumulation of fat in skeletal muscle with age, 34 phosphocholines were determined to be uniquely decreased in elderly relative to young individuals. To establish a model system by which the mechanism of phosphocholine dysregulation could be further investigated, we performed metabolic profiling on *Caenorhabditis elegans*, a nematode worm known to develop sarcopenia. The N2 wild type worm showed comparable age-related changes in phosphocholines. Mutations affecting the *daf-2*, *glp-1*, and *isp-1* genes, which slow aging in *C. elegans* and result in significant delays in the development of sarcopenia, were found to result in a "young" phosphocholine profile. Interestingly, a novel bioinformatics analysis allowing for comparison of dysregulated metabolites unique to each *C. elegans* longevity model, identified 7 metabolites that were similarly dysregulated in all models studied. Four of these metabolites were the same phosphocholines identified to be downregulated in human quadriceps with age. Although alterations in choline metabolism have been implicated in brain senescence, these results show that this metabolic pathway is also important in the development of age-related muscle dysfunction and suggest that unique phosphocholines may play a role in maintaining a youthful phenotype.

86. Seeking Possible Mechanisms by Which combined Postmenopausal Hormone Replacement Therapy (HRT) Preserves Muscle Properties

P.H.A. Ronkainen[1,2](P, N), E. Pöllänen[1,2], M. Horttanainen[1], V. Kovanen[1].
1) Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland
2) Gerontological Research Center, University of Jyväskylä, Jyväskylä, Finland

We have previously reported that combined HRT improves or at least preserves muscle properties among postmenopausal women. Analysis on gene transcripts of the insulin-like growth factor 1 (IGF-1) signaling pathway, known to regulate muscle mass, revealed that HRT modulates the transcription of *IGF-1* and its splice variants. This study aimed at discovering whether the observations are mostly due to the estrogenic or the progestogenic counterpart of combined HRT. C2C12 myotubes were treated with 17β-estradiol (1nM/10nM) or noretisterone acetate (NA, 1nM/10nM). The expression of *IGF-1*, *Akt1* (protein kinase B), *mTOR* (mammalian target of rapamycin), *atrogin-1*, *Foxo1* and *Foxo3* were assessed by quantitative PCR at 2 h, 6 h and 24 h, while the phosphorylation of Akt and mTOR was determined by Western blotting at four time points between 5 min and 2 h. Control cells were collected at each time point including baseline. Data were analyzed by analysis of variance utilizing SPSS software. No statistically significant effects of the treatments on gene expression were found. The expression of several transcripts, however, appeared to change between different time points, but the slope was strikingly similar to that of the control cells. Further, we were unable to identify any effects of the treatments on the phosphorylation of Akt or mTOR. A slight, albeit statistically non-significant, positive effect of 10 nM NA on the amount of p-Akt was observed. In conclusion, the components of a typical combined HRT did not affect the expression of the genes involved in IGF-1 signaling pathway in C2C12 myotubes. Moreover, the activation of the key proteins of this hypertrophic pathway was observed not to change significantly in our model. An interesting notion, however, was evident; careful tracking of control cells along the entire time frame in this kind of experiment is of immense importance.

87. Healthspan Assessment in Ames Dwarf Mice

Lauren B. Sloane (P, G), Steven N. Austad
Barshop Institute for Longevity and Aging Studies, San Antonio, TX

The Ames dwarf (Prop1df) mouse lives 50% longer than littermate controls. The Prop1df mutation eliminates the production of growth hormone, prolactin, and thyroid stimulating hormone from the anterior pituitary. Because these hormone deficiencies might be expected to impact mouse health, we performed a battery of tests of physiological function in young (~5 mo) and older (18-24 mo) Ames dwarf mice. These assays include cognitive evaluation (Y-maze), kinesthetic measures (rotarod performance, gait analysis), metabolic parameters (body composition, VO2, and respiratory quotient), and total spontaneous activity. We discuss both similarities and differences in our findings with previously published assessments of health in the Ames dwarf.

88. A Role for Fibroblast Growth Factor 21 (FGF21) as a Putative Longevity Factor

Ravneet K Boparai (P, G)[1], Oge Arum[1], Michal M Masternak[1], Romesh Khardori[2], Andrzej Bartke[1]
[1]Department of Internal Medicine, Geriatrics Research, Southern Illinois University School of Medicine, Springfield, IL; [2]Department of Internal Medicine, Division of Endocrinology, Metabolism & Molecular Medicine, Southern Illinois University School of Medicine, Springfield, IL

Fibroblast Growth Factor 21 (FGF21) is an atypical member of the FGF19 subfamily that can exert systemic, hormone-like effects. FGF21 signals through the classic FGF receptor complexed with its coreceptor, β-klotho, and their expression has been detected in metabolically relevant tissues such as liver, adipose and pancreas. FGF21 has emerged as a novel metabolic regulator with broad metabolic effects including enhancing insulin sensitivity. Since hepatic expression of FGF21 is robustly induced by fasting via a PPARα-mediated mechanism and Caloric Restriction (CR) is an intervention that has been consistently shown to extend lifespan in various animal

models, the aim of the present study was to determine an association, if any, between FGF21 and longevity. We have addressed this by studying thirty month old Growth Hormone Receptor Knockout (GHRKO) mice and their control littermates subjected to two different dietary restriction regimens, CR and Every Other Day Feeding (EODF) starting at four months of age. The expression and abundance of both FGF21 and its coreceptor, β-klotho were determined in hepatic tissue from these animals. Hepatic expression of FGF21 was found to be significantly elevated in normal mice on CR (1.499 ± 0.17; $P<0.05$) and EODF (2.78 ± 0.49; $P<0.02$) in comparison with ad libitum fed mice (1.00 ± 0.14). However, GHRKO mice which do not exhibit extended longevity in response to CR did not show an induction in FGF21 gene expression in response to either form of dietary restriction. β-klotho expression was also increased in normal mice on CR ($P<0.05$) and EODF ($P<0.03$). These observations suggest that FGF21 might have a role in mediating the beneficial effects of CR on lifespan.

Supported by NIA and Fraternal Order of Eagles

89. Leukocyte Mitochondrial DNA Content is Associated With Depression in Older Women

Moo-Young Kim(P), Yu-Na Son, Duk-Chul Lee
Department of Family Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Depression and suicide in older adults are serious social problems. In an animal model of depression, which is induced by chronic stress, brain mitochondrial function is decreased. The purpose of this study is to investigate whether the mitochondrial DNA content of peripheral blood leukocyte is related to depression in community dwelling older women. A total of 142 community dwelling old women who can carry out daily life independently were recruited in this study. Mitochondrial DNA (mtDNA) copy numbers were measured using real-time PCR methods. Depression was assessed by the 15-item geriatric depression scale (GDS). Depressive cases defined as the subjects whose GDS score was ≥ 6 or who were taking anti-depressant medication. We also measured cognitive function, physical performances (gait speed, chair-stand times, tandem standing times) and metabolic and endocrine factors. The depression group had a significantly lower mtDNA copy number than the control group (81.1(IQR 43.6~130.0) vs 113.8(IQR 46.5~215.6), $P=0.03$). And MMSE score and physical performance score were significantly lower in the depression group than the control group (respectively, 23.8 ± 3.89 vs 25.2 ± 3.71, $P=0.03$; 7.0 ± 2.16 vs 8.1 ± 2.56, $P<0.01$). After adjustment for confounding factors using logistic regression analysis, mtDNA copy number was significantly related to depression (odds ratio 0.49, $P=0.03$). We demonstrated that low leukocyte DNA content is related to depression in older women. It is suggested that mitochondrial dysfunction may be a mechanism of geriatric depression.

90. The Relationship Between Visfatin and Metabolic Syndrome in Postmenopausal Women

Jung-Ha Kim, Sang-Hwan Kim, Jee-Aee Im, Duk Chul Lee (P)
250 Seongsanno, Seodaemun-gu, Seoul, Korea

Objective: The biological role and activity of visfatin, an adipokine mainly produced by visceral fat, have not been fully elucidated. The observed relationships between visfatin and metabolic syndrome are inconsistent. The purpose of this study was to illuminate the relationship between visfatin and metabolic syndrome in postmenopausal women.

Methods: The present study included 129 postmenopausal women. Subjects with cardiovascular disease such as myocardial infarction, transient ischemic attack, and cerebral infarction were excluded from the study sample. Body weight, height, blood pressure (BP), and waist and hip circumference were measured, and biochemical tests were performed.

Results: The mean serum visfatin level (mean±S.D.) of subjects with metabolic syndrome was 2.63 ±1.68 ng/mL, significantly higher than that of subjects without metabolic syndrome ($p<0.01$). As the number of components of metabolic syndrome increased, the concentration of serum visfatin also increased ($p<0.01$). Visfatin concentration was positively correlated with waist circumference ($r=0.269$, $p<0.01$), systolic BP ($r=0.248$, $p<0.01$), diastolic BP ($r=0.257$, $p<0.01$), fasting glucose level ($r=0.271$, $p<0.01$), HOMA-IR ($r=0.313$, $p<0.01$), triglyceride level ($r=0.272$, $p<0.01$), WBC count ($r=0.309$, $p<0.01$), and homocysteine level ($r=0.175$, $p<0.05$). With multiple logistic regression analysis, visfatin was found to be an independent factor associated with metabolic syndrome after adjustment for confounding variables including age and body mass index (BMI).

Conclusions: Serum visfatin was associated with metabolic syndrome in postmenopausal women, suggesting that visfatin may act as the underlying pathophysiology of metabolic syndrome in postmenopausal women.

91. Association Between Serum Adiponectin and Ferritin Level in Apparently Healthy Women

Ji-Won Lee (P, N), Moo Young Kim, Duk-Chul Lee
Seoul, Korea

Aim: Serum adiponectin and ferritin are associated with glucose metabolism, insulin resistance (IR) and oxidative stress, while bilateral relationship between serum ferritin and adiponectin has been unknown. The aim of the study was to evaluate the association between serum adiponectin and ferritin level in apparently healthy women.

Subjects and methods: We evaluated a total of 111 subjects aged 32–68 years old. Clinical and laboratory measurements, including serum levels of their lipid profiles, high-sensitivity C-reactive protein (hs-CRP), fasting glucose levels, fasting insulin levels adiponectin,

ferritin levels and total antioxidant status (TAS) were measured.

Results: Serum adiponectin levels were negatively correlated with body mass index (BMI), homeostatic model assessment of insulin resistance (HOMA-IR), triglyceride, ferritin, TAS and positively correlated with HDL cholesterol levels. Serum ferritin levels were positively correlated with age, BMI, HOMA-IR, TAS and negatively correlated with adiponectin levels. By step-wise multiple regression analysis, serum ferritin, triglyceride, HDL cholesterol levels were found to be independent factors associated with serum adiponectin, and serum adiponectin, TAS, and menopause status independently affected serum ferritin levels.

Conclusions:
Our findings suggest that the relationship between serum ferritin and adiponectin levels might play an important role in glucose metabolism, IR and oxidative stress. Further studies on the causality between adiponectin and ferritin are warranted.

92. Chemical Analysis of Aging: Testing Predictions From Green Theory

Elizabeth L. Ostler,(P) Aamira Iqbal, Declan Naughton, Matthew D. Piper and Linda Partridge
School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, UK.

The Green Theory of Aging postulates that aging is caused by failure to repair a diverse multitude of thermodynamically-stable damage, caused by both normal metabolic processes and damaging agents. Such damage produces a wide variety of difficult-to-repair chemical adducts. Two specific predictions arise from Green Theory: firstly a wide variety of chemical adducts will increase in concentration with age and secondly, organisms maintained under conditions which extend lifespan will display a reduced rate of accumulation of such compounds.

In order to test these predictions, novel spectroscopic and spectrometric methods for the analysis of stable chemical adducts in whole *Drosophila* were developed. These methods were specifically designed to survey the broadest possible range of stable compounds (rather than focusing on specific compounds which might, or might not, be relevant to aging).
We have now used these techniques to assess the effects of a wide variety of parameters on the chemical changes observed during *Drosophila* aging and have shown results consistent with the predictions of Green Theory.[1] We have now extended this analysis to include detailed 1H Nuclear Magnetic Resonance and Mass Spectrometric data.

1. Iqbal A, Piper M, Faragher RGA, Naughton DP, Partridge L & Ostler EL Chemical changes in aging *Drosophila melanogaster*. AGE (2009) **31**, 343. DOI: 10.1007/s11357-009-9105-4.

93. Effects of Dietary Restriction on Short-Lived Saccharomyces Cerevisiae Mutants

Jennifer Schleit (P), Brian K. Kennedy, and Matt Kaeberlein
Department of Pathology, University of Washington, Seattle WA

Dietary Restriction (DR) has been shown to extend life span and enhance stress resistance in multiple organisms. To date, most studies have focused on the mechanisms of life span extension from DR in control populations, with relatively little effort made to explore how diverse genetic populations respond to DR. In a preliminary examination of short-lived Saccharomyces cerevisiae deletion mutants, we observed dramatically varying replicative life span responses to DR. These differential responses to DR could be largely grouped based on the function of the deleted gene. In general, deletion mutants with defective DNA repair showed little or no replicative life span extension from DR. Mutants with impaired mitochondrial functions often had greatly extended replicative life spans in response to DR, with some surpassing the life span observed in wild-type yeast mother cells. In contrast, mutants with altered vacuolar ATPase (V-ATPase) activity had greatly reduced life spans in response to DR. To further investigate these findings, we are taking three parallel approaches. First, the impact of DR on additional short-lived S. cerevisiae mutants defective for a variety of cellular processes is being examined. Second, longevity epistasis analysis is being performed in double mutants containing a life span shortening deletion and a known life span extending mutation. Third, we are exploring potential molecular mechanisms by which different cellular defects influence the longevity response to DR in yeast. Future experiments will expand these studies to the nematode Caenorhabditis elegans. Together these experiments will provide new insight into the molecular mechanisms influencing responses to DR and their role in aging.

94. Age-Dependent Increases in 5'-Adenosine Monophosphate-Activated Protein Kinase, C-JUN-N-Terminal Kinase, and Glycogen Synthase Kinase-3 Beta and Role for Caloric Restriction: Implication for Mitochondrial Energy Substrate Control

Ryan T. Hamilton (P, G), Fei Yin, Enrique Cadenas
University of Southern California School of Pharmacy, Department of Pharmacology and Pharmaceutical Sciences, Los Angeles, CA

Age-dependent hypometabolism precedes the development of Alzheimer's disease (AD) by a decade. Several canonical signaling pathways that converge upon mitochondrial substrate bioavaliability and function include age-dependent activation of JNK and GSK3b phosphorylation and protective functions of AMPK. It is known that both GSK3b and JNK phosphorylation increase with age in Fischer rats and that both pathways inhibit PDH activity yielding decreased glucose-derived substrate bioavailability. These observations supported the hypothesis that the interplay between JNK, GSK3b and AMPK may provide insight into mechanisms of AD centered around substrate bioavailability and that caloric

restriction may shift this paradigm. It was observed that there was an age-dependent increase in AMPKa protein expression while there was an age-dependent decrease in JNK-1, and JNK-2 protein expression whereas AMPKa, JNK-1 and JNK-2 phosphorylation was increased age-dependently in both ad libitum (AL) and short-term caloric restricted (ST-CR) rats. AMPKa phosphorylation was increased at 6 months of age and unchanged at 14 and 26 months versus AL. Citrate lyase (CL), Short chain alcohol dehydrogenase (SChAD), and hydroxy methyl glutaryl coenzyme A-reductase (HMG-CoA-R) were increased age-dependently in the ST-CR and AL rats while ST-CR increased HMG-CoA-R and decreased ACC at both 6 and 14 months. ACC protein expression was decreased with age in both the AL and ST-CR rats while TFP was unchanged except for 14 month ST-CR where there was an attempt to upregulate it that was abolished in the 26 month ST-CR. These findings suggest that aging-dependent inhibition of glucose-dependent substrates by JNK and GSK3b may elevate energy sensing AMPKa leading to a shift to lower lipid synthesis, increased lipid catabolism of HMG-CoA-R substrates by SChAD and increased cholesterol synthesis while the increased cholesterol synthesis needs to be addressed in terms of both its activity and its substrate metabolism by SChAD.

95. Global Analysis of the Liver Mitochondrial Proteome Half-Lives Demonstrates Increase Turnover Rate with Ageing

Dao-Fu Dai(P, G), Nick Schulman, Edward Hsieh, Michael MacCoss, Peter Rabinovitch
University of Washington, Seattle, WA

Impairment of protein homeostasis has been implicated in ageing. However, the changes of mitochondrial protein turnover rate with age are not well understood. We performed a global analysis of liver mitochondrial proteome turnover rates in young and old mice. Mice were fed with a diet containing 50% 2H-leucine for 20 days, followed by regular diet for 12, 24, 36 and 60 hours. The mitochondrial proteome half-lives were estimated by the exponential decay of 2H-leucine-containing peptides. The percentage of 2H-enrichment in leucine-containing peptides was analyzed using a new "Topograph" software, which is able to interpret the isotopomer distribution in peptides after heavy label protein digests. In this manner, we have successfully identified the label status peptides corresponding to more than 500 proteins from liver mitochondria. Of these, the presence of one or more leucine amino-acids allows us to estimate the protein turnover rates for more than 400 proteins simultaneously. This is the first such high-throughput analysis of protein turnover rates. The overall mitochondrial protein turnover rates significantly increased by ~20% with age, as shown by steeper slopes of exponential decay ($p=0.0013$ for Young WT vs. Old WT). This is especially true for components of the electron transport chain and oxidoreductase proteins which are redox-sensitive and more susceptible to oxidative damage. Interestingly, our preliminary data showed that overexpression of catalase targeted to mitochondria (mCAT) significantly reduced the turnover rates of liver mitochondrial proteins in old mice, consistent with the protective effect of mCAT against protein oxidative damage.

96. Mouse Models of Muscle Remodeling

Ted G. Graber (P,N), CN (Joyce) Chen*, Kelsey H.H. Mosser, Wendy M. Bratten, Deborah A. Ferrington, LaDora V. Thompson
University of Minnesota, Minneapolis, MN

Aging is associated with profound loss of muscle mass and ongoing remodeling that involves muscle degeneration and reduced regeneration, which has been linked to increased oxidative damage and altered proteasome function. This study was to investigate whether oxidative stress and proteasome function play a role in muscle remodeling associated with two models of muscle deterioration: dystrophin-/- knockout (mdx) and double knockout, dystrophin-/-/utrophin-/- (dko). Mouse grip strength was used to evaluate muscle performance. Serum creatine kinase (CK) and protein carbonyls (oxyblot) were measured to determine the extent of muscle damage. Myofiber cross-sectional area and central nuclei (CN) were measures of atrophy and regeneration. Proteasome activity and content were evaluated using fluorogenic peptide substrates and western blots. The mdx and dko strains had a 3-fold increase in CK, a 35% decrease in strength, significant muscle atrophy, and a 169-fold increase in CN without any change in oxidatively-damaged proteins in comparison to wt. Muscle proteasome function showed a significant increase in the hydrolysis of fluorogenic peptides in the mdx and dko versus wt. Notably, no difference was observed in total proteasome (alpha 7) content. Comparing the composition of the catalytic beta subunits in the mdx and dko showed an increase in the cytokine-inducible immunoproteasome subunits, LMP2 and LMP7, whereas no change was observed in the content of the standard proteasome subunits, 20Sx and 20Sy. Overall, the muscles of the mdx and dko are functionally compromised, yet are still undergoing remodeling. In conclusion, the novel observation of increased proteasome activity without accumulation of oxidized proteins suggests these changes are part of a compensatory mechanism for responding to stress. Furthermore, this work suggests the increased proteasome function is likely due to an increase in immunoproteasome.

97. Do the Lifestyle Factors that Minimise Inflammation and Optimise Healthy Aging Change Throughout Life?

Judith H Ford (P)
University of South Australia, Adelaide
South Australia

Aging starts at conception and the active growth phase to puberty uses most of the cells' capacity to divide. Maturation usually occurs in the early 20's and in most organs other than the reproductive, growth is slowed to achieve maintenance of tissue function. Maintenance division continues until the dividing cells reach their telomeric limit, when the p53 gene complex is switched on and fatty acid metabolism, especially the fatty acid synthase and stearoyl-CoA desaturase genes are down-

regulated. This is accompanied by mitochondrial dysfunction through the changes in cellular fatty acids[1] and increased inflammation caused by the reduction of long-chain polyunsaturated fatty acids (PUFA). Organ senescence is reached when mitochondrial function is seriously compromised and there is no capacity for renewal. In the female reproductive system, reduced function of granulosa cells is apparent from about age 35 and is accompanied by severe mitochondrial dysfunction, lowered fertility and miscarriage. This can be delayed however by suppressing ovulation, since miscarriage rates were significantly reduced in women who had long-term use of the oral contraceptive pill[2]. Thus it seems likely that the telomeric limit of cells in specific organs can be delayed by lifestyle factors, including calorie restriction, that reduce cell division or telomeric damage. Once the limit is reached, dietary supplementation with long-chain PUFA, including olive oil as a source of oleic acid would seem to be important and from here on mitochondrial function may need to be enhanced. To date, resistance and weight bearing exercise have been demonstrated to be effective in stimulating mitochondrial function as has supplementation with cofactors such as
l-carnitine, co-enzyme Q10 and alpha-lipoic acid. Data will be presented to support the concept of the benefits of staged lifestyle intervention.

1. Ford JH (2010) AGE (in press)
2. Ford JH & MacCormac L (1995) Hum Reprod. 10(6):1397-402

98. Caspase-2 Acts as an Initiator Caspase in Oxidative Stress Induced Apoptosis in Primary Neurons

Meenakshi Tiwari (P, G), Marisa Lopez-Cruzan, William W. Morgan and Brian Herman
Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, TX

The increase in oxidative stress has been associated with neuronal cell death, which is characteristic of many neurodegenerative diseases associated with aging. Caspases play a central role in apoptosis; however, their involvement in oxidative stress-induced neuronal apoptosis remains elusive. Activation of 'initiator' (or 'apical') caspases-2, -8 or -9 is crucial for induction of apoptosis. In the present report, we determined caspase activation upon treatment with oxidative stress-inducing agents namely, hydrogen-peroxide, tertiary-butyl-hydroperoxide, menadione, 6-hydroxydopamine and rotenone in primary cultures of cortical neurons developed from young mice. Using a cell-permeable, biotinylated pan-caspase inhibitor (b-VAD-fmk) that inhibits and 'trap' the apical caspase activated when apoptosis is triggered, we identified caspase-2 as an initiator caspase activated in response to oxidative stress in primary neurons. Loss of caspase-2 inhibited oxidative stress-induced apoptosis. However, significant protection from cell death was observed against rotenone treatment but not with other oxidants. Moreover, the neurons dying in the absence of caspase-2 die a delayed necrotic cell death. Further focusing on the role of caspase-2 in rotenone-induced cell death defined a role of caspase-2 upstream to mitochondria. Loss of caspase-2 inhibited rotenone-induced Bid truncation and Bax activation and subsequently inhibited the release of cytochrome-c and AIF from mitochondria. Further, in caspase-2 knockout neurons, rotenone treatment induced autophagy and inhibition of autophagy abolished the protective effect of loss of caspase-2 during rotenone-induced cell death. Taken together these results indicate that caspase-2 is the initiator caspase during oxidative stress induced cell death, however, loss of caspase-2 provides survival advantage depending upon the oxidant.

99. Methionine Sulfoxide Reductase A (MsrA) Does not Affect Lifespan, but Protects From Metabolic Disease

Adam Salmon[1](P, G), Jennalynn Styskal[1], Florence Nwagwu[1], Yvonne Watkins[1], Viviana Pérez[1,2], Nicholas Musi[3], Arlan Richardson[1,2,4]
[1]The Sam and Ann Barshop Institute for Longevity and Aging Studies; [2]Department of Cellular & Structural Biology; [3]Division of Diabetes, The University of Texas Health Science Center at San Antonio, San Antonio, TX; [4]The Geriatric Research Education and Clinical Center, South Texas Veterans Health Care System, San Antonio, TX

Accumulation of oxidative damage has been thought to be an important mechanism underlying the aging process, the age-related rise in multiple pathologies and the progressive functional decline of various cellular processes. Proteins are particularly susceptible to oxidative stress and oxidation can alter the conformational structure, and thus the function of cellular proteins. Methionine sulfoxide reductase A (MsrA) plays an important role in the antioxidant defense, but is unique in that it repairs protein oxidative damage; MsrA reduces methionine sulfoxide residues to non-oxidized methionine. Mice lacking MsrA (*MsrA*$^{-/-}$) are generally normal in phenotype; *MsrA*$^{-/-}$ mice are indistinguishable from control in several key factors including body weight, glucose homeostasis, and body composition, but differ from normal in that they are sensitive to oxidative stress. Despite this sensitivity to oxidative stress, the lifespan of *MsrA*$^{-/-}$ mice is no different than that of control mice when maintained using optimum husbandry conditions. While MsrA seems to have no effect on lifespan, this enzyme may play an important role in the etiology of certain pathologies or age-related diseases. Obesity and fat accumulation are major risk factors for the development of insulin resistance and other metabolic dysfunctions such as type 2 diabetes and cardiovascular disease. It is thought that obesity-induced oxidative stress may be a primary cause of these diseases. When *MsrA*$^{-/-}$ mice are fed a diet high in fat content, they become significantly more insulin resistant relative to control mice on the same diet. Obese *MsrA*$^{-/-}$ mice show diminished response to insulin in whole animal glucose uptake (insulin tolerance tests) compared to obese control mice as well as a significant reduction in insulin signaling in liver, muscle, and adipose tissue. Additionally, mice overexpressing MsrA may be protected from obesity-induced insulin resistance. It is thought that oxidative stress causes insulin resistance by activating JNK signaling and by elevating production inflammatory cytokines like TNFα and IL-6; these processes can directly inhibit insulin signaling. We

find evidence that the action of MsrA is independent of these mechanismsand our preliminary data suggest that proteins within the insulin signaling pathway may be critical targets of this obesity-induced protein oxidation and may be protected by the activity of MsrA. These findings support a new hypothesis that obesity may lead to insulin resistance through increased oxidation, and thus reduced function, of proteins in the insulin signaling pathway and that protection from protein oxidation may be a possible preventative for many obesity-related diseases.

100. Re-Evaluation of the Free Radical Theory of Aging: Short, Normal and Even Long Lifespan in a SOD Mutant In C. Elegans

Shin Murakami (P), Hana Murakami, Angela Veh, Kelly Cabana, and Danielle Anderson
Aging-Osteopathic Consortium, Department of Basic Sciences, College of Osteopathic Medicine, Touro University-California, CA

The sod-4 gene is an extracellular superoxide dismutase gene, which can scavenge deleterious reactive oxygen species (ROS), superoxide radicals. The free radical theory of aging assumes that ROS, when not removed, causes damage in macromolecules, leading to aging. Based on the hypothesis, it was expected that the sod-4 mutations were short lived. However, previous studies show that the sod-4 knockout mutants have little effect on lifespan, providing evidence against the theory. Using in vivo imaging of ROS, we found that the sod-4 mutant has two subpopulations. The first subpopulation with a normal lifespan showed undetectable levels of ROS, while the second subpopulation with a short lifespan showed a high level of ROS. The short-lived subpopulation caused embryonic lethality and reduced fertility. Overall population in the sod-4 mutation was dominated by the first subpopulation with normal lifespan, which is consistent with the previous studies. Importantly, the results do not contradict, and are even supportive of the free radical theory of aging. Furthermore, the sod-4 mutant showed life extension when the deleterious phenotypes during development were minimized. The life-extension effect is likely a type of hormesis. Taken together, we report an interesting example of a single-gene mutation, which shows different effects on lifespan, depending on the subpopulation and depending on the stage of inactivation.

101. Resveratrol Depends on Red Wine Polyphenols for Antioxidant Activity

Ettore Bergamini (P), Gabriella Cavallini, Alessio Donati, Sara Straniero
Centro di Ricerca di Biologia e Patologia dell'Invecchiamento - University of Pisa
Via Roma, PISA- Italy

Resveratrol (trans-resveratrol, RSV), a stilbene derivative, is said to be endowed with antioxidant, antiaggregant, antiinflammatory, anti-cancer, anti-aging, blood-sugar lowering and beneficial cardiovascular effects. Abundant in red wine, RSV may be responsible for the French paradox, but extremely high doses of the pure substance appear to be required for beneficial activity. RSV is a phytoalexin, i.e. it is produced naturally by several plants when under attack by pathogens such as bacteria or fungi, in order to enhance protection by constitutively occurring polyphenols. Here we studied if red wine polyphenols (RWP) are required for the anti-oxidant effects of RSV.
Isolated rat liver cells were prepared by the collagenase method, preloaded or not with RWP, different doses of RSV or both, and submitted to UVB radiation (Parentini et al., 2002). Release of malondialdehyde (MDA) in the medium and levels of fat soluble antioxidants (FSA) were assayed as described by Guarini et al. (2008). Results showed that radiation significantly increased MDA release and decreased vitamin E, CoQ10 and CoQ9 and dolichol levels in liver cells; that preloading with RWP decreased UVB-induced MDA release and did not protect from FSA depletion; that RSV at a low dose slightly but significantly increased MDA release and FSA depletion, and did not affect neither MDA nor FSA at higher dosage; that RSV in the presence of RWP remarkably decreased UVB-induced MDA release and had no effects on FSA levels. It is concluded that RSV requires RWP at least for antioxidant activity.

102. A Novel Physiological Strategy of Intervention on Aging and Age-Associated Diseases: The DANI Protocol

Ettore Bergamini (P), Gabriella Cavallini, Alessio Donati, Zina Gori
Centro di Ricerca di Biologia e Patologia dell'Invecchiamento - University of Pisa
Via Roma, PISA - Italy

Biological aging, an essential concause of all age-associated diseases, may largely depend on an age-dependent accumulation of altered mitochondria and peroxisomes and a secondary increase in oxidative stress. The discovery that antiaging dietary restriction stimulates autophagy and speeds up the turnover rate of cell components unravelled that this vicious circle can be broken by enhancing the function of autophagy. The administration of Rapamycin and derivatives (e.g. everolimus) is being used to stimulate autophagy via mTOR inhibition in animal studies, but use in humans may be hampered by immunodepressive and toxic effects. A better stimulation of autophagy will be presented, which can be used safely in humans. The treatment (named PISA: Pharmacological stimulation of Suppression of Aging) acts by enhancing the physiological mechanism of autophagy regulation (via a mild caloric restriction and physical activity plus a timed administration of antilipolytic drugs). The beneficial antiaging effects of this treatment can be potentiated by counteracting the deleterious effects of aging on oxidative stress via a temporally appropriate enforcement of antioxidant defences (an appropriately timed consumption of polyunsaturated fatty acids and functional foods). These two different types of antiaging intervention may have additive effects and can be combined to set antiaging protocols (DANI: Dynamic Antiaging Nutritional Intervention) that proved to be quite effective both in rodents and humans .

103. Is the Attenuation of Insoluble Carbonylated Proteins a Marker of Longevity in Long-Lived Species? A Comparative Approach.

Viviana Perez, Shanique Leonard, Arlan Richardson, Steve Austad, Rochelle Buffenstein, and Asish Chaudhuri
Barshop Institute for Longevity and Aging Studies, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Protein carbonyls are irreversible and unrepairable protein modifications that are often observed in elevated level during aging and in age-related diseases. Even the undegradable oxidized protein carbonyls have the propensity to form higher-order aggregates, most of the studies on protein carbonylation in aging have been done with cytosolic fractions. In this study, we tested our working hypothesis using variety of long- and short–lived species, including: laboratory mice [Mus musculus, 4 years], White-footed mouse (Peromyscus leucopus, 8 years], free tail bat [T. brasiliensis, 8y]; NMRs [Heterocephalus glaber, 30 years] that the longer living species have the ability to attenuate the accumulation of increased insoluble protein carbonyls. We have used a fluorescence-based assay to measure the level of protein carbonyl in the cytosolic and insoluble fractions of the liver tissue. As we predicted, short-living mice showed age-related accumulation of oxidized protein carbonyl in the insoluble fraction compared to the level detected in the insoluble fraction of longed-lived species. This phenomenon was also observed in long-living calorie restricted mice when the level was compared to Ad libitum fed mice. All these data therefore, strongly suggest a public mechanism that the attenuated accumulation of protein carbonyl in the insoluble fraction might be a key determinant in modulating the longevity of mammalian species.

104. Calorie Restriction (CR) Protects Against Oxidative Stress-Induced Muscle Atrophy by Preserving Mitochondrial Function and Muscle Integrity Even in the Absence of Antioxidant Enzyme CuZnSOD

Young C. Jang[1,3] (P, G), Michael S. Lustgarten[1,4], Florian Muller[1,3], Chris Hayworth[5], Yuhong Liu[1,3], Arlan Richardson[1,2,3], and Holly Van Remmen[1,2,3]
1. The Sam and Ann Barshop Center for Longevity and Aging Studies 2. The South Texas Veteran Health Care System 3. Dept. of Cellular & Structural Biology 4. Dept. of Physiology, University of Texas Health Science Center at San Antonio 5. Dept. of Neuroscience, University of Texas at Austin

Calorie restriction (CR) has been shown to protect against age-related muscle loss and function (sarcopenia) by reducing reactive oxygen species (ROS) generation and oxidative damage. However, most of the data supporting these observations have been correlation and the direct cause-effect relationship of CR in attenuating oxidative stress has not been thoroughly tested. Therefore, in order to directly test whether CR protects against oxidative stress and sarcopenia *in vivo*, we gave 40% CR diet to age-matched wild-type (WT) and CuZnSOD knockout mice (*Sod1*$^{-/-}$), which exhibit a high oxidative damage and an acceleration of sarcopenia. Compared to *ad libitum* fed *Sod1*$^{-/-}$ mice, a loss of muscle mass, muscle fiber cross sectional area, and fiber morphology are significantly attenuated in *Sod1*$^{-/-}$ CR mice as function of age. Moreover, an increase in nerve sprouting and altered neuromuscular junctions (NMJ) are also significantly reduced in *Sod1*$^{-/-}$ CR skeletal muscle, suggesting CR protects against muscle atrophy by attenuating denervation. As a result, *Sod1*$^{-/-}$ CR mice showed a significantly improved neurological motor function as measured by rotarod performance. Furthermore, skeletal muscle mitochondria isolated from *Sod1*$^{-/-}$ CR, generates a significantly lower level of mitochondrial H_2O_2 (both State I and State II) and decreased mitochondrial respiration and ATP production are restored in *Sod1*$^{-/-}$ CR muscle mitochondria. A decline in endurance exercise capacity in *Sod1*$^{-/-}$ mice was also significantly improved to the level of WT counterpart in *Sod1*$^{-/-}$ CR suggesting overall oxidative capacity is attenuated in *Sod1*$^{-/-}$ CR mice. In an agreement with mitochondrial ROS production, we found that the level of lipid peroxidation (F_2-Isoprostane/4-HNE) and protein oxidation (protein carbonyls) were significantly lower in *Sod1*$^{-/-}$ CR skeletal muscle. Overall, our results demonstrate that CR is a robust anti-aging intervention that attenuates oxidative stress-induced age-related muscle loss that exerts its effect even in the complete absence of important antioxidant enzyme, CuZnSOD.

Supported by NIH P01 AG20591 (H.V.R.) and MDA Grant MDA3879 (H.V.R.)

105. Do Thioredoxin 2 Transgenic and 1 Knockout Mice Extend the Lifespan Through Different Mechanisms?

Ikeno, Y (P)., Cortez, L.A., Webb, C.R., Guerra, J., Mahlke, M., Bhattacharya, A., Zhang, Y., Qi, W., Tominaga, K., Liu, Y., Lee, S., Van Remmen, H., and Richardson, A.
Barshop Institue, UTHSC at San Antonio, San Antonio, TX

Our laboratory has conducted the first detailed study on the effect of overexpressing or down-regulating thioredoxin 1 (Trx1: cytosol) or thioredoxin 2 (Trx2: mitochondria) on aging. Interestingly, we found that the Trx2Tg (Trx2 hemizygous transgenic) mice that overexpress Trx2 in all tissues during aging showed a significant extension of lifespan (25.6%) compared to wild-type mice, although we did not observe a significant increase in survival of the Trx1Tg (Trx1 hemizygous transgenic) mice, when the Trx1 overexpression was maintained over the lifespan. The extension of lifespan of Trx2Tg mice was correlated to less reactive oxygen species (ROS) production from mitochondria and less oxidative stress. These data indicate that overexpressing Trx in the mitochondria may be more important than in the cytosol on aging because mitochondria are a major source of ROS. When we tested the effects of reduced levels of Trx in cytosol or mitochondria on aging, we surprisingly observed
the reversed effects, i.e., a significant increase in survival of the Trx1KO (heterozygous Trx1 knockout) mice (12.6%) compared to wild-type mice while the Trx2KO

(heterozygous Trx2 knockout) mice showed little effects on lifespan. The extension of lifespan of Trx1 KO mice was associated with less cancer compared to wild-type mice at 22-24 months of age. These data indicate that reduced cancer in the Trx1KO mice could be one of the contributing factors of extended lifespan.

Our data 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 (overexpressing catalase in the mitochondria has been shown to increase lifespan but overexpressing catalase in the nucleus or the cytosol has no effect on lifespan); and 2) down-regulating Trx in the cytosol increases lifespan and reduces cancer, but down-regulating Trx in mitochondria had no effect on lifespan or cancer. These paradoxical, but intriguing results could indicate that the 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 grant from the VA Merit Review, American Federation for Aging Research, and Glenn Foundation)

106. Does the Nitration of NGF Trigger Neuronal Damage in Aging and Alzheimer's Disease?

Kristine M. Robinson (P, G), Randall L. Woltjer, Joseph F. Quinn
S.W. Sam Jackson Park Rd.
Portland, Oregon

To better understand how oxidative/nitrative stress contributes to the aging process, specific mechanisms of significant detriment must be identified and parsed away from other well-tolerated pathways. In the CNS, neurons are dependent upon trophic support from neurotrophins such as Nerve Growth Factor (NGF). Paradoxically, we have also shown that NGF can trigger apoptosis in motor neurons in the presence of nitric oxide. Furthermore, we found that oxidation and nitration potentiated NGF toxicity 10,000 fold. Recent studies indicate the precursor to NGF, proNGF, may be the predominant species found in vivo as compared to NGF. Similarly to NGF, we found that oxidation and nitration of proNGF increases the toxicity of proNGF and induces neuritic damage in cultured hippocampal neurons. Post-translational modifications of NGF may be particularly relevant to age-associated neurodegenerative diseases, such as Alzheimer's disease (AD). Both oxidative stress and proNGF are increased in AD. We detected nitrated proNGF in AD frontal cortical tissue, however nitrated-proNGF was not detected in non-demented control samples. Oxidative/nitrative modifications of neurotrophins may represent one pathway by which increased oxidative stress experienced during aging confers significant neurological defects, especially in the context of AD.

107. The Proteasome System in Oxidative Stress and Aging: Are There Common Traits?

Karl A. Rodriguez (P, N), Maria E. Gaczynska, Pawel A. Osmulski
Department of Molecular Medicine, Institute of Biotechnology, University of Texas Health Science Center San Antonio, San Antonio, TX

The proteasome, as an essential protease of the ubiquitin-proteasome pathway (UPP), is responsible for the controlled cleavage of short- and long-lived proteins. The former are factors regulating transcription, cell cycle and apoptosis, among other intracellular metabolic processes. By degrading these types of proteins, the proteasome could be a factor in the metabolic slowdown in aging tissue. In turn, breaking down numerous long-lived proteins, proteasome provides a quality control service for the cell. In fact, one of important tasks of the proteasome is to remove oxidatively damaged proteins in the course of unfolded protein response (UPR). Oxidative stress then may affect proteasomal activity, as the UPP is subjected to the increased load of substrates and damage by free radicals. Importantly, inefficient UPR is considered one of traits of aging. Our previous data supports the notion that there are systematic changes in localization, subunit abundance and peptidolytic activity of proteasomes in liver samples collected from C57BL/6 mice of different ages. We found that the general decline in catalytic activity with age was accompanied by degeneration of nuclear proteasomes and increased relative contribution of microsomes-associated proteasomes involved in UPR. We attempted to compare this "aging signature" with changes related to oxidative stress. We tested subunit composition and peptidolytic activity of proteasomes in livers from 6-month old Sod1-/- mice, and compared them with wild type controls. Data indicates that samples from Sod1-/- liver tissue show a relative decline of proteasome activity and changes in proteasome subunit composition in the nucleus. The relative contribution of proteasome activity in microsomes increased. Similar trends were seen in the liver tissue of old, wild-type mice. The similarities between the patterns of change in old tissue and oxidatively challenged young mutant tissue hint at a common mechanism for the age-related decline in proteasome function.

108. MLC_{3f} Gene Transfer with a Recombinant Adenovirus into Hindlimb Unloaded Fischer-344 Rat Semimembranosus: The Effect of MLC_{3f} on a Single Fiber Size, Force Generation, and Cell Damage

Jong-Hee Kim[1] (P, G), Windy S. Torgerud[1], Kelsey H. Mosser[1], Shuichi Watanabe[2], Hiroyuki Hirai[2], Atsushi Asakura[2], LaDora V. Thompson[1]
[1] Department of Physical Medicine and Rehabilitation and [2] Department of Neurology, University of Minnesota, Minneapolis, MN

There is significant skeletal muscle deterioration with aging and inactivity, such as atrophy, loss of strength, and a decrease in contractile velocity. Even though the molecular mechanisms responsible for muscle deterioration are widely investigated, the underlying mechanisms for the decrease in contractile velocity are not known. We

previously demonstrated that the slowing of velocity in type II fibers with hindlimb unloading (HU) was associated with a decrease in the relative content of the myosin light chain 3f (MLC_{3f}), suggesting alterations in expression levels of key proteins may be a contributing factor for muscle dysfunction. In the current study our goal was to establish a recombinant adenovirus DNA gene transfer *in vivo* that would overexpress MLC_{3f} protein in individual muscle fibers without altering morphological properties (size, damage) and force generating capacity (a contractile property independent of MLC_{3f} content). Using HU to induce muscle atrophy and a reduction in force generation, we examined single fiber size (cross-sectional area), specific force (kN/m^2), cellular damage (i.e., macrophages), and MLC_{3f} content following injection of adenovirus MLC_{3f} and empty vectors. With HU, there is a reduction in diameter (-27%), force (-28%), and relative MLC_{3f} content (-54%), demonstrating the deleterious effects of inactivity. With injection of MLC_{3f} and empty vectors, the muscles did not show an increase in macrophages, providing evidence of no damage. Muscles that received the empty vector with HU showed reductions in diameter (-28%) and force (-21%), which are similar to the HU group without injection. In muscles receiving MLC_{3f} during HU, diameter and force were decreased by 27% and 19%, but MLC_{3f} expression significantly increased (+103%) compared to empty vector treated. In summary, injection of MLC_{3f} into muscles does not influence skeletal muscle morphology or force generating capacity, yet there is an increase in MLC_{3f} expression.

109. SIRT6 Promotes DNA Repair Under Stress by Mono-ADP-Ribosylating PARP1

Vera Gorbunova (P), Zhiyong Mao, Chris Hine, Amita Vaidya, Marina Feigenson, Andrei Seluanov
Department of Biology, University of Rochester, Rochester NY, USA

SIRT6 is a mammalian homolog of the yeast Sir2 deacetylase that promotes longevity in yeast and invertebrates. Mice deficient for SIRT6 exhibit premature aging and genome instability. However, the mechanisms of SIRT6 function in genome maintenance and lifespan regulation are unclear. Here we show that in mammalian cells subjected to oxidative stress SIRT6 is recruited to the sites of DNA double-strand breaks (DSBs) and strongly stimulates DSB repair. SIRT6 physically associates with PARP1 and mono-ADP-ribosylates it, leading to stimulation of PARP1 poly-ADP-ribose polymerase activity. Our results suggest that SIRT6 promotes genome stability by stimulating PARP1 and enhancing DSB repair under oxidative stress. We propose that SIRT6 functions as a regulator integrating oxidative stress signaling and DNA damage response. The hormesis theory states that mild doses of stress may have beneficial effects on the organism by stimulating survival pathways. This theory has been explored extensively by biogerontologists. We hypothesize that SIRT6 serves as a mediator of hormetic response, promoting longevity by stimulating DNA repair under stressful conditions.

110. Inhibition of mTOR Signaling Promotes Mammalian Longevity

Dudley W. Lamming(P), Nada Kalaany, Pekka Katajisto, Maki Saitoh, Deanna Stevens, David A Guertin and David M. Sabatini
Whitehead Institute for Biomedical Research, Cambridge, MA

The mammalian target of rapamycin (mTOR) signaling pathway regulates growth and metabolism in response to the availability of nutrients. The mTOR pathway is highly conserved, and a homologue of the central component of the pathway, the mTOR protein kinase, is found in most eukaryotes, including yeast, worms, flies, plants, mice, and humans. Recent studies have demonstrated that inhibition of mTOR signaling by the clinically used drug rapamycin can extend the lifespan of yeast, flies, and mice. The inhibition of mTOR signaling has been proposed to mimic the effects of calorie restriction, an intervention that promotes health and longevity in mammals, and inhibition of mTOR signaling may therefore be of therapeutic value in the treatment of age-related diseases. Here, we have examined the effects of decreased mTOR signaling on health and longevity by using mice heterozygous for mTOR or for the mTOR complex members Raptor and mLST8. We find that female $mTOR^{+/-}$ $mLST8^{+/-}$ mice have extended lifespan, an effect that may be mediated in part by reduced signaling through the mTORC1 target S6K1.

111. Free Radicals in Aging: Studies of Antioxidants in Models of Diseases of Aging

Robert A. Floyd (P)
Oklahoma Medical Research Foundation
Oklahoma City, OK

Free radicals are considered important in aging and disease of aging. Exacerbated levels of reactive oxygen and nitric oxygen species have been shown to be associated with several diseases of aging including cancer, stroke, Alzheimer's disease and Parkinson's disease. This suggests that antioxidants which quell free radical processes would be useful as agents to abate the diseases processes. In practice, this assumption has proven to be not straight forward and even in some cases completely wrong depending on the antioxidants used and the experimental models studied. Utilizing alpha-phenyl-tert-butylnitrone (PBN) nitrones in many different experimental models we have learned that the biological activity of antioxidants can be quite complex influencing many different biochemical processes other than simply quenching free radicals. We have shown that PBN and its derivatives have neuroprotective activity in experimental models of stroke and that it has anti-cancer activity in experimental models of hepatocellular carcinoma, colon cancer and glioblastoma and in addition more recently we have shown that PBN derivatives when combined with the antioxidant N-acetylcysteine (NAC) acted synergistly in protecting from noise induced hearing loss in chinchillas. Despite the robust activity of PBN-nitrones in many disease models its mechanism of action has not been elucidated. Spin trapping of free radicals is not its primary mode of action. However, its basic anti-inflammatory properties are considered to be

important. Just as the basic mechanistic action of the antioxidant α-tocopherol has proven to be quite complex it is likely that the mechanistic basis of other antioxidants will prove to be unique to each chemical even though operationally in biology they may act as an antioxidant.

112. The Physiological and Molecular Effects of Rapamycin on Heterogeneous Mice

Qingying Meng (P), Kevin Flurkey, Robin Ertl, Mike Astle, David Harrison, Rong Yuan
The Jackson Laboratory, 600 Main Street, Bar Harbor, Maine

It is widely accepted that rapamycin extends longevity in mice by inhibiting the mTOR pathway. Recently, we conducted a cross-sectional study to investigate the effects of both short-term (10 months) and long-term (30 months) rapamycin treatments on a group of heterogeneous mice. Physiological assays showed that mouse bodyweight and tissue weights including quadriceps, brown fat, gonadal fat and visceral fat were not affected by either short- or long-term rapamycin treatment. Both short- and long-term treatment did, however, significantly increase the number of red blood cells, hemoglobin and hematocrit levels in the blood. Flow cytometry revealed that long-term treatment significantly elevated the percentage of naïve CD4 T cells, whereas short-term treatment slightly decreased the percentage of both naïve CD4 and CD8 T cells. Both short- and long-term treatment significantly increased metabolic rate, CO_2 production, and O_2 consumption without increasing physical activity, indicating a much higher basal metabolic rate. In the molecular analyses, our preliminary results showed that p-IGF1R, p-IGF1R/IGF1R, p-AKT and p-AKT/AKT were much higher in the treated mice. Interestingly, in the long-term treated mice, although the increase of p-IGF1R/IGF1R was significant, both p-IGF1R and IGF1R decreased in amount. This might reflect a decline of IGF1/insulin signaling or desensitization of the receptors after long-term rapamycin treatment. Importantly, while we found that IGF1 level was significantly higher in the old control mice than in the young control mice, its level was not altered upon either short- or long-term rapamycin treatment. Thus we hypothesize that in addition to inhibiting the mTOR pathway, rapamycin could also function through the IGF1/insulin pathway and at certain downstream molecules where mTOR and IGF1/insulin pathways could cross talk and provide feedback signaling.

113. A Point Mutation in the Oxidation Sensitive DNA Repair Gene XRCC1 Suppresses Tumor Progression

C Pettan-Brewer[1, 2] (P), J Goh[1], L Enns[1], R Coil[1], J Morton[1] and W Ladiges[1, 2].
School of Medicine, [1]Department of Comparative Medicine and [2]Nathan Shock of Excellence in the Basic Biology of Aging Center, University of Washington, Seattle WA.

DNA damage plays a major role in aging and cancer. There are a number of events that lead to DNA damage including exposure to reactive oxygen substances (ROS) and other reactive metabolites. Variations in the DNA repair gene X-ray repair cross-complementing group 1 (XRCC1) have been increasingly reported in age-associated cancer epidemiology investigations, but have yielded conflicting results and are lacking biological data. XRCC1 is an essential scaffolding protein that interacts with many proteins associated with the repair of oxidation-induced DNA damage. Several polymorphisms and point mutations, including L360R, have been shown to be in the same domain where critical binding with the DNA damage sensor gene Poly (ADP-ribose) polymerase (PARP) occurs. In order to further investigate the biological effects of L360R, we constructed a gene-targeted mouse line and showed the homozygous genotype to be embryonic lethal. We therefore used the heterozygous genotype to determine tumor susceptibility and showed that subcutaneously implanted B16 melanoma tumors developed more slowly in L360R mutant mice compared to wild type littermates (tumor volume 116±11 mm^3 vs 263±21 mm^3 , respectively, $p \leq 0.05$) suggesting host mediated affects. We next used azoxymethane (AOM, 10mg/kg once a week for 6 weeks) to induce colon tumors and showed that after six months the tumor burden was 14.2±3 mm^3 in mutants compared to 22.5±5 mm^3 in wild type littermates ($p \leq 0.05$). These findings suggest the XRCC1 L360R point mutation acts as a tumor suppressor, possibly involving host mediated events affected by aging. The molecular mechanism for the suppression is not yet known, but the XRCC1 L360R mouse is a promising animal model to further investigate cancer and aging related to increased oxidative stress.

114. Anti-Oxidation and Lifespan-Prolongation Activities of CordyMax in Oxidative Stress and Aging Models

Jia-Shi Zhu[1,2,3] (P), Yan Zhang[2], Jieying Yang[2], Ninzhi Tan[2], and Chunsheng Zhao[2]
[1]Pharmanex Research Institute, Provo, UT; [2]Pharmanex Beijing Clinical Pharmacology Center: 2 Xinkang Road, Beijing, China; [3]School of Pharmacy, Shihezi University, Shihezi City, Xinjiang, China

Cordyceps sinensis is traditionally believed as an anti-aging herb in China. We have reported the effects of CordyMax (CM), a mycelia fermentation product of *C. sinensis*, in glucose-lipid-energy metabolisms, endurance enhancement and anti fatigue. In this study we examined the effects of CM in antioxidant and lifespan extension in mice. The antioxidant activity was tested in mice (6 m-o) that received 60 days of vehicle or CM (0.5, 1.0 or 1.5g/kg) by gavage and a single dose of 11 Gry ^{60}Co gamma-radiation on Day 60. Compared to controls, CM increased plasma total thiol-groups, GSH and GSH-peroxidase, and liver CAT, SOD and GSH-reductase (all $p<0.05$). CM reduced liver protein carbonyl-groups and 8-OHdG (both $p<0.05$). To examine the lifespan-prolongation effect of CM, 250 mice (12 m-o, both sexes) were received vehicle or CM (0.5, 1.0 or 1.5g/kg) mixed with the forage. Calorie intake was adjusted twice per week to match the levels for controls. Compared to controls, the 80% survival time was extended 102-137 days in the CM dosage groups, the 50% survival time extended 10-66 days and the 10% survival time extended >45 days (one CM group has not reached the 10% survival yet; 96wks treatment so far). The Kaplan-Meier Survivor analysis revealed the extended lifespan and the reduced risks of normal death by CM. In conclusion,

CM therapy significantly improves the body's antioxidant capacity and extends the lifespan in mice, supporting the traditional belief on the anti-aging function of CM in humans.

115. Diseases that Favor Longevity: Case of Goiter

Svetlana V. Ukraintseva, Konstantin Arbeev, Liubov Arbeeva, Alexander Kulminski, Igor Akushevich Anatoli I. Yashin
Duke University, Center for Population Health and Aging, Durham, NC

Postponed aging and/or increased longevity may be associated with increased risks of some diseases. Such diseases could be among those continuously affecting the rates of metabolism, proliferation, and information processing in body because the decline in these rates is universal characteristic of human aging. Goiter or struma (enlargement of the thyroid gland) is a thyroid disease that chronically affects metabolic rate in body and therefore it might influence the rate of aging-related processes and/or longevity in humans. To investigate the latter possibility we evaluated long-term survival of the Framingham Heart Study (FHS) (4447 individuals, aged 50+) and the Longitudinal Study of Aging Danish Twins (LSADT) (2162 individuals, aged 75+) participants, who have and who don't have a goiter diagnosis or a thyroid disease treatment in medical history. We found that being previously diagnosed with the goiter significantly reduces risk of death from all causes combined in the elderly in both data sets (by 35-40%, on average). In the FHS, 10% individuals without and 20% with goiter survived the age 95. Possible explanations of this phenomenon include: (i) changes in metabolism associated with the goiter affect rates of individual aging-associated changes, so that people with this disease overall age slower; (ii) there are factors that increase the risk of the thyroid disease but at the same time protect organism against other, more fatal pathology, so that the net effect on survival is beneficial. E.g., autoimmune inflammation is important factor of goitrogenesis, however, as recent data show, it may also be protective against some cancers (Martin-Orozco et al. 2009). Conclusion. This study demonstrates for the first time that a chronic health disorder does not always reduce individual robustness and may be associated with substantially improved overall survival and longevity. Next, we are going to test the suggested above two explanations of the favorable effect of goiter on survival in several longitudinal data sets.

Keywords: thyroid, longevity, aging, metabolism, autoimmune inflammation

116. Caenorhabditis Remanei as the Perfect "Aging" Organism: Genetic Variation for Lifespan and Heat, UV and Oxidative Stress Response, and in a Conserved Aging Pathway

Rose M. Reynolds (P), Richard Jovelin, Patrick C. Phillips
University of Oregon, Eugene, OR

There is a growing consensus that one of the most promising methods for advancing our understanding of complex biological processes is to examine how those processes function in a natural system. This understanding may be particularly advantageous for the genetics of longevity since studies of genetically heterogeneous populations can identify genes that have universal effects on prolonged health, rather than those affecting specific genetic backgrounds. In addition, nature's experiments employ larger numbers of individuals and likely include a wider variety of mutations than laboratories can accommodate. This natural "experiment" should lead to identifying natural allelic or gene expression differences that produce individuals that are healthier longer, without negative pleiotropic effects. The model nematode *Caenorhabditis elegans* has served as one of the most powerful systems for uncovering conserved mechanisms through which the aging process can be manipulated in the laboratory. Although *C. elegans* is a well developed model system with flexible genetic and genomic tools, recent studies have shown it is conspicuously lacking in natural genetic diversity on local and world-wide scales, suggesting that it will serve as a poor model for studying variation in aging within natural populations. The closely related soil nematode *C. remanei*, which is dioecious (outcrossing) and readily collected in nature, is an ideal complement to *C. elegans* as a natural system. The *C. remanei* genome has been sequenced and is comparable in size to *C. elegans*, but experiences levels of linkage disequilibrium comparable to *Drosophila melanogaster*. Significantly, *C. remanei* is amenable to the same laboratory and genetic manipulations as *C. elegans.* In addition, this species has both males and females, making it a better model for human aging. We have found significant within-population genetic variation for lifespan and the abilities to withstand heat and oxidative stress, but not for resistance to UV stress. In addition, we have found significant levels of molecular genetic variation within a known aging pathway, the insulin and insulin-like growth factor signaling (IIS) pathway. This variation, and the tractability of *Caenorhabditis* systems, makes *C. remanei* the ideal model system for studying the genetic complexities likely to characterize naturally existing individual differences in aging.

117. Acetaminophen Improves Protein Translational Signaling in Aged Skeletal Muscle

Miaozong Wu (P), Hua Liu, Jacqueline Fannin, Anjaiah Katta, Yeling Wang, Ravi Kumar Arvapalli, Satyanarayana Paturi, Sunil K. Karkala, Kevin M. Rice, and Eric R. Blough

Department of Biological Sciences, Marshall University, Huntington, WV, USA.

Background: Sarcopenia or the age-associated loss of skeletal muscle mass and function has adverse effects on quality of life, disease prevention, and a profound socioeconomic significance. Aged atrophic skeletal muscle exhibits Akt enzymatic dysfunction and reduced mammalian target of rapamycin (mTOR) phosphorylation. Here we determine how aging affects the regulation of signaling molecules thought to reside downstream of Akt/mTOR and whether changes in these molecules, if

present, can be attenuated by pharmacological intervention. Results: Compared to 6- and 27-month old F344BN rats, the expression of the mTOR-complex proteins raptor and GβL and the phosphorylation of negative regulator tuberin/TSC2 (Thr1462) were reduced in the soleus muscles of very aged animals (33-months old). These changes in Akt/mTOR pathway signaling proteins were in turn associated with decreased phosphorylation of S6 kinase p85S6K (Thr412) and eukaryotic translation initiation factor-4E (eIF4E) binding protein-1 (4EBP1, Thr37/46), reduced phosphorylation of S6 ribosomal protein (Ser235/236), and increased inhibition of eIF4E by binding to 4EBP1 as measured by co-immunoprecipitation. Ex vivo incubation of adult muscles with H2O2 mimicked the age-related decreases seen in eIF4E and 4EBP1 phosphorylation while the inclusion of acetaminophen in the muscle bath attenuated this effect. Age-associated alterations in Akt/mTOR pathway signaling and in the phosphorylation of the stress-responsive eIF2α protein were attenuated by chronic acetaminophen treatment (30 mg/kg body weight/day for six months). Conclusion: Aging is associated with impairments in the regulation of proteins thought to be important in controlling mRNA translation and acetaminophen may be useful for the treatment of age-related muscle atrophy by reducing oxidative stress.

118. Aging-Induced Change in Neurotransmitter Levels in Rat Brain: HPLC Study

Mahendra Bishnoi (P, N)
Centre with Potential for Excellence in Biomedical Sciences (CPEBS), Panjab University, Chandigarh, India

Aging is associated with the change in human behavior. Neurotransmitters (catecholamine, indolamine and adenosine) play an important role in the development of many neuropsychiatric illnesses such as depression, psychosis, ADHD, anxiety etc. The aim of present study was to relate the change in the levels of various neurotransmitters in rat brain with aging. HPLC/ECD or UV was used to measure the levels of dopamine, epinephrine, serotonin and adenosine in whole brain homogenates of rats of different age groups (adolescence (1-2 months), adult (4-6 months), aged (12-18 months). There was significant increase in the levels of dopamine, serotonin and adenosine in whole brain homogenates of adult animals as compared to infant, which was then significantly decreased in aged animals as compared to adult animals. Levels of epinephrine were not changed significantly in adult animals as compared to infant but increased in aged animals as compared to adult. The present study provides an insight to altered levels of neurotransmitters with aging that can be useful for the development of drugs for number of neuropsychiatric illnesses.

119. Dysregulation of the Hippocampal Synaptoproteome with Age-Related Cognitive Decline

H. VanGuilder[1] (P, G), C. Van Kirk[1], J. Farley[2], H. Yan[2], W. Sonntag[2], W. Freeman[1]
[1]Department of Pharmacology, Penn State College of Medicine, Hershey Center for Applied Research; [2]Department of Geriatric Medicine, University of Oklahoma Health Science Center

Age-related deficits of cognitive function of varying severity reduce independence and quality of life for aging individuals. Unlike age-related neurodegenerative diseases, cognitive decline occurs with normal aging and is not characterized by neuronal loss, but likely reflects dysregulated neurotransmission. Previous reports have demonstrated altered synapse morphology and electrophysiology in the aged rat hippocampus, but the mechanisms of synaptic dysfunction with cognitive decline remain poorly understood. We have recently identified a number of synaptic proteins that serve as both effectors and regulators of neurotransmission that decrease with advancing age. The goal of this work was to identify alterations in the hippocampal synaptoproteome regulated specifically with age-related cognitive decline in a rodent model of aging. As is observed in humans, there is a range of cognitive impairment in Aged rats, with some aged animals performing similarly to Adult animals on learning and memory tasks while other aged animals demonstrate reduced performance. We used the Morris Water to stratify adult (12 months) and aged (26 months) Fischer x Brown Norway hybrid rats into Intact and Impaired categories prior to hippocampal synaptosome isolation and quantitative proteomic analysis. This examination identified numerous proteins regulated with cognitive decline that may contribute to functional loss, including calcium-binding proteins (CaMKII, calbindin, Necab2) and structural remodeling proteins (NOGO-A, GAP43, MAP2, drebrin) that are necessary for stimulus-induced synaptic plasticity. Interestingly, the neurotransmission-regulating proteins previously identified (SNAREs, PSD95, synaptophysin, etc…) were consistently decreased with aging, but were not different between Aged Intact and Impaired animals. These findings indicate that cognitive decline does not reflect a "more aged" phenotype, but is a distinct age-related phenomenon. The novel targets identified by this work provide a potential mechanism of synaptic dysfunction and cognitive impairment, and provide direction for future intervention studies focused on restoring cognitive function.

120. Disruption of Protein Kinase A Protects Against Age-Induced Cardiac Dysfunction

Linda C Enns (P,G), Kenneth L Bible, Warren C Ladiges
Dept of Comparative Medicine, University of Washington, Seattle, WA

Protein kinase A (PKA) is a gene complex consisting of multiple regulatory and catalytic subunits that mediate signal transduction of G-protein-coupled receptors through activation by adenyl cyclase (AC)-mediated cAMP. The PKA pathway has become of great interest to the study of aging, since we have shown that mutations that cause a reduction in PKA signaling delay the incidence and severity of age-related disease in mice. Among its many roles, PKA is important for the regulation of cardiac contractility, acting downstream of β-adrenergic receptors (βARs) to control calcium transients. We previously showed that loss of the PKA RIIβ regulatory subunit

protects mice against age-related cardiac dysfunction. We were therefore interested in see if disruption of the PKA Cβ catalytic subunit would result in a similar cardiac phenotype. We found that aged (>24 months) WT mice had enlarged hearts that were 45% heavier in males and 25% heavier in females than littermates lacking PKA Cβ (P=0.003 and 0.024). We used echocardiography and doppler imaging to look at diastolic function (Ea/Aa) and myocardial performance index (MPI). By 9 months of age, WT male mice were already showing signs of diastolic dysfunction, which was attenuated in PKA Cβ null littermates. The Ea/Aa and MPI of WT mice was 40% higher, and 40% lower, respectively, than that of Cβ null littermates (P=0.017 and 0.014). Superior Ea/Aa ratios and MPI in the mutants compared to WT continued to be observed up to 24 months of age (P=0.0024 and 0.037). At this age, WT mice also showed other evidence of worsening diastolic function, with increased injection response times of 20.9 ms compared to 16 ms in mutants (P=0.013) and reduced fractional shortening percentages (46.9% for WT compared to 49.4% in mutants (P=0.02). By 24 months of age, WT mice had enlarged left atria, with aorta/left atrium (AO/LA) ratios of 0.63 compared to 0.81 in mutants (P=0.0003). Mice with loss of PKA Cβ catalytic subunit are thus resistant to age-induced diastolic dysfunction associated with impending heart failure.

121. SSeCKS/AKAP12 Prevents Polyploidy/Multinucleation and Rb-Dependent Cellular Senescence by Attenuating PKC Activation

Shin Akakura (P), Peter Nochajski, Lingqiu Gao, Paula Sotomayor, Sei-ichi Matsui and Irwin H. Gelman
Roswell Park Cancer Institute (Buffalo, NY)

SSeCKS/AKAP12 (SSeCKS) is a tumor suppressor which regulates cell cycle progression by scaffolding key mitogenic signaling proteins such as PKC and PKA. SSeCKS is downregulated in many human cancers, and SSeCKS-null mice develop prostatic dysplasia exhibiting the hallmarks of senescence. Here, we show that SSeCKS-null mouse embryonic fibroblasts (KO-MEF) exhibit multinucleation, p16Ink4a/Rb-dependent premature senescence and increased susceptibility to oncogenic transformation. SSeCKS binds to PKC alpha, delta and epsilon isozymes and attenuates their activities. Senescence is likely driven by PKC hyperactivation in the absence of SSeCKS scaffolding, with evidence that PKC alpha induces p16Ink4a/Rb through a MEK-ERK-dependent downregulation of Id1, whereas PKC delta induces cytokinesis defects through the downregulation of the mitotic exit network kinase, WARTS/Lats1. Our data suggest that SSeCKS maintains genomic integrity by attenuating mitogenic and cytokinetic functions of PKC isozymes.

122. The Impact of Aging on the Mouse Bone Marrow Microenvironment

Stephanie N. Zimmer (P), Holly VanRemmen, Vivienne I. Rebel (S. Zimmer)
Department of Cellular & Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, TX

Throughout life, hematopoietic stem cells (HSCs) are responsible for the maintenance and repair of the hematopoietic system. However with age, it is apparent this homeostasis is not properly maintained. Transplantation assays of bone marrow isolated from young and old donors have demonstrated that the number of HSCs increases with age in C57Bl/6 mice. Additionally, old C57Bl/6 mice show skewing of the lineages from lymphopoiesis toward myelopoiesis and a functional decline of the immune system. These cellular changes have been largely attributed to cell autonomous age-associated alterations in the HSC pool. However, HSCs are also regulated cell-extrinsically by the bone marrow microenvironment. Here we determine if the bone marrow microenvironment undergoes age-related changes that may contribute to the hematopoietic phenotype in aged C57Bl/6 mice. The following intriguing observations were made: first, we found that the number of osteoblast precursor cells, measured by colony forming unit-fibroblast assay were higher in old mice compared to young. This is in concordance with previous studies showing a positive correlation between the osteoblasts numbers and HSCs numbers and may explain why the number of HSCs in C57Bl/6 mice increases with age. Second, when purified HSCs were co-cultured on bone marrow stroma cells obtained from young and old mice, we observed that on old stroma significantly more colony forming cells were produced than on young. This result supports the notion that an old microenvironment stimulates HSC production. Third, we analyzed expression levels of a panel of genes in young and old bone marrow stroma and found a number of them were significantly over-expressed in old stroma compared to young. Lastly, long-term rapamycin treatment seemed to prevent these age-associated increases in gene expression levels in bone marrow stroma cells. Together, these results provide evidence that the bone marrow microenvironment under goes significant changes as part of aging.

123. A Quantitative Assessment of the Role of Oxidative Stress During Aging

Nicolas Brandes, Heather L. Tienson (P), and Ursula Jakob
Department of Molecular Cellular and Developmental Biology, University of Michigan
Ann Arbor, MI

The free radical theory of aging states that the progressive decline in aging organisms results from increased oxidative damage to cellular macromolecules. While this theory is well supported by correlative evidence, it is still unclear whether oxidative stress is a cause or consequence of aging. Over the past two years, our lab has developed a highly quantitative mass spectrometric tool called OxICAT, which allows for a global analysis of the oxidation state of proteins within the cell. We have applied this technique to the investigation of protein thiol oxidation in the chronological lifespan of yeast, a model system for post-mitotic cell aging. We found that yeast cells suffer from a sudden loss in redox balance prior to cell death, whose onset is significantly delayed under the life-extending conditions of caloric restriction. With the unique ability to precisely determine the thiol oxidation status of hundreds

of proteins at any given time point, we discovered that general protein oxidation is preceded by the oxidation of a few highly conserved key proteins, including thioredoxin reductase (TRR) and CDC48. TRR is the central player of the thioredoxin system, which controls cellular redox homeostasis and antioxidant capacity. It is regulated by cellular NADPH/NADP+ ratios. CDC48 is a chaperone that plays an equally central role in many different cellular processes, including apoptosis. Oxidation of key cysteines in these proteins correlates to and may even cause the observed loss of redox homeostasis (i.e., thioredoxin reductase) and cell death (i.e., CDC48). Additional studies will reveal the exact relationship between the observed changes in redox homeostasis and aging. They will provide valuable insights into the validity of the free radical theory of aging.

124. Monitoring Oxidative Stress in Aging C. elegans

Maike Thamsen *, Daniela Knoefler * (P, N), Ursula Jakob
Molecular, Cellular and Developmental Biology Department, University of Michigan, Ann Arbor, MI, USA

Aging is a complex physiological process and numerous aging theories have been proposed. One of the leading models is the free radical theory of aging, which suggests that the accumulation of reactive oxygen species, like superoxide and hydrogen peroxide, causes protein, lipid and DNA damage and leads to the observed age-related decline of cells and tissues. To directly monitor the onset and extent of oxidative stress during the lifespan of C. elegans, we utilized two complementary approaches. In the first approach, we use the fluorescent hydrogen peroxide-sensor protein HyPer (Belousov, 2006) to evaluate the accumulation of endogenous hydrogen peroxide in the body wall muscle cells of C. elegans. This ratiometric sensor protein has two excitation maxima, which substantially change in the presence of hydrogen peroxide. With this tool, we are now able to determine and monitor endogenous hydrogen peroxide levels over the whole life span of a worm population. In the second approach, we use a highly quantitative mass spectrometry based thiol trapping technique termed OxICAT to identify the protein targets of oxidative stress in aging animals. This technique allows us to not only detect and quantify oxidative thiol modifications in hundreds of different proteins in a single experiment but enables us to identify the affected proteins and to define their redox-sensitive cysteine(s). Using this technique we determined the precise redox status of countless C. elegans proteins and monitored their age-related changes. The combination of these techniques provides us now with valuable insights into the underlying mechanism of aging and into the role that oxidative stress plays in this process.

Reference: Belousov, V.V., et al., Nat Methods, 2006. 3(4).

*Authors contributed equally to this work

125. An Intervention That Extends Lifespan Abolishes Cognitive Deficits in a Mouse Model of AD

Veronica Galvan (P), Patricia Spilman, Natalia Podlutskaya, Matthew J. Hart, Jayanta Debnath, Olivia Gorostiza, Dale Bredesen, Arlan Richardson, Randy Strong
[1]Department of Physiology, [2]The Barshop Institute for Longevity and Aging Studies,
University of Texas Health Science Center at San Antonio, San Antonio, TX, USA
[3]The Buck Institute for Age Research, Novato, CA, USA

Reduced TOR signaling has been shown to significantly increase lifespan in a variety of organisms. It was recently demonstrated that long-term treatment with rapamycin, an inhibitor of the mTOR pathway, or ablation of the mTOR target p70S6K extends lifespan in mice, possibly by delaying aging. Whether inhibition of the mTOR pathway would delay or prevent age-associated disease such as Alzheimer's disease (AD) remained to be determined. We used rapamycin administration and behavioral tools in a mouse model of AD as well as standard biochemical and immunohistochemical measures in brain tissue to provide answers for this question. Here we show that long-term inhibition of mTOR by rapamycin prevented AD-like cognitive deficits and lowered levels of Aß42, a major toxic species in AD, in the PDAPP(J20) transgenic mouse model. These data indicate that inhibition of the mTOR pathway can reduce Aß42 levels in vivo and block or delay AD in mice. As expected from the inhibition of mTOR, autophagy was increased in neurons of rapamycin-treated transgenic, but not in non-transgenic, PDAPP mice, suggesting that the reduction in Aß and the improvement in cognitive function are due in part to increased autophagy, possibly as a response to high levels of Aß. Our data suggest that inhibition of mTOR by rapamycin, an intervention that extends lifespan in mice, can slow or block AD progression in a transgenic mouse model of the disease. Rapamycin, already used in clinical settings, may be a potentially effective therapeutic agent for the treatment of AD.

126. Altered Levels and Localization of pCaMKII and pCREB in Alzheimer Hippocampi

Lindsay C. Reese (P,N), Wen-Ru Zhang, Giulio Taglialatela
University of Texas Medical Branch, Galveston TX, USA

Alzheimer's Disease (AD) is an insidious age-related neurodegenerative condition infamously known to cause profound memory dysfunction. Currently the 6th leading cause of death, it continues to increase in prevalence. Earlier, effective treatments are necessary to prevent AD from becoming a major public health crisis. The generation of such therapies will require an improved understanding of the initial mechanisms of memory loss in early AD. A growing body of evidence supports oligomeric amyloid-beta mediated calcium dysfunction and downstream effects on kinases and phosphatases. Our lab is interested in elucidating these pathways and have previously studied the role of calcineurin (CaN) in models of AD. Here, we employ immunohistochemistry and immunoblotting to assess the expression and localization of other phosphatases, kinases, and downstream targets in actual

AD brain. Human hippocampi from control, MCI, and AD cases were analyzed with immunoblots and immunohistochemistry. Proteins of interest include calcium/calmodulin activated kinase II (CaMKII), phospho-CaMKII (pCaMKII), calcineurin (CaN/PP2B), and phosphorylated cAMP response element binding (pCREB) While the amount of total CaMKII remains the same across the three conditions, there is a loss of pCaMKII in the dendritic arborizations with an increase in the somatic area of the CA3 region of the hippocampus. This is concurrent with a decrease of pCaMKII / post-synaptic density 95 (PSD-95) colocalization. Furthermore, there is a loss of nuclear pCREB. Both the decrease in dendritic pCaMKII and nuclear pCREB correlate with low cognitive test scores. These data suggest that AD pathogenesis affects the signals leading to the phosphorylation or dephosphorylation of CaMKII and CREB, providing a putative mechanism for the early memory deficits.

127. Naked Mole-Rats as a Model for Alzheimer's Disease

Yael H Edrey (P,N), James Mele, Asish R Chaudhuri, Rochelle Buffenstein
Barshop Institue for Aging and Longevity Studies, University of Texas Health Science Center at San Antonio, TX

Aging is the greatest risk factor for sporadic Alzheimer's disease (AD). This neurodegenerative disease is characterized by dementia and progressively worsening impairments to learning, memory and functionality. The pathological hallmarks are accumulation of beta amyloid (Aβ) plaques and neurofibrillary tangles. A search for an appropriate animal model to assess the mechanisms leading to this devastating disease remains elusive. Aged lab mice and rats do not develop AD, and this may be due to their short lifespan. Here, we propose the naked mole-rat (*Heterocephalus glaber;* NMR) as a new natural model for studying this age-associated disease. NMRs are the longest-lived rodents, living >30 years in captivity. We have examined age-related changes in brain histology and assessed the sequence of Aβ protein in NMRs, levels of this protein and its propensity to aggregate. The sequence of Aβ in NMRs shows greater homology with that of humans than does the sequence of mice. Brain homogenates of NMRs also have a lower propensity to aggregate than those of mice. Furthermore, NMR brain homogenates appear to protect human Aβ from self-aggregation. Taken together, these data suggest there are species differences in Aβ. NMRs may thus prove to be a useful model to help understand the mechanisms of AD as well as provide useful insights into protective mechanisms against this disease.

128. Blueberry Extracts Sequester Toxic Proteins in the Brain Through Induction of Autophagy

Shibu M. Poulose (P, G), Donna Bielinski, Derek Fisher, Barbara Shukitt-Hale, James A. Joseph
USDA-ARS, HNRCA at Tufts University, Boston MA

Diets rich with berries have shown efficacy in enhancing the health of the aging brain, possibly leading to improved cognition and motor abilities. Most contemporary studies have focused on the protective role of these fruits with their antioxidant and anti-inflammatory abilities, where an increase in oxidative stress with age causes widespread cellular damage leading to declines in motor and cognitive abilities. Our current study emphasizes the protective role of blueberry extracts in terms of their propensity to rescue neurons through the induction of autophagy, a protein homeostasis function in the brain and periphery. Recent studies have indicated that autophagy in brain diminishes with aging, leading to disruption of intracellular degradation and recycling of toxic proteins, a known cause for age-related neurodegenerative diseases. Our studies on BV2 microglial cells indicate that blueberry extracts at 0.5 to 2 mg/ml concentrations significantly inhibited mTOR (mammalian target of rapamycin), specifying the activation of autophagy. A dose-dependent inhibition was observed when cells were treated in combination with Bafilomycin A1, a known autophagy inhibitor (mTOR activator) and berry extracts. Further examination of the conversion of MAP1-LC I to MAP1 LC3 II (microtubule-associated protein1 light chain 3), a hallmark of autophagosome formation, indicated an increase in LC3 II formation, with an increasing concentrations of blueberry extracts up to 2mg/ml treated for about 6 hours. Immunofluorescence and western blot analysis indicate the clearance of a polyubiquitin-binding protein p62/SQSTM1, known as sequestosome 1, supporting the sequestration of toxic proteins in the brain. Further studies are being carried out to confirm these effects using hippocampal (H22) and ATG5 deficient fibroblast cells (ATG5-/- MEF) as well as extracts from strawberries and acai berries. However, the current results strongly suggest that besides their antioxidant and anti-inflammatory effects, the benefits of blueberry on brain health also include clearance of cellular toxic accumulations.

129. Hippocampal M1 Receptor Function Associated with Spatial Learning and Memory in Aged Female Rhesus Macaques

Gwendolen E. Haley (P, G), Chris Kroenke, Daniel Schwartz, Steven Kohama, Henryk Urbanski, Jacob Raber
Oregon Health and Science University/Oregon National Primate Research Center, Beaverton, OR, USA

Of the muscarinic acetylcholine receptors, subtype 1 (M1) is the highest expressed in the prefrontal cortex (PFC) and hippocampus, brains regions important for cognition, and might play a role in cognitive function in the elderly. In this study, muscarinic receptor function was assessed in cognitively-characterized aged female rhesus macaques in vivo using a scopolamine challenge pharmacological magnetic resonance imaging (phMRI) and in vitro using M1 receptor binding analysis. Based on their performance in a spatial maze, the animals were classified as good spatial performers (GSP) or poor spatial performers (PSP). In the hippocampus, but not PFC, the GSP group showed a greater increase in BOLD signal after scopolamine challenge than the PSP group. The GSP groups also had a greater number of M1 receptors and higher M1 receptor

binding affinity than the PSP group. Thus, in aged female rhesus macaques, hippocampal M1 receptor function is associated with spatial learning and memory.

130. Hippocampal Synaptosomal miRNAs are Alternatively Regulated with Aging and Cognitive Decline

C. Van Kirk[a](P, N), H. VanGuilder[a], R. Brucklacher[a], W. Sonntag[b], W. Freeman[a]
[a]Department of Pharmacology, Penn State College of Medicine, Hershey Center for Applied Research; [b]Department of Geriatric Medicine, University of Oklahoma Health Science Center

Cognitive decline with aging reduces independence and quality of life in older individuals. The etiology of cognitive decline (which does not involve neurodegeneration like other age-related diseases such as Alzheimer's and Parkinson's) remains unknown. Previously, we have identified a number of hippocampal synaptic protein changes with aging and/or cognitive decline that suggest impaired neurotransmission. However, the regulatory mechanism for these specific protein changes is unknown. To investigate the potential role of miRNA regulation of protein translation with aging and cognitive decline, Adult (12 months) and Aged (26 months) Fisher 144xBrown Norway rats were typed for cognitive performance using the Morris Water Maze task. Using this test, the Aged rats segregated into Cognitively Intact and Cognitively Impaired groups as determined by their mean proximity to platform. To identify changes in miRNA expression with aging and cognitive decline, hippocampal synaptosomal miRNA levels in Adult Cognitively Intact, Aged Cognitively Intact and Aged Cognitively Impaired rats were measured by miRNA microarray. Differentially expressed miRNAs with both aging and cognitive decline were observed. Potential mRNA transcript targets of the most significantly changed miRNAs were determined by bioinformatic analysis. These targets were compared with our existing databases of hippocampal mRNA and protein changes with aging and cognitive decline to determine specific proteins potentially regulated through miRNA expression. Several differentially expressed proteins (e.g. hippocalcin and two 14-3-3 isoforms) were predicted to be regulated by miRNAs altered with aging and/or cognitive decline (e.g. miR-184 and miR-451). The next steps in this study include confirmation of the miRNA discovery findings by qPCR and directed analysis of the potential mRNA binding partners and protein products. This work will provide an increased understanding of the role of miRNAs in protein expression regulation with aging and/or cognitive decline, allowing for better targeted analyses of the molecular mechanisms of aging and cognitive decline.

131. Mechanisms of Telomere Maintenance and Aging

Saumitri Bhattacharyya (P), Dwitiya Sawant and Joanna Groden
The Ohio State University, Comprehensive Cancer Center, Columbus, OH, USA

Mechanisms that control cellular aging include those that protect and elongate the ends of chromosomes or telomeres. There are two types of such mechanisms, those that use the reverse transcriptase complex known as telomerase and those that use recombination-mediated mechanisms and DNA repair proteins in processes known as ALT (alternative lengthening of telomeres). The interplay of these proteins controls cellular aging and impacts how we think about regenerative medicine and cancer therapy. Our published studies have shown that the BLM helicase, mutations in which are responsible for the inherited human chromosome breakage syndrome Bloom's syndrome (BS), and the human telomerase-associated protein 1 (TEP1), discovered through its interaction with the RNA component of the telomerase complex, interact directly to modulate the unwinding of telomeric DNA in vitro (Bhattacharyya et al., 2009). Both are components of a telomeric complex unique to immortalized cells using ALT. We demonstrated that BLM is required for ALT processes of telomere elongation and its interaction with TEP1 is required for ALT as well as to mediate crosstalk between telomerase-positive and ALT pathways of telomere elongation. We investigate the physical and functional interaction between BLM and TEP1 and how each protein contributes to ALT, and the role of TEP1 in suppressing telomerase when ALT is being used in order to understand how cells regulate aging, lifespan and immortality. The medical implications of these findings include developing the abilities to manipulate telomere length, altering rates of cellular aging and treating the diseases associated with aging.

132. A Test of Artificially Selected, Long-Lived Flies as a Prospective Model for Further Life Extension in Drosophila Melanogaster

Robin J. Mockett (P), Jordan L. Ciza, Shruti Puri, Mye Nguyen, Mehran Nisa and Manami Hatanaka
Department of Biomedical Sciences, University of South Alabama, Mobile, AL, USA

Numerous single-gene mutations have been reported to extend the life span of the fruit fly, Drosophila melanogaster, primarily in short-lived genetic backgrounds. The objective of this study was to develop a set of long- and short-lived, high and low fertility fly strains, in which to test the reproducibility of life extension by single-gene mutations. A pre-existing set of stocks was used, in which long and short life spans had been achieved via artificial selection for early or delayed reproduction. These stocks were rendered isogenic, in order to fix or eliminate random mutations, and a visible white-eye marker mutation (w) was introduced, as a basis for future detection of single-gene mutations tagged with a functional w+ allele. The w marker was shown to have no adverse effect on life span or fertility. Conversely, in most but not all lineages, isogeny had a negative effect on longevity and drastically decreased the fertility of the flies. Unexpectedly, none of the fly stocks were significantly longer-lived or more fertile than standard laboratory control strains. The results suggest that the artificially selected stocks have reverted to a relatively weak, ancestral phenotype. Thus, they are currently inferior to standard control strains as a model system in which to test the effects of putative antiaging mutations.

133. DFOXO Modulates the Effects of Dietary Composition and Restriction on Lifespan in Drosophila Melanogaster

Xiaoping Sun (P, G), Luc Poirier, Chunxu Wang, Toshimitsu Komatsu and Tom Alberico and Sige Zou
Laboratory of Experimental Gerontology, National Institute on Aging, Baltimore, MD

Lifespan is influenced by genetic and environmental factors. Dietary manipulation is an environmental intervention that impacts longevity in many organisms. Signaling pathways, such as the Insulin/ Insulin-like signaling (IIS) pathway, which are ultimately regulated by the concentration of specific nutrients, can also influence lifespan. It is unclear, however, if the dietary influence on lifespan is mediated primarily by the concentration of specific components in the diet and/or the energy content of the food, and how the IIS pathway modulates the dietary response. Here we measured the lifespan of flies raised on standard sugar yeast diets that contained either the same energy content but different ratios of sugar and yeast or the same ratio of sugar and yeast but different energy contents. We also studied the affect of overexpressing dFOXO, a downstream gene of the IIS pathway, either specifically in the pericerebral fat body or ubiquitously on the lifespan of flies raised on these diets. We found that the level of dietary protein is a key factor in determining lifespan and that the effect of DR on lifespan can be influenced by dFOXO activity in a diet-, gender- and tissue-dependent manner. Quantitative PCR measurements of female flies ubiquitously overexpressing dFOXO identifies 4E-BP as a molecule whose expression is induced in diets that shorten lifespan. These findings suggest that the dietary influence on lifespan can be modulated by the dFOXO-dependent IIS pathway.

134. Increased Expression of the GluN2B (NR2B) Subunit of the NMDA Receptor in the Frontal Cortex Improves Memory in Aged Mice

B. L. Brim[1] **(P, N)**, R. Haskell[2], R. Awedikian[3], M. Ellinwood[3], L. Jin[1], K. Magnusson[1]
[1]Mol Cell Bio and Biomed Sci., Oregon State Univ., Corvallis, OR; [2]ViraQuest, Inc., North Liberty, IA; [3]Animal Sci., Iowa State Univ., Ames, IA

There are declines in both the mRNA and protein expression of the GluN2B (NR2B) subunit of the *N*-methyl-*D*-aspartate (NMDA) receptor in both the cerebral cortex and hippocampus during aging in C57BL/6 mice. The declines in protein expression of the GluN2B subunit in the frontal cortex correlate with the decline in memory seen in old mice. This study was designed to determine if this decline in memory could be improved by increasing the expression of the GluN2B subunit in the frontal cortex of aged C57BL/6 mice using an adenoviral vector containing the GluN2B subunit and green fluorescent protein (GFP) genes (GluN2B virus). Old (26 month old) male C57BL/6 mice were bilaterally injected with equivalent volumes and concentrations of either: vehicle, control GFP-tagged virus (control virus), or GluN2B virus. The concentration used for either viral vector did not cause inflammation in young (3 month old) or aged mice, as compared to vehicle, and had a duration of at least 21 days. Immunohistochemistry confirmed the presence of neurons with increased protein expression for the GluN2B subunit in the frontal cortex of the mice treated with the GluN2B virus. This co-localized with GFP expression in both young and aged mice. No change in GluN2B subunit protein expression was observed in vehicle or control virus treated mice. The three different treatment groups of aged mice were tested for spatial reference memory, working memory and associative memory (control task) in the Morris water maze starting at 8-9 days post-surgery. The aged mice treated with the GluN2B virus performed significantly better than either vehicle or control virus treated mice overall in the place trials (N=15). There was no significant effect of the GluN2B virus on working memory, reversal or control trial performance. Together, these results suggest that an increased expression of the GluN2B subunit within the frontal cortex could improve reference memory in aged individuals.

Support: *Supported by NIH grant AG16322 to KRM.*

135. Dietary Natural compounds Improve High Glucose-Induced Neuronal Death and Modulate Oxidative Stress and Apoptosis Markers.

Maria-Grazia Martinoli (P), Julie Bournival, Marc-André Francoeur, Fanny Longpré
Cellular Neurobiology, Department of Biochemistry,, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada

In neurons, hyperglycaemia-induced oxidative stress is currently regarded as a possible cause of neurodegeneration and cellular apoptosis. The goal of the present study was to evaluate the effect of two natural compounds, the polyphenol, quercetin, and the lignan, sesamin, against high glucose-induced neuronal cell death. We used a well known dopaminergic cell line, the NGF-differentiated (neuronal) PC12 cells, a cellular model for Parkinson's disease. These cells when incubated with high glucose showed a significant increase in cytotoxicity, as revealed by colorimetric measurements. Then, administration of quercetin or sesamin could prevent neuronal PC12 cells from high glucose-induced cellular death. Since an increased level of reactive oxygen (ROS) and nitrogen species (RNS) is a consequence of enhanced oxidative stress after high glucose treatment, we demonstrated that the production of ROS and RNS diminished after quercetin or sesamin treatments. DNA fragmentation, Bax/Bcl-2 ratio, and nuclear translocation of the apoptosis-inducing factor (AIF) were significantly reduced by quercetin and sesamin. Finally, treatments with quercetin or sesamin reduced poly(ADP-ribose) polymerase (PARP) cleavage, while high glucose administration had no influence on capase-3 cleavage, supporting an involvement of caspase-3 independent pathways. Based on our results, dietary natural compounds should be considered as a complementary nutritional recommendation against oxidative stress-induced neuronal damages. in aging.

This work was supported by a NSERC (Canada) grant to MGM

136. Distinct Nutrient Biomarker Patterns are Associated with Brain Volume and White Matter Hyperintensities in the Oldest Old

Gene L. Bowman (P), Jackilen Shannon, Lisa Silbert, Jeffrey A. Kaye, Joseph F. Quinn
Oregon Health & Science University, Portland, OR

Background: Nutrient biomarker patterns represent combinations of nutrients in circulation. These patterns provide an opportunity to explore the synergy among nutrients, and better reflects overall exposure of brain to nutrition compared to a single nutrient approach. Total brain atrophy and white matter hyperintensities are associated with the aging brain and with an increased risk for cognitive decline. Brain atrophy is used as a surrogate marker of Alzheimer type pathology; white matter hyperintensities are typically considered a marker of cerebrovascular pathology. Plasma antioxidants, fatty acids, B vitamins, lipids and vitamin D have also been associated with age related cognitive performance.

Objective: This study tested the hypothesis that nutrient biomarker patterns defined by factor analysis (principal components analysis) explain significant variance in total brain and white matter hyperintensity volumes in the oldest old.

Methods: A cross-sectional investigation of nutrient biomarker patterns and MRI derived brain volumes was conducted in 40 community dwelling participants (aged 85 – 101 years) of the Oregon Brain Aging Study. The average fasting period before blood draw was 3 hours and MRI was conducted within 1-month proximity to the blood collection. Plasma antioxidants, fatty acids, B vitamins, lipids and 25 hydroxyvitamin D were determined by standard laboratory methods. REGION image analysis software was used for total brain and WMH volume measurements. Multivariate regression analyses were performed to assess the relationship between nutrient biomarker patterns and brain volumes.

Results: Subjects were mean age 93 ± 3.8 (SD) years, 28 (70%) were women, and 5% were carrying an ApoE-e4 allele. Mean Mini Mental State Examination score was 27 ± 3. Principal components analysis with orthogonal rotation resulted in identification of 8 nutrient biomarker factors (patterns) from 30 nutrient biomarkers originally included in the analysis. Nutrient biomarker pattern #1 (most strongly representing high pyrodoxal-5-phosphate, thiamin, riboflavin, folate, ascorbate, alpha-tocopherol, cobalamin, and 25-hydroxyvitamin D) was positively associated with total brain volume after adjustment for age and total intracranial volume ($p = .010$). Nutrient biomarker pattern #5 (most strongly representing high concentrations of eicosapentaenoic acid and docosahexaenoic acid) was negatively associated with total white matter hyperintensities after adjustment for age and total brain volume ($p = .016$).

Conclusion: The two empirically derived nutrient biomarker patterns that were significantly associated with total brain and white matter hyperintensity volumes are distinct. These data suggest two new relationships relevant to health brain aging and nutrition. First, total brain volume may be preserved by maintenance of high B vitamins, ascorbate, alpha-tocopherol and vitamin D collectively. Second, WMH volume may be attenuated by a distinctly different combination of nutrients including EPA and DHA. These two nutrient biomarker patterns may be acting by different mechanisms, both of which may modulate neuroprotection and reduce risk for cognitive decline.

137. Changes in Growth Factors, Matrix Proteins and Signaling in the Aged Kidney

K Sataranatarajan (P, G), MJ Lee, D Feliers, G Ghosh Choudhury, JL Barnes, H Van Remmen, A Richardson and BS Kasinath
Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center, San Antonio, TX

Signaling pathways regulating changes in aging kidney are not well studied. Data in control young female mice (n=6) at 21 ±1.3 wks of age were compared to aged female mice (n=6) at 127±1.1 wks of age (both C57BL6). Ratio of kidney weight to body weight was increased in aged mice by 30% ($p=0.038$) showing renal hypertrophy; glomerular area by morphometry was increased by 54% ($p=0.0011$). Immunoblotting of renal cortical homogenates from aged mice showed increase in contents of TGF beta (2.7-fold, $p=0.005$) and VEGF (2.9-fold, $p=0.02$). By immunoblotting we observed an increase in renal cortical content of fibronectin in aged mice by 2.4-fold ($p<0.01$) with a trend toward increase in fibronectin mRNA. Collagen IV protein content assessed by immunoblotting was also increased by 2.4-fold in aged mice ($p<0.0001$) without changes in its mRNA. Glomerular area stained for collagen IV was also increased by 21%. The initiation phase of mRNA translation, an important regulatory step in protein synthesis, was stimulated in the aged kidney as shown by increase in phosphorylation of a direct mTOR substrate, 4E-BP1 (2.2-fold, $p=0.046$), demonstrating mTOR complex1 activation. Another critical event in initiation phase of translation, phosphorylation of eIF4E was also increased (3.8-fold, $p=0.0001$) in aged mice. Akt is an upstream regulator of mTOR and mTOR complex2 augments Akt phosphorylation at Ser473. Immunoblotting showed that renal cortical phosphorylation of Akt at Ser473 was augmented by1.8-fold in aged mice ($p=0.003$). Analysis of aged male mice showed most of the above-described changes. We conclude that aging in C57BL6 mice is associated with: (1) kidney growth, glomerular hypertrophy and increase in renal cortical matrix proteins. (2) induction of Akt-mTOR-Akt loop. This is associated with activation of important events in initiation phase of mRNA translation. These data suggest that mTOR inhibition may ameliorate adverse effects of aging on the kidney.

138. Sirt1 is Required for the Pathogenesis of Age-Related Hearing Loss in Mice

Shinichi Someya[1,2] (P, G) and Tomas A. Prolla[1]
[1]Departments of Genetics & Medical Genetics, University of Wisconsin, Madison, WI; [2]Department of Applied Biological Chemistry, University of Tokyo, Tokyo, Japan

Age-related hearing loss (AHL), known as presbycusis, is a universal feature of mammalian aging and is the most common sensory disorder in the elderly. AHL affects over 40% of people over 65 years of age in the US and is projected to afflict more than 28 million Americans by 2030. Due to the high prevalence of this disorder, AHL is a major social and health problem. Caloric restriction extends lifespan in numerous species. In yeast, this effect requires Sir2, a member of the sirtuin family of NAD+-dependent deacetylases. In mammals, it is becoming apparent that the Sir2 ortholog, Sirt1, is a key regulator of cell survival in response to stress. Surprisingly, we found that Sirt1 was required for the pathogenesis of AHL in mice. Auditory Brainstem Response (ABR) hearing analysis revealed that 12-month-old *Sirt1*$^{+/-}$ mice displayed normal hearing or slight hearing loss at low, middle, and high frequencies while age-matched wild-type (WT) mice displayed severe hearing loss at these frequencies. In agreement with the ABR hearing test results, middle-aged *Sirt1*$^{+/-}$ mice displayed only minor loss of neurons and hair cells in the cochlea, while age-matched WT mice displayed severe loss of neurons and hair cell. Cell counting also revealed that the mean neuron survival of basal cochlear turns from middle-aged *Sirt1*+/- mice were significantly higher than that of age-matched WT mice. In addition, the mean outer hair cell survival rate of basal cochlear turns from middle-aged *Sirt1*+/- mice were significantly higher than that of age-matched WT mice. Oxidative stress and apoptosis studies are currently ongoing. Together, our findings provide evidence that Sirt1 promotes AHL.

139. Age Related Changes in Human Tear Lipid

Douglas Borchman (P), Gary N. Foulks, Marta C. Yappert
Kentucky Lions Eye Center, Univeristy of Louisville, Lousiville KY

Lipids (meibum) coat the surface of the tear film stabilizing it and keep it from evaporating. Infants have an unusually stable tear film and they do not blink for extended periods of time. Younger people have lower meibum viscosity, higher meibum volume, and a lower rate of tear evaporation. Since age-related changes in human meibum composition and conformation have never been investigated, as a basis for the study of lipid associated changes with meibomian gland dysfunction leading to dry eye symptoms, we used the power of infrared and NMR spectroscopy to characterize composition, hydrocarbon chain conformation and packing in meibum from humans without dry eye symptoms in relation to age.

Meibum from normal human donors ranging in age from 1 to 88 years of age was studied. Human meibum order and phase transition temperatures decreased with age. The decrease was related to more protein in samples from younger donors. Meibum from babies contained more branched chains and CH3 groups than children and adults. Principal component analysis (PCA) was successfully applied to a set of training spectra of human meibum to predict the age of meibum donors. This indicates that changes in constituents of the meibum spectra (eigenvectors) were due to age-related compositional differences. The spectral features of the two major eigenvectors indicate that with increasing age, meibum contains more wax, double bonds and terminal CH3 groups, and is less ordered. The environment of the carbonyl band becomes less polar with increasing age. Compositional and structural changes in human meibum with age provide insight into the age related stability of the human tear film and serves as a foundation to examine meibum conformational differences in meibum from people with meibomian gland dysfunction related to dry eye symptoms.

140. Ghrelin Receptor Null Mice Have Reduced Visceral Fat and Improved Insulin Sensitivity during Aging

Ligen Lin[1,3] (P), Pradip K. Saha[5], Iyabo Osifeso[1,3], Longjiang Shao[2], Alexander G. A. Smith[2], Owen P. McGuinness[6], Lawrence Chan[4,5] and Roy G. Smith[7], Yuxiang Sun[1, 2, 3, 4]*
[1]USDA/ARS Children's Nutrition Research Center, [2]Huffington Center on Aging; [3]Department of Pediatrics, [4]Department of Molecular and Cellular Biology, [5]Department of Medicine, Baylor College of Medicine, Houston, TX, 77030; [6]Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicines, [7]Department of Metabolism and Aging, The Scripps Research Institute (Florida)

Aging is associated with a higher incidence of Type 2 diabetes; one in five Americans over age 65 has diabetes. Loss of lean mass and accumulation of fat, particularly visceral fat, during aging result in increased insulin resistance. Insulin resistance is a major pathogenic factor for Type 2 diabetes. Ghrelin is the only circulating orexigenic hormone known to increase growth hormone release, stimulate appetite and promote obesity. We have shown that ghrelin's effects on GH release and appetite are mediated through GHS-R. More interestingly, we have found that ghrelin deletion increases glucose-induced insulin secretion and improves peripheral insulin sensitivity, and we have demonstrated that ghrelin deletion partially rescues the diabetic phenotype of leptin-deficient *ob/ob* mice. Acute ghrelin infusion has been shown to induce lipolysis and insulin resistance independently of GH. Ghrelin receptor *Ghsr-/-* mice have reduced body weight, and body composition analysis suggests this may be primarily due to reduced abdominal fat. To determine whether deletion of the ghrelin receptor would improve age-associated insulin resistance, we performed insulin tolerance tests (ITT) on young (2 month), middle aged (9-12 months) and old (24-30 month) wild-type (WT) and *Ghsr-/-* mice to evaluate the effects of insulin on blood glucose. Young WT and *Ghsr*-null mice were both sensitive to insulin, and the difference between WT and *Ghsr*-null was not pronounced. As the mice aged, WT mice showed a marked increase in insulin resistance, whereas the *Ghsr*-null mice remained sensitive to insulin.

Hyperinsulinemic-euglycemic clamps further demonstrated that the null mice have reduced glucose production, increased glucose infusion, and increased glucose uptake in skeletal muscle. In addition, we performed hyperglycemic and hypoglycemic clamps. *Ghsr-/-* mice secrete less insulin during hyperglycemic clamps, and require higher glucose infusion during hypoglycemic clamps. All functional studies support that *Ghsr-/-* mice have improved insulin sensitivity. In line with the functional data, old *Ghsr-/-* mice have significantly reduced epididymal fat (more than 50%) and reduced liver steatosis. Also, old *Ghsr-/-* mice have lower plasma cholesterol, triglyceride, free fatty acid and leptin. Consistently, the expression of adipocyte differentiation and lipid regulatory genes was reduced in the epididymal fat of old *Ghsr-/-* mice. Together, the data suggest that the reduced adipocyte differentiation may be, at least in part, the underlying mechanism that mediates the insulin-sensitive phenotype of *Ghsr-/-* mice. Hence, inactivation of GHS-R signaling reduces visceral fat and prevents age-associated insulin resistance, and GHS-R antagonists may have beneficial effects in preventing age-dependent onset of Type 2 diabetes.

Financial Support: We gratefully acknowledge the support of NIH/NIA 29740 (RGS), NIH/NIA grant 1R03AG029641-01 (YS) and USDA grant (YS).

141. Insulin Resistance in Rapamycin-Fed Mice: Lifespan and Insulin Signaling may not be Directly Linked

JennaLynn Styskal[1] (P, N), Adam Salmon[1], Elizabeth Fernandez[1], Vivian Diaz[1], Randy Strong[1,2,3], Dave Sharp[1,3], Arlan Richardson[1,2,3]
[1]The Sam and Ann Barshop Institute for Longevity and Aging Studies, [2]Dept. of Cellular & Structural Biology, Univ. Texas Health Sci. Ctr. at San Antonio, San Antonio, TX, USA, and [3]South Texas Veterans Health Care System, San Antonio, TX, USA

The aging process is ubiquitous among mammals and is the primary risk factor for the development of numerous health-related issues. One pathway which has emerged as an important regulator of the aging process is the target of rapamycin (TOR) pathway. Reduction of signaling through this pathway has been shown to extend lifespan of several invertebrate models, and recently reduction of the pathway using the TOR inhibitor rapamycin has been shown to extend longevity in mice as well as decrease the incidence of several age-related pathologies. Recent evidence also shows an interaction between the mammalian TOR (mTOR) and the insulin signaling pathway which itself is linked to several age-related diseases including diabetes. In this study, we tested whether treatment with rapamycin, which can inhibit mTOR signaling, may contribute to maintenance of insulin sensitivity in mice under both normal conditions or when challenged with high fat feeding.

We found that mice fed rapamycin on a low fat diet showed no difference in weight gain from those fed a low fat diet alone. However, mice fed a diet high in fat (45% kCal from fat) with rapamycin gained significantly more weight than those fed high fat diet alone. The increase in weight was comprised mostly of increased fat mass as measured by quantitative magnetic resonance analysis. Surprisingly, rapamycin also decreased glucose tolerance and increased insulin resistance in mice on both low and high fat diets, relative to their non-rapamycin fed controls; this was prevalent in both short term (< 8 weeks) and long term (> 18 weeks) feeding. This effect of rapamycin-feeding on insulin resistance was reversible; upon removal of rapamycin from the diet, glucose tolerance and insulin resistance of previously rapamycin fed animals became comparable to levels found in mice fed low fat or high fat diets alone. The reduction in insulin resistance in rapamycin-fed animals was correlated with reduced insulin-stimulated signaling in the insulin signaling pathway. We found that rapamycin treatment caused reduced phosphorylation of both insulin Receptor (InR) and Akt with administration of insulin under high fat fed conditions. Further, phosphorylation of the Glycogen Synthase Kinase 3 (GSK3) protein, typically inhibited by Akt, is increased in mice treated with rapamycin on high fat diets relative to mice fed high fat diet alone Overall, our results show that rapamycin can have a detrimental effect on insulin resistance, particularly in conjunction with obesity and high fat diets. Furthermore, these findings suggest that the effects of rapamycin on lifespan occur despite detrimental effects of this drug on insulin resistance, suggesting the possibility that lifespan could be extended further with concomitant treatment with insulin sensitizing agents.

142. FAT10 (UBD): A Novel Regulator of Adipose Mass, Inflammation and Aging

Allon Canaan[1] (P), Jason Defuria[2], Hui-Young Lee[3], Varman T. Samuel[3], Martin S. Obin[2], Sherman M. Weissman[1]
[1]Deptments of Genetics and [3]Internal Medicine-Section of Endocrinology at Yale University School of Medicine, New Haven, CT. [2]Obesity and Metabolism Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA.

Visceral adipose tissue is negatively associated with life span in mammals, and emerging evidences implicates reduction in fat mass as a mechanism underlying the anti-aging effect of caloric restriction. Here we report that FAT10ko mice display reduced adipose mass, improved metabolic profile and lifespan extension. FAT10 expression is highly induced by inflammatory mediators (TNF-α, LPS, INF-γ), suggesting a potential role for FAT10 in the cellular response to inflammatory/prooxidant stress. Notably, FAT10 expression is repressed by p53, a tumor suppressor with roles in lifespan extension and intriguingly, adipocyte development. Hence, we initiated studies of FAT10's potential role in adipose tissue and metabolic homeostasis, inflammation and aging. FAT10ko mice exhibited delayed onset of aging biomarkers (grey hair, sarcopenia, decreased activity) as well as increased life span. FAT10ko mice (24 months) are leaner, with significantly reduced adipose mass as compared with age-matched WT mice. This was also manifested in young (10 weeks) FAT10ko mice, which weigh less and are more

metabolically active than WT mice, as demonstrated by higher respiratory exchange ratio, caloric intake, and energy expenditure. MRI and necropsy revealed that young FAT10ko mice contain ~40% less adipose tissue than young WT mice, with concomitantly increased lean mass. Intraperitoneal glucose tolerance test revealed significantly enhanced glucose tolerance which coincided with reduced circulating insulin levels. Illumina RNA-Seq analysis identified FAT10 as the third most highly up-regulated gene in intra-abdominal adipose tissue of obese, insulin resistant WT mice. Obesity-associated FAT10 gene up-regulation during 12 weeks of high fat diet (HFD) occurred selectively in adipocytes (>100-fold increase by QPCR), coinciding with increasing adiposity, macrophage infiltration and adipose tissue TNF-α expression. Importantly, FAT10ko mice made obese by extended (15 weeks) HFD feeding exhibited reduced AT and hepatic inflammatory gene expression. Together these observations implicate FAT10 in the metabolic and inflammatory stresses of aging.

143. Antagonistic Pleiotropy with Yeast Longevity: Slow and Delayed Living

Joe R Delaney (P, N), Chris J Murakami, Brian K Kennedy, Matt R Kaeberlein
University Washington, Seattle, WA, USA

Why should unicellular organisms age? If species which fission for reproduction aged, they would die out simultaneously as siblings reach their replicative potential and undergo clonal senescence. Saccharomyces cerevisiae bud asymmetrically, allowing for age to be reset in the daughter cells as they bud from the mother cells. Here we show that budding yeast may have evolved this mechanism to achieve faster growth rates, presumably by selectively packaging damaged components into the progenitor cell. We perform a comprehensive screen on published long lived alleles and show wild type yeast directly outcompetes long lived mutants during periodic cycles of nutrient addition and deprivation. We assay these alleles for doubling times and find ~40% are slow growing, of which ~95% are due to a G1 delay. Combining this competition screen with growth rate data, we were able to determine which alleles were defective in growth rate and/or starvation survival. Many aging genes clearly act in an antagonistic pleiotropic manner; they allow fast divisions early in life at the cost of continued replicative potential in late life. Equally interesting are the numerous mutants which have no readily visible competitive defect. We screen these mutants to find novel data for the evolution of aging, ranging from heat shock sensitivity, failure to grow in glycerol, and a variety of other defects data mined from previous publications.

144. Replicative Life Span Extension by Dietary Restriction in Yeast Requires the Golgi Calcium/Manganese ATPase PMR1

George L. Sutphin (P, N), and Matt Kaeberlein
University of Washington, Department of Pathology, Seattle, WA

PMR1 encodes a golgi apparatus calcium/manganese ATPase. In the budding yeast *Saccharomyces cerevisiae*, Pmr1 is responsible for transporting calcium and manganese from the cytosol into the golgi lumen. Dietary restriction (DR), defined as a reduction in nutrients without malnutrition, extends life span in a variety of organisms and is the best studied intervention for increasing longevity. In yeast, DR can be achieved by reducing media glucose from 2% to 0.05% and results in increased replicative life span (RLS), the number of cell divisions a cell undergoes before senescing. We recently discovered that strains lacking *PMR1*have dramatically shortened RLS when subject to DR, suggesting that *PMR1* is necessary for RLS extension by DR in yeast. Deletion of *PMR1* similarly shortens RLS of strains lacking Tor1, a nutrient-responsive central regulator of cell growth and translation that acts downstream of DR with respect to aging. Strains lacking Pmr1 are unable to grow in liquid under conditions that increase respiration, including media containing either glycerol or 0.05% glucose as a carbon source, suggesting a role for respiration in the response to DR. *PMR1* mutants have abnormal vacuolar morphology and many *pmr1* phenotypes are shared by vacuolar mutants, including strains lacking vacuolar genes involved in protein sorting and genes encoding subunits of the vacuolar H^+-ATPase. Both suggest a link to vacuolar function. The functions of Pmr1 in calcium and manganese transport can be uncoupled and have distinct roles in the cell. Calcium is required for proper function of enzymes in the protein secretory system and has been linked to the unfolded protein response, while manganese can interfere with enzymatic activity in the cytoplasm and is required for glycosylation in the golgi. The work presented is the ongoing effort to identify the relevant molecular mechanisms linking *PMR1* to DR with respect to RLS.

145. Testing the Somatic Theory of Aging: Relevance of KEAP1-NRF2 Pathway and Cell-Cycle Arrest Among the Mice and the Long-Lived Naked Mole-Rat

James Mele (P, G) and Rochelle Buffenstein
Barshop Institue for Aging and Longevity Studies, University of Texas Health Science Center at San Antonio, TX

Mechanisms facilitating successful aging (delayed onset and slow rates of decline) remain elusive, yet few studies have exploited the striking differences in maximum lifespan even among similar sized phylogenetically related species. Within rodents, mice live 3.5 yrs whereas the similar-sized naked mole-rat lives an order of magnitude longer, living more than 30 yrs. Furthermore, this long-living rodent shows markedly attenuated age-related declines in reproduction and physiology, and no incidence of spontaneous neoplasia. We hypothesize that retarded aging processes may have resulted from superior somatic maintenance, and that prolonged species longevity correlates with enhanced stress resistance to genotoxic agents, better induction and coordination of detoxifying and repair pathways and more robust cellular senescence. We have addressed this by comparing the responses of two rodent species with widely divergent longevity, namely naked mole-rats and mice to cellular stressors. Unlike

previous studies that simply measured cell viability to assess the role of cellular stress resistance as a determinant of species longevity we examine the mechanisms induced in response to damaging stressors that may contribute to enhanced cellular resilience to cellular insults. We examine the Nrf2-Keap1 detoxification pathway, resistance to buthionine sulifoximine mediated glutathione depletion, and entry into cellular senescence following chromium treatment. Preliminary data reveal that the naked mole-rat is not only more resistant to toxins but appear to have elevated levels of constitutively active Nrf2 relative to shorter lived-species (mice), and are resistant to glutathione depletion. Furthermore, cells isolated from naked mole-rats appear to enter prolonged cell cycle arrest, enabling better DNA repair. Should this fail, naked mole-rat cells undergo permanent growth arrest (senescence). In contrast, cells isolated from mice appear to continue replicating under potentially damaging conditions perhaps leading to greater incidence of mutation and the high levels of cancer observed in this short-lived species. Elevated Nrf2-ARE signaling and more stringent control of the cell cycle point to a highly responsive quality control system that may contribute to the preservation of genomic and somatic integrity, absence of cancer and extraordinary longevity of this species. Thus our data reflect that efficiency of somatic maintenance is a common mechanism regulating slow and successful aging.

146. The GLUN1$_{0XX}$ (NR1-A) Splice Variant of the NMDA Receptor is Involved in Spatial Reference but not Working Memory

Siba Das (P, N), Brenna Brim and Kathy Magnusson
Department of Biomedical Science, College of Veterinary Medicine, Oregon State University, Corvallis, OR, USA.

GluN1 subunit of the NMDA receptor shows age-related changes in its expression pattern which also correlates with spatial memory performance in mice. Aged C57/Bl mice show an age-related increase in mRNA expression of one of the splice forms of the GluN1 subunit, GluN1$_{0XX}$. This increase in expression is associated with good performance in reference and working memory tasks. The present study was undertaken to determine if the GluN1$_{0XX}$ splice form is required for good performance in reference and working memory tasks in young mice. Mice were injected with 5µl of either siRNA, control RNA or vehicle alone into ventro-lateral orbital regions of both sides of the brain using a stereotaxic apparatus. A fourth group of mice did not receive any injections. Four days post-injection, mice were tested for their performance in a spatial reference memory task for 4 days using the Morris water maze. Mice meant for the spatial working memory task were tested in the water maze for two sessions a day for eight days before the injection and then for two sessions a day for four more days post-injection. Results indicated an overall decline in performance in the reference memory task in the mice receiving siRNA against the GluN1$_{0XX}$ splice form, as compared to the mice injected with control RNA (N=12, p=.0379). There was no significant decline in the performance of mice in the working memory tasks following siRNA administration. These results suggest an important role of the GluN1$_{0XX}$ splice variant in orbital regions for spatial reference memory.

Support Contributed By: NIH grants AG16322 to K.R.M.

147. Upregulation of the NRF2 Cytoprotective Pathway contributes to Species Longevity

Kaitlyn N. Lewis (P,N), James Mele, Yael Edrey, Sung-A Kim, John D.Hayes and Rochelle Buffenstein
STCBM Building, San Antonio, TX, USA

. The transcription factor Nrf2 (nuclear factor-erythroid 2-related factor-2) is conclusively linked to numerous cytoprotective mechanisms that bolster an organism's response to endogenous (oxidative stress) and environmental (pesticides) stressors. Present in all tissues, Nrf2 regulates constitutive expression of over 200 cytoprotective genes, including antioxidant and detoxification enzymes. We hypothesize that the Nrf2 signaling pathway is an important guardian of somatic integrity and plays an important role in lifespan determination. Basal levels of Nrf2 are regulated by Keap1 (Kelch-like ECH-associated protein 1) mediated proteasomal degradation rather than by *de novo* protein synthesis. Under stressful conditions, redox-sensitive cycteine modifications inactivate Keap1, reducing proteasomal Nrf2 degradation and increasing the half-life and size of the Nrf2 pool, facilitating upregulated Nrf2-signaling and enhanced synthesis of cytoprotective proteins. Here we show a positive correlation between species longevity and constitutive Nrf2-mediated cytoprotection in a comparative study using three similar-sized rodents with a 10-fold range in maximum lifespan of species (MLS). The exceptionally long-lived naked mole-rat (MLSP 30 years) has significantly higher basal levels of Nrf2 protein, accompanied by greater antioxidant response element (ARE) binding and enhanced activity of Nrf2-target genes, GST and NQO1 than both the intermediate-lived white-footed mouse (MLS 8 years) and the short-lived C57Bl/6 laboratory mouse(MLSP 3 years), with the intermediate-lived species showing intermediate values. The 4-fold lower Keap1 levels in mole-rats may facilitate their enhanced cytoprotective phenotype. This constitutively primed cytoprotective readiness may explain enhanced resistance to cytotoxins, and contribute to the cancer-free good health and prolonged lifespan of mole-rats. Similarly caloric-restricted and dwarf mouse models of lifespan-extension also show evidence of upregulated Nrf2-dependent components suggesting that enhanced Nrf2 signaling may be a general mechanism for abrogated aging.

148. Mice Hypomorphic for the Igf1 Allele are Resistant to Weight Gain Induced by High Fat Diet

Adam B. Salmon, Yuji Ikeno, Roger McCarter, Christian Sell (P)
1) The Sam and Ann Barshop Institute for Longevity and Aging Research, and
2) Department of Pathology, University of Texas Health Sciences Center at San Antonio, San Antonio, TX
3) Pennsylvania State University, State College, PA.
4) Drexel University College of Medicine, Department of Pathology, 245 N 15th Street, Philadelphia, PA 19102.

Diets high in fat content can produce an obese, insulin resistant phenotype in mice that in many ways is similar to the response of humans to long-term intake of high fat, high calorie diets. In this study, mice hypomorphic for the Igf1 allele were examined for their response to high fat feeding. We found that Igf1 hypomorphs display an insulin resistant phenotype on standard rodent diet but gain significantly less weight than normal controls when placed on a high fat diet. In control animals, insulin response was significantly impaired by high fat feeding, however, Igf1 hypomorphs showed a much smaller shift in insulin response. Gluconeogenesis was elevated in the Igf1 hypomorphs relative to controls on both normal and high fat diet. Together, these results indicate that reduction in the circulating and tissue IGF-1 levels can produce a metabolic phenotype that increases peripheral insulin resistance but renders animals resistant to the deleterious effects of high fat feeding. These results suggest that an unappreciated level of cross talk between the IGF-1 and insulin signaling system can impact the response to dietary changes.

149. Testing the Oxidative Stress Hypothesis of Aging in Primate Fibroblast Cell Lines: Inverse Correlation Between Species Longevity and Cellular ROS Production

Zoltan Ungvari, Andrej Podlutsky, Natalia Podlutskaya, William E. Sonntag, Steven Merlin, Eva E. R. Philipp, Kristian Doyle, Antonio Davila, Steven N. Austad, Anna Csiszar (P)
1) Reynolds Oklahoma Center on Aging, Department of Geriatric Medicine, University of Oklahoma Health Science Center, Oklahoma City OK 73104
2) The Sam and Ann Barshop Institute for Longevity and Aging Studies, The University of Texas Health Science Center, San Antonio, Texas 78245

Predictions of the oxidative stress theory of aging was tested assessing reactive oxygen species (ROS) production and oxidative stress resistance in cultured fibroblasts from 13 primate species ranging in body size from 0.25 to 120 kg and in longevity from 20 to 90 years. We assessed both basal and stress-induced ROS production in fibroblasts from 5 great apes (human, chimpanzee, bonobo, gorilla, and orangutan), 4 Old World monkeys (baboon, rhesus and crested black macaques, and patas monkey), 3 New World monkeys (common marmoset, red-bellied tamarin, and woolly monkey), and 1 lemur (ring-tailed lemur). Measurements of cellular MitoSox fluorescence, an indicator of mitochondrial superoxide (O2.-) generation, showed an inverse correlation between longevity and steady state or metabolic-stress-induced superoxide production. Assessment of cellular H2O2 production revealed a similar pattern. Fibroblasts from longer-lived primate species also exhibited superior resistance to high glucose and H2O2-induced apoptotic cell death than cells from shorter-living primates. Thus, increased longevity in this sample of primates is associated with decreased cellular ROS generation and increased resistance to a variety of stressors, which accords with predictions of the oxidative stress hypothesis of aging.

150. Computational Aids for Systems Biology of Aging

Pat Langley (P)
Computer Science & Engineering
Arizona State University, Tempe AZ, USA

Aging arises from the gradual accumulation of organismic and cellular damage, along with alterations that accompany its repair. These changes result from complex interactions among a variety of mechanisms that challenge the scientific community's understanding. We maintain that a computational systems approach to aging will help clarify the processes that underlie senescence, enable predictions about the factors that influence it, and ease the extension of models as new findings emerge. To this end, we have developed an interactive software environment that represents and interprets hypotheses and phenomena about aging. The modeling formalism includes commands for declaring locations, quantities that occur in them, qualitative causal influences between variables, and empirical findings that describe observed relations. Users can enter this content in constrained English and display the resulting model in the same format. The environment also includes an interpreter that answers queries about relations between variables, generates predictions that it compares
known phenomena, and explain its reasoning in terms of causal chains. Users can easily revise model elements to analyze sources of explanatory power and to incorporate new hypotheses and findings. We have used this modeling environment to formalize a number
of compartments from Furber's (2009) network diagram of aging
(http://www.legendarypharma.com/chartbg.html). This exercise has let us identify and correct errors in the software, as well as improve the user interface. It has also clarified aspects of Furber's diagram, forcing the resolution of ambiguities. In future work, we plan to extend the modeling environment to specify when one
causal pathway dominates another, organize causal influences into higher-level processes, and make the software available over the Web
so that biologists can access, use, and revise models remotely. We also plan to provide a graphical interface that lets users visualize models and their relation to empirical phenomena.

151. Systems Biology of Human Aging – Network Model 2010

John D. Furber (P)
Legendary Pharmaceuticals, Gainesville FL, USA

The many observable signs of human senescence have been hypothesized by various researchers to result from several primary causes. Close 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. We present a network diagram to aid in conceptualizing the many processes and interactions among them, including 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
In addition, several researchers have proposed to adapt the network model's contents into an interactive website with links to references and background materials. A symposium to promote this development was held at Arizona State University, December 2008; abstracts are at http://circas.asu.edu/symposia/aging/ .
A second symposium was held 8-9 Dec 2009 at the National Institute on Aging in Baltimore, Maryland. This network model includes both intracellular and extracellular processes. It ranges in scale from the molecular to the whole-body level. Important pathways include:
• Extracellular proteins become damaged.
• Lysosomes accumulate reactive, crosslinked lipofuscin.
• Mitochondrial DNA mutates.
• Lamin-A progerin in nucleus.
• Nuclear envelope pore proteins oxidized.
• Nuclear mutations, telomere shortening, chromosome breaks, chromatin alterations and epigenetic DNA adducts change gene expression.
• Oxidized aggregates in cytoplasm.
• Proteasomes.
• Redox poise increases.
• Inflammatory cascades.
• Neuroendocrine and immune systems.
• ER stress.

152. Absence of Dietary Carotenoids and N-3 Fatty Acids Promotes Age-Related Macular Degeneration in Rhesus Monkeys

Martha Neuringer (P), Peter J. Francis, Laurie Renner, Alison Weiss, Brett G. Jeffrey
Oregon National Primate Research Center
Oregon Health & Science University, Beaverton, OR, USA

Age-related macular degeneration is the leading cause of vision loss in the elderly. Its pathogenesis involves cumulative oxidative damage, inflammation and activation of the complement system. Macaque monkeys can provide a uniquely valuable model for AMD because they possess a macula and commonly develop early to intermediate stages of AMD, marked by the appearance of subretinal deposits called drusen. However, monkeys almost never spontaneously develop the advanced atrophic or neovascular stages of AMD. This could be due diets very low in fat and high in nutrients thought to be important for retinal health such as the carotenoids lutein and zeaxanthin and n-3 fatty acids. Lutein and zeaxathin are yellow pigments that accumulate in the macula to filter damaging blue light and are also powerful antioxidants. N-3 fatty acids are also present in the retina at high levels where they act as anti-inflammatory and neuroprotective agents. We followed 19 rhesus monkeys that from birth until 14-16 years of age were fed diets lacking carotenoids and therefore had no macular pigment. Eight received a diet also deficient in n–3 fatty acids and the remaining 11 received adequate n–3 fatty acids. Monkeys fed carotenoid-free diets showed increased prevalence of drusen at early ages. Two animals in the n–3 deficient group developed atrophic changes in the macula by 15-16 years of age (equivalent to 45-48 human years), including areas of RPE disruption with pigmentary changes. We also found histological evidence of increased macular lipofuscin in other monkeys on the same diets. Given that atrophic macular disease is extremely rare in monkeys, its appearance at a relatively young age in monkeys deficient in carotenoids and n–3 fatty acids supports the role of these nutrients as significant factors for the prevention of AMD.

153. The Effect of Visceral Fat Removal on Metabolism in GHRKO and Normal Mice

Reyhan Westbrook (P), Michal Masternak, April D. Strader, Andrzej Bartke,
Southern Illinois University School of Medicine, Springfield, IL

Visceral obesity has been linked to insulin resistance and metabolic syndrome. In rats surgical removal of visceral fat improves insulin sensitivity and extends longevity. Growth hormone receptor knock-out (GHRKO) mice are obese and yet hypersensitive to insulin and long-lived. It was of interest to remove most of the epididymal and perinnephric fat from adult GHRKO and normal mice (n=8 per group) and observe changes in metabolic characteristics related to longevity including oxygen consumption (VO2), and Respiratory Quotient (RQ) using indirect calorimetry. After undergoing either visceral fat removal (VFR) or a sham surgery mice were given two weeks to recoup from surgery and tested in the AccuScan Instruments, Inc. PhysioScan Metabolic System. After a 24 hr acclimation period, mice were monitored in the metabolic chambers for 24 hours with ad libitum access to food, and then for a second 24 hour period without food. Gas samples were collected from the chambers, and analyzed every five minutes per animal. VFR decreased VO2 in normal animals ($p=0.0004$). Conversely, VFR transiently increased VO2 in GHRKO mice ($p=0.04$). Under fed conditions, VFR caused decreased RQ compared to sham surgeries during the dark period in normal animals ($p=0.0199$), however VFR caused increased RQ in GHRKO mice compared to GHRKO mice with a sham surgeries during both the dark ($p=0.0197$) and light ($p=0.0003$) periods. A similar effect on RQ was observed under fasted conditions. The observed genotype/intervention interaction suggests differing effects visceral fat on oxidative phosphorylation, and fuel selection in GHRKO vs. normal mice.

154. Multi-Platform Radial-Arm Water Maze Deficits Following High-Energy Particle Irradiation, A Model of Accelerated Aging

Marshall G. Miller (P), Barbara Shukitt-Hale, Bernard M. Rabin, Kirsty Carrihill-Knoll, James A. Joseph
Jean Mayer Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Exposure to high-energy particles has a deleterious effect on neural processes and produces behavioral deficits similar to those observed in aged animals. To explore the effect of high-energy particles on spatial memory behavior, rats were exposed to 0 cGy, 150 cGy, or 200 cGy (n = 15/group) of 56Fe radiation. Five weeks later, learning was assessed using a multiple platform version of the radial arm

water maze in which four arms always contained a hidden, submersible platform and four arms never contained a platform. During testing, rats were required to swim to a hidden platform and, after 15 s of orientation, the platform was submerged. Rats were required to locate all four hidden platforms before being returned to their home cage. Acquisition consisted of three trials per day for five consecutive days with an additional day of testing after a 40-day retention period. Trials were analyzed for reference memory errors (entry into never-escape arms) and working memory errors (re-entry into escape arms). During acquisition, no group differences in reference memory were observed, however irradiated rats were slower to reduce working memory errors across training days. Furthermore, long-term retention testing revealed a trend in the hypothesized direction for a 56Fe dose-effect on reference memory errors during the critical 1st retention trial. Rats who received the highest dose of radiation also showed a trend toward committing more working memory errors across the 2nd and 3rd retention trials where interference from earlier trials is increased. These findings suggest that 56Fe irradiation may serve as a useful, if subtle, model of accelerated aging and demonstrate the potential utility of this novel variant of the radial-arm water maze.

155. Damage Assays Rather Than Biomarkers of Aging

Benjamin P. Best (P)
24355 Sorrentino Court, Clinton Township, MI, USA

"Biological age" and "biomarkers of aging" are not meaningful concepts. Because aging consists of multiple forms of damage, there can be no single biomarker. Correlations of aging phenotype or maximum lifespan with specific forms of damage indicate the contribution of those forms of damage to aging. Epistemological problems with discerning an aging phenotype or
accelerated aging does not mean that genetic manipulation or exogenous agents can't alter the
rate of forms of damage contributing to aging. Rather than seeking general biomarkers of aging
based on the assumption of a single underlying deteriorating factor ("biological aging"),
biogerontologists should seek many assays of aging damage as a means of understanding, predicting, and possibly intervening in aging.

156. Pilot Studies to Find Measurable Effects of Meditation

Alfred B. Ordman (P)
Biochemistry Program, Beloit College, Beloit, WI, USA

Most chronic disease is caused by poor nutrition. Besides reactive oxygen species proposed by Denham Harman, inflammation is the second major mechanism by which poor nutrition generates age-associated disease. Stress can be a major cause of chronic inflammation. The ongoing study described here seeks measurable indices through which meditation can increase consciousness and reduce stress. Meditation may direct consciousness to the present moment. In the process, functional MRI has shown that the brain is activated to generate an empathic response to another's pain. Many simple tests have been tried with a group of students who are trained to meditate for 10 weeks. In the first round of testing, pulse rate, balance, reaction time, calculation rate and accuracy, and memory were measured. In the second round, a control group was added and quality of the meditation experience was evaluated over the weeks training occurred. For the future, a blood protocol is being developed. Stress has been shown to be associated with shorter telomeres in humans, while multivitamin and perhaps vitamin C and E users have longer telomeres. Consumption of 4-legged animal products has been shown to generate chronic inflammation in humans. In order to evaluate the effect of meditation on stress, behavioral and nutritional characteristics will need to be evaluated while selecting study participants and throughout the evaluation period. Among the parameters of interest are dietary factors like consumption of trans-fats and 4-legged animal products, behavioral characteristics like response to stress, and blood measurements including telomere length, blood levels of vitamins C and E, c-reactive protein, glucocorticoids, LDL, HDL, and measures of reactive oxygen species such as 8-OH-deoxyguanosine, protein carbonyls, thiobarbituric reactive substances, and Heinz body formation in red blood cells.

157. Body Height is Associated with Cognitive Function in community Dwelling Old Women

Moo Young Kim, M.D., Ji-Won Lee, M.D., Duk Chul Lee, M.D., Ph.D
250 Seongsanno, Seodaemun-gu, Seoul, 120-752, Korea

Background: There are growing evidences that structural and functional brain reserves may be crucial in cognitive function of late life. In old men, body height as a important marker of growth and development, is related to late life cognitive decline or dementia. The purpose of this study is to examine the relationship of body height to cognitive function in community dwelling old women.

Methods: A total of 150 community dwelling old women who can carry out daily life independently were recruited in this study. We measured height, weight and blood pressure with automatic device and investigated medical history and behavioral habits. We obtained fasting blood samples for the glucose and lipid profile tests and measured physical performance including gait speed, low extremity strength and balance. The Korean version of Mini Mental State Examination (K-MMSE) were used for the assessment of cognitive function.

Results: The acceptable cognition group whose K-MMSE score was over 24 is taller than the impaired cognition group whose K-MMSE score was less than 24(mean height 150.9±6.1, 148.0±5.4, respectively, P value=0.004). In Pearson correlation analysis, body height was positively associated with K-MMSE score ($r=0.342$, $P<0.001$). Multiple linear regression analysis showed that body height independently related to K-MMSE score after adjustment of age, waist circumference, systolic blood pressure, diabetes, hyperlipidemia, alcohol drinking, residential district, education, gait speed($\beta=0.102$, $P=0.028$).

Conclusion: Body height was independently associated with cognitive function in community dwelling old women. For the evaluation of the relationship between height and cognition in diverse cohorts, many studies will be necessary.

158. Disease Dissection and Dietogenesis of Paradoxical Protective Pathophysiologies (3DP)

Narayan deVera, M.D (P)
University of Pennsylvania School of Medicine, Philadelphia, PA, and 207 Norman Place, Santa Monica, CA

3DP is a three dimensional, sub-cellular analysis of various pathophysiologic consequences involving diet, symptomatology, and longevity, correlated with clinical and laboratory research reported between 375 B.C. and 1978 A.D., and predicated upon the belief that modern technological advancements cannot succeed unless their foundation of application includes an awareness of the ancient wisdoms derived from all relevant clinical experiences. From Hippocrates' assertion and axiomatic dual discovery that symptoms onset whenever the same "strong food" (meat or grain) is eaten twice in one day, and diseases manifest whenever that dietary practice is steadily maintained over time, to Sir William Harvey's analysis of the circulation, to A. I. Ringer's 1913 publication demonstrating the correct, physiologic amount of daily dietary protein to be merely twenty grams and reversing the worst chronic cases of psoriasis with his "time honored principle," and to this author's clinical results and research between 1973 and 1978, we define a true foundation of application for twenty-first century technologies, which is the assimilation of a comprehensive molecular and physiologic model, completely detailed in the poster, that explains all enigmatic parameters concerning high blood pressure, as well as the pathogeneses of obesity and cancer, conditions generally preceding and following the onset of hypertension, and which together constitute a continuous chronological spectrum of pathophysiologic responses to excessive dietary protein. One logical conclusion of the model was a prediction, later verified, that the genetic defect in cystic fibrosis resulted in a missing phenyl-alanine amino acid in an enzyme called antigenase. The model also reveals astonishing paradoxes that obesity, elevated cholesterol, hypertension, and cancer each prolong the body's longevity because their processes are slower in manifestation time relative to what would otherwise be much more rapid and critical failures within key organs and capillaries, sparing them from intense internal traumas.

Key words: Longevity, pathogenesis, antigenase
Other information: Flag IntraGlobal is an NGO engaged in medical humanitarian efforts in Africa and India to lower the high mortality rates of women and children

159. 2002-2010 Blueberry Health Study Report: Memory Data Analysis Suggests that 100 Participants Conducting 100 Measurements Each Year Can Document a 0.2% Annual Change During a Two-Year Study at 95% Confidence

Diana J. Burns[1], David L. Doiron[1], Howard A. Raphaelson[1], Kathy Hull[2], James A. Joseph[3], Amy C. Kokesh[4], Bruce S. Kristal[5], Alec Pruchnicki[6], Barrie S. Sachs[7], Roseanne Schnoll[8], Joseph Vogelman[9], Anthony Wetherell[10], Rolf J. Martin[5,11] (P)
[1]Mansfield Senior Center, CT; [2]New Fairfield Senior Center, New Fairfield, CT; [3]Human Nutrition Research Center on Aging at Tufts University, Boston, MA; [4]Raleigh, NC; [5]Brigham and Women's Hospital, Boston, MA; [6]St. Vincent's Hospital, NY, NY; [7]HR Herbs, Teas and Gifts, Sherman, CT; [8]Health & Nutrition Sciences, Brooklyn College, Brooklyn, NY; [9]Orentreich Foundation for the Advancement of Science, Cold-Spring-on-Hudson, NY; [10]Defence Sci & Tech Lab, UK (retired); [11]MMT Corporation, Sherman. Contact: Blueberrystudy@gmail.com. Web site: Blueberrystudy.com

BACKGROUND: To investigate health effects of blueberry consumption, volunteers in CT and NY have been consuming half to one cup daily of frozen (thawed but not cooked) wild Maine blueberries since 2002 while conducting online measurements of memory, decision speed and other cognitive skills. One of the primary goals of this study is to determine the feasibility of long-term aging/longevity studies such as that described by Alex Comfort in 1969. A key question, addressed by this analysis, is whether sufficient statistical power can be obtained at affordable cost with annual 1-month, 2-month or 3-month periods during which daily cognitive measurements are conducted. **METHODS:** Word recognition and other cognitive skills have been measured at Blueberrystudy.com since 2002. Face recognition and spatial pattern recognition have recently been added to the online test battery. Standard deviations for daily word recall data sets were analyzed and found to average 2.50% due in part to ceiling effects. Simulated data sets with an average within-person relative percent standard deviation of 5% (including a 2.5% safety margin) were then constructed for 100 participants conducting 10, 30, 60 and 100 daily measurements each year over a two year period. Two-tailed Student's t-tests and Kolmogorov-Smirnov tests were performed on the simulated data to determine if a 0.2% change could be detected. **RESULTS:** According to both statistical tests, a 0.2% difference can be detected at 95% confidence with a replication rate at $p < 0.05$ of 80% if 100 or more measurements are completed each year. Distributions of simulated data were generally but not always consistent with a normal distribution according to the Kolmogorov-Smirnov test.
CONCLUSION: Approximately 100 repeated measurements each year can provide the statistical power needed for a low cost Alex Comfort-style test battery to measure annual changes when interventions to slow decline or improve performance are evaluated.

160. The Kronos Science Laboratory-Blueberry Study-Memtrax Cognitive Assessment Reliability Study

Susan Kaib[1], S. Mitchell Harman[2], J. Wesson Ashford[3-4], Anthony Wetherell[5], Michael Klvana[6], Rolf J. Martin[6] (P)
[1]Kronos Science, Phoenix, AZ; [2]Kronos Longevity Research Institute, Phoenix, AZ; [3]Department of Veterans Affairs (VA) Palo Alto Health Care System, Palo Alto, CA; [4]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University, CA; [5]Defence Science & Technology Laboratory, UK (retired); [6]MMT Corporation, Sherman, CT.

Following Alex Comfort's 1969 description of a test battery to measure human aging (Lancet 294(7635):1411-15) and Richard Hochschild's development of H-SCAN equipment for estimating biological age (cf. J. Gerontol. 45, 6, B187 1990), both including a number of different cognitive measurements, the Kronos Science Laboratory offered H-SCAN measurements to its clients in 2001 and J.W. Ashford and collaborators developed the online Memtrax image recognition test as a rapid screening tool for Alzheimer's Disease (www.medafile.com), and beginning in 2002 the Blueberry Health Study ["BBS"] offered regular online cognitive assessments to participants consuming 1 cup/day of wild Maine blueberries. The Kronos, Memtrax and Blueberry groups have now received Institutional Review Board approval to directly compare their measurements by determining test-retest reliability and within-person standard deviation for each assessment within an experimental test battery. During this study, the purpose of which is to gather data to power a more definitive study, offline and/or online adaptations of the following assessments will be completed in ten 30-minute measurement periods during a two week period: H-SCAN highest audible pitch, reaction time and movement, vibrotactile sensation and visual accommodation, Memtrax image recognition, BBS word and face recognition, and delayed pattern-match to sample and arithmetic assessments included in the ANAM test battery developed by the Department of Defense (Arch Clin Neuropsychol. 2007 Feb;22 Suppl 1:S15-37). To minimize order effects, assessments will be rotated each day according to a Latin square design. Non-memory assessments will serve as spacers to reduce interference between memory assessments. Offline H-SCAN assessments will be conducted by 28 participants at KSL and KLRI in Phoenix, AZ. Online assessments are open to participants without geographic limit and include optional forward and reverse number recall measurements. The approved protocol and measurement pages are available for review and comment at www.blueberrystudy.com/KSL/BBS/Memtrax.

161. Towards a Systems Theory of Aging

Vincent E. Giuliano (P, G)
Wayland Massachusetts

A comprehensive systems theory of aging must embrace the validated teachings of multiple existing special theories of aging, theories that range from oxidative damage to loss of mitochondrial function to neurological degeneration to telomere shortening and cell senescence to decline in hormone levels. The author has characterized 14 such major theories and an additional 7 candidate ones. While each such theory is correct in its own framework of reference, on the surface most seem to be largely independent of the others. However, on the levels of molecular biology and genomics a rich network of links exists among these theories. The author suggests two overarching frameworks for integrating and clarifying existing understandings from the diverse theories of aging. One framework is lifelong programmed changes in global gene expression due to DNA methylation, histone acytelation and other epigenomic modifications. For example, aging-related decline of efficacy of DNA repair machinery might possibly result from promoter methylation of the Mms22 gene, resulting in increasing susceptibility to oxidative damage with age. Promoter methylation of the P21 and P53 apoptosis genes can result in increased susceptibility to cancers. The second framework sees aging as decline in functioning of the stem cell supply chain, the chain where adult stem and progenitor cells progressively differentiate as-needed into other cells of increased specificity and decreased pluripotency, resulting in lifelong renewal of somatic cell types. As the supplies of multipotent mesenchymal and haemopoietic stem cells available in their niches for differentiation decline because of their replicative senescence, for example, fewer progenitor and somatic cells are available to replace ones that have died or become senescent. The presentation will embody insights developed over a multi-year period and described in the author's online treatise ANTI-AGING FIREWALLS – THE SCIENCE AND TECHNOLOGY OF LONGEVITY .

162. Effects of Cranial Irradiation and the Antioxidant Alpha-Lipoic Acid on Hippocampal-Dependent Learning and Memory of Mice in the Water Maze

Laura E. Villasana and Jacob Raber
Oregon Health & Science University, Portland, Oregon

In both humans and animals, cranial irradiation results in impairments in hippocampus-dependent learning and memory that might be similar to and even contribute to age-related cognitive decline. 56Fe irradiation, the form of radiation astronauts encounter in space, results in long-term increases in ROS which may be contribute to radiation-induced changes in hippocampus-dependent learning and memory. Although conventionally ROS are thought to only have negative effects on cognitive function, increasing evidence supports that they are also required for learning and memory. Therefore, the effects of preventing or attenuating radiation-induced increases in ROS on cognition are not clear. To address this, mice were irradiated or sham-irradiated at 9 months of age and fed a diet rich in the antioxidant alpha lipoic acid (ALA) or regular diet two-weeks prior to irradiation and throughout cognitive testing to assess hippocampus-dependent learning and memory in the water maze (WM). B!
ecause our earlier data showed that female mice are more susceptible to the effects of irradiation on cognitive function than male mice, female and male mice were used to assess whether their response to ALA is sex-dependent. In agreement with the dual role of ROS in cognitive

function, in both male and female mice, ALA prevented radiation-induced impairments in spatial memory retention in the WM probe trials but ALA treatment caused cognitive impairments in sham-irradiated mice. These data support that there might be a fine balance in ROS that determines the direction of its effects on spatial learning and memory under specific conditions. This balance should be carefully considered with regard to consumption of antioxidants under normal physiological conditions and those that involve environmental challenges associated with increases in ROS.

163. Effects of Short or Long-Term Rapamycin Feeding in Bl6 Mice

T. J. Curiel(P, G), V. Hurez, L. Sun, S. Thibodeaux, H. van Remmen, P. Hornsby, A. Richardson, Z. D. Sharp
University of Texas Health Science Center, San Antonio, TX

Rapamycin inhibits mammalian target of rapamycin (mTOR) and prolongs life in mice through unknown mechanisms. We tested the hypothesis that rapamycin increases regulatory T cell (Treg) function thereby reducing age-related inflammation in BL6 mice. Rapamycin was fed in encapsulated microspheres in mouse chow as described. Mice of either sex fed rapamycin exhibited slightly reduced total CD3+ T cells and reduced CD4+ and CD8+ T cells in spleens and lymph nodes compared to mice fed control chow, whether started at 2-3 months, 6 months or 22 months of age, and whether fed for 2 weeks or up to 12 months. Rapamycin consistently increased the total percentage of cells expressing Foxp3, the nuclear transcription factor associated with Treg function, but effected a consistent slight reduction in CD4+CD25+Foxp3+ phenotypic Treg prevalence. In all cases, the capacity of Tregs to suppress T cell proliferation in vitro was equivalent in mice fed rapamycin or control chow. Rapamycin increased CD4+ T cell CCR7 and CD62L expression, suggesting reduced T cell activation. Rapamycin also reduced T cell PD-1, suggesting improved effector function, and reduced dendritic cell and myeloid cell B7-H1, a molecule that we have linked to age-related inflammation. Caloric restriction (CR) produced results equivalent to rapamycin except CR did not reduce B7-H1, and CR effects on PD-1 expression remain under study. CR plus rapamycin was equivalent to either intervention alone. In addition to T cells, myeloid cells can also be pro-inflammatory. Rapamycin had variable effects on myeloid cell numbers and differentiation that requires further study. These preliminary studies suggest that rapamycin reduces T cell activation, which could reduce age-related inflammation, simultaneously improving effector function. Rapamycin effects on Treg-mediated proinflammatory cytokine inhibition are under study, as are rapamycin effects on dendritic and myeloid cell capacity to induce proinflammatory cytokines.

164. Age-Dependent Increase in Cholesterol Efflux, Clearance, and Catabolism in the Aging Intact Female 3xtg Mouse Model of Alzheimer's Disease

Ryan T. Hamilton[1] (P,G), Amanda J. Compadre[1], Julian Lemus[1], Esosa Agbonwaneten[1], Jia Yao[1], Ronald W. Irwin[1], Roberta Diaz Brinton[1,2]
[1] Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, Los Angeles, CA, USA and [2] Department of Neuroscience, University of Southern California, Los Angeles, CA USA

Dysregulation of cholesterol homeostasis is an antecedent to the development of Alzheimer's pathology. Elevated neuronal membrane cholesterol induces an aging-dependent production of amyloid beta that leads to amyloid plaque formation in vivo. This study proposes that cholesterol trafficking, efflux and catabolism is increased in the triple transgenic AD (3xTgAD) model. To test this hypothesis entorhinal cortex sections (C2) were analyzed by western blot in intact female non-transgenic (nonTg) and 3xTgAD mice. 3xTgAD mice had elevated levels of 24-S-hydroxylase (CYP46) and ATP binding cassette protein 1 (ABCA1) at all ages while nonTG mice had an age-dependent increase in both. Apolipoprotein E and F increased age-dependently in the 3xTgAD while it was unchanged in the nonTG. Cholesterol uptake by apolipoprotein E-receptor appeared to be unchanged at all ages in both mice whereas low density lipoprotein-receptor decreased age dependently in both. Lysosomal trafficking of cholesterol by Niemman Pick C1 was decreased age dependently in both. Mitochondrial cholesterol trafficking proteins steroid activated receptor and peripheral benzodiazopine receptor had a dose dependent increase with age in the 3xTgAD while was unchanged in the nonTg. These findings suggest that cholesterol and lipid efflux, clearance and catabolism pathways are upregulated while uptake and lysosomal trafficking are decreased suggesting that cholesterol steady states appear to be associated with the mitochondrial and extracellular compartments in the 3xTgAD mice.

165. **Healthspan Promotion by SRT1720 in C57Bl/6J Mice**

Robin K. Minor[1],(P), Theresa Ward[1], Andrew Levette[1], James Ellis[2], David Sinclair[3] and Rafael de Cabo[1]
[1] Laboratory of Experimental Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, MD ; [2] Sirtris Pharmaceuticals Inc., A GSK Company, Cambridge, MA; [3] Department of Pathology and Glenn Labs for Aging Research, Harvard Medical School, Boston, MA

Sirtuins operate in key pathways that react to energy availability and regulate metabolism and stress resistance. These NAD^+-dependent deacetylase enzymes are conserved across eukaryotes with Sirt1 currently the focus of considerable research for its role in healthspan and lifespan in mammals. It has also been proposed that the beneficial effects of calorie restriction (CR) may be the result of Sirt1 activation. While Sirt1 is associated with improved health and longevity in rodent models of

obesity, whether Sirt1 activation will confer equal benefits in non-obese models is unclear. Here, we tested the effects of long-term treatment with SRT1720 on health and longevity in mice. Four diet groups were compared: standard diet (SD) controls, SD with a low dose of SRT1720, SD with a high dose of SRT1720, and calorie-restricted mice. While SRT1720 has been shown to improve glucose homeostasis in models of obesity, we show here that glucose uptake during an OGTT was also improved by SRT1720 in healthy, standard-diet fed mice as well. During 72h in sealed chambers measuring gas respiration the mice on SRT1720 showed reduced O_2 intake intermediate to that of CR, suggesting optimization of energy utilization. Mean lifespan was extended by 5% in high-dose SRT1720-treated mice and 3% by CR; neither treatment resulted in increased maximum lifespan. These findings suggest that the effects of CR and Sirt1 activation on oxygen consumption and glucose homeostasis do not directly result in maximum lifespan extension in healthy mice, although they are associated with a reduction in premature death and increased mean lifespan. Funded by the NIA/NIH Intramural Research Program.

Membership Directory

2010

Abbo, Fred
fredabbo@mac.com

Adamo, Martin L.
UTHSCSA
adamo@biochem.uthscsa.edu

Agrawal, Anshu
University of California, Irvine
aagrawal@uci.edu

Anderson, Rozalyn
University of Wisconsin
rmanderson5@wisc.edu

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

Appleby, James
jappleby@geron.org

Arking, Robert
Wayne State University
aa2210@wayne.edu

Balin, Arthur K.
Chesley Office Campus
akbalin@aol.com

Barron, Alexander
Oregon Health and Science Univeristy
barronal@ohsu.edu

Bartke, Andrzej
Southern Illinois University
abartke@siumed.edu

Bergman, Elliot
ebergman2@earthlink.net

Best, Benjamin
Cryonics Institute
contact2@benbest.net

Bickford, Paula
University of South Florida
pbickfor@hsc.usf.edu

Bleicher, Eberhard
bleicher@onlinehome.de

Blumberg, Jeffrey B.
Tufts University
jeffrey.blumberg@tufts.edu

Bonilha, Vera L.
Cleveland Clinic
bonilhav@ccf.org

Borchman, Douglas
University of Louisville
borchman@louisville.edu

Brewer, Gregory J.
Southern Illinois University
gbrewer@siumed.edu

Brim, Brenna
Oregon State
brenna.brim@gmail.com

Brown-Borg, Holly
University of North Dakota
brownbrg@medicine.nodak.edu

Buckwalter, Marion
Stanford University
marion.buckwalter@stanford.edu

Burton, Dominick
University of Miami
dburton@med.miami.edu

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

Chein, Edmund

Chou, Chia-Ching
UMDNJ-RWJMS
chouc2@umdnj.edu

Cini, Donna
drcini@balin.com

Citron, Bruce
Bay Pines VA Medical Center
bruce.citron@med.va.gov

Cockrell, Robert C.
Laguna Beach Longeivty Inst.
rcockrell@cox.net

Cohen, Harvey Jay
Duke University Medical Center
harvey.cohen@duke.edu

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

Conover, Cheryl A.
Mayo Foundation for Medical Research
conover.cheryl@mayo.edu

Cooney, Craig
UAMS
cooneycraiga@uams.edu

Corn, Joshua A.
Jean Carper's Stop Aging Now
josh@stopagingnow.com

Das, Siba
Oregon State University
dass@onid.orst.edu

de Grey, Aubrey
SENSFoundation
aubrey@sens.org

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

Desai, Varsha
NCTR
varsha.desai@fda.hhs.gov

DeVera, Narayan
FLAG IntraGlobal
globalfig1@yahoo.com

Dixit, Vishwa D.
LSU System
vishwa.dixit@pbrc.edu

Dong, Yuqing
Clemson University
ydong@clemson.edu

Duriancik, David
Michigan State University
durianci@msu.edu

Edrey, Yael
Barshop Institute
edrey@uthscsa.edu

Effros, Rita
UCLA
reffros@mednet.ucla.edu

Engelmann, Flora
Oregon Health and Science Univeristy
engelmaf@ohsu.edu

Fahy, Gregory M.
Intervene Biomedical
intervene@sbcglobal.net

Farrar, Roger P.
University of Texas at Austin
rfarrar@mail.utexas.edu

Ferris , Steven H.
NYU Langone Medical Center
steven.ferris@med.nyu.edu

Floyd, Robert A.
Oklahoma Medical Research Foundation
robert-floyd@omrf.ouhsc.edu

Fontana, Luigi
Washington University School of Medicine
lfontana@dom.wustl.edu

Ford, Christopher
University of Manchester
christopher.ford@postgrad.manchester.ac.uk

Ford, Judith
University of South Australia
judy.ford@unisa.edu.au

Forster, Michael J.
University North Texas Health Sci. Ctr.
forsterm@hsc.unt.edu

Freeman, Willard
Penn State College of Medicine
wfreeman@psu.edu

Fukagawa, Kazumi
Ryogoku Eye Clinic
br5k-fkgw@asahi-net.or.jp

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

Gorbunova, Vera
University of Rochester
vera.gorbunova@rochester.edu

Goto, Sataro
Juntendo University Graduate School
gotosataro@sakura.juntendo.ac.jp

Graber, Ted
University of Minnesota
grab0170@umn.edu

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

Hansen, Barbara C.
University of South Florida
bchansen@aol.com

Harman, Denham
Univ of Nebraska School of Medicine

Harman, Helen

Harman, S. Mitchell
Kronos Longevity Research Institute
mitch.harman@kronosinstitute.org

Harper, James
University of Michigan
jmharper@umich.edu

Harris, Peggy
Case Western Reserve Univeristy
Peggy.Harris@case.edu

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

Hayflick, Leonard
University of California, San Francisco
len@gene.com

Hepple, Russ
University of Calgary
hepple@ucalgary.ca

Herring, Bert
Fast-5 Corporation
bherring@fast-5.com

Holloszy, John O.
Washington University School of Med.
jhollosz@wustl.edu

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

Ikeno, Yuji
University of Texas Health Science Center at San Antonio
ikeno@uthscsa.edu

Ingram, Donald K.
Pennington Biomedical Research Center
Donald.Ingram@pbrc.edu

Jazwinski, S. Michal
Tulane University Health Sciences Center
sjazwins@tulane.edu

Johnson, Thomas
University of Colorado at Boulder
tom.johnson@colorado.edu

Joseph, James A.
USDA/HNRCA at Tufts
James.joseph@tufts.edu

Jurivich, Donald A.
University of Illinois-Chicago
jurivich@uic.edu

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

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

Kasinath, Balakuntalam
University of Texas Health Science Center
kasinath@uthscsa.edu

Kekich, David
Maximum Life Foundation
kekich@maxlife.org

Kikta, Evelyn
Vita Nutritionals, LLC
evelyn@vitanutritionals.com

Kim, Jong-Hee
University of Minnesota
kimx2355@umn.edu

Kindy, Mark
kindyms@musc.edu

Kuchel, George
University of Connecticut
kuchel@uchc.edu

Ladiges, Warren
University of Washington
wladiges@u.washington.edu

Lamming, Dudley
dlamming@gmail.com

Le Couteur, David S
University of Sydney
dlecouteur@med.usyd.edu.au

Lee, Ji Won
Yonsei University
indi5645@medimail.co.kr
Lee, Duk C.
Yonsei University College of Medicine
faith@yuhs.ac

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

Lewis, Kaitlyn
UTHSCSA
lewisKN@uthscsa.edu

Li, Gang
University of Arizona
gli@email.arizona.edu

Liang, Hanyu
Texas Diabetes Institute
liangh0@uthscsa.edu

Liao, Chen-Yu
Barshop Institute
liaoc@uthscsa.edu

Longo, Dan L.
New England Journal of Medicine
dlongo@nejm.org

Luebke, Jennifer
Boston University School of Medicine
jluebke@bu.edu

MacKay, Vivian
University of Washington
vlm2@u.washington.edu

Magnusson, Kathy
Oregon State University
kathy.magnusson@oregonstate.edu

Maroon, Joseph
UPMC-Presbyterian Hospital
maroonjc@upmc.edu

Martin, George M.
University of Washington
gmmartin@u.washington.edu

Martin, Rolf
Burke/Cornell Medical Research Inst.
rmartin@burke.org

Martinoli, Maria-Grazia
Universite du Quebec
martinol@uqtr.ca

Masternak, Michal
SIU School of Medicine
mmasternak@siumed.edu

Mattison, Julie
NIA
mattisonj@mail.nih.gov

Mele, James
UTHSCSA
jahana3@hotmail.com

Meng, Qingying
The Jackson Laboratory
mengqingying@hotmail.com

Messaoudi, Ilhem
Oregon Health and Science University
messaoud@ohsu.edu

Meydani, Mohsen
Tufts University
mohsen.meydani@tufts.edu

Meydani, Simin Nikbin
Tufts University
simin.meydani@tufts.edu

Miller, Richard A.
University of Michigan
millerr@umich.edu

Miller, Dana
dlmiller@fhcrc.org

Minor, Robin
NIA/NIH
minorro@grc.nia.nih.gov

Mockett, Robin J.
University of South Alabama
mockett@usouthal.edu

Navas, Placido
Universidad Pablo de Olavide
pnavas@upo.es

Nikolich-Zugich, Janko
University of Arizona, College of Medicine
nikolich@email.arizona.edu

Noda, Yasuko
Okayama University Medical School
yasukon@md.okayama-u.ac.jp

Ookhtens, Murad
KECK School of Medicine, USC
murad.ookhtens@usc.edu

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

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

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

Park , Jeong
University of Texas Health Science Ctr.
p1205@hotmail.com

Parker, Lambert
Integrative Longivity Inst.of Virginia
drparker@infaneeta.com

Patti, Gary
The Scripps Research Institue
gjpattij@gmail.com

Pearson, Kevin
University of Kentucky
kevin.pearson@uky.edu

Perrott, Kevin
University of Alberta
kevin@kevsplace.net

Pignolo, Robert
University of Pennsylvania, School of Medicine
pignolo@mail.med.upenn.edu

Pistell, Paul
Pennington Biomedical Research Center
paul.pistell@pbrc.edu

Pöllänen, Eija
University of Jyvaskyla
eija.pollanen@jyu.fi

Poulsen, Henrik E.
Dept. of Clin Pharm.
hepo@rh.dk

Pratt, Loretta A.
The Sally Balin Medical Center
prattbalin@aol.com

Primmer, Stanley R.
stanley_primmer@hotmail.com

Rabin , Bernard
UMBC
rabin@umbc.edu

Rabinovitch, Peter
University of Washington
petersr@u.washington.edu

Rae, Michael
SENS Foundation
mikalra@lycos.com

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

Ran, Qitao
University of Texas Health Science Ctr.
ran@uthscsa.edu
Raphaelson, Howard
hraphaelson@mba1959.hbs.edu

Reisberg, Barry
NYU Med. Ctr
barry.reisberg@med.nyu.edu

Rendon, Samantha
University Texas Health Science Center San Antonio
rendons@uthscsa.edu

Renkema, Kristin
University of Arizona
krenkema@email.arizona.edu

Reynolds, Rose M.
University of Oregon
reynolds@uoregon.edu

Rioux, Pierre
kilio@ureach.com

Rollo, Christopher
McMaster University
rollocd@mcmaster.ca

Romanick, Mark
Univ. of North Dakota School of Med
mromanic@medicine.nodak.edu

Ronkainen, Paula
Paula.h.a.ronkainen@jyu.fi

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

Ross, Ian
University of California Santa Barbara
ross@lifesci.ucsb.edu

Rudd, Brian
University of Arizona
ruddb@email.arizona.edu

Rusnacko, Dale T.

Saito, Hiroshi
University of Kentucky
hiroshi.saito@uky.edu

Salbe, Arline
Kronos Longevity Research Institute
asalbe@gmail.com

Salmon, Adam B.
University of Texas Health Science Ctr. SA
salmona@uthscsa.edu

Samadder, Partha P
University of Arizona
partha@email.arizona.edu

Scarpace, Philip
University of Florida
scarpace@ufl.edu

Seals, Douglas
University of Colorado
seals@colorado.edu

Seluanov, Andrei
University of Rochester
aseluano@mail.rochester.edu

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

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

Shi, Yun
UTHSCSA
shiy@uthscsa.edu

Shigemitsu, Toshiro
Shigemitsu Eye Clinic and Research Foundation
eyeshige@blue.ocn.ne.jp

Shimokawa, Isao
Nagasaki University Graduate School of BS
shimo@nagasaki-u.ac.jp

Shivshankar, Pooja
UTHSCSA
shivshankar@uthscsa.edu

Shukitt-Hale, Barbara
USDA/HNRCA
barbara.hale@tufts.edu

Simpkins, James W.
University of North Texas Health Science Ctr.
jsimpkin@hsc.unt.edu

Sloane, Lauren
UT Health Science Center San Antonio
sloane@uthscsa.edu

Smith, Mark A.
Case Western Reserve University
mark.smith@case.edu

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

Someya, Shinichi
University of Wisconsin - Madison
someya@wisc.edu

Sonntag, William
Oklahoma University Health Science Center
william-sonntag@ouhsc.edu

Spiegel, Paul M.
pms314@aya.yale.edu

Stanislav, Doubal
Charles University
doubal@faf.cuni.cz

Stern, David
CR Society
drstern@comcast.net

Stimpson, Stephen A.
GlaxoSmithKline
stephen.a.stimpson@gsk.com

Sullivan, Thomas J.
The Sullivan Company
tjsullivan@thesullivancompany.com

Sutphin, George
University of Washington
lothos@u.washington.edu

Taguchi, Akiko
Children's Hospital Boston
akiko.taguchi@childrens.harvard.edu

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

Tamasan, Delia
Smart People Foundation
smartpeoplefoundation@gmail.com

Thompson, LaDora
University of Minnesota
thomp067@umn.edu

Traustadottir, Tinna
Kronos Longevity Research Institute
tinna.traustadottir@kronosinstitute.org

Treadwell, Benjamin V.
benmar58@embarqmail.com

Troen, Aron
Tufts University
aron.troen@tufts.edu

Troen, Bruce
troen@miami.edu

Tsitouras, Panayiotis
Kronos Longevity Reseach Insitutue
tsitouras@kronosinstitute.org

Tsubota, Kazuo
Keio University School of Medicine
tsubota@sc.itc.keio.ac.jp

Tumer, Nihal
University of Florida
ntumer@ufl.edu

Uhrlaub, Jennifer
University of Arizona
juhrlaub@email.arizona.edu

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

Vaughan, William
Advanced Food Concepts
billvaughan@mac.com

Villasana, Laura
Oregon Health and Science University
Villasan@ohsu.edu

Voytko, Mary Lou
Wake Forest University School of Medicine
mlvoytko@wfubmc.edu

Wakfer, Paul A.
MoreLife
paul@morelife.org

Wanagat, Jonathan
University of Washington
jwanagat@u.washington.edu

Warner, Huber
University of Minnesota, College of Biological Sciences
warne033@umn.edu

Wasserman, Dean H.
Vein Treatment Center of New Jersey
info@veintreatmentcenternj.com

Watson, Kenneth
University of New England
kwatson2@une.edu.au

Watson, Rachel
University of Manchester
rachel.watson@manchester.ac.uk

Wolf, Norman S.
University of Washington
normwolf@u.washington.edu

Wu, Dayong
Tufts University
dayong.wu@tufts.edu

Wu, Miaozong
Marshall University
wum@marshall.edu

Yen, Kelvin
University of Massachusetts
kelvin.yen@mssm.edu

Zamzow , Daniel
Oregon State University
drzamzow@hotmail.com

Zheng, Ling
University of Southern California
lzheng@usc.edu

Zou, Sige
NIA
zous@grc.nia.nih.gov