THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

AGING SYMPOSIUM

FROM CHROMOSOMES TO COMMUNITIES: INTEGRATING AGING RESEARCH

October 9-10, 2019

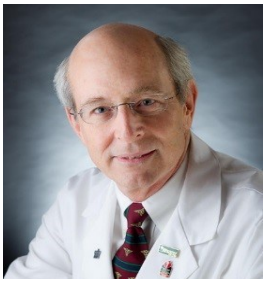
UAB Alumni House

Alzheimer's Disease Center | Comprehensive Center for Healthy Aging | Evelyn F. McKnight Brain Institute | Nathan Shock Center

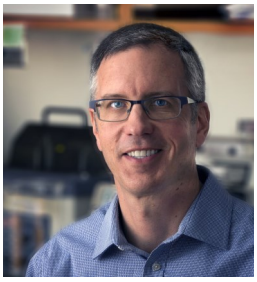
Welcome to the UAB Aging Symposium, From Chromosomes to Communities: Integrating Aging Research! We are excited that you are here. Our hope is that this year's symposium offers fresh and exciting ideas, and an opportunity to develop new collaborations to integrate all the different disciplines for the advancing of aging research.

Steven Austad, PhD
Distinguished Professor & Chair
Director, UAB Nathan Shock Center of Excellence in the Basic Biology of Aging
UAB Department of Biology

Cynthia J. Brown, MD, MSPH, AGSF
Professor of Medicine and Director,
Division of Gerontology, Geriatrics, and Palliative Care
Comprehensive Center for Healthy Aging
UAB Department of Medicine



Ronald M. Lazar, PhD, FAHA, FAAN
Evelyn F. McKnight Endowed Chair
Professor of Neurology
Director, Evelyn F. McKnight Brain Institute at UAB
Director, Division of Neuropsychology



Erik Roberson, MD, PhD
Patsy W. and Charles A. Collat Professor of Neuroscience
Director, Alzheimer's Disease Center
Director, Center for Neurodegeneration and Experimental Therapeutics
Associate Director, Evelyn F. McKnight Brain Institute
UAB Departments of Neurology and Neurobiology

AGENDA

October 9, 2019

7:30 – 8:00 AM	REGISTRATION and CONTINENTAL BREAKFAST
8:00 – 8:10 AM	WELCOME and PLENARY SPEAKER INTRODUCTION **Christopher Brown, PhD**
8:10 – 9:00 AM	PLENARY TALK **Richard Hodes, MD** *From Bench to Bedside: Exploring the Research Continuum at NIA*

Session I: Disparities

9:00 – 9:05 AM	**Session Chair: Cynthia J. Brown, MD, MSPH, AGSF**
9:05 – 9:55 AM	KEYNOTE SPEAKER **Peggye Dilworth- Anderson, PhD** *Academic and Community Partnerships: Creating Processes of Readiness and Sustainability*
9:55 – 10:20 AM	BREAK
10:20 – 10:45 AM	**Virginia Howard, PhD** *Early Life Contributions to Later Life Health Disparities*
10:45 – 11:10 AM	**Mona Fouad, MD, MPH** *Community-Based Approaches to Address Health Disparities*
11:10 – 11:30 AM	DATA BLITZ David Drummer **refer to page 21 for his abstract* Kaleen Lavin **refer to page 31 for her abstract* Lisa Roberts **refer to page 37 for her abstract*
11:30 – 12:30 PM	LUNCH

Session II: CELL SENESCENCE

12:30 – 12:35 PM	**Session Chair: Erik Roberson, MD, PhD**
12:35 – 1:25 PM	KEYNOTE SPEAKER **Darren Baker, PhD, MS** *From chromosome misegregation tumor models to senescence in age-related disease*
1:25 – 1:35 PM	BREAK
1:35 – 2:00 PM	**Melissa Harris, PhD** *Using mouse models of hair graying to discover novel stem cell-related mechanisms that contribute to variation in aging phenotypes.*
2:00 – 2:25 PM	**Victor Thannickal, MD** *Targeting Cellular Senescence in Idiopathic Pulmonary Fibrosis.*

AGENDA

2:25 – 2:35 PM	DATA BLITZ Hunter Dean **refer to page 20 for his abstract* Mackenzie Fowler **refer to page 23 for her abstract* Katherine Kruckow **refer to page 29 for her abstract*
2:35 – 2:50 PM	BREAK with REFRESHMENTS
Session III: Resilience	
2:50 – 2:55 PM	**Session Chair: Steven Austad, PhD**
2:55 – 3:45 PM	KEYNOTE SPEAKER **Luigi Ferrucci, MD, PhD** *Longitudinal Study Section, Clinical Research Branch, National Institute on Aging*
3:45 – 3:55 PM	BREAK
3:55 – 4:20PM	**Jeremy Herskowitz, PhD** *Synaptic Resilience to Alzheimer's disease*
4:20 – 4:45 PM	**Cynthia J. Brown, MD, MSPH, AGSF** *Life-Space Mobility as a Measure of Resilience*
4:45 – 4:55 PM	DATA BLITZ Mary Bell *r**efer to page 17 for her abstract* Zongliang Yue **refer to page 51 for his abstract*
4:55 – 5:00 PM	REMARKS **Erik Roberson, MD, PhD**
5:00 PM	TRAVEL TIME and TRANSPORTATION * The Florentine Building, 2nd floor Ballroom 2101 2nd Ave N, Birmingham, AL 35203
Poster Session & Reception	
6:00 – 8:30 PM	RECEPTION and POSTER SESSION
8:30 PM	POSTER AWARDS **Cynthia J. Brown, MD, MSPH, AGSF**
8:45 PM	TRANSPORTATION TO HOTEL FOR OUT-OF-TOWN GUESTS ARRIVES*

October 10, 2019

7:30 – 8:00 AM	REGISTRATION FOR NEW ATTENDEES and CONTINENTAL BREAKFAST

Session IV: Systematic Sources of Inflamation

8:00 – 8:05 AM	**Session Chair: Ronald M. Lazar, PhD, FAHA, FAAN**
8:05 – 8:55 AM	KEYNOTE SPEAKER **Costantino Iadecola, MD** *Neurovascular pathways to cognitive impairment: from bench to bedside*
8:55 – 9:25 AM	**Thomas Buford, PhD** *Connections between the renin-angiotensin system, gut microbiome, and age -related disability*
9:25 – 9:55 AM	**Carlos Orihuela, PhD** *Inflammaging contributes to age-dependent macrophage dysfunction*
9:55 – 10:15 AM	BREAK

NIH Panel Discussion:

10:15 – 11:45AM	Panel Moderator: Steven Austad, PhD **NIH Panel: John Haaga, PhD, Evan Hadley, MD, Max Guo, PhD**
11:45 - 11:55 AM	CLOSING REMARKS and ADJOURN **Steven Austad, PhD**

***The schedule for complimentary transportation to symposium sessions for out of town guests is below:**

Shuttle from Homewood Suites to Alumni House	Shuttle departing at 7:15 and 7:30 AM both mornings
Shuttle from Alumni House to Poster Session	Bus will begin loading at 5:15 PM
Shuttle from Poster Session to Homewood Suites	Bus will begin loading at 8:45 PM

PLENARY SPEAKER

Richard Hodes, MD

Director, National Institute on Aging (NIA)

Richard J. Hodes, M.D., is the Director of the National Institute on Aging (NIA) at the National Institutes of Health (NIH). Dr. Hodes, a leading researcher in the field of immunology, was named to head the NIA in 1993.

Under Dr. Hodes' stewardship, the NIA budget has grown to $3 billion, reflecting increased public interest in aging as America and the world grow older. Dr. Hodes has devoted his tenure to the development of a strong, diverse, and balanced research program, focusing on the genetics and biology of aging, basic and clinical studies aimed at reducing disease and disability, including Alzheimer's disease and related dementias; age-related cognitive change; and investigations of the behavioral and social aspects of aging. Cutting-edge research conducted and supported by the NIA, often in collaboration across institutes at the NIH, has helped to revolutionize the way we think about these conditions.

Dr. Hodes' research laboratory in the National Cancer Institute focuses on the cellular and molecular mechanisms that regulate the immune response. A graduate of Yale University, Dr. Hodes received his M.D. from Harvard Medical School.

From Bench to Bedside: Exploring the Research Continuum at NIA

The National Institute on Aging (NIA) leads the Nation's biomedical research enterprise in the field of aging and is the designated Federal lead on Alzheimer's disease (AD) related dementias (ADRD) research. NIA's research agenda for these areas has expanded in recent years with substantial increases in Congressional appropriations. NIA supports broad, multidisciplinary aging research programs in which research moves through a pipeline from studies of basic mechanisms to applications in clinical trials, as well as research on care and caregiving. This presentation will review the diverse types of aging and AD/ADRD research, programs, and infrastructure that the NIA is currently supporting. The presentation will also outline the impact of recent investments on the AD/ADRD research field as a whole, including new funding opportunities available to researchers.

SESSION ONE: KEYNOTE SPEAKER

Peggye Dilworth-Anderson, PhD

Professor, Health Policy & Management
Gillings School of Global Public Health
University of North Carolina- Chapel Hill

Dr. Dilworth-Anderson is professor of Health Policy & Management at the Gillings School of Global Public Health, University of North Carolina- Chapel Hill. Her research focus is on health disparities and Alzheimer's disease with an emphasis on building knowledge for the scientific and lay community to inform conducting culturally relevant research and disseminating information about Alzheimer's disease and related disorders in medically underserved diverse populations.

In recognition of her research in aging, Dr. Dilworth-Anderson received the Pearmain Prize for Excellence in Research on Aging from the University of Southern California (USC) Roybal Institute on Aging. This award exemplifies outstanding contributions to the field of translational aging research and its import to issues directly relating to older people. UNC awarded her the University Diversity Award in recognition of her commitment to diversity and inclusion in research, teaching and leadership. She received the Ronald & Nancy Reagan Alzheimer's Research Award for her research contributions on Alzheimer's disease in medically underserved populations from the Alzheimer's Association.

Dr. Dilworth-Anderson has served in numerous leadership roles, some of which include: President of Gerontological Society of America. Member: Global Council on Brain Health, Committees of the National Academies of Sciences, Engineering, and Medicine; National Alzheimer's Association Medical and Scientific Council; Board of Directors of the National Alzheimer's Association and Eastern North Carolina Chapter; National Research Advisory Council of the Institute on Aging/NIH.

Having a strong commitment to supporting the next generation of researchers in aging, Dr. Dilworth-Anderson has dedicated many years to training and mentoring graduate and medical students, fellows, and junior and mid-career faculty interested in the field of aging. In recognition of her mentoring, she received the Minority Task Force Mentor Award from the Gerontological Society of America and the UNC Faculty- to- Faculty Mentoring Award from the Carolina Women's Leadership Council.

A graduate of Tuskegee Institute, Dr. Dilworth-Anderson received her master's and doctorate degrees in sociology from Northwestern University and post-doctoral training from the Midwest Council of Social Research in Aging. She is a fellow of the Gerontological Society and National Council on Family Relations.

Academic and Community Partnerships: Creating Processes of Readiness and Sustainability
This presentation will focus on the "readiness" of scientists and communities to engage in moving from chromosomes to communities. The goal is to provide evidence on facilitators and barriers that support and impede building capacity within communities and among scientists to partner in planning and conducting research as well as addressing the health needs of communities. The presentation will be informed by The Circle of Influence Model of community linkage, which seeks to implement community-academic partnered participatory research (CAPPR), thereby empowering diverse communities to engage with academic scientists in an ethical, bidirectional, mutually beneficial and informed research process. The Circle of Influence model supports universities and communities in exerting more control over the research enterprise and in creating sustained connections that can improve the future health and well-being of the people living in targeted regions.

SESSION ONE: UAB SPEAKERS

Virginia J. Howard, PhD, FAHA, FSCT
Professor of Epidemiology, School of Public Health

Dr. Howard is a stroke epidemiologist with over 30 years' experience in multicenter, multidisciplinary clinical trials and longitudinal cohort studies with a focus on stroke, stroke risk factors, and health disparities.

Early Life Contributions to Later Life Health Disparities
Looking at health disparities and factors associated with them, this presentation will summarize some findings from REGARDS related to early life factors and later life occurrences of stroke, stroke risk factors, and cognitive impairment.

Mona N. Fouad, MD, MPH
Senior Associate Dean for Diversity and Inclusion, School of Medicine
Professor and Director, Division of Preventive Medicine
Director, UAB Minority Health and Health Disparities Research Center

Dr. Fouad is recognized nationally as a leader in health disparities research and served as a member of the NIH National Advisory Council on Minority Health and Health Disparities and is currently a member of the National Academy of Medicine. Dr. Fouad's career has focused on the health of minority and underserved populations, including efforts to increase involvement of special and underrepresented populations in research.

Community-Based Approaches to Address Health Disparities
Health Disparities are differences in health and health outcomes that adversely affect disadvantaged populations. For example, across ethnicities and geographic regions, individuals with lower income and education have higher rates of chronic disease and unhealthy behaviors than those with higher income and education. Because health disparities are complex, arising from interactions among race, age, gender, biological factors, health behavior, social status, and access to resources, interventions that fail to account for the full context are unlikely to be successful in reducing disparities. In contrast, community-based approaches involve researchers working with communities to identify the factors driving health disparities and then developing practical, community-based solutions to address them. The community-based approach rests on true academic-community partnerships that combine the evidence-based, data-driven expertise of academic research with the resources and abilities of community residents to produce successful prevention and health promotion programs. Dr. Fouad will present several examples and discuss how these examples can inform research on aging and health.

SESSION TWO: KEYNOTE SPEAKER

Darren Baker, PhD, M.S.

Associate Professor in Biochemistry and Molecular Biology
Assistant Professor in Pediatrics and Adolescent Medicine
Mayo Clinic

Work in the Baker laboratory is focused on understanding the mechanistic contribution of senescent cells to various age-related diseases through the use and development of in vivo mouse models.

From chromosome misegregation tumor models to senescence in age-related disease

Perhaps the single greatest risk factor for the development of chronic degenerative diseases in people is advancing age. A potential molecular mechanistic explanation of this relationship is that fundamental processes of aging actively promote tissue dysfunction and age-associated diseases. One plausible culprit may be the accumulation of senescent cells, as recent studies have found cellular senescence is a fundamental process of aging that often associates with disease states. These cells are thought to disrupt normal tissue functions through both cell intrinsic and extrinsic mechanisms. Importantly, cells with features reminiscent of senescence have been found in a variety of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, suggesting that senescent cells may contribute to neurodegenerative pathology. Several years ago, through the use of genetically modified mice to develop cancer, we demonstrated that premature aging is caused by the accumulation of senescent cells. Recently, using mice prone to neurodegeneration due to neurofibrillary tangle deposition, we find that senescent cells actively promote the initiation, progression, and severity of symptoms. Through elimination of these cells, by either genetic or pharmacological means, we were able to dramatically attenuate disease pathology. These data suggest that these cells may be potential therapeutic targets for intervention in debilitating age-related diseases.

SESSION TWO: UAB SPEAKERS

Melissa Harris, PhD

Assistant Professor, Department of Biology

Dr Harris' lab is interested in the cell biology, genetics and genomics of stem cells, aging, pigmentation biology, and tissue regeneration.

Using mouse models of hair graying to discover novel stem cell-related mechanisms that contribute to variation in aging phenotypes.

In the field of aging biology, a long-standing debate has focused on distinguishing between what is aging and what is disease, but one issue most aging biologists can agree on is that all humans age a little differently. With this in mind, my lab is focused on answering the question, "Why do we age the way we do?" We would like to understand whether there is a way we can measure variability in aging phenotypes so as to tailor prevention or therapeutic strategies to promote healthy aging on an individual basis. Here we propose to address this question using melanocyte stem cells (McSCs) and hair graying mouse models.

Within the lab, hair graying mouse models serve as an unbiased approach to identify environmental and molecular perturbations that lead to somatic stem cell dysfunction and disruption of adult tissue regeneration. Previously, we demonstrated the utility of this scheme to better define the transcriptional roles of SOX10 and MITF in McSC maintenance and to identify genetic alterations associated with resistance to hair graying. Currently we are exploring the influence of innate immune suppression, stress hormones, and the regulation of stem cell quiescence on McSC activation and hair repigmentation. Individually, each of these hair graying mouse models informs us on critical mechanisms important in the homeostasis of regenerative tissues, both in the acute and aging sense, and provides insight into disease. Altogether our work suggests that not only are there many ways to induce hair graying, but also that our genetic background will influence how we respond. My lab seeks to understand how a combination of mechanisms can explain variability in an aging phenotype and how we might use this information towards better diagnostics.

Victor Thannickal, MD

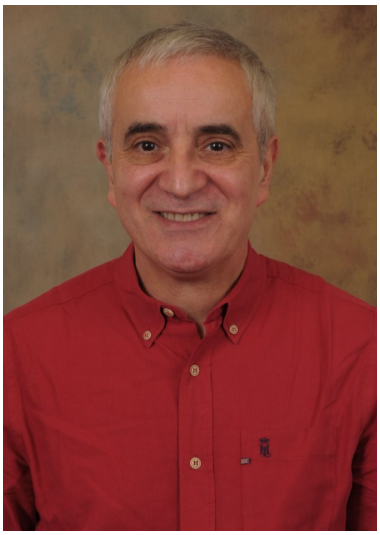
Professor of Medicine
Director of the Division of Pulmonary, Allergy and Critical Care Medicine
Vice Chair for Research in the Department of Medicine

Dr. Thannickal's research is focused on cellular and molecular mechanisms of lung repair and regeneration. This work has advanced fundamental understanding of myofibroblast origins, differentiation, and survival in pulmonary fibrosis.

Targeting Cellular Senescence in Idiopathic Pulmonary Fibrosis.

Emerging data support the concept that aging and age-related diseases are associated with an accumulation of senescent cells in tissues/organs. Idio-pathic pulmonary fibrosis is an age-related lung disease in which senescence of epithelial cells and fibroblasts have been demonstrated. Here, we present pre-clinical studies to support targeting senescent cells to resolve fibrogenic responses to lung injury.

SESSION THREE: KEYNOTE SPEAKER



Luigi Ferrucci, MD, PhD

Scientific Director, Longitudinal Study Section, Clinical Research Branch, National Institute on Aging (NIA)

Dr. Luigi Ferrucci is a geriatrician and an epidemiologist who conducts research on the biological and phenotypical pathways leading to progressive physical and cognitive decline in older persons.

Measuring Aging in the Baltimore Longitudinal Study of Aging

The human curiosity about the origin of aging and frailty is probably as old the human race and has become stronger and stronger with time. Initial attempts to study aging in human through a "scientific method" was based on a comparison of the characteristics of younger and older persons. This work was generally considered of great philosophical importance but little practical utility. In fact, most people believed that aging just occurs, it is irreversible, and little or nothing can be do about it. Although a lot of good science has been produced comparing people of different age, this method has substantial limitations because people of different age have been exposed to different environment and, therefore, the true effect of aging can never be dissected. The Baltimore Longitudinal Study of Aging (BLSA) was designed to address this problem and minimize the effect of secular trends and, to some extent, the biasing effect of selective survival of the most fit individuals by following participants with multiple visits over time. Nathan Shock designed the BLSA to discriminate "normal aging" from "disease", but most recently has become clear that aging and most age-related diseases share the same root in the biology of aging and, therefore, a clear-cut discrimination between aging and disease is not possible. In this presentation, I will share with the audience how the data collected in the BLSA was adapted to this new paradigm, in the attempt to connect mechanisms of aging biology, phenotypes typical of aging and their functional consequence. The fact that aging has been recognized as the most important mechanism of disease bring the study of aging at the front of medical research.

SESSION THREE: UAB SPEAKERS

Jeremy H. Herskowitz, Ph.D.

Associate Professor of Neurology
Patsy W. and Charles A. Collat Scholar in Neuroscience

Our team conducts research on Alzheimer's disease (AD) and Frontotemporal dementia (FTD) and is committed to identifying better therapeutic targets and finding more effective treatments for these devastating disorders. We formulate and test mechanistic hypotheses on AD and FTD pathogenesis by incorporating cellular and animal models with synergistic studies using postmortem human brain tissue samples.

Synaptic Resilience to Alzheimer's disease

Exciting advances in neuroimaging and other biomarker assays provide the means to detect Alzheimer's disease (AD) pathology in vivo and yield crucial evidence that the pathological processes of AD initiate years to decades prior to clinical dementia onset. Yet, approximately 30%-50% of individuals who come to autopsy without dementia have high levels of AD pathology. It is hypothesized that such individuals exhibit cognitive resilience that protects against dementia. How cognitively normal older individuals with AD pathology withstand the development of dementia has remained one of the most pivotal, unanswered questions in the field. Our research aims to understand cellular mechanisms of cognitive resilience and how these mechanisms can be exploited for therapeutics to delay or prevent dementia in AD patients.

Cynthia J. Brown, MD, MSPH

Gwen McWhorter, Ed.D., Endowed Chair in Geriatric Medicine
Professor and Director, Comprehensive Center for Healthy Aging
Division of Gerontology, Geriatrics, and Palliative Care

Dr. Brown is a board-certified Geriatrician and former physical therapist whose research has focused on hospital and community mobility. She leads the Comprehensive Center for Healthy Aging as well as the Division of Gerontology, Geriatrics, and Palliative Care at UAB.

Life-Space Mobility as a Measure of Resilience

Mobility is an important measure of overall health and resilience. While performance-based measures of mobility such as gait speed are predictive of adverse outcomes, they can be difficult to incorporate into clinical practice. The University of Alabama at Birmingham (UAB) Study of Aging Life-Space Assessment (LSA) is a self-reported measure that assesses mobility in the community in which persons report distance, frequency, and independence of movement ranging from one's room to beyond one's town. The LSA, which has been validated for in-person and telephone administration, measures the full continuum of mobility in community-dwelling older adults. We will present data regarding the association of life-space and adverse outcomes including nursing home placement and mortality, as well as show the impact of emergency department visits and hospitalization on life-space mobility.

SESSION FOUR: KEYNOTE SPEAKER

Costantino Iadecola, MD

Director, Feill Family Brain and Mind Research Institute
Anne Parrish Titzell Professor of Neurology
Professor of Neuroscience
Cornell University, Weill Cornell Medical College

Costantino Iadecola, M.D. is the Director and Chair of the Feil Family Brain and Mind Research Institute and the Anne Parrish Titzell Professor of Neurology at Weill Cornell Medicine. A pioneer in establishing the concept of neurovascular unit, Dr. Iadecola has championed the involvement of neurovascular dysfunction in neurodegenerative diseases, and the role of innate immunity and the microbiome in ischemic brain injury. He has published over 350 papers in peer-reviewed journals and plays a leadership role in research organizations and funding agencies in the US and abroad. Dr. Iadecola has received the McHenry Award from the American Academy of Neurology, two Jacob Javits Awards from the National Institutes of Health, the Willis Award - the highest honor in stroke research bestowed by the American Heart Association (AHA), the Zenith Fellow Award from the Alzheimer's Association, and the Excellence Award in Hypertension Research (Novartis) from the Hypertension Council of the AHA, In 2015, Dr. Iadecola was elected to the Association of American Physicians. In 2018, Clarivate Analytics (Web of Science) listed Dr. Iadecola as one of world's "Highly Cited Researchers" for ranking in the top one percent of the most-cited authors in the field of neuroscience and behavioral sciences (2006-2016). In 2019 was elected Distinguished Scientist by the American Heart Association.

Neurovascular pathways to cognitive impairment: from bench to bedside

The brain lacks energy reserves and is vitally dependent on a continuous and well-regulated delivery oxygen and glucose through the cerebral blood supply. Structural and functional alterations of cerebral blood vessels have emerged as a key correlate of conditions associated with cognitive impairment. The concept of "neurovascular unit" (NVU) was introduced in 2001 to highlight the close developmental, structural, and functional interactions between brain cells and cerebral blood vessels, and their coordinated reaction to injury. Comprised of neurons, glia, perivascular cells, e.g., perivascular macrophages, and vascular cells (endothelium, smooth muscle cells, and pericytes), the NVU is responsible for matching the delivery of blood to the brain with local energy needs dictated by brain activity. The NVU is also involved in regulating the molecular exchange between blood and brain (blood-brain barrier), clearance of metabolic byproducts through perivascular, paravascular and transvascular routes, trafficking of immune cells, and trophic support to brain cells (matrix, growth factors, etc.). NVU dysfunction, involving not just flow regulation but also other NVU functions, is central to the pathobiology of dementia and alters the homeostasis of the brain microenvironment in regions involved in cognition leading to cognitive impairment. Thus, neurovascular dysfunction is observed not only in vascular cognitive impairment, but also in Alzheimer's disease, attesting to the significant overlap between these conditions. In addition, major risk factors for cognitive impairment, such as hypertension, ApoE4 genotype, and high salt intake, are also associated with neurovascular dysfunction. Although activation of innate immunity, vascular oxidative stress and inflammation are major pathogenic factors, the underlying molecular mechanisms and their link to cognitive impairment remain poorly understood, and are a fruitful area of research with major diagnostic and therapeutic implications for both vascular and neurodegenerative dementias.

SESSION FOUR: UAB SPEAKERS

Thomas W. Buford, PhD, FACSM, FAHA, FGSA

Associate Professor and Endowed Scholar
Department of Medicine; Division of Gerontology, Geriatrics, and Palliative Care
Associate Director, Center for Exercise Medicine & Nathan Shock Center

Dr. Buford is a translational scientist with interests in identifying efficacious interventions to improve physical and cognitive functions in late life to ultimately improve health and preserve independence among older adults.

Connections between the renin-angiotensin system, gut microbiome, and age-related disability

The renin-angiotensin system (RAS) is commonly recognized for its role in the maintenance of blood pressure, however it has important implications for the maintenance of functional abilities in late life. This talk will discuss findings from across the translational research spectrum (i.e. animal studies to clinical trials) with relevance to the prevention of late-life disability, including recent and ongoing work related to the gut microbiome – now widely recognized to play an important role in human health.

Carlos J. Orihuela, PhD

Professor, Department of Microbiology, School of Medicine

A former recipient of the Glenn Award for Research in Biological Mechanisms of Aging, his research is focused on the host-pathogen interactions that are responsible for the increased susceptibility of the elderly to community-acquired pneumonia.

Inflammaging contributes to age-dependent macrophage dysfunction

Advance age is associated with chronic low-grade inflammation. “Inflammaging” is now understood to enhance the susceptibility of elderly to pneumonia in a variety of ways including increased expression of bacterial ligands on host cells, a muted cytokine response by alveolar macrophages exposed to bacterial products, and reduced killing capacity or clearance of bacteria by immune cells. New data suggests that age-dependent macrophage dysfunction is not due to intrinsic defects, but instead the result of homeostatic suppressors meant to prevent injury associated with chronic inflammation. Ongoing studies are focused on characterizing these negative regulators and their individual and combined impact on host immunity during aging.

NIH PANEL

John Haaga

Director, Division of Behavioral and Social Research, National Institute on Aging (NIA)

John Haaga has served since May 2016 as Director of the Division of Behavioral and Social Research in the National Institute on Aging. From 2004 to 2015 he was Deputy Director, and from April 2015 Acting Director, of the division. He leads NIA's extramural program funding research in economics, demography, epidemiology, cognitive science and social neurosciences, behavioral genetics, and health services research related to aging. This program includes major data collection and dissemination in the United States and cross-national comparative research on global health and aging. Dr. Haaga also serves as coordinator for the trans-NIH Common Fund Program in Health Economics. He teaches at the University of Maryland, School of Public Policy, and has previously taught at Georgetown University and the Defense Intelligence College.

Before joining NIA, he was Director of Domestic Programs and of the NIH-funded Center for Public Information on Population Research at the Population Reference Bureau, a nonprofit research and education organization. During 1994-97 he was staff director for the Committee on Population of the National Academy of Sciences. He has served as President of the Association of Population Centers and Secretary-Treasurer and elected member of the Board of Directors for the Population Association of America. From 1991 to 1994 he directed extension research in family planning and maternal and child health at the International Centre for Diarrhoeal Disease Research, Bangladesh. During the 1980s, Dr. Haaga was a Policy Analyst in RAND and a Research Associate for the Cornell University International Nutrition program. He has lived and worked in Bangladesh, Malaysia and Kenya, and worked for short periods in Indonesia, India, Kenya, Lesotho and Botswana. His PhD in Public Policy was awarded by the RAND Graduate School, and he has a BA (first-class honors) in Modern History from Oxford University and an MA in Inter-

Evan Hadley

Director, Division of Geriatrics and Clinical Gerontology ,National Institute on Aging (NIA)

Dr. Hadley is Director of the National Institute on Aging's Division of Geriatrics and Clinical Gerontology, which supports clinical and translational research on aging throughout the U.S. He received his M.D. from the University of Pennsylvania, and completed a research fellowship in NIA's Gerontology Research Center in 1980. Since then he has been responsible for developing NIA research programs on a variety of topics including physical frailty, comorbidity, prevention and treatment of diseases in older persons, clinical trials of interventions against disabling conditions, factors promoting healthy aging over the life span, and strategies to translate genomic and physiologic findings on age-related outcomes into interventions that delay adverse aging changes.

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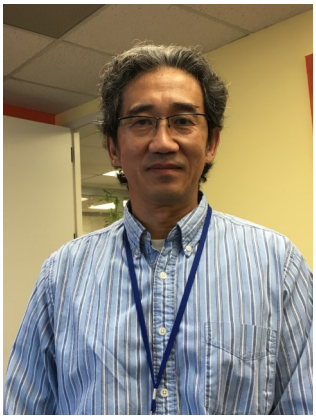
NIH PANEL



Max Guo, Ph.D

Chief of the Genetics and Cell Biology Branch, Division of Aging Biology at the National Institute on Aging (NIA)

Trained as a molecular biologist and geneticist, Dr Guo obtained a PhD in Biochemistry on study of RNA splicing with Dr. Alan Lambowitz from the Ohio State University in 1992. He did his postdoctoral training on oncogenes with Dr. J. Michael Bishop at University of California at San Francisco. Before joining NIH as a Program Officer in 2002, he was an Assistant Professor of Cancer Biology at the Sidney Kimmel Comprehensive Cancer Center of Johns Hopkins Medical School. He was a Program Officer of Genetics and Genomics at National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Heart, Lung and Blood Institute (NHLBI) from 2002 to 2007. From 2008-2011, he was the Deputy Director of the Division of Metabolism and Health Effects, NIAAA. He joined NIA in 2011, responsible for the genetics and chromatin portfolio.

POSTER ABSTRACTS

Tau-SH3 interactions are critical for amyloid-β toxicity in primary neurons

Adam R. Aldaher, Jonathan R. Roth, Travis Rush, Samantha J. Thompson, J. Nicholas Cochran, and Erik D. Roberson

Affiliations to come

The microtubule-associated protein Tau is strongly implicated in Alzheimer's disease (AD) and aggregates into neurofibrillary tangles in AD. Genetic reduction of Tau is protective in several animal models of AD and cell culture models of amyloid-β (Aβ) toxicity, making it an exciting therapeutic target for treating AD. Evidence indicates that Tau's interaction with Fyn kinase and other SH3 domain-containing proteins, which bind to PxxP motifs in Tau's proline-rich domain, may contribute to AD deficits and Aβ toxicity. Hence, we sought to determine if inhibiting Tau-SH3 interactions ameliorates Aβ toxicity. We developed a peptide inhibitor of Tau -SH3 interactions and a proximity ligation assay (PLA)-based target engagement assay. We used membrane trafficking and neurite degeneration assays to see if inhibiting Tau-SH3 interactions ameliorate Aβ induced toxicity in rat primary hippocampal neurons. We verified that the reduction of Tau ameliorates Aβ toxicity in neurons. From PLA, we identified a peptide inhibitor that reduced Tau-Sh3 interactions in HEK-293 cells and primary neurons. In primary neurons, endogenous Tau-Fyn interaction was present primarily in neurites and was reduced by the peptide inhibitor, demonstrating target engagement. The peptide inhibitor reduces Tau-SH3 interactions in neurons and ameliorates Aβ toxicity by both used membrane trafficking and neurite degeneration assays. The results show that inhibiting Tau-SH3 interactions ameliorates Aβ toxicity, indicating that Tau-SH3 interactions allow for Aβ toxicity and that inhibiting Tau-Sh3 interactions is a potential treatment for AD.

Nasal Dendritic Cell-Targeting System Enhances Influenza Virus-Specific Recall Secretory IgA Ab Responses In Aging

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The elderly have already experienced various pathogens and thus possess pathogen-specific Abs, whose titers are too low to combat reinfection. Thus, it would be of great benefit to the aged population if one could use an innate adjuvant system alone, without vaccine, in order to enhance mucosal immunity against past respiratory infections. We tested whether a combined plasmid Flt3 ligand (pFL) and CpG ODN adjuvant, which is targeting dendritic cells would enhance influenza virus-specific recall antibody (Ab) responses without a need for additional vaccination. Young adult mice were nasally infected with B/Brisbane or immunized with A/Puerto Rico/8/34 (PR8) hemagglutinin (HA) plus cholera toxin (CT) as mucosal adjuvant three times at weekly intervals. Over six months later, these mice were given nasal pFL and CpG ODN only (double signaling system). For positive controls, inactivated B/Brisbane or PR8 HA plus CT was given nasal route. Nasal washes, saliva and plasma samples were collected 7 days later and influenza virus HA-specific IgA Ab responses were evaluated. Mice treated with nasal double signaling system showed significantly increased and comparable levels of anti-HA secretory IgA Ab responses in the external secretions when compared with those responses seen in positive controls. The increase in total IgG Ab responses in mice given pFL and CpG ODN were limited when compared with those seen after primary nasal infection. Total plasma IgE Ab titers in mice given nasal pFL and CpG ODN only were the same as IgE levels seen in naïve mice. These results suggest that nasal pFL and CpG ODN alone can enhance pre-existing Ag-specific Ab responses without adverse effects in the elderly.

POSTER ABSTRACTS

Methods to estimate underlying blood pressure: The Atherosclerosis Risk in Communities (ARIC) Study

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Antihypertensive medications complicate studies of blood pressure (BP) natural history; BP if untreated ("underlying BP") needs to be estimated. Our objectives were to compare validity of five missing data imputation methods to estimate underlying BP and longitudinal associations of underlying BP and age. We simulated BP treatment in untreated hypertensive participants from Atherosclerosis Risk in Communities (ARIC) in visits 1–5 (1987–2013) using matched treated hypertensive participants. The underlying BP was imputed: #1, set as missing; #2, add 10 mmHg for systolic, 5 mmHg for diastolic; #3, add medication class- specific constant; #4, truncated normal regression; and #5, truncated normal regression including prior visit data. Longitudinal associations were estimated using linear mixed models of imputed underlying BP for simulated treated and measured BP for untreated participants. Method 3 was the best-performing for systolic BP; lowest relative bias (5.3% for intercept at age 50, 0% for age coefficient) and average deviation from expected (0.04 to -1.79). Method 2 performed best for diastolic BP; lowest relative bias (0.6% intercept at age 50, 33.3% age <60, 9.1% age 60+) and average deviation (-1.25 to -1.68). Methods 4 and 5 were comparable or slightly inferior. In conclusion, constant addition methods yielded valid and precise underlying BP and longitudinal associations.

ACES - ACE Inhibitors Combined with Exercise for Hypertensive Seniors: Design of a Randomized Controlled Trial

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Antihypertensive medications targeting the renin–angiotensin system have been associated with improvements in physical function, particularly when combined with exercise. However, randomized controlled trials (RCT) are needed to confirm this hypothesis. Therefore, the primary aim of this RCT is to determine if the choice of first-line antihypertensive medication, influence functional and cardiovascular risk factor responses to exercise among older adults with hypertension. This three-arm, multi-site, triple-masked RCT will enroll 213 (n=71/ arm) inactive, community-dwelling adults ≥ 60 years of age with hypertension and functional limitations to a 32-week intervention study. Participants will be randomly assigned to one antihypertensive medication: i) Perindopril (8 mg/qd), ii) Losartan (100 mg/qd), or iii) Hydrochlorothiazide (25 mg/qd). Additionally, all participants will also engage in a structured 20-week center (2x 45 minutes/ week) and home-based (60 minutes/week) aerobic exercise intervention, implemented before and after a 6-week observational phase. Outcomes will be assessed at weeks 0, 2, 6, 16, 26, and 32 post-randomization. The primary outcome is the change in gait speed. Changes in exercise capacity, body mass and composition, and circulating indices of cardiovascular risk will also be assessed as secondary outcomes. Linear mixed effects model with primary intent-to-treat analyses will be conducted to compare the change in gait speed from baseline to the end of intervention among the three groups at the significance level of 0.05. In addition, sensitivity and sub-group analysis will also be conducted to evaluate the effect of potential confounding variables and sub-group differences. This RCT is expected to differentiate the effect of three first-line medications on functional status and cardiovascular risk factors, when combined with regular exercise training and thus, may have potential implications for antihypertensive prescription guidelines to millions of American older adults with hypertension.

POSTER ABSTRACTS

Effects of Metformin on heterogeneity in resistance training-induced muscle hypertrophy

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Resistance training has been shown to increase muscle mass and strength. However, our laboratory has previously demonstrated heterogeneity in response to resistance training (RT), and the molecular signatures underlying this variation are of great interest. Metformin is a commonly prescribed drug to treat type 2 diabetes and increase insulin sensitivity. Because of the potential additional effects of metformin treatment on muscle inflammation in the aged muscle, this two-site, randomized controlled trial examined the influence of metformin on responsiveness to RT (parent clinical trial: "Metformin to Augment Strength Training Effective Response in Seniors," MASTERS, R01AG046920). 94 individuals were randomized to 1700mg Metformin (n=46) or placebo (n=48) for two weeks before and throughout 14 weeks of progressive RT. Muscle biopsies of the vastus lateralis were obtained pre and post intervention to measure molecular and cellular changes in response to RT +/- Metformin. Thigh muscle mass, measured by dual X-ray absorptiometry (DXA), was assessed before and after RT, and the change in bilateral thigh mass normalized to femur length was calculated. Metformin inhibited resistance training-induced improvements in muscle mass and muscle quality. Furthermore, Metformin treatment had a profound impact on response heterogeneity, such that those randomized to metformin were more likely to be classified as "poor" or "non"-responder to RT, using a K-means clustering algorithm. In ongoing analyses we are leveraging RNA-Seq and studies of muscle stem cell biology and tissue-resident macrophages to further examine potential mediators of responder status in individuals randomized to placebo and/or metformin.

Characterization of the age-related DNA methylome and development of an epigenetic age predictor in medaka (Oryzias latipes)

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Age specific patterning of DNA methylation ("epigenetic aging") is the single best marker of biological age as it is strongly correlated with chronological age, the onset of age-related disease, and all-cause mortality. Epigenetic age predictors use loci specific changes in the status of DNA methylation across the genome to predict chronological age with astonishing accuracy. Discrepancies between chronological and epigenetic or "biological" age can be used to explore the molecular underpinnings that determine different aging trajectories. Further, important life history characteristics such as the onset of reproductive maturity and senescence are associated with epigenetic age, suggesting that accelerated epigenetic aging may have implications on the timing of ecologically important life history events. We aimed to identify and describe the age-related DNA methylome and develop an epigenetic clock for a model fish species, medaka (Oryzias latipes), using reduced representation bisulfite sequencing of 2-, 6-, and 12 -month old animals. Our findings suggest that a substantial portion of methylation changes correlate with chronological age, with a greater proportion of change occurring early in life relative to late. Using just 39 of these age-associated loci, we have developed a model that is highly predictive of chronological age (cor = 0.9495) and provides the ability to assess biological age acceleration in the response to environmental factors. Further, our characterization of the age-related loci demonstrates the genomic distribution and functional associations of the age-related methylome, contributing towards ongoing research attempting to elucidate the functional role of DNA methylation in aging.

POSTER ABSTRACTS

Improving Everyday Cognitive Function in Patients with Stroke and Vascular Cognitive Impairment: Combining Cognitive Speed of Processing Training with the Transfer Package and Shaping of CI Therapy: Results of First Two Subjects

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Purpose: We propose to develop a novel intervention to improve speed of cognitive processing in everyday situations outside the treatment setting for people with stroke and vascular cognitive impairment (VCI). The new treatment combines two repeatedly validated and well-researched rehabilitation treatments, Speed of Cognitive Processing Training (SOPT) and the Transfer Package (TP) of CI Movement Therapy, to produce a marked improvement in the transfer of cognitive improvement from the treatment setting to instrumental activities of daily living (IADL) in everyday life situations, and also in retention of the treatment effect. Conventional treatments are of limited effect in these two areas.

Method: There were 2 pilot subjects; one male with chronic left hemisphere stroke with moderate impairment (MoCA Score — 10), one with vascular cognitive mild impairment (MoCA Score — 21)

Protocol: Ten 2.5 hour sessions were given 2-4 times/wk. Sessions consisted of 1 hour Speed of Cognitive Training followed by 1½ hours of techniques derived from CI Therapy including: 1) training by the technique of shaping of cognitive IADL (e.g., making purchases, speaking on the phone, selecting items from a crowded shelf), 2) homework tasks monitored for compliance, 3) daily review of 18 cognitive activities performed in everyday situations, 4) problem solving discussion.

Results: Both participants improved substantially on the Cognitive Task Activity Log (CTAL), which elicits data on the independence and quality of 18 important IADL. Both participants are engaging in more than 10 (S_1) or 20 (S_2) activities not engaged in before training.

Conclusion: The combination of SOPT and the techniques of CI Therapy (training by shaping of IADL in the laboratory and the TP) appears to be a promising treatment for mild to moderate cognitive impairment.

Future Directions:
1. Determine retention over the course of one year.
2. Duplicate procedure in 8 more pilot subjects (10 in all).

Components of social support mediate racial disparity on diabetes distress within older African and Caucasian Americans.

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Background: Approximately 30.3 million Americans are living with diabetes with 90 – 95% classified as Type 2. African Americans (AAs) have a higher prevalence of diabetes than Caucasian Americans (CAs) and higher levels of diabetes-related distress. Potential factors to explain this disparity are the specific types of social support individuals receive. This study examined various components of social support as mediators of the association of race with diabetes distress.

Methods: Data were collected as a part of the University of Alabama at Birmingham (UAB) Diabetes and Aging Study of Health (DASH) via phone interviews with participants who were 65 and older and self-reported having diabetes. A series of linear regression models tested social support variables as mediators of the direct effect of race on diabetes distress.

Results: The analytic sample included 148 participants (74 AA, 74 CA) with an average age of 72.7 years. After controlling for age, gender, marital status and education, AA race was significantly associated with higher levels of diabetes distress, $p < .05$. The one social support component that differed by race and predicted diabetes distress was negative interaction. When negative interaction was added to the initial model, the direct effect of AA race on diabetes distress was no longer significant (57.70% of the direct effect explained) suggesting full mediation.

Conclusion: Results suggest that racial differences related to the types of social support received may partly explain the disparity between AAs and CAs on diabetes distress. These findings elucidate the need for research investigating the unique role of social support on diabetes-related outcomes for ethnic/racial minority groups.

POSTER ABSTRACTS

Autofluorescence of Lipofuscin in the Salivary Gland of the Aging Fruit Fly, D. melanogaster

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The purpose of this project was to visualize and quantify damaged material known as lipofuscin in the salivary gland of Drosophila melanogaster. It was hypothesized that autofluorescence at an excitation wavelength of 488 nm and emission ratio of 610/510 nm, indicative of lipofuscin, would be greater in old (55-76 d) than in young (10-14 d) adult fly salivary glands. Dissections were performed on male and female flies of three strains: y w, w1118 and Oregon R. Images of both tubular and distal segments of the salivary gland were acquired using a Nikon A1R confocal microscope, and NIS Elements software was used to quantify lipofuscin granules. In both parts of the salivary gland from both sexes and all three fly strains, the 610/510 nm emission ratio was higher in old than in young flies, by 9-115%. The increase was statistically significant in 3/6 comparisons for the tubular portion of the gland and 4/6 for its distal end. The results obtained provide strong evidence for accumulation of lipofuscin in the salivary gland of aging D. melanogaster.

Enhanced skeletal muscle proteostasis as a determinant of CNS protein quality control and neural function in the aging brain

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Proteostasis is essential for cell health and viability, and involves complex and highly conserved networks that regulate protein translation, protein folding, and protein degradation. A decline in proteostasis function is one of the features of aging tissues, particularly of the central nervous system (CNS). Indeed, the aging brain is particularly sensitive to proteotoxic stress, as demonstrated by the high number of age-associated neurodegenerative disorders characterized by protein misfolding and aggregation, including Alzheimer's disease (AD). The regulation of non-cell autonomous proteostasis has recently arisen as a novel mechanism for the modulation of systemic homeostasis in worms and flies, and is postulated to have important organismal effects on metabolism and aging. However, to date, there are no studies addressing the existence and activity of these pathways in mammals, and their potential effects on the aging brain. Transcription Factor E-B (TFEB) is a powerful master transcription factor regulator of proteostasis, integrating autophagy and bioenergetics. We recently derived transgenic mice that moderately overexpress TFEB in skeletal muscle, and discovered that the resulting enhanced skeletal muscle proteostasis function can significantly ameliorate proteotoxicity in the CNS and also improve cognition and memory in aging mice. We have also uncovered changes in soluble TFEB muscle-secreted factors (myokines), suggesting a potential modulation of the observed neuroprotective effects. Our current work aims to characterize these targets and validate their therapeutic potential for diseases of the aging CNS.

POSTER ABSTRACTS

Dendritic spine plasticity as a mechanism of cognitive resilience against Alzheimer's disease pathology.

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Neuroimaging and other biomarker assays suggest that the pathological processes of Alzheimer's disease (AD) initiate years prior to clinical dementia onset. However some 30%-50% of older individuals that harbor AD pathology do not become symptomatic in their lifetime. It is hypothesized that such individuals exhibit cognitive resilience that protects against AD dementia. We hypothesized that in cases with AD pathology structural changes in dendritic spines would distinguish individuals that had or did not have clinical dementia. We compared dendritic spines within layers II and III pyramidal neuron dendrites in Brodmann Area 46 dorsolateral prefrontal cortex using the Golgi-Cox technique in 12 age-matched pathology-free controls, 8 controls with AD pathology (CAD), and 21 AD cases. We used highly optimized methods to trace impregnated dendrites from brightfield microscopy images which enabled accurate three-dimensional digital reconstruction of dendritic structure for morphologic analyses. Spine density was similar among control and CAD cases but reduced significantly in AD. Thin and mushroom spines were reduced significantly in AD compared to CAD brains, whereas stubby spine density was decreased significantly in CAD and AD compared to controls. Increased spine extent distinguished CAD cases from controls and AD. Linear regression analysis of all cases indicated that spine density was not associated with neuritic plaque score but did display negative correlation with Braak staging. These observations provide cellular evidence to support the hypothesis that dendritic spine plasticity is a mechanism of cognitive resilience that protects older individuals with AD pathology from developing dementia.

Frontotemporal Dementia–Associated Variants in TREM2 Destabilize the Apical Ligand-Binding Region of the Immunoglobulin Domain

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Single nucleotide variations in Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) have been linked to both late-onset Alzheimer's disease and behavioral variant frontotemporal dementia (FTD), which either can present in isolation or can occur with cystic bone lipomas in a condition called Nasu-Hakola disease. Models of the extracellular domain of TREM2 show that Nasu-Hakola disease–associated mutations are grossly inactivating by truncation, frameshift, or unfolding, that Alzheimer's disease–associated variants localize to a putative ligand-interacting region (PLIR) on the extracellular surface, and that FTD-associated variants are found in the hydrophobic core. However, while these FTD-associated residues are predicted to play a role in steric packing of the extracellular domain of TREM2, how they ultimately lead to disease remains unknown. Here, we used *in silico* molecular modeling to investigate all-atom models of TREM2 and characterize the effects on conformation and dynamical motion of FTD-associated T96K, D86V, and T66M variants compared to the benign N68K variant and wildtype. Our model, which is based on a published 2.2 Å resolution crystal structure of the TREM2 extracellular domain, finds that FTD-associated variants cause localized instability in three loops adjacent to the PLIR that correspond to the complementarity-determining regions (CDRs) of antibodies. This instability ultimately disrupts tethering between these CDRs and the core of the immunoglobulin domain, exposing a group of otherwise-buried, positively charged residues. This instability and exposure of these positively charged residues is most severe following introduction of the T66M variant that can cause FTD even in the heterozygous state and is less severe following introduction of variants that are less strongly tied to FTD. Thus, our results provide further evidence that the proposed loss-of-function caused by FTD-associated variants may be driven by altered conformational stability of the ligand-interacting CDR and, ultimately, loss of affinity or specificity for TREM2 ligands.

POSTER ABSTRACTS

Impact of an aged host's physiological milieu on RNA virus pathogenicity

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Elderly individuals often exhibit greater incidence, severity, and mortality rates to infection with some RNA viruses. Studies in mammalian systems have shown that infection of an aged host promotes rapid changes of the viral genome that lead to increased pathogenicity via mechanisms that are not fully understood. Hence, the aging population could represent a potential pool for the emergence of new, pathogenic viral strains. A better understanding of the interactions between viruses and their aged hosts is required to uncover the mechanisms that are compromising the aged organism's ability to survive infection.

Our lab utilizes *Drosophila melanogaster* as an experimental model and focuses on aged host-virus interactions using the RNA-containing Flock House Virus (FHV). We tested whether FHV passage in the aged host affects its pathogenicity using hemolymph (insect blood) transfer experiments. Transferring hemolymph from older, FHV-infected hosts led to the more rapid death of young recipients in comparison to hemolymph transferred from younger, FHV-infected flies. We determined the virus titers in transferred samples using the 50% Tissue culture Infective Dose method and observed comparable virus loads in hemolymph extracted from young and aged FHV-infected flies. Furthermore, adding the virus externally to hemolymph samples, we found similar mortality rates in recipients that were injected with either young hemolymph/FHV or aged hemolymph/FHV. This suggests the possible existence of factors in the *milieu* of the aged fly that enhance virus pathogenicity specifically during its replication in the aged host.

Our long-term goals include using sequencing techniques to examine the potential accumulation of mutations in the genome of FHV passed through an older host and investigating the factors in the aged fly responsible for the increased pathogenicity. Gaining further understanding of interactions between viruses and their aged host could unravel fundamental mechanisms that may lead to preventing the emergence of novel viral strains.

Characterization of Muscle Inflammation Susceptibility: A Potential Prognostic Factor for Optimal Post-surgical Rehabilitation.

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Many individuals with end-stage osteoarthritis undergo elective total hip/knee arthroplasty (THA/TKA) to relieve pain, improve mobility and quality of life. However, ~30-35% suffer long- term mobility impairment which we hypothesize may result from blunted restoration of muscle mass and function. THA/TKA rehabilitation requires regeneration of muscle damaged during surgery, and regrowth of atrophied muscle from reduced loading/activation, all inhibited by chronic muscle inflammation. Our lab illustrated a profound basal skeletal muscle pro-inflammatory state in some individuals (based on TWEAK receptor (FN14) gene expression), termed muscle inflammation susceptibility (MuIS), which we predict is an important prognostic indicator of successful rehabilitation. As part of a 5-year, randomized controlled trial, the goal is to phenotype the initial cohort of MuIS$^{(+)}$ and MuIS$^{(-)}$ participants. 84 participants (29M/55F; 62±8yrs; BMI 30.7±5.4kg/m^2) undergoing THA/TKA were assessed. Of these, 37 were clustered as MuIS$^{(+)}$ (n=23, 4-fold higher FN14 mRNA) or MuIS$^{(-)}$ (n=14). Comparisons were made using two-tailed T- tests; alpha P≤0.05. Thigh muscle mass (TMM), quadriceps power and torque were lower on the surgical (SX) leg (P<0.05). Additionally, myofiber type IIx distribution and type II cross-sectional area were greater in the SX leg and MuIS$^{(+)}$ group respectively (P<0.05). Tumor necrosis factor-**a** receptor and interleukin-6 receptor trended higher in MuIS$^{(+)}$ (P>0.05). Preliminary results suggest the SX legs of patients undergoing TKA/THA exhibit exaggerated inflammation, accompanied by lower TMM, torque and power. The MuIS$^{(+)}$ group exhibits further exacerbated pro-inflammatory signaling, highlighting the profound impact of muscle inflammation and emphasizing potential value in perioperative MuIS status assessment to inform optimal post-surgical care.

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POSTER ABSTRACTS

The Role of Fibroblast Growth Factor 23 in Cellular Senescence in the COPD Bronchial Epithelium

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Chronic obstructive pulmonary disease (COPD) has become a global epidemic which disproportionally affects elderly populations and is associated with accelerated aging. COPD is characterized by airway inflammation, loss of alveolar-capillary units and progressive decline in lung function. COPD airways show elevated levels of pro-inflammatory Fibroblast growth factor-23 (FGF-23) and deficiency in Klotho, a co-receptor for FGF-23 and anti-aging protein. COPD is a disease of aging and the FGF23/klotho is an aging pathway, we hypothesize that FGF-23 combined with klotho deficiency promotes bronchial cellular senescence in COPD. This study, two models were used; 1) an *in vivo* aged murine model and 2) an *in vitro* human bronchial epithelial cell culture model (Beas2b). 18 month old mice were exposed to cigarette smoke or air for 3 weeks to induce airway inflammation. Lungs were examined for expression levels of inflammation markers (IL-6), senescence markers (p16, p21) and klotho. The results showed a decrease in IL-6, p16 and p21 and klotho expression mRNA levels in smoked aged mice when compared to aged control mice. In the in vitro study, Beas2b cells were exposed to FGF-23 and cigarette smoke extract (CSE) for a time course of 24, 48 and 72 hours. The results showed an increases in p21 protein levels when compared to non-treated controls. These results suggest that FGF23/ Klotho signaling plays a role in airway inflammation and senescence in the aged mouse lung. Further studies are needed to understand how FGF-23/klotho signaling contributes to airway inflammation and cellular senescence in the pathogenesis of COPD.

Development of a Culturally-Based Palliative Care Tele-Consult Program to Meet the Unique Cultural Values and Preferences of Rural African American and White Rural Elders With Serious Illness and their Families: A Program By The Community For the Community. *PHASE I: Determination of Cultural Values and Preferences*

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Background: Lack of respect for cultural differences may compromise care for seriously ill minority patients, yet culturally appropriate models of palliative care (PC) are not currently available, especially in rural areas. Therefore, developing a model of PC that reaches rural communities through telehealth and takes into consideration the cultural preferences of rural African Americans (AA) and Whites is crucial.

Design: A Community Advisory Group (CAG) (4 AA and 4 White) from Beaufort, South Carolina advised the research team. Based on CAG recommendations, multiple focus group recruitment methods were implemented, and separate focus groups (2 sessions each) held for each ethnic group. Sessions focused on care received by their loved one during their recent serious illness. All sessions were recorded, transcribed, and analyzed using systematic thematic analysis.

Results: Themes in White and AA groups included those that were (a) Equivalent (e.g., plea for doctors to treat patients and family respectfully, clarity about medication use and dosage, and initial discomfort with telehealth). (b) Similar, but with variation (e.g., AA considered the church central to all aspects of life, AA had fears that hospice staff would take charge in the patient's home, W reported ongoing support by the hospice chaplain). (c) Divergent (e.g., AA families were committed to caring for loved ones at home, W caregivers felt guilt at leaving loved one in nursing home, AAs were distrustful of the medical system and of physicians, concerns about sharing of prognosis, and in AA group, death was not discussed at homes).

Conclusions and Relevance: Understanding the cultural values of different ethnic or cultural groups is the first step towards being able to design programs that meet the cultural tenets and preferences of unique groups. All themes were reported to CAG, and in Phase II used to develop a feasible, culturally-based palliative care tele-consult.

POSTER ABSTRACTS

Investigation of sex differences in longevity of daf-16 mutant C. elegans

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This project is exploring sex differences in longevity observed in *C. elegans*. The model has two natural sexes, males (XO) and hermaphrodites (XX). The hermaphrodites are basically self-fertile females who have the ability to make a limited number of sperm for internal self-fertilization. Previous studies have shown that wildtype (N2) *C. elegans* males live longer than hermaphrodites. Mechanisms underlying these sex-specific effects of longevity can be evaluated by investigating longevity-modulating mutant strains that have historically been solely characterized in hermaphrodites, including the *daf-16(m27)* mutant in the insulin-signaling pathway. The hypothesis tested was males have increased longevity compared to hermaphrodites in both wildtype and daf-16(m27) mutant populations. We generated and propagated N2 males by using a heat stress procedure to induce meiotic chromosome nondisjunction. A breeding scheme was devised and carried out to create a homozygous *daf-16(m27)* population. Homozygosity of the mutant population was verified using PCR-based genotyping and Sanger sequencing. To observe and study individual animals across their lifespan, a liquid 96-well lifespan assay was developed and used in this study with *daf-16(m27)* hermaphrodites (n = 81) and males (n = 31) and wildtype N2 hermaphrodites (n = 85) and males (n = 27). There was a difference in median survival between N2 and *daf-16(m27)* strains with no observed sex difference, respectively 21 and 16 days. There was a difference in maximum survival between N2 and *daf-16(m27)* strains and observed sex differences (N2 hermaphrodites, 37 days; N2 males, 26 days; *daf-16(m27)* hermaphrodites, 26; *daf-16(m27)* males, 23). Findings reveal there is a significant decrease in longevity for the *daf-16(m27)* males compared to the *daf-16(m27)* hermaphrodites (p = 0.01, Log-rank test). This experiment is being replicated and is currently underway.

Progression of Alzheimer's disease by previous cancer history

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Background: Some studies suggest cancer survivors have decreased risk of developing Alzheimer's disease (AD). However, adverse effects of cancer and its treatments, especially in later-life, include cognitive deficits in domains affected by AD. Little is known about how previous cancer exposure affects AD progression.

Methods: We utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to evaluate progression to AD by self-reported all-cancer, breast, prostate, colorectal, or non-melanoma skin cancer history. Random linear mixed effects models were used to examine baseline differences and rates of progression on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) by cancer history. Age at AD onset was examined using consensus clinical diagnoses with Cox proportional hazards regression.

Results: Among 1271 participants, all-cancer exposed were older and more likely to be White compared to cancer unexposed. Mixed models revealed no significant differences in progression over time, but did reveal significantly lower baseline ADAS-Cog score, indicating better cognition at a given age of onset in cancer survivors. Cox models indicated cancer survivors had significantly later age of AD onset (HR: 0.67, 95% CI: 0.53-0.85) after adjustment for covariates.

Conclusion: Cancer survivors begin with better cognition and later age of AD onset, but progress similar to cancer unexposed participants, indicating that differences in AD between cancer exposed and unexposed patients emerge early in the disease course. This analysis provides information, beyond previous studies' cross-sectional examinations, on longitudinal progression by cancer exposure. Further investigation is warranted with data poised to stratify by cancer treatment and severity.

KEYWORDS: Alzheimer's disease, mild cognitive impairment, disease progression; cancer, cognitive impairment; ADNI

POSTER ABSTRACTS

Investigating the role of the double-stranded RNA transporter SID-1 in a Parkinson's Disease model

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Parkinson's Disease (PD) is the second-most common neurodegenerative disease in humans, impacting more than 10 million individuals globally. PD negatively affects motor and cognitive functioning as a result of the selective loss of dopaminergic (DA) neurons in the brain, and it is predicted to increase in prevalence given an aging population. The neurodegeneration of DA neurons in PD is linked to the protein alpha-synuclein (α-syn) in humans, which misfolds and aggregates into plaques. The Caldwell Lab has created a model of PD by overexpressing human α-syn exclusively in the DA neurons of the nematode Caenorhabditis elegans (C. elegans), and as a result these worms exhibit progressive, age-dependent degeneration of DA neurons, similar to the pathology seen in PD patients. Here, we investigate the role that the double-stranded RNA (dsRNA) transporter SID-1 plays in DA neurodegeneration, DA neuron function, and lifespan. Our results indicate that a sid-1 mutation increases the function of DA neurons in an a-syn background compared to α-syn only controls, as determined by Basal Slowing Response (BSR) assays, which test the functionality of the DA neurons by quantitatively determining the extent of slowing when worms encounter food. In addition, our data reveal that this mutation of sid-1 in an α-syn background provides protection against dopaminergic neurodegeneration as compared to worms without the sid-1 mutation. Although sid-1 mutants in an α-syn background experience increased neuronal function and neuroprotection, they experience decreased lifespan. However, overexpression of sid-1 specifically in the DA neurons rescues this decrease in lifespan caused by the sid-1 mutation. These results show that neuroprotection of DA neurons does not necessarily equate to longevity, and suggests that the transport and subsequent silencing of dsRNAs may be implicated in PD. Further insight into these mechanisms could lead to critical discoveries of new methods and therapeutic treatments for PD.

Associations of Satisfaction with Social Support and Physician Trust with Greater Self-Efficacy in Older Adults Living with Diabetes

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Background: Previous literature asserts that higher perceived self-efficacy in managing one's diabetes may partially ameliorate the difficulties faced by people living with diabetes, their caregivers, and their loved ones. Diabetes is one of the most prevalent chronic conditions that burdens older adults living in the United States. This is particularly true in the Deep South region of the United States where diabetes-related health outcomes may be especially dire for older African Americans (AA) compared to Caucasian Americans (CA).

Method: Data were collected as part of the University of Alabama at Birmingham (UAB) Diabetes and Aging Study of Health (DASH). Older adults sixty-five years of age and older who self-reported living with diabetes provided verbal consent and participated in telephone interviews. Correlational analyses were conducted to look at the bivariate associations of psychosocial variables (e.g., multiple-item scales of social support and negative interaction with members of the social support network, perceived discrimination and physician trust) with the outcome of self-efficacy in dealing with diabetes. Additionally, a multiple linear regression model examined the covariate-adjusted associations of psychosocial variables with self-efficacy.

Results: The sample included 148 participants (74 AA, 74 CA) with an average age of 72.7 years. Negative interaction and perceived discrimination were negatively associated with perceived diabetes self-management (self-efficacy), whereas satisfaction with social support and physician trust were positively associated with diabetes self-management in bivariate correlations, p's < .05. The results of the covariate-adjusted regression model showed that there was no racial difference on self-efficacy. However, higher levels of satisfaction with social support and physician trust were each significant predictors of self-efficacy.

Conclusion: These findings suggest the importance of satisfaction with social support and physician trust for older AAs and CAs living with diabetes. These factors are potentially modifiable, therefore interventions targeted to make improvements on these domains should be explored.

POSTER ABSTRACTS

Resveratrol and exercise to treat functional limitations in late life (RESTORES): A pilot randomized controlled trial

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Problem: Evaluate the safety and feasibility of combining exercise (EX) and resveratrol to treat older adults with physical function limitations.

Methods: Pilot randomized, controlled trial (RCT) of community-dwelling adults (N=60), 72±6 years old with objective functional limitations were randomized to 12 weeks of either (1) EX + placebo, (2) EX + 500 mg/day resveratrol, or (3) EX
1,000 mg/day resveratrol. EX consisted of two sessions a week for 12 weeks of center-based walking and whole-body resistance training. Safety was assessed primarily through adverse events, and feasibility through exercise session, and supplement (placebo or resveratrol) adherence. Physical function outcomes included the 4-m usual-paced gait speed and the six- minute fast-paced walk test. Physical function data represent unadjusted within group mean differences at week 12 with 95% confidence intervals.

Results: Adverse events were similar between groups (n=8 EX + placebo, n=12 EX + 500 mg/day resveratrol, and n=7 EX + 1,000 mg/day resveratrol). Exercise session adherence across groups was 76.39±28.97% while supplement adherence across groups was 85.15±16.17%. The relative change of EX + placebo group for the 4-m gait speed was -0.035 m/sec (-0.107, 0.036). The change for EX + 500 mg/day resveratrol was 0.029 m/sec (-0.101, 0.042) while EX + 1,000 mg/day resveratrol group change was 0.036 m/sec (-0.037, 0.109).The within group change in six-minute walk test for the EX + placebo group was 8.959 m (-13.04, 31) while the EX + 500 mg/day resveratrol was 21.466 m (-1, 43.9), and the EX + 1,000 mg resveratrol group was 32.932 m (9.9, 56).

Conclusions: The pilot RCT indicated that combined EX + resveratrol was safe and feasible for older adults with functional limitations.

Future Directions: Although the physical function results from the EX + 1,000 mg/day resveratrol group are promising, a fully-powered trial is necessary to definitively evaluate these outcomes.

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POSTER ABSTRACTS

Tryptophan metabolism is differently regulated between large and small dogs

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Companion dogs have recently been promoted as an animal model for the study of aging due to their similar disease profile to humans, the sophistication of health assessment and disease diagnosis, and the shared environments with their owners. In addition, dogs show an interesting life history trait pattern where smaller individuals are up to two-fold longer-lived than their larger counterparts. While some of the mechanisms underlying this size and longevity trade-off are strongly suspected (i.e. growth hormone/IGF-I), there are likely a number of undiscovered mechanisms, as well. Accordingly, we have completed a large-scale global metabolomic profiling of dogs encompassing a range of sizes and ages from three cities across the United States. We found a surprisingly strong location signal in the metabolome, stronger in fact than any signal related to age, breed, or sex. However, after controlling for the effects of location, tryptophan metabolism emerged as significantly associated with weight of the dogs, with small dogs having significantly higher levels of tryptophan pathway metabolites. Overall, our results point toward novel, testable hypotheses about the underlying physiological mechanisms that influence size and longevity in the companion dog and suggest that dogs may be useful in sorting out the complexities of the tryptophan metabolic network.

CRISPR/Cas9-Mediated Loss-of-Function in Growth Hormone-Releasing Hormone Alters Physiological and Metabolic Profile in Mice

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Previously, we demonstrated that growth hormone releasing hormone (GHRH) deficient mice have dramatically increase lifespan and improved metabolic homeostasis. However, this knock-out mouse model was generated with embryonic stem cell based gene -targeting method which can result in passenger mutations. For this study, we targeted GHRH with CRISPR/Cas9 technology to avoid this pitfall and studied metabolism and physiology of this mouse model. $GHRH^{-/-}$ mice have significantly reduced expression of growth hormone in pituitary gland and insulin-like growth factor-1 (IGF-1) in liver demonstrating successful disruption of growth hormone (GH) pathway. $GHRH^{-/-}$ mice have significantly lower body weight and higher insulin sensitivity compared to $GHRH^{+/+}$ mice. To obtain meaningful interpretation of the physiological data, in addition to studying absolute values, we used generalized linear modeling (GLM) which is the most widely accepted method when comparing with animals with different body size/ composition. $GHRH^{-/-}$ mice have dramatically decreased lean mass, bone mineral content and density, while having a significantly higher fat mass compared $GHRH^{+/+}$ mice as measured by dual-energy X-ray absorptiometry (DXA). We recorded respiratory exchanges by using indirect calorimetry method as a means to measure energy expenditure and metabolic rate. $GHRH^{-/-}$ mice have significantly decreased oxygen consumption, carbon dioxide production, and energy expenditure compared to $GHRH^{+/+}$mice. Respiratory exchange ratio (RER), which is calculated by division of carbon dioxide production with oxygen consumption, provides insight into the relative participation of lipids, carbohydrates, and proteins in energy production. $GHRH^{-/-}$ mice have significantly lower RER during the light cycle compared to $GHRH^{+/+}$ mice suggesting a higher activity in lipid metabolism $GHRH^{-/-}$ mice in a circadian-dependent manner. We conclude that novel CRISPR/Cas9 $GHRH^{-/-}$ mice are presenting consistent physiological and metabolic characteristics, which might explain long lifespan of GHRH deficient in mice.

POSTER ABSTRACTS

The cellular significance of the long non-coding RNA Neat1 in an Alzheimer's disease model

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The impact of excess amyloid-β (Aβ) on astrocyte function is inadequately explored despite their critical role in maintaining homeostasis of the neuronal microenvironment and in processes underlying learning and memory. Accumulation of hippocampal Aβ results in a reactive astrocyte state detrimental to cognitive function. We believe that altered epigenetic regulation of astrocyte function by the long non-coding RNA *Neat1* is both a consequence of and contributor to various pathologies associated with Alzheimer's disease (AD). Our lab has demonstrated that Neat1 mediates neuronal histone methylation and age-related memory impairment and that reducing *Neat1* expression rescues these memory deficits. These studies prompted us to ask if *Neat1* contributes to AD-associated cognitive decline and if so, if *Neat1* might serve as a therapeutic target. Previous studies have shown that *Neat1* expression is elevated in the hippocampus of patients with Alzheimer's disease, while knock down of *Neat1* in glial cell lines results in impaired Aβ uptake. My overarching hypothesis is that Neat1 epigenetically regulates astrocyte-specific genes involved in hippocampus-dependent memory formation in a model of AD. Using magnetically activated cell sorting, we have been able to isolate microglia and astrocyte fractions from an aged mouse model of AD. Preliminary data suggests elevated Neat1 expression in the hippocampus of the hAPP-J20 mouse model of AD, both in whole extracts and in cell-type specific analyses. There is an urgent need to understand underlying mechanisms that contribute to cognitive decline in AD, and to generate therapies that

Early weight loss and hypothalamic dysfunction in Alzheimer's disease

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Background: While cognitive deficits are the major manifestation of Alzheimer's disease (AD), weight loss can precede the cognitive decline in the preclinical stage of AD, where amyloid-beta (Aβ) and tau have accumulated but cognition is intact. As the mechanisms underlying the weight loss are unclear, we hypothesize that early Aβ accumulation disrupts hypothalamic circuits that regulate body weight and alter signaling of the fat hormone leptin. In prior studies, compared to wild-type littermates, Tg2576 mice with Aβ pathology had lower body weight, lower plasma leptin levels, and dysfunction of leptin-responsive hypothalamic neurons prior to memory impairment. Here, we examined whether alterations in plasma leptin levels and hypothalamic atrophy are found in individuals with preclinical AD.

Methods: Cognitively intact (CDR=0) non-obese (body mass index, BMI<30) volunteers (age>50 years) from the Healthy Aging & Senile Dementia and Adult Children Study (Missouri, USA) with 3T MRI scans and fasting plasma samples were included. Preclinical AD was defined by established cerebrospinal fluid (CSF) criteria. Plasma leptin levels were measured by immunoassays. Hypothalamic volumes were measured in T1-weighted MRI scans by manual segmentation (MRIcron) and voxel-based morphometry (SPM8).

Results: Compared to controls, male preclinical AD subjects have lower BMI and lower plasma leptin levels, which were associated with CSF $A\beta_{1-42}$ levels. Interestingly, there were no differences in BMI and plasma leptin levels between female preclinical AD and controls. While total hypothalamic volumes trended lower in preclinical AD, there was significantly reduced gray matter densities in specific regions within the hypothalamus of preclinical AD subjects compared to controls.

Conclusions: Together with our mouse studies, these results suggest that hypothalamic leptin signaling dysfunction occurs early in AD. Although the findings need verification in additional cohorts and the mechanisms defined including any sex differences, these findings may provide key insights into the mechanisms underlying weight loss in AD.

POSTER ABSTRACTS

Feasibility of Online Synchronous Caregiver Dementia Coaching for Rejection-of-Care Behaviors

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Problem: Two-thirds of family caregivers of persons living with dementia have encountered rejection-of-care (ROC) behavior, usually during assistance with activities of daily living.

Purpose: To describe the feasibility of an online videoconferencing platform to help caregivers prevent and reduce ROC behavior

Design: Quasi-experimental.

Sample: Twenty-six family caregivers: 54% female, 77% white, 62% spouses (31% wives, 31% husbands), mean age 65 years, and college-educated (92%). Their care recipients were 61% female, 77% white, mean age of 76 years, and college-educated (88%).

Procedure: Family caregivers who endorsed problematic ROC behaviors in their care recipients participated in six online, individual, synchronous, sequential, and weekly 1-hour coaching sessions. We measured general burden (Zarit Burden Inventory) and the frequency, severity, and associated distress of responsive behaviors (Neuropsychiatric Inventory Questionnaire). Data collection intervals were before coaching (baseline), immediately after the final session (Time 1), and six weeks (Time 2) and 12 weeks (Time 3) after the final session, respectively.

Results: Caregivers reported less overall distress scores at Time 2 compared to baseline: 13.58 (SD 6.44) versus 17.42 (SD 6.90), t=2.56, p=0.017). Distress scores returned to baseline by Time 3. Caregivers reported less severe ROC behavior at Time 2 which was not statistically significant. Burden remained unchanged throughout the 24 weeks.

Conclusion: Virtual caregiver coaching that targets ROC behavior is feasible. Qualitative review of the encounters suggests that a longer period of intervention and an outcome measure more sensitive to ROC effects on activities of daily living may be needed in future studies.

Circadian regulation of mitophagy in the heart

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The circadian clock in the heart is essential for cardiomyocyte function and metabolism, evidence suggest that there is a decline of circadian regulation in aging heart. Essential to provide the energy for heart structure and function are the abundant mitochondria. Prior studies have indicated that mitochondrial function is perturbed in the heart of the mice carrying aberrant circadian clock regulators. Furthermore, some of the key proteins involved in mitochondrial dynamics and mitochondrial quality control (autophagy of the mitochondria or mitophagy) are also circadian dependent. These studies have led us to hypothesize that the circadian clock in the heart, which could be perturbed during aging, regulates mitochondrial dynamics and mitophagy. To test the hypothesis in vivo, we have performed electron microscopy to measure mitochondrial morphology, and confocal microscopy with the Mito-QC mice (which carry a mitochondrial targeted protein that are both red and green fluorescent with the green fluorescence sensitive to the acidic environment of the lysosome) to measure mitophagy at different times of the day. As a proof of concept, mice were fasted; 24 hours fasting appeared to increase mitophagy in the heart. Ongoing studies are currently utilizing this model to investigate whether mitophagy changes over a 24 hr period in the heart, whether genetic disruption of the cardiomyocyte clock influences mitophagy, and whether there is a dysregulation of clock regulation of mitophagy in aging heart.

POSTER ABSTRACTS

Predicting Balance status in Parkinson's Disease with Laboratory Measures of Stability

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Background: Balance impairment in individuals with Parkinson's disease (PD) can lead to falling and serious consequences. Comprehensive balance assessment quantifying Center of Mass (COM) control relative with base of support (BOS) can reflect how the nervous system controls balance function and has the potential to identify balance problem and direct interventions.

Purpose: To determine which combination of laboratory measures of stability could predict balance status.

Methods: Sixty PD participants (age=58-74 years) were recruited for a high intensity progressive resistance exercise training study. Here, we report a secondary analysis of participants' pre-intervention assessment. Individuals with PD were grouped based on an established cut-score of the Mini-BESTest for distinguishing fall risk: impaired balance (n=25), or no balance impairment (n=35). Individuals completed the following assessments: 1) three 30-second standing balance trials while standing on force plate: (i) with eyes opened, (ii) with eyes closed, and (iii) with eyes opened and feet together to quantify static balance control. The average and variability of the 95% ellipse area of center of pressure (m2) during the 30s trial was calculated. 2) To quantify dynamic balance control, participants were asked to walk on the treadmill at their own comfortable and maximum walking speeds (CWS and MWS) for 30 seconds while a motion capture system collected kinematics. Average value and variability of margin of stability (MOS) and COM's position were quantified. Data were compared using parametric and non-parametric statistics. Pearson's and Kendall tau correlations were used to assess relationships between the laboratory measures of stability and the mini-BEST score and balance status. Prediction of impaired balance status was evaluated using logistic regression.

Results: Compared to those with no balance impairment, PD participants with impaired balance had greater sway areas in all conditions ($p<0.05$) and greater values of the entire laboratory measures of dynamic stability during walking ($p<0.001$) except COM's position and MOS at both walking speeds in an anteroposterior direction. The mini-BEST score was negatively correlated with some laboratory measures of stability ($r=-0.63$ - -0.33, $p<0.05$). Finally, sway area with feet together condition and Normalized MOSAP Variability at MWS were predictors on the balance status.

Conclusion: Our quantitative data showed that individuals with balance impairment demonstrated worse COM control both statically and dynamically in sagittal and frontal planes. Two potential predictors for balance status were established that may help researchers and clinicians identify those with whom to prioritize intervention for individuals with PD living in the community.

Dissection of the inflammatory status of hearts in aging mice with invasive pneumococcal disease

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The elderly are at increased risk for dying from pneumonia. In addition, pneumonia survivors are at enhanced risk for disability and mortality well after the infection is cleared. One-in-four adults hospitalized for *Streptococcus pneumoniae*, the leading cause of community-acquired pneumonia, experiences an adverse cardiac event during hospitalization and survivors are also at increased risk for cardiac-related death for up to 10 years following hospitalization. One potential reason for this increased susceptibility to infection during advance age is inflamm-aging, the low but chronic increase in inflammation in tissues and blood during aging. Previously inflamm-aging was shown to enhance susceptibility to pneumonia by increasing the expression of bacterial ligands on lung epithelial cells and inhibiting toll-like receptor activation. Importantly, the mechanisms that impact age-related susceptibility to heart infection and damage remain unknown. To understand the age-related inflammatory changes in context of the heart, aged (18 months and older) and young (3-6 month) hearts from uninfected and infected C57Bl/6J mice were examined for differences in the activation status MAPK and NFκB via immuno-blot, cytokine levels via ELISA, and bacterial burden and cardiac damage by histology, respectively. We determined that aged mice have higher baseline levels of NFκB and MAPK activation and thickening of vascular walls within the heart suggestive of endothelial cell dysfunction. Importantly, aged mice failed to respond as efficiently to *S. pneumoniae* infection. This was demonstrated by aged mice having drastically increased bacterial burden (>100-fold) within the blood, and a dampened cytokine response within heart tissue compared to young mice. Ongoing studies are focused on revealing alterations in immune cell populations in the heart via flow cytometry. The results of these studies will help serve as the beginning of understanding how inflammation in hearts during aging impacts susceptibility to bacterial infections, such as invasive pneumococcal cardiac infections.

POSTER ABSTRACTS

Classical and lectin complement pathways and markers of inflammation for investigation of susceptibility to infections among healthy older adults

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Background: Innate immune responses and host-bacterial interactions are key factors in inflammaging, and complement protein C1q and inflammatory cytokines IL-6 and TNF-α have been identified as potential biomarkers for frailty and disease. In addition, older adults are disproportionately affected by acute infections caused by serotypes of Streptococcus pneumoniae that interact with ficolin-2 (L-ficolin), a lectin complement pathway component. To investigate these possibilities, we performed a detailed between-group comparison of the classical and lectin complement pathways and measured aging biomarkers among healthy younger versus older adults.

Methods: n=30 younger (ages 19-54) and n=27 older (age ≥70) adults without significant smoking history or chronic diseases affecting immune function were included. We compared mean levels of classical (CH50, C1q, C3, C4) and lectin (MBL, CL-L1, MASP-1/2/3, MAp44, MAp19, H/M/L-ficolins) complement pathway components, as well as inflammatory markers (IL-6, TNF-α, CRP) between groups using two-sample t-tests. Demographic variables were compared between groups using Pearson Chi-square. Linear regression was used to adjust for the effects of sex and race.

Results: C1q levels were higher among younger adults. Mean C1q levels were significantly higher in the younger group, both before (722.7 vs 651.4 units/ml, P = 0.002) and after (714.8 vs 662.8 units/ml, P = 0.028) adjustment for the effects of sex and race. C1q levels were significantly higher in nonwhite participants compared to white participants in the younger group (750.7 vs 679.0 units/ml, P = 0.022). IL-6 and TNF- α were significantly higher among the older adults in both unadjusted and adjusted analyses. There were no significant differences in other complement pathway components between groups.

Discussion: Unexpectedly, we observed higher C1q in the younger adults. In addition, we found a significant association between race and C1q levels. These findings have implications for use of C1q as a biomarker in the study of aging-related degenerative disease.

POSTER ABSTRACTS

Impact of Exercise Rehabilitation on Skeletal Muscle Transcriptional Programs in Parkinson's Disease

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Parkinson's disease (PD) is the most common motor neurodegenerative disease, and neuromuscular function deficits associated with PD contribute to disability. Targeting these symptoms, our laboratory has successfully used 16-wk high-intensity resistance exercise as rehabilitative training (RT) in individuals with PD. We observed significant improvements in muscle mass, strength, power, motor unit activation and total score on the 39-item PD Questionnaire (PDQ-39), providing encouraging evidence of potential symptom reversal through RT. In order to characterize the transcriptome-wide transducers of this intervention in PD, we generated RNA-seq data from skeletal muscle of a subset of these individuals [4M/1W, 67±2yr, Hoehn & Yahr stages 2 (n=3) and 3 (n=2)] before and after 16-wk high intensity RT. Following RT, 302 genes were significantly upregulated, notably related to remodeling and nervous system/ muscle development. Additionally, 404 genes, primarily negative regulators of muscle adaptation, were downregulated. Next, we used Pathway-Level Information ExtractoR (PLIER) to reveal coordinated gene programs (as latent variables, LV) that differed in skeletal muscle among young (YA), old (OA) healthy adult muscle (n=12 per cohort), and PD subjects pre- vs post-RT. Notably, the LV4 gene program was significantly lower at baseline in PD than YA, tended to be lower in OA, and was significantly increased by exercise. LV4 genes are associated with angiogenesis, axon guidance, and muscle remodeling. The LV16 program was higher in both PD and OA than YA and was reduced by 16-wk RT in PD; functional annotations suggest involvement in denervation, autophagy, and cell death. This approach enabled identification of two novel skeletal muscle transcriptional programs that are dysregulated by PD and aging, respectively. Encouragingly, RT has a normalizing effect on both programs in individuals with PD. Findings provide direction towards elucidating the molecular mechanisms responsible for RT-induced improvements in symptom severity and optimizing exercise regimens for individuals with PD. Supported by NICHD T32-HD-071866.

Accumulation of Dementia Risk Factors Alters Brain Regions of Episodic Memory: An fMRI Analysis

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Background: Research suggests that genetic, lifestyle, and environmental factors enhance one's risk for developing Alzheimer's disease and related dementias (ADRD). However, it is not known how an accumulation of multiple risk factors alters brain function. One barrier to this research is that increased risk for ADRD affects the cerebrovascular system, thus decoupling neural activity from the fMRI blood oxygen level dependent (BOLD) signal, which many previous studies did not calibrate for. We hypothesized that as the number of ADRD risk factors increase, brain regions within the medial temporal lobes and the default mode network (DMN) would exhibit altered brain activity during an episodic memory retrieval task. To reduce the influence of non-neural influences on the BOLD signal, several steps were taken to calibrate fMRI BOLD activity.

Methods: Participants from 50 to 70 years old, were recruited with varying levels of risk for dementia. A neuropsychological battery was performed to screen out possible dementia. Using fMRI, brain activity was assessed while participants completed a memory task by viewing a pair of pictures, followed by an alternative-forced-choice test, where participants viewed a picture cue and had to determine which of four pictures was paired with the cue.

Result: After correcting the fMRI BOLD signal, whole-brain analyses revealed that increased dementia risk was negatively associated with brain activity in the hippocampus—a task positive region—and was positively associated with the lateral parietal cortex—a task negative region.

Conclusion: We found evidence that adults with an accumulation of risk factors for dementia exhibit decreased modulation of brain activity in critical regions underlying episodic memory. These findings call into question previous studies that did not calibrate the BOLD signal and found compensatory hyperactivity in these regions. Instead, cumulative risk likely represents early dysfunction of the default mode and brain regions underlying episodic memory.

POSTER ABSTRACTS

PAI-1 regulation of alveolar type II cell senescence, SASP secretion, and SASP-mediated activation of alveolar macrophages in fibrotic lung

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Senescence of alveolar type II (ATII) cells, progenitors of the alveolar epithelium, is implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF), an aging-related progressive fatal lung disorder. The mechanism underlying ATII cell senescence and the mechanism whereby senescent ATII cells contribute to lung fibrosis, however, remain poorly understood. Our previous studies showed that increased expression of plasminogen activator inhibitor 1 (PAI-1), a serine protease inhibitor that plays a critical role in hemostasis and in the development of lung fibrosis, mediates bleomycin-induced ATII cell senescence *in vivo* and *in vitro* through activation of p53-p21-pRb cell cycle repression pathway and the development of lung fibrosis in mice. Our new data further show that PAI-1 mediates TGF-b1-induced ATII cell senescence though inducing p16, not p53, cell cycle repressor. PAI-1 also modulates TGF-b1-induced senescence associated secretary phenotype (SASP) in ATII cells as well as ATII cell SASP-mediated activation of alveolar macrophages. Together, our results suggest that increases in PAI-1 expression contributes importantly to ATII cell senescence in fibrotic lung induced by different stimuli through activating different cell cycle repression pathways. Our data also suggest that ATII cell SASP may promote lung fibrosis by activating alveolar macrophages.

Dose-response trial to counteract skeletal muscle atrophy in older adults via resistance exercise training

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Purpose: We investigated the effects of manipulating resistance exercise training (RT) volume on skeletal muscle hypertrophy responsiveness in older adults with aging-related muscle atrophy. Eighty-three elderly individuals (>65 years; women = 44) completed 10-wk of RT.

Methods: In an intra-subject experimental design, we randomly allocated each leg to one (1X) or four (4X) sets of 8-15 maximum knee extension repetitions 2x/wk. Quadriceps cross sectional area (qCSA) was assessed by magnetic resonance imaging before and after the intervention. Individuals were then classified as low- or high-responders based on individual change in qCSA in the 1X leg considering the typical error of measure (minimal difference [MD] = 3.27%;
<MD: low-responder, >MD: high-responder).

Results: Sixty percent of the individuals were classified as low-responders; among those, 80% increased qCSA in response to 4X. Of the 40% classified as high-responders on 1X, the 4X prescription on the contralateral leg further augmented the hypertrophic response in 50% of these individuals, while 30% realized no additional benefit of 4X and 20% actually had a blunted response to 4X vs. 1X.

Conclusions: our results demonstrate that increases in RT volume can be an effective strategy to decrease the number of low-responders and even augment the hypertrophic response in some; however, higher RT volume may be detrimental for a small proportion of older adults.

Future directions: Our ongoing research is focused on potential molecular and cellular mechanisms driving low-responsiveness. Future trials should also test the effects of manipulating other prescription variables (e.g., exercise load, frequency, duration), along with considering other behavioral and environmental factors (dietary control, etc).

POSTER ABSTRACTS

Physical therapy referrals among adult patients hospitalized in acute care

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Purpose: To assess physical therapy (PT) referral patterns during hospitalization in acute care as they relate to changes in patient activities of daily living (ADL) from baseline before hospitalization to current status.

Methods: Data were collected prospectively from electronic health records of consecutively hospitalized patients aged ≥ 50 years admitted to three medical wards at UAB Hospital between August 20, 2018 and October 22, 2018. The primary outcomes were physician order for acute care PT and ADL scores at baseline (2 weeks prior to admission) and current (at time of PT referral or at discharge if no referral). Association between ADL decline and PT referral was assessed using logistic regression, adjusted for sex; race/ethnicity; and age.

Results: The study cohort consisted of 323 patients with a mean age of 67.7 (SD, 11.5) years. Among the 323 patients, 152 (47%) were female, 134 (42%) were black, 148 (46%) declined in ADL from baseline to current and 230 (71%) received referral to acute care PT. Approximately 15% of patients with ADL decline did not receive a PT referral, but experiencing ADL decline was associated with a significantly greater occurrence of PT referral compared to not experiencing ADL decline (adjusted odds ratio, 4.41; 95% CI, 2.47–7.87). Of the 175 patients without ADL decline from baseline to current, 102 (58%) were referred to acute care PT. Forty-two (41%) of these patients maintained complete ADL independence from baseline to current.

Conclusions: Acute care in-patients in need of the specialized care of a physical therapist are receiving referral to this service, however other patients who may not benefit from therapy are also being referred suggesting a need for improved standardization of the referral process for better healthcare utilization.

Autofluorescence in Tissues of Aging Adult Drosophila melanogaster

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Age-related accumulation of the autofluorescent age pigment, lipofuscin, is well documented, but its distribution in live cells within intact organs and its abundance in relation to other fluorophores in the organism are less well documented. The goal of this study is to provide that information for adult *Drosophila melanogaster*, using confocal laser scanning microscopy. Images have been obtained from freshly dissected tissues isolated from both sexes of Oregon R wild type, w^{1118} and y w mutant flies after excitation at seven wavelengths (range: 405 – 643 nm). Distinctive, nonlipofuscin-like emission has been observed for the cuticle, trachea and developing embryos. Lipofuscin-like fluorescence is most prominent in the Malpighian tubules and some regions of the gut, where its abundance increases on average with adult age. The brain and salivary gland contain lesser amounts of material with a lipofuscin-like morphology and emission spectrum, but the difference between age groups is frequently statistically significant even in small samples (n = 3-6). Quantification of fluorescent material has been hampered because emissions from most tissues are close to the detection limit of the instrument. The results generally do not differ markedly by sex or genotype.

Preliminary conclusions are that lipofuscin can be observed by this method in many organs of *D. melanogaster,* a significant, quantifiable buildup is demonstrable in some cases in aging adults, but there is also appreciable inter-individual variation among the flies. Establishing the magnitude, location and consistency among animals of lipofuscin accumulation should aid in predicting whether further interventions to prevent or reverse oxidative damage will be effective in slowing the aging process and increasing healthy longevity.

POSTER ABSTRACTS

Variations in Referrals, Assessments and Treatment of Alzheimer's Disease of African Americans in the Deep South

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Introduction: Beyond general prevalence, racial disparities in Alzheimer's disease (AD) remain a significant concern. In particular, although African Americans are known to be at higher risk of AD and its associated comorbidities, it is unknown what barriers exist with respect to treatment and assessment such as neuroimaging for pathologic hallmarks of AD. With the advent of data warehousing and clinical informatics, numerous tools exist to evaluate patterns of patient engagement with respect to demographics. This study used the clinical repository Informatics for Integrating Biology and the
Bedside (i2b2) for the University of Alabama at Birmingham (UAB) Health System to investigate patterns of African American engagement and representation in clinical visits for AD.

Methods: The local implementation of i2b2 for UAB was used to characterize medical encounters from October, 2015 to October, 2018 to investigate AD-related encounters for African American and non- African Americans patients. Comparisons included neuroimaging rates such as PET for AD pathology and volumetric MRI, encounters by commonly treating departments and prescription rates for cognitive enhancing medications. These rates were then compared against expected rates of engagement for African American across the entire UAB Health System and compared using contingency table techniques.

Results: The proportion of African Americans seen for AD across the UAB Health System (21.8%) did not differ from the proportion of African Americans over the age of 65 living in the Birmingham metro area (19.6%). However, there was an underrepresentation of African Americans receiving amyloid or FDG PET for AD evaluation (7.0-8.0%), which was not observed for other imaging modalities including brain MRI or PET for Epilepsy. When referral patterns were examined, African Americans were underrepresented in the Memory Disorders clinic population (11.1%) but overrepresented within the General Medicine (36.6%) and Geriatrics departments (33.5%).

Conclusions: Although African Americans with AD are not underrepresented at this academic medical center, they appear to be less frequently referred for advanced neuroimaging including amyloid or FDG PET. This is likely the result of underrepresentation in referrals to the Memory Disorders specialty clinic, where most of these advanced neuroimaging examinations are ordered.

A Regulatory Intersection of Dopamine and miRNA Transport in C. elegans Parkinson's Disease Models

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A recent whole exome sequencing study involving familial Parkinson's disease (PD) revealed in sequence variation among patients in the human TNK2 gene, which encodes a non-receptor tyrosine kinase. I functions to prevent the endocytosis of the dopamine (DA) reuptake transporter (DAT) in mammals. Based on the location of the 4 SNPs discovered in the *TNK2* gene, we postulate that the altered TNK2 protein eludes being targeted for degradation by its cognate E3 ubiquitin ligase, NEDD4, and its prolonged activity is deleterious for DA neurons. *Caenorhabditis elegans* possess an ortholog of TNK2, termed SID-3, which modulates the internalization of dsRNA into the cytoplasm, possibly via the conserved dsRNA transporter SID-1. Taken together, we hypothesize that TNK2/SID-3 co-regulates the import of DA and dsRNA. To test this, we modulated the activity of SID-3 in *C. elegans* genetically, with a knockout mutation, and pharmacologically, using both Aim-100 (a TNK2 inhibitor) and NAB2 (a NEDD4 activator) in assays involving 6-hydroxydopamine (6-OHDA) exposures, a-synuclein (a-syn) overexpression in the DA neurons, and RNAi studies targeting GFP. Our results indicate that the DA neurons of *sid-3(ok973)* mutants are protected from 6-OHDA and a-syn toxicity. Treatments with Aim-100 and NAB2 protected the DA neurons of *C. elegans* from both insults. Furthermore, NAB2-induced protection was abolished in mutants of the NEDD4 homolog *wwp-1(gk372).* Interestingly, Aim-100, but not NAB2, prevented RNAi of GFP in body wall muscles, thereby indicating a putative tissue-associated distinction in the regulation of SID-3. Our studies indicate that SID-3 functionally behaves as its mammalian homolog to regulate internalization of DAT, and that the loss of SID-3 activity is both neuroprotective and impedes RNAi. The regulatory intersection of neurotransmission and epigenetic modulation exemplified by these studies may represent a cellular nexus of gene-by-environmental interaction underlying neurodegeneration, with TNK2 at its center as a potentially druggable therapeutic target.

POSTER ABSTRACTS

The Impact of Change in BMI on the Obesity Paradox in COPD

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Background: Chronic Obstructive Pulmonary Disease (COPD) is a disease of accelerated aging of the lung. Although the primary risk factor is smoking, being overweight or obese is also associated with increased risk. But COPD patients who are overweight or obese have a lower risk of death, termed the obesity paradox. Change in BMI (DBMI) may be more reflective of disease pathology. We evaluated whether significant gain and loss of BMI are associated with survival to disentangle the obesity paradox.

Methods: Longitudinal data from two visits approximately 5-years apart in 4,047 current and former smokers (greater than 10 pack-years) was analyzed. A standard deviation of +/- 10% in DBMI was observed in 2,204 subjects with normal lung function (GOLD 0) who reported no unintentional weight-loss. DBMI was then coded as a categorical variable (loss, gain with no change as the reference) in 1,843 participants with COPD. Kaplan-Meier and Cox-proportional hazard models were used to evaluate the relationship between DBMI and mortality. Cox-proportional hazard models were adjusted for age, sex, smoking duration and BMI category.

Results: Participants with COPD who lost greater than 10% BMI had a higher risk of death (HR: 2.0, 95% CI 1.5-2.7, P<.0001). Participants with COPD who gained more than 10% of their BMI experienced no difference in survival.

Conclusions: Our findings indicate COPD patients who lose more than 10% of their BMI over 5-years are at significant increased risk of death independent of BMI. Patients who gained more than 10% BMI did not differ in their survival experience compared with those with no significant change. The obesity paradox in COPD may be explained to some degree by considering longitudinal BMI.

POSTER ABSTRACTS

Runx2 deficiency in hypertrophic chondrocytes impair resorption of cartilage and bone

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Runx2 transcription factor play an obligatory for chondrocytes and osteoblast differentiation. Increase in cartilage degradation and bone resorption lead to arthritis and osteoporosis. Runx2 expression is progressively increased from immature to hypertrophic chondrocytes (HC). However, the role of Runx2 in HC is unknown. We used Col10-Cre transgenic mice for HC-specific ablation of the Runx2 gene. HC-specific Runx2 null ($Runx2^{HC/HC}$) mice were born alive and survive to adulthood with well-developed skeleton but extremities are poorly mineralized. The overall length of long bones was shorter in mutant littermates. Histological analysis of 3-day old limbs showed the length of HC zone was double in $Runx2^{HC/HC}$ mice. Alcian-blue staining revealed the accumulation of cartilage matrix up to the mid-diaphysis of long bone. Consistent with poor cartilage resorption, a significant decrease in the expression of matrix-degrading enzymes was noted in mutant mice. Surprisingly, Von kossa staining revealed increased mineralization beneath the growth-plate in $Runx2^{HC/HC}$ mice. Micro-CT analysis confirmed a 3-fold increase in the trabecular bone while trabecular-thickness remained unchanged. Consistently, a 55% increase in trabecular-number and 25% decrease in trabecular-space were observed in mutant littermates. Cortical bones, however, were comparable among the littermates. To better understand increased trabecular bone, we evaluated osteoclasts activity. TRAP staining revealed a 30% decrease in the number of osteoclasts in $Runx2^{HC/HC}$ bones which supported by the decrease Rankl/Opg ratio. Analysis of 2.5-month old littermates revealed a locally osteopetrotic phenotype and sustained accumulation of cartilage in the mutant bones. Histomorphometric analysis of 2.5-months old femur showed osteoclasts number, erosion surface and osteoclast surface was decreased by 44%, 38%, and 15% respectively in mutant mice. Interestingly, osteoblast number and surface were also decreased by 10% and 14% respectively in $Runx2^{HC/HC}$ bone. Runx2 plays an essential role in cartilage resorption and homeostasis of trabecular bone that is independent of hypertrophic maturation of chondrocytes.

Drosophila melanogaster as a model for exercise research

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Exercise is an important part of a healthy lifestyle, and adequate physical activity is considered essential to maintain health – both mental and physical – during the aging process. While the importance of physical activity for healthy aging is clear, it is much less clear what type of exercise treatments to prescribe for individual patients to obtain optimal outcomes. To answer this question and to take into account environmental and genetic variables impacting exercise outcomes, additional in-depth studies are needed. Model organisms are positioned ideally to address these questions, as many environmental factors can be controlled and genetically well-defined populations are available. We use the fruit fly *Drosophila melanogaster* as a model for the study of exercise and the factors contributing to variation in exercise response. To date, we have used the Drosophila Genetics Reference Panel 2 (DGRP2) population to identify genetic variants associated with basal animal activity levels, exercise-induced activity levels, as well as two exercise response variables, mass and physical fitness as measured by climbing ability. We find that these variables are impacted by hundreds of genetic loci, many of which act in a sex-specific fashion. Here, we present the results from our on-going analyses on the type of genes contributing to the response to exercise.

POSTER ABSTRACTS

Lipopolysaccharide Binding Protein is Associated with CVD Risk in Older Adults

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Background: Intestinal (i.e. "gut") permeability may be related to cardiovascular disease (CVD) risk, but biomarkers for gut permeability are limited and associations with CVD risk are unknown – particularly among older adults.

Purpose: This cross-sectional study aimed to determine if serum biomarkers related to gut permeability [intestinal fatty acid-binding protein (iFABP)] and bacterial toxin clearing [cluster of differentiation 14 (CD14), lipopolysaccharide binding protein (LBP)] are associated with CVD risk among older adults.

Methods: Older adults (n = 38, 72.0 ± 7.1 years old) were stratified by CVD risk category (Adult Treatment Panel: moderate, high-moderate, high). One-way ANOVAs determined differences in each biomarker by risk category, and associations with risk score were evaluated with Pearson correlations.

Results: LBP ($p < 0.001$), but not iFABP and CD14 (p's > 0.05), was significantly different between CVD risk categories. Post-hoc tests indicated LBP was higher in the moderate risk compared to both higher risk categories ($p < 0.005$). Evaluation of LBP and individual components in the risk score demonstrated a moderate, positive correlation of LBP with total cholesterol ($r = 0.326$, $p = 0.046$).

Conclusion: Higher circulating concentrations of LBP were associated with lower CVD risk among older adults. Further, total cholesterol was positively associated with circulating levels of LBP – notable as cholesterol assists LBP in clearing bacterial toxins from circulation by transporting toxins for removal. These data suggest LBP may be a key component in reducing CVD risk in older adults.

Roles for the Heterochromatin Protein 1 family at active transcription start sites

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Genome instability is a hallmark of aging which can be induced by mutations in chromatin proteins or epigenetic changes to cellular transcriptional programs. One way genome stability can be maintained is through the formation and maintenance of heterochromatin. In metazoans, members of the Heterochromatin Protein 1 (HP1) family are critical for heterochromatin formation. Most eukaryotic genomes have several HP1 family members. In *Drosophila melanogaster*, there are three somatically expressed HP1 proteins: HP1a, HP1B and HP1C. In addition to their roles in chromatin structures, these proteins also function in transcriptional regulation, but the degree to which transcriptional regulation by HP1 proteins contributes to genome stability is not known. Here, we characterize the endogenous binding targets of all three somatically expressed HP1 proteins. We find that HP1 protein binding targets are expressed at high levels and display signatures of promoter proximal pausing. We observe a release from pausing upon depletion of HP1a. Additionally, we find that HP1 proteins share a majority of their binding sites, suggesting their activity may be coordinated in the regulation of these genes. Finally, we report a strong association between HP1-bound genes and the formation of R-loops, DNA/RNA hybrid structures that are associated with genome instability. Together, these data help to clarify the function of HP1 proteins in transcriptional regulation and suggest these functions may contribute to genome stability.

POSTER ABSTRACTS

Age-dependent Role of Toll-6 in Survival to Viral Infection in Drosophila melanogaster

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The immune system, which defends the body against harmful pathogens, undergoes age-related alterations resulting immunosenescence. Following virus infection, older individuals tend to exhibit higher mortality rates in comparison with younger individuals. However, whether immunosenescence is solely responsible for that is unknown. *Drosophila melanogaster* is a powerful model organism for the study of innate immunity and can be used to study the impact of aging on antiviral immune reactions. Similar to humans, older flies are more sensitive to infection than younger flies. In order to identify genes encoding such factors, we looked for variations in the genome that associate with the altered ability to survive infection at old age. We identified a polymorphism in the gene encoding the receptor Toll-6, an ortholog of human Toll-Like Receptors (TLRs), which plays a role in innate immunity. In flies, the Toll-6 receptor is involved in early neural development; however, it has not previously been implicated to function in either aging, nor antiviral immunity. Following injection of the RNA-containing Flock House Virus (FHV), older *Toll-6* null mutants display higher mortality rates in comparison to older wild-type flies. No difference in mortality following FHV infection was seen in younger individuals, suggesting an age-dependent role for this receptor in survival to virus infection. We are currently conducting experiments to identify the mechanisms by which *toll-6* expression promotes the survival of the aged fly, and to determine whether this depends on neurotrophin signaling.
Understanding how aging alters organismal ability to fight infection and identifying new factors that mediate resistance to viral infection may lead to novel therapies to improve the health of the elderly.

Effect of Endurance Exercise on Nrf2 Signaling in Aging Myocardium

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Introduction: Nuclear factor erythroid 2 related factor 2 (Nrf2) signaling maintains the redox homeostasis and its activation is shown to suppress cardiac maladaptation. Earlier we reported that acute endurance exercise (2 days) evoked Nrf2-dependent antioxidant cytoprotection in young WT animals but not in aged WT animals. Here, we determined the effect of chronic endurance exercise (EE)-mediated cardiac adaptation in aged mice with and without Nrf2.

Methods: Age-matched WT and Nrf2-null mice ($Nrf2^{-/-}$) (>22 months) were subjected to 6 weeks of EE (25 meter/min, 12% grade). The myocardial redox status, levels of antioxidant genes and proteins along with immunochemical detection of protein- DMPO or GSH-NEM adducts, and total ubiquitination were assessed. ECG and Echocardiography were performed to assess cardiac function.

Results: At a sedentary state, loss of Nrf2 resulted in significant downregulation of antioxidant genes ($p<0.05$) (*Nqo1, Ho1, Gclm, Cat, and Gst-α)* with decreased GSH-NEM immuno- fluorescence signals. $Nrf2^{-/-}$ mice subjected to CEE showed an either similar or more pronounced reduction in the transcript levels of *Gclc, Nqo1, Gsr, and Gst-α* in relation to WT littermates. Interestingly, the $Nrf2^{-/-}$ hearts had a substantial reduction in G6PD and CAT proteins while their gene levels were unchanged. Of note, there was a significant decline in GSH along with a pronounced increase in protein-DMPO adducts and ubiquitination in $Nrf2^{-/-}$ hearts after EE. Subsequently, there was a significant upregulation of hypertrophy genes (Anf, Bnf, and β-Mhc) ($p < 0.05$) in the $Nrf2^{-/-}$ hearts in relation to WT mice after EE. Moreover, the aged $Nrf2^{-/-}$ mice exhibited a higher degree of cardiac remodeling in association with a significant decrease in fractional shortening, pronounced ST segment upon EE compared to age-matched WT littermates.

Conclusions: While both the WT and Nrf2 knockout mice exhibit hypertrophy after EE, the older $Nrf2^{-/-}$ hearts showed ventricular remodeling coupled with profound diastolic dysfunction.

POSTER ABSTRACTS

Functional connectivity in the Healthy Oldest Old: Findings from the McKnight Brain Aging Registry

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Measuring relationships among brain regions using functional connectivity metrics has been a successful biomarker of disease and has been shown to relate to cognitive function. The majority of work has been performed in younger adult populations and older populations with mean age under 85. Little work has described functional connections in the oldest-old.

There are two main benefits of characterizing functional connectivity in healthy oldest-old populations: it allows us to characterize what a healthy oldest old brain should look like by identifying typical distributions of functional connectivity metrics and because these participants have relatively large variability on cognitive metrics, we can examine how variability in cognition relates to functional connections.

Data were acquired as part of the McKnight Brain Aging Registry, across the four McKnight Brain Research Foundation sites. For this analysis, 62 community-dwelling, cognitively unimpaired older adults, ages 85-99 were included who had undergone structural and BOLD resting state MRI scans. Cortical surfaces were rendered for each participant and BOLD scans were preprocessed using Ciftify algorithms. Functional connectivity was measured within three well-characterized networks: Default Mode Network, Cingulo-Opercular Network, and Fronto-Parietal Network. Brain network functioning is an important avenue for aging and cognitive research since network infrastructure, including network integration and segregation, is likely to have a large impact on cognition.

We found that this cohort of healthy oldest old participants showed strong, reproducible connectivity networks for the three networks we tested. Further, level of connectivity within the frontoparietal network was positively associated with score on the MOCA, consistent with a contribution of cortical network integrity to performance on this task of generalized cognition.
This work shows feasibility for examining connectivity in the healthy oldest old and helps set the stage for understanding how individual variability in connectivity relate to cognitive performance in this oldest-old cohort.

The Metabolic and Cognitive Characteristics of a Novel Rat Model for Alzheimer's Disease

Hemant Srivastava and Liou Y. Sun

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Alzheimer's disease (AD), among elderly, is the leading neurological disorder and the third highest cause of death in the U.S. Interestingly, there has been a recent surge in literature suggesting neurodegeneration in AD is linked to metabolic differences and insulin dysregulation. Furthermore, studies suggest Type-2 diabetes (T2D) affected adults have an increased risk of developing AD; AD is also linked to Type-3 diabetes, which involves insulin dysregulation in the brain. In this study, we analyzed peripheral insulin dysregulation, glucose sensitivity, body composition, and brain metabolism with a recently established animal model for AD: the TgF344-AD rat. Body composition differences amongst both sexes and genotypes of rats were revealed alongside slight differences in young rats' insulin and glucose sensitivity. Additionally, abnormalities were observed in the brain's insulin regulation through analysis of total brain homogenates Western Blots for insulin receptor substrate (IRS-1), protein kinase B (Akt), Glycogen Synthase Kinase 3 alpha/beta (GSK-3???), and phosphoinositide-dependent protein kinase 1 (PDK-1) for young male rats. Observed differences in molecular metabolic protein levels are notably seen earlier than the onset of dementia-like symptoms which were established through Morris Water Maze results. Additionally, sex and genotype differences are seen during anxiety evaluating tests such as the Open Field Test and Elevated plus Maze. In conclusion, it is likely that insulin/glucose dysregulation pathways originating in the CNS occurring prior to AD onset, are possibly linked to AD pathology, impacting males and females differently.

POSTER ABSTRACTS

Anti-aging properties of melatonin and its metabolites

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Using cultured human epidermal keratinocytes (HEKn), we have investigated the influence of melatonin and 6-hydroxymelatonin on an expression of genes involved in the process of aging. Primary cultures of HEKn were incubated for 24 hours in the presence of melatonin or 6-hydroxymelatonin at 10^{-5} M concentration or solvent (control), RNA was isolated and submitted for RNA sequencing at Novogene company. The Gene Set Enrichment Analysis (GSEA) of RNA-Seq data has indicated that the tested compounds have anti-aging properties. We also noticed an overrepresentation of the Telomere elongation and Circadian clock gene sets (Reactome FI Viz). Differential expression analysis with DESeq2 software indicated upregulation of *DNA2 gene* (fold change= 2.4), which have a connection with telomere extension, and upregulation of KLK1 gene (fold change= 3.3), that codes kallikrein 1, the protein involved in ACEI pathway. It has been reported that Angiotensin-Converting-Enzyme Inhibitors (ACEIs) administered to hypertensive rats double the lifespan of these animals. In humans, ACEIs prevent against both hallmarks of aging: organ fibrosis and cardiac hypertrophy. The differential expression analysis has also identified melatonin downregulation of SIRT4 gene (fold change= -6.4) and 6-hydroxymelatonin (fold change= -4.1). SIRT4 belongs to the sirtuins gene family that codes proteins associated with aging process. GSEA analysis has also shown overexpression of FGFR1 signaling after melatonin treatment (enriched score: 0.90). In addition, 6-hydroxymelatonin upregulated myokine genes: IL6 (fold change= 2.1) and IL15 (fold change= 7.3).

We suggest that both melatonin and 6-hydroxymelatonin may have anti-aging properties but these compounds differ in their particular mechanism of action.

Vitamin D3 hydroxyderivatives may have anti-aging activities

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Retrospective analysis of recently reported by us microarray data on vitamin D3 (D3) induced changes in cultured human keratinocytes (In J Mol Sci 2018, 19 (10), 3072) indicated that D3 hydroxyderivatives stimulate expression of genes involved in anti-aging activities. Briefly, primary neonatal human epidermal keratinocytes were treated with 10^{-7} M of either $1,25(OH)_2D_3$ (classical active form of D3) or $20,23(OH)_2D_3$ (non-calcemic form of D3) or vehicle, RNA was isolated and submitted for gene expression analysis by Illumina's HumanWG-6 chip/arrays. Analysis of the data showed that 24-hour incubation of keratinocytes with $20,23(OH)_2D_3$ elevated *FOXO3* gene expression (2.3 fold). FOXO3 protein is associated with NAD metabolism, sirtuins and aging pathway (Wiki pathways analysis). The $20,23(OH)_2D_3$ also stimulated SIRT1 expression (1.9 fold). Note that activation of SIRT1 leads to mTOR inhibition, and this mechanism is connected with anti-aging properties.

Furthermore, we noted upregulation of the kallikrein gene family by $1,25(OH)_2D_3$ after 24- hour treatment, including stimulation of *KLK6* (25 fold), *KLK13* (3.1 fold), *KLK3* (2.1 fold), *KLK9* (2.0 fold), *KLK5* (2.0 fold), *KLK7* (1.8 fold) and *KLK10* (1.8 fold). Also after 6-hour incubation with $1,25(OH)_2D_3$ the upregulation of *KLK6* (3.3 fold), *KLK13 (*1.9 fold) and *KLK3 (*1.9 fold) was seen. Kallikreins are proteins involved in Angiotensin-Converting-Enzyme Inhibitor (ACEI) pathway. Interestingly, ACEIs administered to hypertensive rats double lifespan of these animals. In humas, ACEIs prevent against hallmarks of aging such as organ fibrosis and cardiac hypertrophy.

Therefore, we suggest that $1,25(OH)_2D_3$ and $20,23(OH)_2D_3$ may have anti-aging properties through action on different pathways.

POSTER ABSTRACTS

Angiotensin (1-7) Expressing Lactobacillus Dose-Dependently Benefits the Gut-Brain Axis in Aged Rats

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Aging is associated with gut dysbiosis – a condition linked with altered central nervous system function (i.e the "gut-brain axis"). Age-related health benefits have been ascribed to the renin-angiotensin system (RAS), mediated partially via the angiotensin (1-7) or Ang(1-7) axis. This pre-clinical study explored dosing of a genetically modified probiotic expressing Ang(1-7) – which we previously showed to induce dose-dependent increases in circulating Ang(1-7) – in modulating the gut-brain axis. Twenty-nine male F344BN rats were randomized at 24 months of age to receive oral gavage of Ang(1-7) Lactobacillus paracasei (LP) zero (control), one, three, or seven times/week over 28 days. At day 29, samples of feces, serum and pre-frontal cortex (PFC) were collected. Microbiome taxonomic analysis of fecal samples was performed via 16S-based PCR. Serum samples were analyzed for tryptophan and downstream metabolites via LC-MS. PFC was evaluated for mRNA expression of select inflammatory cytokines. PCoA revealed that groups differed in the overall fecal microbiota community structure as determined by Unweighted UniFrac. Indices of alpha-diversity, including richness and phylogenetic diversity, displayed significant group differences – with the most dramatic effects observed in the 3-times/week group. Compared to control, serum serotonin and 2-Picolinic Acid were significantly increased in the 3-times/week group. The 3-times/week regimen also significantly reduced COX2, IL1β, and TNFα mRNA expression, and 7-times/week reduced COX2 and IL1β expression in PFC. Therefore, we conclude that short-term treatment with Ang(1-7) LP dose-dependently benefits the gut-brain axis in aged rats, with 3-times/week appearing to be the optimal dosing regimen.

The Effect of Short-Term Feed Restriction on Spatial Memory: Development of a Novel Galliform Model

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The *status quo* as it pertains to aging and memory research is the use of rodents as animal models. However, there is evidence that these species are, in general, not as well adapted for aging research, including Alzheimer's disease. Therefore, there is a critical need to advance our knowledge by carefully choosing additional species that can better represent the physiologically and evolutionarily relevant space. In this study, we evaluated the effect of short-term feed restriction on spatial short-term memory in chickens. Six one-day-old broiler chickens were reared using normal management practices. Starting at 2 weeks of age (WOA), birds were placed in a custom-made 8-arm radial maze (RAM) for training purposes. The RAM had an apothem of 24.1 cm. Each arm was 60.5 x 19.5 cm (L x H). At 3 WOA birds were feed restricted (40% of the feed consumed by full fed birds) for one week. Spatial short-term memory was assessed using the 8-baited arms for 600 seconds via an automated video tracking system (EthoVision®). Variables were analyzed using non-parametric procedures in SAS and included: **F8** (The correct choices in the RAM out of the first 8 choices made); **OALL** (The overall number of RAM arm choices made); **TxO** (The ratio of total time required to complete a session to the total number of entries), **Velocity** (The speed at which the bird traveled in the RAM), **Time** (The time required to complete the trial) and **NPC** (The total number of pellets consumed). Feed restricted birds increased OALL (P = 0.038), Velocity (P = 0.048) and tended to increase NPC (P = 0.12) as compared to full fed birds. Our results indicate that the development of a galliform model to study memory and aging is feasible. Additionally, we concluded that short-term feed restriction improved spatial memory in chickens.

POSTER ABSTRACTS

Cultural Values, Preferences, and Goals of End-of-Life Care of Family Members of Patients with Life-Limiting Illness in Kumasi, Ghana: A Community-Based Study

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Original Research Background: Understanding patient and family cultural values, preferences and goals of care in patients with life-threatening illness is the first step in ensuring the provision of goal-concordant care. Palliative care (PC) programs are at their infancy in Ghana, with three PC physicians and four nurses at Komfo Anoyke Teaching Hospital (KATH) in Kumasi, a city of 1.5m people. Ghana has a collectivist culture in which families and communities, not the individual, is central. Little is known about End of Life (EoL) care values, care preferences and goals of care.

Research Objective: To gain an understanding of cultural values, preferences and goals of care of family caregivers of patients who had received EoL care at KATH.

Method: Community Based Participatory Research served as the study's guiding principles. An 8 member Community Advisory Group advised on focus group implementation including meeting site, topics of discussion, ethical considerations, and recruitment methods. The focus group included nine family members and focused on care received by their loved one during their recent serious illness. This session was recorded, transcribed and analyzed using a systematic thematic analysis.

Results: Emergent themes included problems related to healthcare system: unreliable access to doctors, high cost of care (self-pay is the main method), challenges of getting diagnosed, pain and symptom burden, and poor doctor-patient-caregiver communication. Three cultural values emerged: caregivers' pivotal role in caring for loved ones; discussion of prognosis requiring involvement of others, and key role of God/faith in illness and dying processes.

Conclusion: This pilot study provided PC physicians insight into values, preferences and goals of care, and provided community caregivers the opportunity to participate at the start of designing a culturally-based EOL care program.

Implications for research, policy or practice: Understanding community values and preferences is the first step towards building programs that ensure culturally-based goal-concordant care. Overcoming the systemic barriers will require longer-term efforts.

POSTER ABSTRACTS

African American Communities Speak to Palliative Care Clinicians: Evaluation of an Innovative Community-Developed Communication Skills Training Program

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Original Research Background: Lack of understanding of cultural differences may significantly compromise care at end-of-life (EOL) for minority patients. Cultural competence among clinicians increases the likelihood of providing quality care, leads to higher patient satisfaction, and reduces health disparities.

Research Objectives: (1) Evaluate the feasibility of delivering a community-developed and theory-based training program focusing on the cultural aspects of EOL care in rural, Southern African Americans (SAA) to Palliative Care (PC) clinicians; (2) Assess the effect of this program on PC clinicians' knowledge of SAA cultural values towards EOL care and confidence in ability to change practice.

Methods: The 3-hour training consists of: Overview of relevance of culture to EOL; debriefing of three videos developed by SAA pastors and healthcare professionals featuring key messages for communicating with and providing culturally appropriate care to SAAs with serious illness; a skills-based and reflective communication training program; and a discussion with an AA chaplain on the importance of faith and religious community among SAAs.

Results: Feasibility: Twenty-three of 30 UAB PC clinicians participated in the training. Adherence to training protocol was high.

Knowledge: Clinicians' self-reported knowledge of SAAs attitude towards EOL care significantly increased on 9/18 measures (e.g., attitudes of being told prognosis; decision-making style; and family and community resources). Confidence: Clinicians scored 9 out of 12 items measuring confidence to chance practice [1 (least) to 5 (most)] as 4.0+ (e.g., asking how they wished to hear about prognosis; ensuring all those wanted are included in discussions). Only one item scored 3.4 or less.

Conclusion: A community-developed and theory-based training program was feasible to administer and resulted in significant changes in multiple areas of clinician knowledge of SAA, and a high level of confidence in changing practice.

Implications for research, policy or practice: Long term efficacy will be examined in a RCT. If effective, it can serve as a model for

Exposure to an Environmental Contributor of Parkinson's Disease: S. venezuelae impacts lifespan and mitochondrial dynamics in C. elegans

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Parkinson's Disease (PD) is characterized by the loss of dopaminergic (DA) neurons and the formation of protein inclusions that contain the α-synuclein (α-syn) protein. Overexpression of human α-syn in the eight DA neurons of *C. elegans* causes neurodegeneration in an age- and dose-dependent manner, similar to that observed in human pathology. Only 5-10% of PD cases have a direct genetic origin; however, exposure to herbicides, pesticides, and interaction with soil are all potential risk factors. A soil bacterium, *Streptomyces venezuelae (S. ven),* produces a secondary metabolite that causes age- and dose- dependent DA neurodegeneration in *C. elegans*; it also exacerbates α-syn-induced DA neurodegeneration. Initial studies from our lab determined that exposure to the *S. ven* metabolite caused oxidative stress and upregulation of reactive oxygen species (ROS). These studies identified the metabolite worked through the transcription factor *daf-16* to activate *sod-3.* We also found that *S. ven* toxicity negatively impacts mitochondrial function, associated with increased mitochondrial fragmentation. To determine whether the metabolite impaired the longevity of worms, we subjected wild-type (WT) worms to lifespan assays. We discovered that exposure to the *S. ven* metabolite caused a decrease in *C. elegans* lifespan. However, further studies revealed metabolite exposure at lower concentrations, caused lifespan extension, suggesting a hormetic effect. Notably, *daf-16* mutants displayed no significant differences between solvent control and metabolite at both high and low concentrations in lifespan assays, suggesting the hormetic response is *daf-16* dependent. We additionally investigated the impacts of S.ven metabolite on the aging process of *C. elegans* mitochondrial fission and fusion mutants, *drp-1* and *fzo-1*, respectively. We found exposure to S.ven increased lifespan in a *drp-1* mutant background, suggesting that this cellular pathway, which we have shown to be upregulated in response to *S.ven* exposure, might be important for combating toxicants following chronic exposure.

POSTER ABSTRACTS

Diagnostic Electrophysiology of the Aging eye

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Aging and age-related changes in the brain are known to parallel functional and anatomical changes in the eye. The electroretinogram (ERG) and ocular coherence tomography (OCT) are readily available diagnostic tests of retinal function and structure. This study explores the potential of combining ERG and OCT tests to monitor retinal ganglion cells in normal aging. The photopic negative response (PhNR) and pattern electroretinogram (PERG) both contain responses from retinal ganglion cells. Ganglion cells process visual information in the retina and transmit signals to the brain. The PERG uses a reversing black and white checkerboard stimulus. Preliminary results show that reducing the contrast or size of the stimulus leads to a reduction in the response. How does aging affects these results?

Optical coherence tomography (OCT) will be used to gather a retinal thickness scan of the macular region to measure the ganglion cell volume. The central retinal ganglion cell population will be dominated by the midget cells serving the foveal cones, and losses here might be expected to correlate with decreased signals coming from the finer checkerboard patterns. Our results will measure changes in ganglion cell layer volume across 3 decades in normal females.

Beta-amyloid plaques along with other complications of Alzheimer's disease result in the interruption in retinal signaling and death of retinal ganglion cells. We will compare ERG and OCT findings from 10 normal females from two age groups, 22-30 and 50 -65, to ascertain if ganglion cell layer volume loss is an age-related and a reliable indicator of ganglion cell function as measured by ERG. As our results will serve as prelude to studies of neurodegenerative diseases. An increased knowledge of electrophysiological tests could help identify diseases before the appearance of clinical symptoms, which could have incalculable value in diagnosis and monitoring of disease progression or therapeutic intervention.

The assessment of a microplate system for measuring individual real-time respiration in small, multicellular organisms

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The ability to measure oxygen consumption rates of a living organism in real-time provides an indirect method of monitoring dynamic changes in metabolism reflecting organismal level mitochondrial function during development, aging, and/or dysfunctional/ dysregulated physiologic states. In this study, we assessed the Loligo Systems microplate system for measuring individual respiration in small organisms. The organisms included were adult nematodes (*Caenorhabditis elegans,* N2), zebrafish embryos (*Danio rerio, AB)*, and adult fruit flies (*Drosophila melanogaster, w^{1118}*). Organism(s) were placed inside 80 µL glass chambers on a 24-well microplate atop a 24-channel optical fluorescence oxygen reading device for real-time oxygen consumption rate measurements. Adult nematodes and zebrafish embryos were in liquid culture, M9 buffer and egg water respectively, and the adult flies were in room air. The microplate and reader were placed inside an incubator for temperature control at 25.3 °C. A soft silicone gasket with a thin liner was used to seal the chambers. Reference standard oxygen consumption (respiration) of single and multiple *C. elegans* adults (n = 1 – 4 animals/well, ~1 mm long adult), *D. rerio* embryos (n = 1 – 4 animals/well, total mass range estimate/well 0.065 – 0.26 mg), and *D. melanogaster* adults (n = 1 – 2 animals/well, total mass range estimate/well 0.219 – 0.608 mg) in the microplate system were achieved. Significant differences across numbers of animals/well and by sex were observed. Validation experiments of the oxygen consumption rates measured in *C. elegans* in parallel with Seahorse extracellular flux (XF) experiments are underway. The Loligo Systems microplate system offers a non-invasive and non-destructive method to measure real-time respiration in smaller organisms. These data provide preliminary evidence for utility of the system for a variety of biomedical applications that relate to organismal and mitochondrial function/dysfunction, including research in the basic biology of aging in these highly-utilized, pre-clinical, genetic model organisms.

POSTER ABSTRACTS

The loss of Alzheimer's disease risk gene BIN1 in inhibitory neurons induces network hyperexcitability

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Alzheimer's Disease is the world's leading cause of dementia. Multiple genome-wide association studies (GWAS) have identified bridging integrator 1 (*BIN1*) locus as the second leading genetic risk locus for AD; however, the role of BIN1 in AD remains unclear. Studies have confirmed that neuronal BIN1 isoform expression is reduced in AD patients, and in cultured neurons, the loss of BIN1 induced increased amyloid beta (Aβ) and tau aggregation. This suggests that BIN1 loss contributes to AD pathogenesis making BIN1 a critical target for further investigation *in vivo*. Furthermore, nearly half of AD patients exhibit an increase in epileptiform activity, which we suggest may be related to BIN1 loss.

We generated a BIN1 knockout mouse model with BIN1 absent in the whole brain using Nestin-Cre driven floxed BIN1 recombination. We used this mouse model to measure pharmacologically induced seizure susceptibility and discovered that BIN1 loss in the brain leads to network hyperexcitability. To investigate the role of BIN1 in specific cells, we also generated mice lacking BIN1 in either excitatory neurons or inhibitory neurons. We discovered that the network hyperexcitability present in mice lacking BIN1 in the whole brain was recapitulated in mice lacking BIN1 in inhibitory neurons but not excitatory neurons. BIN1 loss in inhibitory neurons also induced behavioral deficits and increased mortality. This study demonstrates that BIN1 loss in the whole brain and in inhibitory neurons may contribute to network hyperexcitability, elucidating BIN1's potential role in the epileptiform activity observed in AD patients.

Synergistic analysis of dendritic spine morphology and the synaptic proteome in human entorhinal cortex uncovers mechanisms of synapse loss in Alzheimer's disease

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Amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) of the microtubule-associated protein tau are the pathological hallmarks of AD; however, synapse or dendritic spine loss correlates more strongly with cognitive impairment than plaques or NFTs. Approximately one-third of individuals that come to autopsy in their eighties have Aβ plaques and tau NFTs, yet did not have dementia in life. These cognitively normal individuals with AD pathology (CAD) were likely in preclinical stages of AD. Unlike individuals with AD dementia, CAD cases do not exhibit dendritic spine loss in the prefrontal cortex. NFT burden negatively correlates with dendritic spine loss, suggesting that tau contributes to synapse loss in AD. In this study, we asked whether the entorhinal cortex (EC), one of the earliest regions to exhibit tau pathology, shows alterations in dendritic spine density and morphology in AD. Dendrites in postmortem human EC samples from 20 normal controls, 6 CAD cases, and 24 AD cases were visualized using the Golgi–Cox technique and spines were imaged using high-resolution brightfield microscopy. Neurolucida 360 was employed for three-dimensional dendrite reconstruction and dendritic spine morphometry analysis. CAD cases maintained spine density at levels similar to healthy controls, while spine density was reduced in AD patients. To begin to understand the mechanisms of EC synapse loss in AD, we undertook a systems approach to identify synaptic proteins that are differentially expressed in AD and associated with dendritic spine density and morphology. EC synaptosomal fractions were isolated from 20 normal controls, 7 CAD cases, and 31 AD cases. Liquid chromatography coupled with tandem mass spectrometry-based proteomics was performed on synaptosomes, followed by weighted protein co-expression network analysis. Resulting modules were correlated with numerous traits, including clinical data, spine density and morphology, and neuropathology to reveal protein targets that associate with EC synapse loss in AD.

POSTER ABSTRACTS

Large multi-center study reveals robust and replicable evidence for dysbiosis of gut microbiome in PD

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Introduction: The human gut harbors billions of microbial cells whose collective genomes make up the human gut microbiome. Multiple studies have confirmed changes in the gut microbiomes of Parkinson Disease (PD) patients but produced varied lists for specific microorganisms altered in PD. Inconsistent findings might be due to differences in study populations and methodological differences. Even when analyzing the same dataset using multiple analytical methods, different results can be produced.

Purpose: We aimed to detect gut microorganism-PD associations that are robust to different analytical methods and replicable across datasets.

Methods: PD and neurologically healthy control subjects were enrolled from NeuroGenetics Research Consortium (NGRC) affiliated movement disorder clinics in Seattle,WA, Albany,NY, and Atlanta,GA (dataset1: 201 PD, 132 controls) and Birmingham,AL (dataset2: 323 PD, 184 controls). We extracted DNA from stool and sequenced for 16S rRNA gene V4 amplicons. Amplicon sequences were processed using DADA2 bioinformatics pipeline. We tested relative abundances of 626 genera for association with PD. Associations were considered significant and replicated if they reached multiple testing corrected significance with two statistical methods (ANCOM and KW) in both datasets with and without adjustment for covariates.

Results: The findings that were significant and replicated in both datasets included reduced levels of butyrate producing genera from *Lachnospiraceae* and *Ruminococcaceae* families, elevated abundance of opportunistic pathogens, and elevated levels of *Lactobacillus* and *Bifidobacterium* in PD.

Conclusion: We detected gut microorganism–PD associations that were robust to different analytical methods and consistent across datasets. Reduction in butyrate producing genera was consistent with the literature and may not be specific to PD. Higher abundance of opportunistic pathogens in PD is consistent with Braak's hypothesis. Results caution against the use of probiotics to self-medicate because the main commercial probiotics, *Bifidobacterium* and *Lactobacillus*, may already be abnormally high in PD.
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Amyloid β hijacks norepinephrine signaling to activate the pathogenic GSK3β/tau cascade

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The brain noradrenergic system is critical for normal cognition and is affected early in Alzheimer's disease (AD). Here we reveal, for the first time, a direct role of norepinephrine signaling in connecting Aβ and tau, the two key pathological components in AD. Aβ oligomers bind to an allosteric site on α_{2A}AR to redirect norepinephrine-elicited signaling to GSK3β activation and tau hyperphosphorylation. This norepinephrine-dependent mechanism sensitizes pathological GSK3β/tau activation in response to nanomolar accumulations of extracellular Aβ, which is 50-100 fold lower than levels required to activate GSK3β by Aβ alone. The significance of our findings is supported *in vivo* from analyzing human tissue samples and longitudinal clinical data, and two mouse models. Our study provides new insights into mechanisms underlying Aβ proteotoxicity, which have strong implications for the interpretation of Aβ clearance trial results and future drug design, and for understanding the selective vulnerability of noradrenergic neurons in AD.

POSTER ABSTRACTS

The Alzheimer's Disease Risk Gene BIN1 Regulates Network Hyperexcitability

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The *BIN1* gene is the second leading genetic risk factor for late onset Alzheimer's disease after *APOE*. BIN1 has been studied substantially outside the brain, however much is currently unknown about it's role in the brain. We previously determined that BIN1 controls seizure susceptibility. More specifically, mice lacking BIN1 in excitatory neurons were less susceptible to seizures. Because seizure susceptibility is a function of network hyperexcitability our focus here was to determine whether BIN1 regulates network hyperexcitability through analysis of gross dendritic tree morphology. Whole-cell patch clamp recordings of mouse CA1 pyramidal excitatory neurons lacking BIN1 were performed. These cells fired less action potentials and received fewer excitatory synaptic inputs. CA1 excitatory pyramidal neurons lacking BIN1 were stained using a biocytin fill protocol and then imaged via confocal microscopy. Z-stack confocal images were used to reconstruct the neurons in Neurolucida 360 software. Sholl analysis was then performed on the reconstructed neurons. No significant differences were observed between excitatory neuron BIN1 knockouts and controls, however preliminary results showed that excitatory knockouts tended to be more complex. The data inconclusively suggest that BIN1 loss increases excitatory neuron complexity, thereby decreasing action potential propensity by reducing electrical resistance of the neuron and making it harder to fire action potentials. Future studies will continue to investigate BIN1 loss in excitatory neurons and if BIN1 loss in the whole brain and in inhibitory neurons specifically affects excitatory and inhibitory neuron complexity. Also, molecular analysis of changes in presynaptic and postsynaptic markers will be evaluated as possible contributors to changes in synaptic transmission and intrinsic neuronal excitability.

Hypertension among Older Americans in the Southeast: Baseline findings from the UAB Study of Aging

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The high rates of hypertension (HTN) or high-blood pressure (HBP) among African Americans (AA) has been recognized for many years. Blood pressure (BP) is normally higher on average among AAs vs. European Americans (EA) and the age of HTN diagnosis is earlier for AAs. Although there are similarities between both groups for treatment, racial differences persist with diagnosis and prevalence of HTN. The reasons for these racial health disparities remain unknown, thus it is important to use frameworks to investigate differences in factors related to HTN among older AAs and EAs to inform disease prevention and treatment. The current study examines contextual, individual, and behavioral factors that explain racial differences in HBP among a sample of older adults living in the southeastern United States. The study employs Andersen's Behavioral Model of Health Services Utilization, which posits predisposing, enabling, and need factors at the individual and contextual levels and performance of health behaviors determines health outcomes. Subjects are 1,000 participants in the UAB Study of Aging (1999 – 2009), a population-based, longitudinal study of community-dwelling older adults designed to identify factors associated with mobility restriction. Participants self-reported diagnosis of HTN at baseline, followed by medical validation. Descriptive statistics characterize the sample. Logistic regression ascertains predictors of HTN among study variables, controlling for geodemographic and other factors informed from the scientific literature. Researchers conducted data analysis using SAS 9.4. Preliminary results from baseline data finds older AAs reported a greater prevalence of HTN (83.7%) when compared to older EAs (59.8%). Older AAs reported 3.44 greater odds of having HTN compared to older EAs. Researchers investigated the influence of individual, contextual, and behavioral factors in contributing to the HTN disparity. Results may inform practical, multilevel interventions leading to successful interventions that will close the disparity gap between AAs and EAs.

POSTER ABSTRACTS

Fatigue is Independently Associated with Functional Status Limitations in Older Adults with Cancer – results from the Cancer and Aging Resilience Evaluation (CARE) Registry

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Introduction: Fatigue is an indicator of frailty among older adults, compromising independent living. The burden of fatigue and its impact on functional well-being in older adults with cancer remains understudied. We addressed this gap in older adults with cancer seen at a single center.

Methods: Patients completed a modified geriatric assessment (GA) survey (CARE) that included the PROMIS® global health 10 (assesses fatigue). We examined the prevalence of fatigue, bivariate associations between those with/without moderate/severe fatigue, and logistic regression of the association between moderate/severe fatigue and limitations in Instrumental Activities of Daily Living (IADL) and Activities of Daily Living (ADL) adjusting for age, sex, race/ethnicity, education, cancer type and stage, pain, comorbid conditions, and time from cancer diagnosis.

Results: A total of 495 participants completed the CARE survey at a mean age of 70y; 56.7% were male; 23.3% Black. Tumor types included colon [22.1%], pancreatic [17.8%], rectal [8.7%], other [51.4%]; mostly advanced stages (70% stage III/IV). Overall, 289 (58.4%) patients reported moderate/severe fatigue. Patients with moderate/severe fatigue were more likely (p<0.0001) to report IADL and ADL limitations (66.1 vs. 27.6% and 25.1 vs 6.5%, respectively), ≥1 fall (29.6% vs. 12.2%), limitations in walking one block (71.4% vs. 26.0%), limitations in social activities (60.9% vs. 20.6%), depression (27.1% vs. 6%), moderate/severe pain (63.2% vs. 24.1%), ≥3 comorbid conditions (41.3% vs. 24.1%). In multivariable analyses (adjusting for factors in methods), the odds of IADL and ADL impairment in those with moderate/severe fatigue were 2.7-fold (95%CI 1.7-4.4, p<0.001) and 2.8-fold (95%CI 1.4-5.5, p=0.004), respectively, compared with those with no/mild fatigue.

Conclusions: Over half of older adults with cancer report moderate/severe fatigue that is associated with numerous GA impairments and independently associated with functional status limitations. Further understanding of the multifaceted aspects of fatigue and development of targeted interventions combating fatigue are needed.

POSTER ABSTRACTS

Downregulated Expression of Heme Metabolism Genes in Chronic Obstructive Pulmonary Disease Cachexia

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Chronic Obstructive Pulmonary Disease (COPD) is defined by accelerated lung function decline and is most prevalent in aged populations. Interestingly, many limiters of quality of life for patients with COPD are not directly correlated with lung function. In particular, cachexia (a form of muscle wasting) is associated with reduced quality of life and increased risk of death in COPD. The underlying mechanism of how cachexia develops and contributes to poor outcomes for COPD patients remains elusive. COPD cachexia may be associated with underlying gene expression changes that could provide valuable insights for surveillance and drug development. Our goal was to identify gene expression signatures associated with COPD cachexia in current and former smokers. We analyzed RNA-sequencing data from a discovery cohort (COPDGene Study N=400) with replication using Affymetrix array data in an independent study (ECLIPSE Study N=140). In COPDGene, cachexia was defined as weight loss >5% in the past 12 months or low body mass index (BMI) and 1/3 criteria: decreased muscle, anemia, and low fat-free mass index (FFMI). In ECLIPSE, cachexia was defined as weight loss > 5% in the past 12 months or low BMI and 3/5 criteria: decreased muscle strength, anorexia, abnormal biochemistry (anemia or high CRP), fatigue, and low FFMI. Differential gene expression was performed comparing cachectic and non-cachectic subjects with COPD, adjusting for confounders including age and sex. COPD cachexia prevalence was 13.7% in COPDGene and 7.9% in ECLIPSE. In COPDGene, 23 genes were significantly differentially expressed (FDR-$p<0.05$) in cachectic versus non-cachectic COPD patients. Replication analyses revealed 14/23 genes significantly replicated ($p<0.05$) being downregulated in both cohorts. Many of these downregulated genes were involved with heme metabolism (*ALAS2, ANK1, TNS1, SPTB, TRIM58, PPP2R5*) and biosynthesis (*ALAS2, SLC25A39*). Impaired heme biosynthesis may contribute to cachexia through free-iron buildup, oxidative tissue damage, and aberrant repair.

POSTER ABSTRACTS

Wealth and Obesity Among U.S. Adults Entering Midlife

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Objective: This study examines the relationship between wealth and obesity among adults entering midlife and whether this relationship varies by gender, race, and measure of wealth.

Methods: The data were obtained from the National Longitudinal Survey of Youth 1979 (NLSY-79). Population-averaged models were used to examine the associations between multiple measures of wealth and obesity among 6,979 respondents while controlling for education, occupation, income, and relevant sociodemographic variables.

Results: The analysis found a robust association between wealth and midlife obesity as well as heterogeneity in the wealth-obesity association across gender, race, and measure of wealth. With the exception of Black men, net worth generally had a significant and inverse relationship with obesity. The net worth-obesity association was largest among women and was driven primarily by home value—in addition to savings and debt for Black women. Although home value was significant for White men, the components of wealth were generally unrelated to obesity among men.

Conclusions: The association between wealth can obesity was generally robust but also complex, depending on gender, race, and measure of wealth. Research that does not consider multiple components of wealth may overlook the importance of economic resources in shaping obesity rates in the U.S. population.

Keywords: obesity, health disparities, socioeconomic status, SES, wealth, race, gender

An Observation of Mouth Care Provided to Elderly Long-Term Care Facility Residents with Dementia

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The purpose of this project is to describe observed mouth care provided by certified nursing assistants (CNAs) to residents with dementia in long-term care (LTC). CNAs are responsible for performing oral care in LTC. However, many residents with dementia resist care, which leads to an overall decline in oral health. We performed a secondary analysis of data from the Managing Oral Hygiene Using Threat Reduction (MOUTh) randomized clinical trial, which included residents with dementia living in nine facilities in Alabama and Pennsylvania. CNAs were observed performing mouth care over a one-week period prior to delivery of the MOUTh intervention. Data collected during this period included resident demographics, duration in the facility, length of mouth care, mean score for oral care, frequency of care-resistant behaviors, and oral health assessment scores (OHAT). Descriptive statistics were used to characterize both the residents who received the mouth care and the mouth care performed by CNAs. Data from 100 residents were analyzed. Residents were primarily female (76%) Caucasians (84%), age 81.55 ± 10.43 years, and had lived in LTCF approximately 2 years (22.66 ± 23.63 months). Mouth care sessions lasted an average of 2.53 ± 1.27 minutes with mouth care successfully completed in 79.8% of attempts. CRB scores averaged 31.50 ± 49.93. OHAT scores were reduced from a mean of 5.35 to 3.94. Consistent mouth care was shown to decrease OHAT scores significantly, therefore, decreasing the risks associated with an unhealthy oral cavity. Interventions to promote mouth care by CNAs to residents with dementia may be warranted.

POSTER ABSTRACTS

The discovery of novel drugs associated with aging using BEERE (Biomedical Entity Expansion, Ranking, and Explorations)

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Background: Aging increases vulnerability to age-associated disease. Genetics studies have been performed in understanding the mechanisms of aging process and the etiology of age-associated diseases. Although hundreds of aging-associated gene candidates reported in genome-wide association study or gene ontology are well investigated, there are still two puzzles for conventional hypothesis-driven researchers to solve. Which extended knowledge and insights including the gene, diseases, drugs, phenotypic features and clinical attributes from the list of the variations we can reveal? Are there any novel functional genes cohesively interact to the driver variants we can investigate? We motivated by the need to develop a web server called Biomedical Entity Expansion, Ranking, and Explorations (BEERE).

Result: The input was 243 genetic candidates associated with aging from PAGER database. In the conjunction of 243 genetic candidates and the term 'aging', BEERE expanded and ranked 665 drug candidates with semantic relationships to aging or the genetics candidates mined in PubMed articles. 92 drugs in drugBank to be significant in BEERE ranking. We classified the drugs into the beneficial effect category, harmful effect category, and unknown effect category. And the consensus targets of 13 drugs directly associated to aging in beneficial effect category are highly related to 'apoptotic signaling in response to DNA damage' through 'NFkB Signaling' and 'ccr5 signaling in macrophage'. 3 drugs, Tretinoin, Simvastatin, and Indole-3-carbinol, are indirectly associated with aging in beneficial effect category. Tretinoin interferes known hub genes JUN, FOS, PTGS2 and EPO which are induced by hypoxia. Simvastatin interferes 'NFkB Signaling Network' through TP53, AKT1, IL6, IL1B, STAT3, BAX, CCL2, VCAM1, and PTEN. Indole-3-carbinol interferes 'apoptosis anti-apoptosis network' through targeting TP53, BAX, DDIT3, PTEN, and SIRT1.

Conclusion: We expect that BEERE to be a popular tool in understanding molecular mechanisms and accelerating drug discovery in complex diseases.

Organ-specific insulin sensitivity in growth hormone-releasing hormone deficient mice

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Released insulin participates in many metabolic actions, such as glycogen deposition in liver and skeletal muscles, stimulation of lipogenesis and inhibition of lipolysis, repression of gluconeogenesis in liver, but mainly functions to increase glucose uptake through binding to insulin receptor on the cell surface of metabolically active tissues. Insulin-stimulated insulin receptor substrate can trigger two major signaling pathways phosphatidylinositol 3 kinase (PI3K)/AKT pathway and mitogen-activated kinases (MAPK) signaling pathway (also known as ERK). Our data shows that growth hormone-releasing hormone deficient ($GHRH^{-/-}$) mice have dramatically extended life span and robustly increased insulin sensitivity. However, insulin sensitivity in metabolically active tissues and other organs remains unclear in this aging model. We observed that insulin significantly enhanced activation of AKT1 and ERK1/2 in metabolically active tissues, including liver, skeletal muscle, subcutaneous adipose tissue, visceral adipose tissue and interscapular brown adipose tissue in mice lacking GHRH. Meanwhile, insulin-mediated phosphorylation of AKT1 is detected in spleen and lung, while insulin-stimulated activation of ERK1/2 is found in kidney in $GHRH^{-/-}$ mice. We noted that insulin sensitivity was attenuated in cortex in GHRH deficient mice, furthermore, insulin-stimulated expression of pERK1/2 decreases in $GHRH^{-/-}$ mice compared with WT. Our data shows that glycogen synthesis in liver and skeletal muscle significantly increases; however, glycolysis is dramatically reduced in $GHRH^{-/-}$ mice. We found that phosphorylated-glycogen synthesis kinase 3α/β, which acts downstream of AKT, is upregulated in liver and skeletal muscle in GHRH deficient mice. These data indicate that GHRH deficient mice have increased insulin sensitivity not only in metabolically active tissues, but also in spleen, lung, and kidney, and increase of glycogen synthesis in mice lacking GHRH results from inactivation of glycogen synthesis kinase 3α/β.

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