Fall **2020**

THE CHRONOS CHRONICLE:

The Newsletter of the Aging Institute

The Hemidemisemiquaver*

***In music, a note lasting for a 64th of a beat. Hence, as below, a very short note.**

Welcome to the first installment of our semiannual newsletter that details the progress of the Aging Institute of the University of Pittsburgh School of Medicine and UPMC. In 2019, for the first time in human history, the number of people on the planet over the age of 65 exceeded the number of people under the age of 5. Moreover, in the United States, in the next 40 years, the number of seniors will likely double, with an expected 95 million Americans over the age of 65 by 2060.

The Aging Institute brings together basic, translational, and clinical scientists who seek to uncover the basic mechanisms underlying human aging and to develop novel therapeutic strategies to slow or reverse the aging process. Within our walls, researchers are hoping to solve the greatest unanswered biological puzzle — how and why do we age? The answer to that question will likely provide a completely new set of therapies that can help delay or prevent a wide range of age-related diseases and provide not necessarily a longer life, but rather, a life freer of debilitating diseases.

The Aging Institute received a significant investment from UPMC Immune Transplant and Therapy Center and the University of Pittsburgh to expand scientific investigation into the basic biology of aging. As part of this commitment, approximately 30,000 square feet of laboratory and office space was renovated at Bridgeside Point 1, part of the South Side research and technology center along the Monongahela River, to house this expanded research program. The Aging Institute now houses the laboratories of 14 talented principal investigators in a highly collaborative and interactive environment. These investigators work alongside postdoctoral scientists, graduate and medical students, and professional staff. Our research focuses on the fundamental biology of aging, such as the role of DNA damage and mitochondrial dysfunction in the aging process, as well as how aging contributes to a range of common diseases, including heart disease and neurodegenerative conditions.

The strength of the Aging Institute lies with our multidisciplinary team of scientists who have primary appointments within various basic science departments and clinical divisions, within the University of Pittsburgh School of Medicine and UPMC. We are also home to an on-site high throughput drug discovery facility that allows for screening of various small molecules (drugs) that may have therapeutic benefit. Excitingly, some of those molecules, developed within our laboratories, are proceeding toward clinical trials in the next few years. Moreover, the clinical efforts of the Institute, led by my colleague **Anne Newman, MD, MPH**, are embarking on innovative trials that leverage the basic biology of aging to test novel treatments that improve the quality of life for our seniors.

I hope you enjoy reading about the people who work in our Institute and some of their recent accomplishments. Some people have compared aging to the weather, in that everyone talks about it but no one does anything about it. We, at the Aging Institute, beg to differ.

Toren Finkel, MD, PhD
Director, Aging Institute, University of Pittsburgh/UPMC
Professor of Medicine, Division of Cardiology
G. Nicholas Beckwith III and Dorothy B. Beckwith Chair in Translational Medicine

AGING INSTITUTE

University of Pittsburgh and UPMC

Faculty Spotlight: Dr. Anne B. Newman

By Samaneh Farsijani, PhD

Anne Newman, MD, MPH, is the chair of the Department of Epidemiology at the University of Pittsburgh and Katherine M. Detre Endowed Chair of Population Health Sciences. Dr. Newman is also the clinical director of the Aging Institute, director of the Center for Aging and Population Health, and co-director of the Claude D. Pepper Older Americans Independence Center.

Dr. Newman is an internationally known scientist and geriatrician. She has published more than 700 peer-reviewed publications and has mentored several trainees in the field of aging and epidemiology, including me. For this issue of the Aging Institute Update, I am glad to present my Zoom interview with Dr. Newman to highlight her career path as well as to learn more about her successful career and mentorship.

When did you first identify yourself as a scientist?

I like research and clinical practice both. When we started the Health, Aging, and Body Composition (Health ABC) cohort study, I was doing clinical practice and research at the same time. Over time, I moved more toward research from clinical practice as I was having challenges with doing both: being paged constantly for patient emergencies or asked to refill prescriptions while leading a large cohort. It was really when I felt that there were lots of people who could take care of patients, but there wasn't anybody else who could fix the research project.

What are you currently working on?

My research today focuses on identifying biologic predictors of healthy aging and disability in large cohorts of older adults in the community.

Do you think aging can be delayed? What in your opinion is a good intervention to delay aging?

I do not think aging can be delayed. I think it can be slowed, which is different. Delay implies that there is an onset, but there is no discrete onset. Aging is a process that begins at conception. In terms of good interventions to slow aging, I think there are a lot of things across the whole life span that are important, beginning with a healthy pregnancy, but physical activity is the only intervention that has been tested in human clinical trials.

What interventions are you currently testing?

We hope to start the "TAME" trial in fall 2020, to test the effect of metformin in mitigating the aging process. We are also trying to launch a trial on clazakizumab, which is an IL-6 monoclonal antibody, in older adults.

What advice do you have for young early career scientists?

To do what is most interesting to them. To read about things that you want to learn about. To publish your work.

You have had several successful trainees. What mentoring advice would you give to other scientists?

I think of mentoring as with my children. I give them what I can, but I hope that they can develop relationships with other adults, their teachers, their friends' parents and learn from them. It takes a village to raise a child. I feel the same way about mentoring. This will also help develop a collaborative scientific approach.

What has been a highlight of your career?

There are many highlights. I think the best time was when we were putting the Health ABC study together. It was a lot of intellectual fun and new collaborations with other investigators, namely Stephen Kritchevsky, Steven Cummings, Tamara Harris, and many others. Those were the great days.

What are your aims going forward?

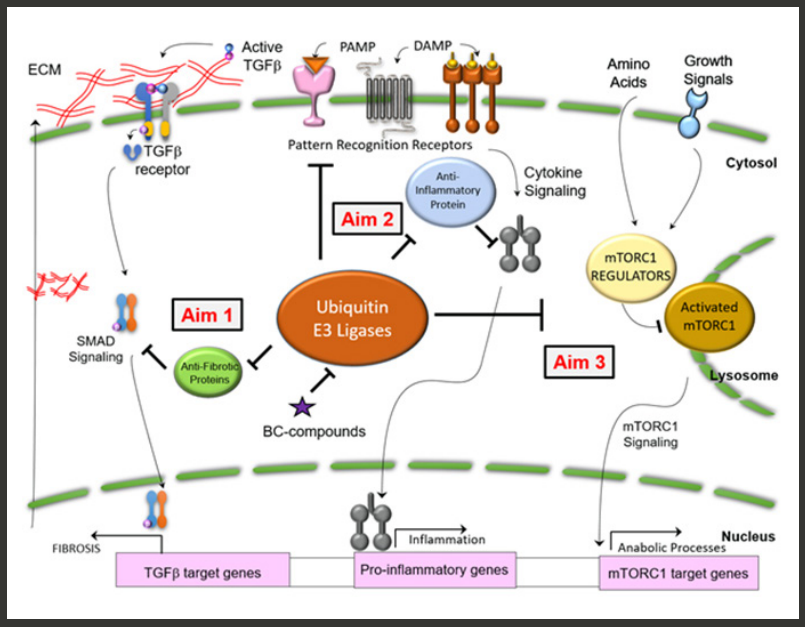
What I really expect to see is a series of studies that have different ways of altering the aging process. My goal is to develop a clinical trial platform to test new agents in older adults.

Trainee Spotlight: Congratulations to Dr. Travis Lear

Congratulations to **Travis Lear, PhD**, who successfully defended his dissertation in April 2020 and earned a doctorate from the School of Public Health in the Department of Environmental and Occupational Health. Dr. Lear was a graduate student in the lab of **Beibei (Bill) Chen, PhD**, at the Aging Institute. His thesis was on ubiquitin E3 ligases in interstitial lung fibrosis in idiopathic pulmonary fibrosis (IPF) and scleroderma, inflammation, and innate immunity. While in graduate school, Dr. Lear also uncovered a role for ubiquitin E3 ligase in nutrient sensing. He plans to continue investigating the role of proteolytic regulation of nutrient sensing in aging. Dysregulated nutrient sensing is a hallmark of aging, and he believes that the role of how E3 ligases contribute to metabolic dysregulation and nutrient sensing dysfunction in aging is not fully uncovered.

Dr. Lear has been a successful trainee with approximately 20 publications from his graduate work, and was awarded a National Institutes of Health F31 Individual Fellowship. He has also won several awards for his graduate work including the Outstanding Doctoral Student Departmental Award in 2020. He is currently supported by the T32 training program in the Vascular Medicine Institute, Department of Medicine. In the past few months, he has been actively working on repurposing FDA-approved drugs against SARS-CoV-2. In addition, he has also applied for the very competitive and prestigious NIH Director's Early Independence Award (DP5) that supports exceptional postgraduate trainees to transition into independence.

Outside of lab, Dr. Lear enjoys reading and learning about, and exploring history — he sometimes wonders what would have happened if he followed that path instead of science. He enjoys watching sports like baseball and is trying to get back into running when he can.



Faculty Update: Welcome Dr. Andrey Parkhitko

The Aging Institute welcomed **Andrey Parkhitko, PhD**, a molecular biologist from Harvard Medical School, on Sept. 1, 2020.

Dr. Parkhitko received his initial training in Moscow, Russia, prior to coming to the United States to join the laboratory of **Elizabeth Henske, MD**, at Brigham and Women's Hospital/Harvard Medical School for his master's degree and later his doctorate. During this time, Dr. Parkhitko studied how autophagy, a process of degrading and recycling internal contents, can serve as a protective mechanism in cancer cells with constitutive activation of mammalian target of rapamycin (mTOR), a central regulator of cellular growth. He also studied how both autophagy and mTOR contribute to the reprogramming of metabolism in cancer cells.

Upon completion of his doctorate, Dr. Parkhitko joined the lab of **Norbert Perrimon, PhD**, at Harvard Medical School to study how metabolism changes during aging. He chose to use Drosophila because it offers great genetic tools, has a relatively short lifespan, and includes good models for cancer and neurodegeneration. Using metabolomic approaches to study the age-related metabolic changes and by combining metabolomics and a genetic screen, Dr. Parkhitko identified several novel genes involved in methionine and tyrosine metabolism that extend lifespan when downregulated.

In his laboratory at the Aging Institute, Dr. Parkhitko plans to use integrative research approaches to advance understanding of the metabolic mechanisms related to aging and age-related diseases using both Drosophila and mice as model systems. He will apply advanced Drosophila genetics tools, newly developed CRISPR techniques, and state-of-the-art methods to measure metabolic fluxes to dissect the metabolic networks that are involved in aging and the age-dependent decline of tissue homeostasis and tissue functions. Ultimately, his goal is to translate his findings in Drosophila to facilitate the development of novel molecular interventions for human age-dependent diseases.

UPMC Senior Services: News and Updates

Western Pennsylvania Regional Health Collaborative

In response to the impact of COVID-19 on vulnerable long-term care residents, the Western Pennsylvania Regional Response Health Collaboration Program brings together UPMC, Allegheny Health Network, the Jewish Healthcare Foundation, and the Healthcare Council of Western Pennsylvania, in addition to several local health systems including Excela Health, St. Clair Hospital, and Penn Highlands Healthcare, to address the needs of long-term care facilities in the southwestern and portions of the northwest regions of Pennsylvania. This collaboration was developed due to successful legislation crafted by UPMC partners, including **Deborah Brodine**, president of both UPMC Western Psychiatric Hospital and UPMC Senior Services, and **David Nace, MD**, clinical chief of Geriatric Medicine, director of Long-Term Care with the University of Pittsburgh, and chief of medical affairs for UPMC Senior Communities, and supports facilities through:

- **Onsite COVID-19 testing**
- **Educational training on infection control, cohorting practices, and personal protective equipment (PPE) use recommendations**
- **Coordinated clinical response efforts through on-site infection control assessments, contact tracing, and rapid response to changes in infection rate**
- **Obtaining emergency staffing augmentation, emergency PPE, and identification of alternative care sites when needed**

UPMC: For additional information contact **412-648-6714** and **wprrhc@upmc.edu**.

AHN: For additional information contact **866-496-1766** and **RRHC@ahn.org**.

Introducing the New UPMC Senior Services Website

Visit **UPMC.com/SeniorServices** for the latest information on the help and referral line, and education and community outreach efforts of UMPC Senior Services. Our portfolio of educational programming continues to grow as UPMC Senior Services joins forces with the Education and Consultative Services of UPMC Western Psychiatric Hospital. Both groups will continue to offer best-practice programming and state-of-the-art training to professionals, students, and members of the community.

2020 Celebrating Senior Champions

Celebrating Senior Champions went virtual for 2020! UPMC Senior Services honored distinguished individuals and organizations with a special on-line event on Thursday, Oct. 22. Hosted by Master of Ceremonies and Pittsburgh Steelers great Robin Cole, the event was a blend of favorite elements from previous celebrations and new features suited to the virtual experience, including tributes to honorees, a Silent Auction, a Split the Cash Raffle, a prize drawing for ticket holders, and commemorative swag bags for all ticket holders. Visit **UPMC.com/Services/Senior-communities/Senior-champions**.

Scott Lammie

Hill House Association
and program transition partners
Emma Lucas-Darby

Richard Morycz, PhD

World-Renowned Experts Visit the Aging Institute

Jan Vijg, PhD, professor and the Lola and Saul Kramer Chair in Molecular Genetics at the Albert Einstein College of Medicine in New York, visited the Aging Institute in January 2020.

Dr. Vijg has published approximately 300 scientific articles and is inventor or co-inventor on eight patents. Dr. Vijg is the recipient of several prestigious awards, such as the Nathan Shock New Investigator Award of The Gerontological Society of America (1994) and the Irving S. Wright Award of Distinction of the American Federation for Aging Research (2012). He gave a fantastic seminar at the Aging Institute on his work entitled, "Single-Cell Genomics in Studying Genome Instability Imaging." Dr. Vijg has dedicated his career to carefully measuring and understanding the incidence and accumulation of nuclear DNA mutations with age. Traditionally, measuring DNA mutation in bulk (heterogenous population of) cells and tissues has been extremely challenging.

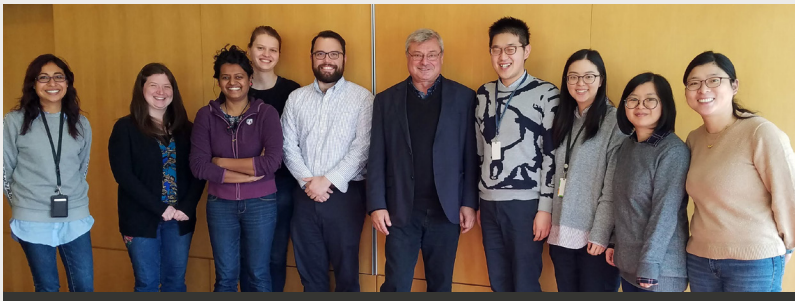
Dr. Vijg with members of the Aging Institute.

However, Dr. Vijg and his team have developed state-of-the-art tools to examine nuclear DNA mutations in single cells. This provides us with an opportunity to understand how and when stochastic mutations occur and accumulate, as well as the consequence of such mutations on tissue health.

Additionally, he took time to meet with trainees, during which he shared the challenges and triumphs on his career path from a postdoc to principal investigator. Several of the trainees commented that they had a very insightful lunch with Dr. Vijg. He challenged the trainees to dig deeper and asked why they particularly chose to study aging. They discussed, 'Can we really solve aging? Can we cure aging, delay it or reverse it?' He encouraged the trainees to pursue global possibilities with a view to creating bridges and breaking down walls that hinder research regionally. The faculty at the Aging Institute also had an opportunity to discuss their science and talk about collaborative opportunities with Dr. Vijg. We hope to share fruits from some of our collaborations in the near future.

John M. Sedivy, PhD, director of the Brown University Center on the Biology of Aging, visited the Aging Institute in November 2019. Dr. Sedivy is a leading expert on cellular senescence and organismal aging, and has published more than 140 articles. He presented his recent work at the Aging Institute seminar series: "Activation of Endogenous Retro Transposable Elements as a Mechanism Contributing to Age-Associated Sterile Inflammation."

His work highlights that cellular senescence, one of the most prominent hallmarks of aging, is accompanied by an "activation" of retrotransposable elements (RTE). RTEs, also known as "jumping genes," are DNA sequences that can move around the genome and cause chaos by disrupting gene expression and driving genomic instability. These RTEs are usually repressed in our genome, but his team found that during cellular senescence that occurs with age, LINE-1 (L1) RTEs become transcriptionally derepressed and activate type-I interferon (IFN-I) response. This IFN-I response contributes to the maintenance of the senescence-associated secretory phenotype (SASP). SASP defines the ability of senescent cells to secrete a variety of proinflammatory cytokines, immune modulators, growth factors, and proteases that often induce age-associated inflammation (inflammaging). Chronic inflammation with age leads to higher susceptibility to chronic morbidity, disability, frailty, and premature death. Interestingly, treatment of "old" mice with the nucleoside reverse transcriptase inhibitor (a treatment for HIV and hepatitis), lamivudine, downregulated IFN-I activation and sterile inflammation in several tissues. Based on these findings, Dr. Sedivy proposes that RTE activation is an important component of sterile inflammation associated with age and that L1 RTE is a relevant target for the treatment of age-related diseases.



Dr. Sedivy with members of the Aging Institute.

During his visit, Dr. Sedivy had lunch with our trainees at the Aging Institute and shared insights into how to have a productive research career, how to network, and how to become a successful principal investigator. Dr. Sedivy also met with several investigators, exchanging ideas about aging and age-related diseases. Although Dr. Sedivy's visit to the Aging Institute was short, it was definitely productive.

University of Pittsburgh and UPMC

AGING INSTITUTE RESEARCH SEMINAR SERIES

Visiting Speakers, Fall 2020

Virtual Presentations | 2nd Thursday of the Month | Noon to 1:00 p.m.

SEP 10

Chemical biology of protein aggregation in membraneless organelles and the stressed proteome

Xin Zhang, PhD

Associate Professor of Chemistry, Biochemistry and Molecular Biology
Paul Berg Early Career Professor
Pennsylvania State University

OCT 22

Pathophysiological causes of senescence and rejuvenation by in vivo reprogramming

Manuel Serrano, PhD

ICREA Research Professor at Institut De Recerca Biomèdica (IRB Barcelona)
Director of the Institute for Research in Biomedicine (IRB Barcelona)

NOV 12

Mitochondria as signaling organelles

Navdeep Chandel, PhD

David W. Cugell Professor of Medicine, Division of Pulmonary & Critical Care Medicine
Professor of Biochemistry and Molecular Genetics
Feinberg School of Medicine, Northwestern University

DEC 10

Modulating selective autophagy for health-span extension

Ana Maria Cuervo, MD, PhD

The Robert and Renee Belfer Chair for the Study of Neurodegenerative Diseases
Professor, Department of Developmental and Molecular Biology
Co-Director, Institute for Aging Research
Albert Einstein College of Medicine

Scan QR Code to register or visit
https://bit.ly/RegisterPittAging2020

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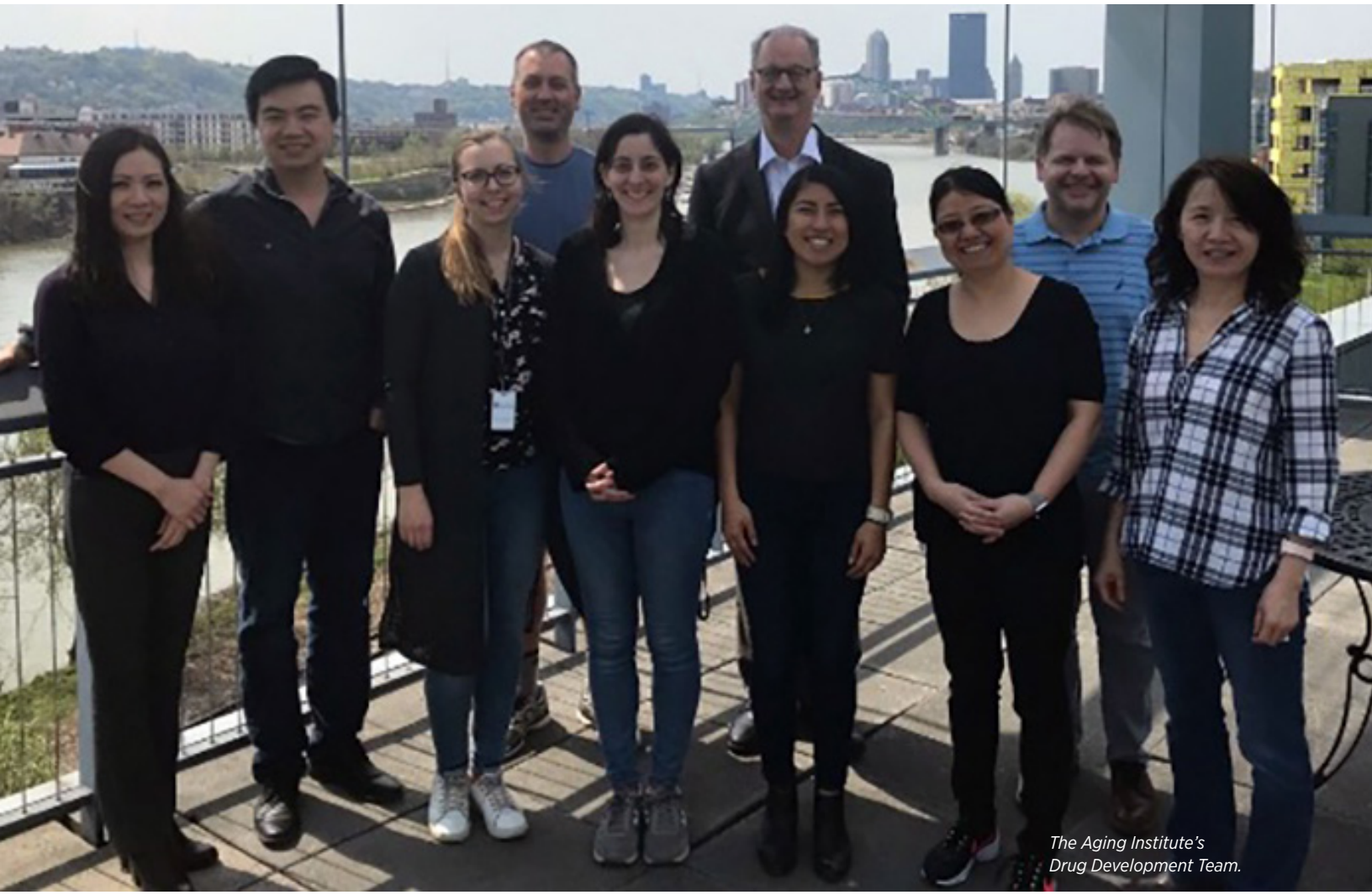
University of Pittsburgh | Department of Medicine, School of Medicine

UPMC LIFE CHANGING MEDICINE

Highlighted Grants at the Aging Institute



The Aging Institute's Drug Development Team.

The Aging Institute's **Drug Discovery Team** Receives Grant Funding to Identify FDA-Approved Drugs that can be Repurposed to Combat COVID-19

While mostly focusing on aging biology, the recent outbreak of COVID-19 represented a unique challenge to the scientific community. As such, we decided we had to do our part in helping to develop new therapies to combat this worldwide epidemic. We were fortunate that the Jewish Healthcare Foundation, a Pittsburgh-based philanthropic organization, was able to support this initiative, which allowed us to redirect our efforts in drug discovery to fight this pandemic. SARS-CoV-2 (2019-nCoV) is the pathogenic coronavirus responsible for the global pandemic of COVID-19 disease. Given its rapid spread, coupled with the high burden of acute respiratory failure and death, there is an urgent need for additional therapies. We believed that the most rapid and effective near-term approach was to identify currently FDA-approved drugs that can be repurposed to block viral entry and infectious spread. The question was, how could we identify such agents?

Our approach was to execute a high throughput screen (HTS) in our state-of-the-art chemical screening facility that identified a small subset of FDA-approved compounds that effectively reduce the surface expression of TMPRSS2. The surface protein TMPRSS2 is a critical host protein required for efficient SARS-CoV-2 viral entry. Without TMPRSS2 expression, Sars-CoV-2 cannot enter cells. Consistent with this, the FDA-approved agents we identified were able to dramatically limit SARS-CoV-2 cellular entry. The results are now under editorial review at a major scientific journal. As such, with the help of the Jewish Healthcare Foundation we were able to identify a new approach to treating COVID-19 infection by repurposing existing FDA-approved drugs to fight this viral infection. Our labs are currently expanding these efforts to try and obtain additional agents that might be useful to block viral infection, a strategy that is critical until an effective vaccine can be identified.

Dr. Stacey Rizzo Received Grant Funding to Investigate the Role of Lifespan Interventions on the Regulation and Progression of Alzheimer's Disease

A recently awarded grant by the National Institute on Aging to **Stacey Rizzo, PhD**, **Toren Finkel, MD, PhD**, **Yuan Liu, PhD**, and collaborator **Afonso Silva, PhD**, in the Department of Neurobiology at the University of Pittsburgh will investigate the role of lifespan interventions on the regulation and progression of Alzheimer's disease.

Alzheimer's disease affects an estimated 50 million patients worldwide, with the number expected to triple over the next 30 years. Unfortunately, to date there are no treatments that stop or prevent Alzheimer's disease. This may in part be due to our limited understanding of the mechanisms that precede the pathogenesis of Alzheimer's disease that are distinct from normal healthy aging.

Aging is not a uniform process, and how different biological systems, tissues, and cell types change throughout a lifespan as well as how they may become dysregulated with disease progression is not known. Notably, the immune system becomes dysregulated with aging that leads to chronic inflammation. Several aging-related disorders share this common condition, including cancers, diabetes, cardiovascular disease, and neurodegenerative disorders including Alzheimer's disease.

While systemic inflammation may be a result of an aging immune system, other processes involved in regulating the immune system to keep it in check are also impaired with aging. Notably, the process of autophagy which is responsible for recycling degraded cellular components is also impaired with aging and in diseases. The overall aims of this proposal are therefore to understand the processes underlying dysregulation of the autophagy-inflammation network in aging biology and how chronic inflammation due to this dysregulation may contribute to Alzheimer's disease. We hypothesize that interventions that target the shared feature of systemic inflammation in the biology of aging and Alzheimer's disease, via regulation of the autophagy-inflammation network, may have potential as therapeutic agents for the prevention of conversion to disease pathogenesis in Alzheimer's disease as well as improve health span and longevity in aging populations. Specifically, for these studies, we will focus on dissecting out the differences in systemic inflammation between healthy aging and that which manifests with Alzheimer's disease progression. In addition to evaluating how different cell types in the brain contribute to aging and Alzheimer's disease pathology, we will also evaluate the potential of novel compounds that target both autophagy and inflammation processes for their ability to prevent Alzheimer's disease and cognitive deficits in mouse models engineered for human genetic risk factors for Alzheimer's disease including ApoE4.

As part of the research plan, the team will use the Aging Institute's Preclinical Phenotyping Core (PPC) facility to conduct behavioral and cognitive testing in the mouse models. The PPC is a state-of-the-art core facility under the direction of Dr. Rizzo that provides University of Pittsburgh researchers access to specialized instrumentation for evaluating behavioral characteristics in animal models of human disorders. This includes a suite of cognitive tests that are analogous to the types of cognitive assessments conducted in human Alzheimer's patients. In addition the PPC has specific expertise in evaluating features of normal healthy aging in mouse models including frailty assessments, hearing, vision, and motor activity that will help understand if the interventions being tested can not only prevent and/or treat Alzheimer's disease, but also slow down the processes of aging.

The long-term goal of the team is to identify therapeutic agents that can prevent Alzheimer's disease. Findings from these studies will provide both mechanistic insight into the autophagy-inflammation network involved in regulating normal healthy aging and in Alzheimer's disease progression, and evaluate the potential of novel interventions as potential therapeutics for the prevention of Alzheimer's disease.

Dr. Rizzo and members of the Aging Institute Investigative Team.

Additional **New Grants** at the Aging Institute

Principal Investigator	Grant Title	Grant Type	Funding Agency
Yvonne S. Eisele, PhD	"Improve the diagnosis and outcome of cardiac transthyretin-related amyloidosis"		The Pittsburgh Foundation
Shihui Liu, MD, PhD	Defining cellular receptors for the Bacillus cereus hemolysin BL toxin (HBL) and the development of anti-HBL therapies	R01	National Institutes of Health
Shihui Liu, MD, PhD	Molecular mechanisms and novel biological-based therapies for anthrax lethal toxin-induced mortality	R56	National Institutes of Health
Ana Mora, MD	Senescence and the validation of new therapeutic concepts for lung fibrosis		Boehringer Pharmaceuticals
Shiori Sekine, PhD	"The development of the chemical-biological tool to delineate the molecular mechanism maintaining the mitochondrial membrane homeostasis"		Samuel & Emma Winters Foundation
Shiori Sekine, PhD	The Pharmacological and Genetical Delineation of Mitochondrial PINK1 Import Regulation		University of Pittsburgh Competitive Medical Research Fund
Yusuke Sekine, PhD	"Molecular links between acetyl-CoA metabolism and the nucleolar stress response"		Samuel & Emma Winters Foundation
Yusuke Sekine, PhD	Deciphering Molecular Links between Acetyl-CoA Fluctuations and a Cellular Hallmark of Aging		University of Pittsburgh Competitive Medical Research Fund
Matthew Steinhauser, MD	A new modality to image tumor metabolic heterogeneity at subcellular resolution	DP2	National Institutes of Health
Bokai Zhu, PhD	Hepatic 12h-to-24h reprogramming drives NAFLD		Pittsburgh Liver Research Center/NIH P30

Highlighted Manuscripts at the Aging Institute

Dr. Bokai Zhu Sheds New Light on the '12-Hour Oscillation' and Receives National Institutes of Health Director's New Innovator Award

Bokai Zhu, PhD, assistant professor of medicine at the Aging Institute, was awarded the National Institutes of Health Director's New Innovator Award (DP2) in October 2020. This award is a highly prestigious and competitive research initiative designed to support exceptionally creative, early-career investigators who propose innovative, high-impact projects. Dr. Zhu's lab is studying a new form of "molecular" oscillation that cycles with a period of 12 hours. These 12-hour ultradian oscillations are both functionally and genetically distinct from the well-known 24-hour circadian rhythms in mammals. **Heather Ballance, PhD**, a postdoctoral fellow in Dr. Zhu's lab, along with collaborators recently published a research article in *PLoS Biology* that sheds new light on the regulation, function, and evolutionary origin of these intriguing 12-hour oscillations.

In the recent study, Dr. Zhu's lab set out to identify a dedicated cell-autonomous 12-hour pacemaker that is responsible for the establishment and maintenance of the mammalian 12-hour rhythms. They found that liver-specific deletion of XBP1, a transcription factor well known for its role in endoplasmic reticulum (ER) stress response, drastically impaired 12-hour rhythms of gene expression without affecting circadian gene expression. This study raised a new vehicle-cargo hypothesis that delineates the distinct functions of 12h versus circadian rhythms. The vehicle-cargo hypothesis argues that the 12-hour pacemaker accommodates demands for increased gene expression/processing at the two biological "rush hours" by elevating the global traffic capacity (and/or the rate) of the central dogma information flow (CEDIF) [all the way from transcription in the nucleus to protein trafficking and sorting in the endoplasmic reticulum and Golgi]. This connects and tunes rates of mRNA and protein processing to the 12h cycle of metabolic stress (thus acting as the vehicle). The circadian clock, on the other hand, dictates the particular genes/gene products processed at each rush hour (thus acting as the cargo). An everyday metaphor would be the fluctuating daily traffic on the highway: the 12h biological rhythm is analogous to the oscillatory operating capacity of the highway, which increases during the two rush hours (by opening the HOV lane, for example), whereas the function of the circadian clock is likened to determining which cars actually go on the highway at each rush hour.

In addition to the novel biology, Dr. Zhu's discovery of a 12h-clock pacemaker also has philosophical implications, which lie in the concept of "musica universalis" that was first proposed by the famous Greek mathematician Pythagoras. He claimed that the movements of celestial bodies follow mathematical equations and resonate to produce an inaudible harmony of music, and the harmonious sounds that men make were a mere approximation of this larger harmony of the universe. Since the circadian rhythm is synchronized to the 24h light/dark cycle coinciding with the Earth's rotation, and the mammalian 12h clock may have evolved from the circatidal clock, which is in turn entrained by the 12h tidal cues orchestrated mainly by the moon, it is apparent that the biological rhythms are also in tune to the rhythms of the universe. In other words, the biological rhythms are also part of "musica universalis."

With the new DP2 grant, Dr. Zhu's lab aims to answer some tantalizing questions on the 12-hour ultradian pacemaker in the next five years. For example, Dr. Zhu is interested in identifying potential endocrine and paracrine hormones that can synchronize the 12-hour pacemakers in different tissues/organs in mice. Characterization of such humoral factors will likely lead to the discovery of long sought factors regulating non-cell-autonomous UPR in mammals. Another future area of the lab is using an "omics" approach to comprehensively characterize both the mRNA and protein substrates that are subject to 12-hour CEDIF regulation, and determine how 12-hour regulation of CEDIF may alter during aging and in aging-related diseases.

Dr. Gang Li — Developing Techniques to Identify Functional Single Nucleotide Polymorphisms

Gang Li, PhD, assistant professor of medicine at the Aging Institute, has worked to develop techniques to identify functional single nucleotide polymorphisms (fSNPs) and recently published an article in Nature Communications. There has been a huge public investment in genome-wide associated studies (GWAS). These studies have identified numerous common genetic variants. Most of these genetic variants are SNPs, a substitution of a single nucleotide at a specific position in the human genome. The challenge with GWAS is the inability to specify which disease-associated SNP's are functional (ie, responsible for causing the disease). Given this, utilization of data from GWAS studies to help guide therapies has been limited. Without knowing the causative functional SNPs (fSNP), understanding the underlying mechanisms of disease is difficult. The inability to translate GWAS data into information that can be used for therapies is one of the greatest current challenges in human genetics.

To meet the challenge, Dr. Li and his team have developed a potentially transformative approach with three novel techniques to not only identify fSNPs but also characterize these fSNPs by identifying the fSNP-bound proteins that regulate risk gene expression. In this approach, they use Reel-seq (Regulatory element-sequencing) to identify fSNPs in a high-throughput fashion; SDCP-MS (SNP-specific DNA competition pulldown-mass spectrometry) to identify fSNP-bound proteins with a high specificity; and AIDP-Wb (allele-imbalanced DNA pulldown-Western blot) to validate both the fSNP and its binding proteins simultaneously on a single Western blot by detecting allele-specific protein:fSNP binding.

To demonstrate the feasibility of this approach, Dr. Li's group applied Reel-seq to a DNA library containing 4316 SNPs on 177 breast cancer-associated loci and identified 521 candidate fSNPs. As proof of principle, they verified 12 fSNPs on three well-characterized loci, they are FGFR2, MAP3K1, and BABAM1. Next, using SDCP-MS and AIDP-Wb, they rapidly identified multiple regulatory factors that can modulate FGFR2 expression via binding to the fSNPs on the FGFR2 locus. Their results suggest that sequential application of Reel-seq, SDCP-MS, and AIDP-Wb can greatly help to translate large sets of GWAS data into biological mechanisms. Currently, Dr. Li's group has applied this approach to many other age-related diseases, such as Alzheimer's disease and cardiovascular diseases. "Once we understand the underlying mechanisms, we will be able to identify the best target for drug development for these diseases," says Dr. Li.

Thank You from the Aging Institute Team

Contact the Aging Institute

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