Research: Impacting and Expanding Knowledge

Midwestern University

Tomorrow's Healthcare Team

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555 31st Street | Downers Grove, Illinois 60515

19555 North 59th Avenue | Glendale, Arizona 85308

2021

Message from the President

Dear Friends of Midwestern University,

In this edition of Research: Impacting and Expanding Knowledge you are introduced to the exciting exploration being conducted by our faculty and students as they develop research plans, collect and analyze data, and persist through the challenges and opportunities presented. Research at Midwestern University is an important component in preparing the next generation of healthcare providers. It is the ability to expand knowledge, go search for answers that previously were only a hypothesis, while linking the art of teaching with the science of discovery.

Teaching students, instilling in them a desire for scientific discovery is a major focus of the Midwestern University faculty. Students work closely with their faculty mentors as they are encouraged to present and publish their work and develop lifetime skills that can only enhance their careers. It is the loyal and dedicated faculty that make this possible by sharing their vision, confidence, and outcomes with their students. All of our colleges and programs participate in forms of research and scholarship. It is with this concerted effort that we obtained $5,231,304 in total active grants during Calendar Year 2021. Many of our senior faculty members contributed to this growing grant fulfillment while teaching full time, mentoring students, and actively publishing. They should all be congratulated for making 2021 a significant year in discovery.

Sincerely,

Kathleen H. Goeppinger, Ph.D.

Kathleen H. Goeppinger, Ph.D.
President and Chief Executive Officer, Midwestern University

Expanding Research and Impacting Knowledge

GRANTS: $5,231,304 in Grants for Calendar Year 2021

Midwestern University
Tomorrow's Healthcare Team

$33.3 Million
Commitment to Research Activities*
in Fiscal Year 2021

$1.6 Million
in Extramural Funding Expenditures
in Fiscal Year 2021

105 Student Research Fellowships
funded at $552,350
in Fiscal Year 2021

* *Includes direct and indirect costs. For 2021, this equates to 7.7% of the University budget.*

Principle Investigators and Projects Awarded Grants Exceeding $400,000:

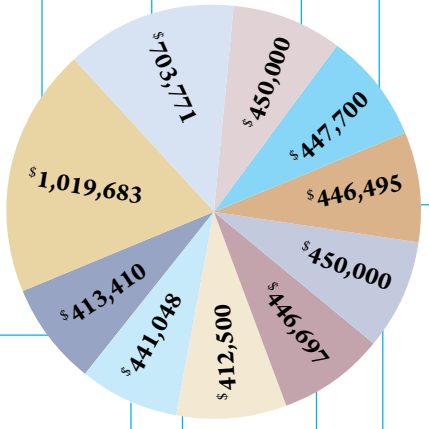
Dr. Chongwoo Kim
College of Graduate Studies
Title: The Role of SAM Polymerization in Polycomb-dependent Chromatin Structures[Δ]

Dr. Chad VanDenBerg
Clinical Research Services
Title: Multiplexed In-solution Serological Tests for SARS-CoV-2, Human Coronaviruses and Other Respiratory Pathogens[†]

Dr. Ashlesh Murthy
College of Veterinary Medicine
Title: Mechanisms of CD8+ T Cell-mediated Chlamydia-induced Reproductive Pathology[Δ]

Dr. Ann Revill
College of Graduate Studies
Title: Cholinergic Modulation of XII Motoneurons and XII Premotoneurons[Δ]

Dr. Brina Lopez
College of Veterinary Medicine
Title: Host-Pathogen Interaction During Cryptosporidiosis - A Model for Disease Pathogenesis and Discovery of Effective Therapeutics[§]



Dr. John Vandenbrooks
College of Graduate Studies
Title: Elucidating the Role of Rhipicephalus sanguineus (the Brown Dog Tick) as a Vector for Rocky Mountain Spotted Fever (RMSF) Transmission in Arizona[#]

Dr. Mitra Esfandiarei
College of Graduate Studies
Title: Targeting Endothelial Dysfunction in a Genetic Mouse Model of Aortic Aneurysm: Implications for Prevention and Therapy[Δ]

Dr. Marc Scheetz
College of Pharmacy
Title: Quantifying Renal Injury Among the Most Commonly Used Antibiotic Combinations[Δ]

Dr. Joshua Edwards
College of Graduate Studies
Title: Mechanisms of Cadmium-Induced Dysglycemia[Δ]

Dr. Minsub Shim
College of Graduate Studies
Title: Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-Induced Long-term Adverse Sequelae[Δ]

Funding sources: *[Δ]National Institute of Health Awards; [§]USDA National Institute of Food and Agriculture; [#]Arizona Biomedical Research Center; [†]Leidos/ASU/NIH*

Core Facility Provides Research Hub for Students, Faculty

The Midwestern University Glendale Campus Core Facility was formed in 2019 to provide access to shared research instrumentation and acquire new technologies that are out of reach to individual investigators. The Core Facility is actively funded by Midwestern University to support research, foster collaborative projects, drive scientific innovation, and engage our community by hosting STEM education programs. This facility is located in the Foothills Science Center and currently supports molecular and cellular analyses, histological sectioning, microscopic imaging, and multi-dimensional visualization. Staff maintain the shared equipment, provide training and technical advice to researchers, and work with researchers to develop scientific protocols. The university has continuously added new equipment and resources to strategically adapt to the changing needs of Midwestern's research community and new core facilities are being designed and developed to be deployed in the near future. The Core Facility support the diverse needs of faculty, staff, and students in a broad array of scientific disciplines and serves as a centralized hub for research support across the Glendale Campus.

For more information about these and other research projects, visit the Research section on the Midwestern University website at: ***https://www.midwestern.edu/research.xml.***

MWU Grants Funded from $100,000 - $400,000

Investigator/s	College(s)	Title	Total	Agency
Baab, K.	**CGS**	Testing Adaptive Hypotheses of Plio-Pleistocene Hominin Craniofacial Evolution	**$330,021**	National Science Foundation
Eckman, D., Jones, C., Jones, T.B., Vallejo-Elias, J. Virden, T. & Powell, J.	**CGS & CHS-GD**	Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4Targeted-Replacement Mice	**$225,000**	AZ Dept. of Health Services through the AZ Biomedical Research Commission
Ellermeier, J.	**CGS**	Genetic Regulation of the Twin Arginine Translocation System in Salmonella enterica serovar Typhimurium	**$150,000**	NIH-R03
Jadavji, N.	**CGS**	Identification of Developmental Factors Involved in Ischemic Stroke Outcomes in Adulthood and Old Age	**$152,735**	American Heart Association
O'Neill, M.	**CGS**	Collaborative Research: The Effects of Musculoskeletal Design on Bipedal Walking and Running Performance in Humans, Chimpanzees and Early Hominins	**$239,935**	National Science Foundation
Riede, T.	**CGS**	Collaborative Research: Evolution of Long-distance Communication in Vocal Rodents	**$193,774**	National Science Foundation
Riede, T.	**CGS**	The Role of Vocal Ligament in Fundamental Frequency and Adduction Control	**$201,055**	NIH-R01 Subcontract from the University of Utah
Townsend, K.E.B.	**CGS**	Collaborative Research: After the Bridgerian Crash - An Integrated Analysis of Mammalian Paleocommunities and Paleoecologies During the Middle Eocene	**$239,596**	National Science Foundation
Elbayoumi, T. and Yao, M.	**COP**	Atrial Fibrillation Strategically Focused Research Network: Atrial Substrate in Atrial Fibrillation and AF-associated Brain Disease	**$126,979**	American Heart Association Subcontract from Northwestern University
Gulati, A.	**COP**	Mentor and Train PCCM and NPM Fellows for Scholarly Activity	**$170,000**	Advocate Health & Hospitals
Scheetz, M.	**COP**	AKI001 Vancomycin (MEEK) and AKI002Liposomal Vancomycin	**$265,452**	Nevakar, Inc.
Vasudevan, B.	**AZCOPT**	A Multi-center, Double-masked, Randomized, Placebo-controlled, Phase 3 Study of the Safety and Efficacy of Atropine 0.1% and 0.01% Ophthalmic Solutions Administered with a Microdose Dispenser for the Reduction of Pediatric Myopia Progression (The CHAPERONE Study)	**$313,000**	Eyenovia
Vasudevan, B.	**AZCOPT**	Effect of LipiFlow on Ocular Surface Disease Management with Cataract Surgery	**$273,000**	Johnson & Johnson Surgical Services
Rice, S.	**CCO**	A Multi-center, Double-masked, Randomized, Placebo-controlled, Phase 3 Study of the Safety and Efficacy of Atropine 0.1% and 0.01% Ophthalmic Solutions Administered with a Microdose Dispenser for the Reduction of Pediatric Myopia Progression (The CHAPERONE Study)	**$313,000**	Eyenovia

The goals of the Center are to:

- Submit interdisciplinary extramural grants annually.
- Publish meritorious research.
- Train multiple students per year, assist them in successfully presenting and publishing their research, and support their success in seeking post-graduate training and education.
- Train multiple residents/fellows per year, resulting in meaningful publication and presentation of their research and support their success in obtaining high quality positions upon completion of their training.

Pharmacometrics Center of Excellence Pairs Innovative Research, Mentorship

Primary research areas currently include:

- Antibiotic safety and efficacy
- Prevention of drug induced kidney injury
- Development of novel therapeutics

The Midwestern University Pharmacometrics Center of Excellence opened on the Downers Grove Campus in the summer of 2018 after earning approval from Kathleen H. Goeppinger, Ph.D., President and Chief Executive Officer of Midwestern University. Since then, the Center has increased the number of funded extramural research grants, published peer-reviewed research, trained Midwestern students to uphold rigorous research standards, and mentored Postdoctoral fellows who will become future career scientists and leaders.

The Center is led by Marc Scheetz, Pharm.D., M.Sc., BCPS, Professor of Pharmacy and Pharmacology, and is comprised of a team of pharmacologists, translational scientists, synthetic chemists, and clinicians. The Center focuses on pharmacometrics, which involves the quantitative study of medication effects on both humans and animals. In-silico methods such as computer modeling and computer simulation are used to improve and refine approaches from preclinical studies through the clinical environment. The Center also helps foster collaborative approaches that pair clinicians and scientists committed to improving the health of people and animals utilizing the principles of One Health.

The approved mission of the Center is to design innovative strategies that maximize safe and effective pharmacotherapy for patients and develop the next

generation of translational clinicians and scientists through advanced pharmacometric education. Since the Center's inception, a total of 45 extramural grants/contracts requesting $14.9 million have been submitted. Of these, 11 (24%) were funded for a total of $848,395. During the last fiscal year, a total of 38 peer-reviewed manuscripts were accepted for publication in various high-tier journals. In addition, 24 students had the opportunity to work with Center leaders and faculty members on advanced research projects, and three first-year Postdoctoral fellows were engaged in conducting important research that will contribute to the body of scientific knowledge. Dr. Scheetz is a co-principal investigator for a new project funded for $3.7M by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH). In the study, AMPLE-Antibiotics in MODS: Personalizing Exposures, their team will enroll children with multiple organ dysfunction syndrome from 15 intensive care units across the United States. The team will devise new dosing schemes to improve the safety and efficacy of antibiotics for these most critically ill children.

The future goals of the Center include continuing to advance educational opportunities at Midwestern University and enhancing the University's reputation for scientific excellence. "We are excited to continue our work with our MWU students to make current drugs safer for patients by innovating delivery approaches and developing new therapeutics," Dr. Scheetz said.

Long-Term Research Idea Leads to Several New Patents

"These drugs that can be taken by mouth have the ability to prevent challenging solid tumors, such as liver, lung, and pancreatic cancer, from spreading in the body."

Project: Aspartyl(asparaginyl)-beta-hydroxylase (ASPH) Inhibitor Patents

Principle Investigator: Mark Olsen, Ph.D., College of Pharmacy, Glendale Campus, Associate Professor, Pharmaceutical Sciences

Project Summary:
As a way of encouraging groundbreaking research and contributing to society as a whole, Midwestern University provides support for faculty members seeking to obtain U.S. patents for well-conceived inventions that are significantly developed and likely to lead to commercialization. With the support of Midwestern University, Mark Olsen, Ph.D. (CPG), Associate Professor, Pharmaceutical Sciences, has successfully received 11 patents with several more pending that could provide additional hope to people afflicted by cancer.

In 2008, Dr. Olsen accepted a medicinal chemistry position at Midwestern University's College of Pharmacy on the Glendale Campus. At the time, he was in possession of a series of intriguing modified molecules that were based on work he did in the mid-1980s with a former mentor. Dr. Olsen subsequently modified and investigated his molecules further when he undertook his new position at Midwestern. The molecules had the potential to lead to the development of new anti-metastatic cancer drugs that could stop the ability of some cancers to spread throughout the body.

Fourteen years later and with strong support from the College of Pharmacy, the Office of Research and Sponsored Programs, the Office of General Counsel, and Kathleen H. Goeppinger, Ph.D., President and Chief Executive Officer of Midwestern University, Dr. Olsen's hope for the molecules has proven correct. He has successfully developed a family of Aspartyl(asparaginyl)-beta-hydroxylase (ASPH) inhibitors that have demonstrated the ability to suppress cancer metastasis. This work has led to more than 10 academic papers and a series of U.S. patents that cover different aspects of the invention.

"Most cancer patients don't die of the initial tumor, they pass away due to the cancer spreading to other organs," Dr. Olsen said. "These drugs that can be taken by mouth have the ability to prevent challenging solid tumors, such as liver, lung, and pancreatic cancer, from spreading in the body."

Dr. Olsen added that just having a new drug is not satisfactory. "There must also be a way to determine which patients would benefit from the drug, and which ones would not. To address this issue, we've engineered a monoclonal antibody to ASPH to provide a comprehensive diagnostic and therapeutic patent portfolio suitable for proper investment," he added. To commercialize these findings, Dr. Olsen is planning to create a pharmaceutical company, Crenae Therapeutics, with venture capital funding. As part of the Midwestern University faculty, Dr. Olsen will continue to work on developing new pharmaceutical treatments that can benefit others.

The Story Behind Accelerated Aging Effects of Cancer Therapies

"While an accumulating body of evidence supports the hypothesis that cancer treatments including chemotherapy and radiation are associated with accelerated aging, its underlying mechanisms remain elusive."

Project: Cyclooxygenase-2 Signaling in Cell Senescence and its Role in Chemotherapy-induced Long-term Adverse Sequelae

Principal Investigator: Minsub Shim, Ph.D., College of Graduate Studies, Glendale Campus, Associate Professor, Biochemistry and Molecular Genetics

Consultants: Thomas Broderick, Ph.D., Professor, Pathology, College of Graduate Studies; Tony Tullot, M.D., Chair, Pathology, College of Graduate Studies

Grant: $450,000 NIH-R15 (REAP)

Dates: 12/1/2019 to 11/30/2022

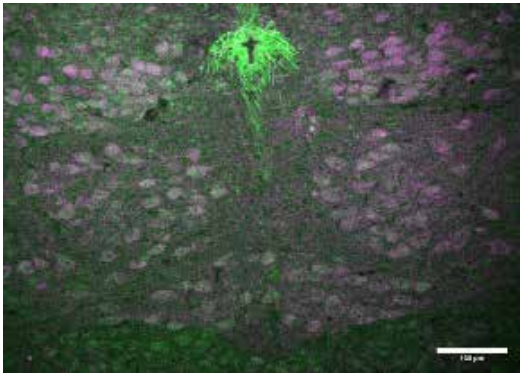
Project Summary:
Childhood cancers have grown increasingly prevalent in the United States over the past 40 years. With this increase in incidence, the survival rate has also risen, climbing above 80% in 2015. The increased survival rates brought with them an unfortunate consequence: the late effects of cancer therapy.

Survivors of childhood cancers often have an early occurrence of health conditions associated with aging, including neurocognitive decline, cardiovascular and respiratory diseases, endocrine and metabolic disorders, musculoskeletal complications, premature skin and ocular changes, and early onset of frailty, known as the late effects of cancer therapy. While an accumulating body of evidence supports the hypothesis that cancer treatments including chemotherapy and radiation are associated with accelerated aging, its underlying mechanisms remain elusive, partially due to a lack of animal models.

This project focuses on elucidating the molecular mechanisms by which chemotherapy causes adverse long-term side effects. Dr. Shim hypothesizes that cyclooxygenase-2 (COX-2), a key enzyme in the synthesis of bioactive lipids, plays an important role in the aging process and that targeting the COX-2 signaling can effectively suppress chemotherapy-induced aging. Using a novel mouse model that mimics the late effects of chemotherapy in the survivors of childhood cancer, Dr. Shim found that inhibition of COX-2 ameliorates aging phenotypes, and he is currently investigating how COX-2 regulates cellular senescence – the phenomenon where cellular division eventually ceases, inhibiting tissue repair and regeneration.

"Current estimates indicate that there are over 400,000 survivors of childhood cancer living in the United States," Dr. Shim says. "Given that survival rates are improving due to advances in treatment, this growing population is at increased risk for a number of chronic or even life-threatening health conditions. Our proposed studies can lead to the development of more effective strategies to prevent the late effects of chemotherapy, which could increase the quality of life in childhood cancer survivors."

Researcher Seeks to Understand Fundamental Cause of Sleep Apnea



"We must understand the basic science mechanisms that contribute to the normal, and eventually pathological, loss of airway tone during sleep to look for new ways to treat sleep apnea."

Project: Cholinergic Modulation of XII Motoneurons and XII Premotoneurons

Principal Investigator: Ann Revill, Ph.D., College of Graduate Studies, Glendale Campus, Assistant Professor, Physiology

Co-investigator: Nicole J. Francis, Ph.D., Associate Research Professor, Department of Biochemistry, Université de Montréal

Grant: $ 447,700 NIH-R15

Dates: 7/20/20 to 6/30/2022

Project Summary:
It is estimated that 12% of the U.S. population suffers from sleep apnea, and 80% of those people have not yet received a diagnosis. People with sleep apnea experience a decreased quality of life, lost productivity, increased risk of cardiovascular disease and stroke, and increased accident risk. Dr. Revill and her team of researchers are using grant funding from the National Institute of Health (NIH) to examine the root cause of sleep apnea.

During sleep, the loss of upper airway muscle tone can make the upper airway susceptible to collapse, which then leads to obstructive sleep apnea, characterized by repeated periods (up to hundreds per night) of low or no airflow ("apnea"). While some loss of airway tone during sleep is normal, it is not normal for the airway to completely collapse. Typically, tongue muscle activity during the drawing in of a breath, or inspiration, dilates and stiffens the airway to keep it open. However, during sleep, there's a reduced activity in the motoneurons that control the upper airway muscles, including the tongue. This contributes causally to obstructive sleep apnea. The reduced activity of the tongue motoneurons is hypothesized to be due to sleep-specific activation of the muscarinic acetylcholine receptors; these receptors can either increase or decrease the activity of cells, depending on several factors such as age.

Dr. Revill's lab will explore this hypothesis by examining the cellular and synaptic mechanisms that are modulated by muscarinic acetylcholine receptors in the tongue motoneurons, as well as the premotoneurons that provide the breathing drive to motoneurons. "We will use powerful electrophysiological techniques to record from individual neurons as well as populations of neurons in combination with a transgenic mouse model to test our hypotheses," Dr. Revill said. "The overarching goal is to determine how muscarinic acetylcholine receptor modulation changes across maturation from birth until adulthood. This fundamental information will be essential to next explore the mechanisms that contribute to reductions in airway tone during sleep."

In addition to the multitude of health concerns for people with sleep apnea, the economic impact is also monumental. In 2015, the total economic impact of sleep apnea was estimated to be $162 billion, including treatment costs as well as costs associated with undiagnosed sleep apnea. "We must understand the basic science mechanisms that contribute to the normal, and eventually pathological, loss of airway tone during sleep to look for new ways to treat sleep apnea," Dr. Revill added.

Understanding Why and How the Immune System Sometimes Attacks Healthy Cells

"Gap junctions between infected and healthy cells could allow antigenic proteins of pathogens to travel between them, creating an immune response that attacks healthy cells."

Project: Gap Junction-Mediated Antigen Transport Via Epithelial Connexin-43 Contributes to CD8+ T cell Activation and Immunopathology

Principle Investigator: Ashlesh Murthy, M.D., Ph.D., College of Veterinary Medicine, Associate Dean

Co-investigators: Weidang Li, M.D., Ph.D., College of Veterinary Medicine, Research Instructor; Srikanth Manam, M.S., College of Veterinary Medicine, Senior Research Specialist. Collaborators: Bruce Nicholson, Ph.D., UT Health Long School of Medicine, San Antonio, TX

Grant: $450,00 NIH-R15 (REAP)

Dates: 7/1/2019 to 6/30/2022

Project Summary:
The immune response is the body's natural method of fighting diseases and infections. By removing pathogens, which are microbes that carry infectious material to cells and cause illnesses, the immune system helps to regulate cell health and maintain homeostasis.

Immune cells identify these pathogens by means of antigenic proteins found on the pathogen's surface or those secreted out of the pathogen into the host. The detection of these proteins causes immune cells to manufacture peptides called cytokines, which create an inflammatory response in and around the infected cells. Sometimes, however, inflammation caused by an excess of these cytokines can extend beyond the infected cells to affect healthy cells, which result in pathological conditions such as inflammation during infection, hypersensitivity, and autoimmune diseases. Why, then, do the immune cells generate cytokines that intrude on healthy cells?

Dr. Murthy's research postulates that a specific type of immune cell – CD8+ T cells– might generate an excess of pro-inflammatory TNF-α cytokines that affect healthy cells because antigenic proteins from pathogens are transported to them via what is

called a "gap junction." Gap junctions are channels that connect the cytoplasms of two adjacent cells. Normally, antigenic proteins from intracellular pathogens cannot easily bridge the gap between cells on their own because they have to tediously cross multiple barriers of the lipid bilayers that makes up the host cell membranes. However, when groups of host proteins called connexins accumulate and interface across cell membranes (creating a "connexon"), a gap junction forms that could allow antigenic proteins of pathogens to travel from an infected cell to a healthy one. The presence of these antigen proteins in the healthy cell, then, would cause the CD8+ T cells to erroneously generate more cytokines and create a pathogenic reaction beyond the infected area.

By using a strain of the intracellular bacterium Chlamydia in mice to track the progression of infection and immune response, Dr. Murthy's group hopes to show the effects of gap junction transmission of antigen proteins to healthy cells and the subsequent immune response. "Understanding these effects will help us create safer, yet still efficacious, vaccines and immunotherapies," Dr. Murthy says, "as well as help us identify new targets for mitigating immune-induced disorders."

Midwestern University

Tomorrow's Healthcare Team

Downers Grove Colleges

Chicago College of Osteopathic Medicine

College of Pharmacy, Downers Grove

College of Dental Medicine - Illinois

Chicago College of Optometry

College of Health Sciences
- Physician Assistant
- Physical Therapy
- Occupational Therapy
- Clinical Psychology
- Speech-Language Pathology

College of Graduate Studies
- Biomedical Sciences
- Public Health
- Precision Medicine

Glendale Colleges

Arizona College of Osteopathic Medicine

College of Pharmacy, Glendale

College of Dental Medicine - Arizona

Arizona College of Optometry

College of Veterinary Medicine

College of Health Sciences
- Physician Assistant
- Physical Therapy
- Occupational Therapy
- Nurse Anesthesia
- Graduate Nursing
- Cardiovascular Science
- Clinical Psychology
- Speech-Language Pathology

Arizona College of Podiatric Medicine

College of Graduate Studies
- Biomedical Sciences
- Public Health
- Precision Medicine