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.
President and Chief Executive Officer, Midwestern University
**Expanding Research and Impacting Knowledge**

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

**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 StructuresΔ

- **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 PathologyΔ

- **Dr. Ann Revill**
  - College of Graduate Studies
  - Title: Cholinergic Modulation of XII Motoneurons and XII PremotoneuronsΔ

- **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. Chongwoo Kim**
  - College of Graduate Studies
  - Title: The Role of SAM Polymerization in Polycomb-dependent Chromatin StructuresΔ

- **Dr. Marc Scheetz**
  - College of Pharmacy
  - Title: Quantifying Renal Injury Among the Most Commonly Used Antibiotic CombinationsΔ

- **Dr. Joshua Edwards**
  - College of Graduate Studies
  - Title: Mechanisms of Cadmium-Induced Dysglycemia§

- **Dr. Mitra Esfandiarei**
  - College of Graduate Studies
  - Title: Targeting Endothelial Dysfunction in a Genetic Mouse Model of Aortic Aneurysm: Implications for Prevention and TherapyΔ

- **Dr. Joshua Edwards**
  - College of Graduate Studies
  - Title: Mechanisms of Cadmium-Induced Dysglycemia§

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

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**Funding Sources:**
- ΔNational Institute of Health Awards
- §USDA National Institute of Food and Agriculture
- *Arizona Biomedical Research Center
- †Leidos/ASU/NIH

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**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

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* Includes direct and indirect costs. For 2021, this equates to 7.7% of the University budget.
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.
<table>
<thead>
<tr>
<th>Investigator/s</th>
<th>College(s)</th>
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<tr>
<td>Baab, K.</td>
<td>CGS</td>
<td>Testing Adaptive Hypotheses of Plio-Pleistocene Hominin Craniofacial Evolution</td>
<td>$330,021</td>
<td>National Science Foundation</td>
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<td>Eckman, D., Jones, C., Jones, T.B., Vallejo-Elias, J. Virden, T. &amp; Powell, J.</td>
<td>CGS &amp; CHS-GD</td>
<td>Cerebrovascular Dysfunction and Cognitive Decline in Aging APOE2, APOE3 and APOE4 Targeted-Replacement Mice</td>
<td>$225,000</td>
<td>AZ Dept. of Health Services through the AZ Biomedical Research Commission</td>
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<td>Ellermeier, J.</td>
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<td>Jadavji, N.</td>
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<td>Identification of Developmental Factors Involved in Ischemic Stroke Outcomes in Adulthood and Old Age</td>
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<td>O’Neill, M.</td>
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<td>Collaborative Research: The Effects of Musculoskeletal Design on Bipedal Walking and Running Performance in Humans, Chimpanzees and Early Hominins</td>
<td>$239,935</td>
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<td>Collaborative Research: Evolution of Long-distance Communication in Vocal Rodents</td>
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<td>Riede, T.</td>
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<td>The Role of Vocal Ligament in Fundamental Frequency and Adduction Control</td>
<td>$201,055</td>
<td>NIH-R01 Subcontract from the University of Utah</td>
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<td>Townsend, K.E.B.</td>
<td>CGS</td>
<td>Collaborative Research: After the Bridgerian Crash - An Integrated Analysis of Mammalian Paleocommunities and Paleoecologies During the Middle Eocene</td>
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<td>National Science Foundation</td>
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<td>Elbayoumi, T. and Yao, M.</td>
<td>COP</td>
<td>Atrial Fibrillation Strategically Focused Research Network: Atrial Substrate in Atrial Fibrillation and AF-associated Brain Disease</td>
<td>$126,979</td>
<td>American Heart Association Subcontract from Northwestern University</td>
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<td>Gulati, A.</td>
<td>COP</td>
<td>Mentor and Train PCCM and NPM Fellows for Scholarly Activity</td>
<td>$170,000</td>
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<td>Scheetz, M.</td>
<td>COP</td>
<td>AKI001 Vancomycin (MEEK) and AKI002 Liposomal Vancomycin</td>
<td>$265,452</td>
<td>Nevakar, Inc.</td>
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<td>Vasudevan, B.</td>
<td>AZCOPT</td>
<td>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)</td>
<td>$313,000</td>
<td>Eyenovia</td>
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<tr>
<td>Vasudevan, B.</td>
<td>AZCOPT</td>
<td>Effect of LipiFlow on Ocular Surface Disease Management with Cataract Surgery</td>
<td>$273,000</td>
<td>Johnson &amp; Johnson Surgical Services</td>
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<tr>
<td>Rice, S.</td>
<td>CCO</td>
<td>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)</td>
<td>$313,000</td>
<td>Eyenovia</td>
</tr>
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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 medications and treatments. The Center continues to foster collaborative approaches that pair clinicians and scientists committed to improving the health of people and animals utilizing the principles of One Health.
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.
“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.”
“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.
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:** $450,000 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.”
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