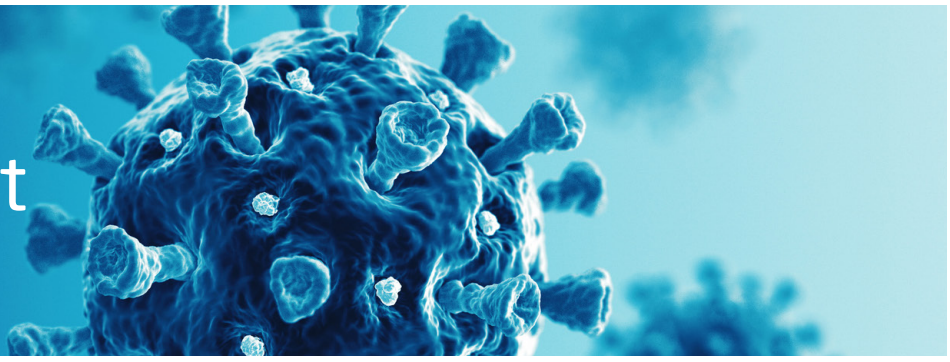
Breakthroughs

Feinberg School of Medicine Research Office

February 2023

Studying the Lasting Impact of COVID-19



By Olivia Dimmer

Feinberg scientists continue to investigate the lasting impact of the COVID-19 pandemic, from utilizing sentinel surveillance to monitor SARS-CoV-2 transmission rates to developing new approaches to monoclonal antibody therapy.

Using sentinel surveillance to monitor SARS-CoV-2 transmission

Sentinel surveillance, or having limited participants report data that may be generalized to an entire population, may help indicate increasing transmission of SARS-CoV-2 earlier than current COVID-19 surveillance efforts, according to a Northwestern Medicine study published in *Nature Communications.*

"We were really thrilled to work with the Illinois Department of Public Health and the Chicago Department of Public Health to test out new ideas around surveillance. Situational awareness is critical during outbreaks so that we can make decisions based on the latest and best data possible," said Jaline Gerardin, PhD, assistant professor of Preventive Medicine in the Division of Epidemiology and senior author of the study.

Since the beginning of the pandemic, COVID-19 surveillance efforts conducted by public health agencies have helped inform public health preparedness and response efforts. However, these systems often fail to accurately reflect fluctuating rates of SARS-CoV-2 transmission in communities.

In the current study, Gerardin's team aimed to determine if a novel sentinel surveillance system of outpatient SARS-CoV-2 testing data could more accurately assess increasing rates of disease transmission.

For this system, investigators used data from outpatient SARS-CoV-2 testing sites in Chicago. Patients were tested between September 2020 and June 2021 and reported symptom onset within four days preceding their test.

Overall, the investigators found that trends in sentinel cases were in good agreement with transmission rates obtained from local hospital data. Furthermore, transmission rates could be assessed approximately nine days sooner with sentinel surveillance than with hospital admissions.

Targeting internal protein in virus clears SARS-CoV-2, offers promising efficacy as variants emerge

An entirely new approach to monoclonal antibody therapy shows that targeting the more genetically stable internal protein of the SARS-CoV-2 virus rather than the surface spike protein can also clear SARS-CoV-2, according to a study from Northwestern Medicine and the University of Illinois at Chicago (UIC), published in the *Journal of Clinical Investigation.*

Some monoclonal antibody treatments have stopped working because the spike viral protein undergoes high rates of mutation, rendering some viral variants resistant to current antibody therapies. The novel approach could provide a new armament in treatments that could preserve effectiveness as the spike protein mutates.

This is the first time that therapeutic monoclonal antibodies have targeted an internal rather than a surface protein.

"These results may also contribute to the development of combined antibody therapies for SARS-CoV-2 as well as other viral diseases such as HIV by targeting unconventional viral proteins that are not typically targeted by monoclonal antibody therapies," said co-corresponding author Pablo Penaloza-MacMaster, PhD, assistant professor of Microbiology-Immunology.

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Northwestern Medicine®

Covid-19 *(continued from cover page)*

The first author is Tanushree Dangi, PhD, a research associate in the Penaloza-MacMaster laboratory.

All the monoclonal antibody therapies for SARS-CoV-2 are based only on the surface spike protein because this viral protein mediates entry into the cell.

"It's like a key and lock system to enter the cell," Penaloza-MacMaster said. "You want to have antibodies that prevent the key – the spike – from entering the lock. But the key has been changing as the virus mutates, and some antibody treatments are no longer effective at blocking the key from opening the lock. The current antibody therapies could lose efficacy in the future. We asked whether targeting the internal part of the virus by an antibody therapy would confer protection."

The nucleocapsid protein is present inside SARS-CoV-2, but when a cell gets infected, the nucleocapsid protein is exposed to the cell surface. The nucleocapsid is among the most abundant proteins in SARS-CoV-2, making it an excellent target for antibodies that can then recruit cells of the immune system.

Postacute complications of SARS-CoV-2 infection in children

Postacute sequelae of SARS-CoV-2 infection (PASC), more commonly known as "long COVID," or symptoms that manifest weeks or months after primary SARS-CoV-2 infection, has emerged as a well-known complication in adults but has remained understudied in pediatric patients.

A recent study published in *JAMA Pediatrics* found that PASC is uncommon in children with SARS-CoV-2 infection and presents features that differ from adults.

"The strengths of our analysis are being able to use a national pediatric electronic health data network (PEDSnet) as the source of this information and defining specific pediatric syndromes from the high background rate of symptoms and complaints that make studies of long COVID so challenging," said Ravi Jhaveri, MD, division head and the Virginia H. Rogers Professor of Infectious Disease in the Department of Pediatrics, who was also co-author of the study.

In the current study, investigators analyzed electronic health record data from more than 650,000 pediatric patients across the U.S. who underwent viral testing for SARS-CoV-2 between March 2020 through October 2021. Of these patients, nine percent tested positive, and 91 percent tested negative.

Using statistical analysis, the investigators found that the symptom, condition and medication most strongly associated with SARS-CoV-2 infection were loss of taste and smell, myocarditis and cough and cold medications.

Furthermore, the incidence of at least one systemic, syndromic or medication feature of PASC was 41.9 percent among children who tested positive versus 38.2 percent among children who tested negative, with an incidence proportion difference of 3.7 percent.

"Our findings suggest that the burden and risk windows of PASC may differ between children and adults. Future studies, including long-term prospective studies, such as the National Institutes of Health RECOVER Initiative, are needed to fully elucidate PASC phenotypes," the authors wrote.

New study reports the longest follow-up period of neurologic symptoms impacting non-hospitalized COVID-19 'long-haulers'

Most non-hospitalized COVID-19 "long-haulers" at the Northwestern Medicine Neuro COVID-19 Clinic continued to experience symptoms such as brain fog, numbness and tingling, headache, dizziness, blurred vision, tinnitus and fatigue an average of 15 months after disease onset, according to a study published in *Annals of Clinical and Translational Neurology.*

Scientists analyzed patients six to nine months after their initial visit to the Neuro COVID-19 Clinic and discovered heart rate, blood pressure variation and gastrointestinal symptoms increased in so-called long-haulers, while loss of taste and smell decreased overall.

"This new study is novel and reports the longest follow-up period of neurologic symptoms impacting non-hospitalized patients suffering from long-COVID anywhere in the world," said Igor Koralnik, MD, chief of Neuro-infectious Diseases and Global Neurology in the Department of Neurology, who oversees the Neuro COVID-19 Clinic. "We were surprised by the persistence of most of the debilitating neurologic symptoms of our patients, and by the late appearance of symptoms that suggest dysfunction of the autonomic nervous system."

Feinberg medical students Sareen Ali, Anthony Kang, Tulsi Patel and Jeffrey Clark were the lead authors of the study, and team members at the Neuro COVID-19 clinic.

Melissa Rohman contributed to this article.

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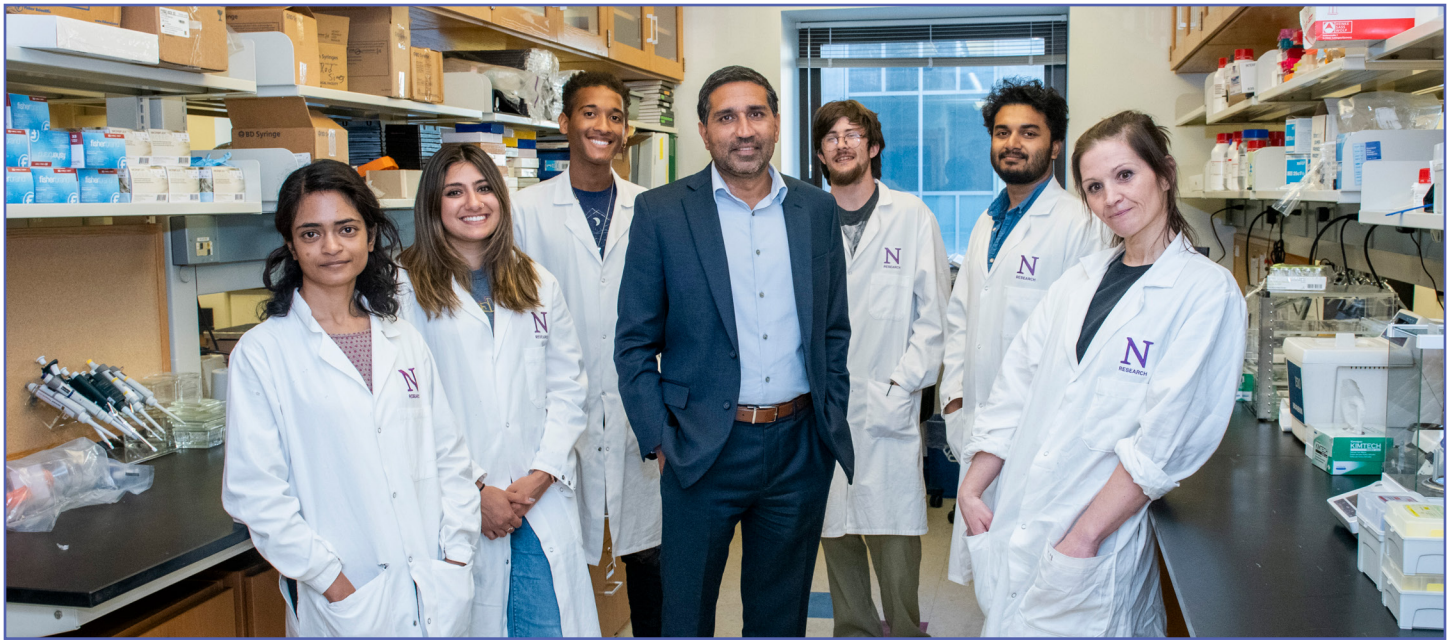


Medical School Establishes New Center for Psychiatric Neuroscience

By Olivia Dimmer

Feinberg has established the Center for Psychiatric Neuroscience, a collaborative hub created to unite interdisciplinary scientists to understand neural mechanisms underlying mental illness, elucidate mechanisms of psychotropic drug action and develop novel therapeutics.

Sachin Patel, MD, PhD, chair of the Department of Psychiatry and Behavioral Sciences, and the Lizzie Gilman Professor of Psychiatry and Behavioral Sciences, will serve as director of the center.

“Cultivating a Department of Psychiatry integrated with robust translational neuroscience research is extremely important for the future of our field,” Patel said. “This is a unique opportunity to synergize with the existing neuroscience infrastructure including the Departments of Neuroscience, Pharmacology, Neurobiology and other areas to establish a center that’s really at the intersection between mental health and neuroscience.”

In addition to serving as a platform for recruiting new faculty to Feinberg, the center will be a focal point for current Northwestern faculty with an interest in utilizing neuroscience approaches to better understand pathophysiological mechanisms of mental illness.

While center investigators are focused broadly in mental health neuroscience, recently recruited faculty will be especially focused on understanding stress-related psychiatric disorders and their comorbidity with substance use disorders and the neural basis of trauma memory formation and expression important for understanding disorders such as PTSD, Patel said.

“So far, we’ve focused on understanding important environmental risk factors, such as stress, which is a major risk factor for pretty much all psychiatric disorders and is ubiquitous in our society,” Patel said. “We want to understand how that environmental pressure interacts with the brain to lead to increases in susceptibility to developing psychiatric disorders. Ultimately by uncovering those mechanisms, we hope to potentially reveal mechanisms for intervention and mitigate some of the effects of stress on psychiatric illnesses.”

The center will also host educational events and provide technological resources and support for scientists studying translational neuroscience and psychiatry, he said.

Patel’s own research has focused on the body’s endogenous endocannabinoid system, as well as understanding how cannabis affects neurobehavioral processes and the pharmacology of cannabis as it relates to pathophysiology and mental health treatment.

Information about the center can be found at the Center for Psychiatric Neuroscience website and Northwestern faculty or trainees can apply to become a member through the center’s membership application.

Listen to an episode of the Breakthroughs Podcast on this topic.

Graduate Student/Post-Doc Events and Opportunities

Institute for Sexual and Gender Minority Health and Wellbeing 2023 Postdoctoral Fellow Showcase

March 2, Noon to 1:00 p.m.

This year showcases the work of the three newest postdoctoral fellows: Michael Curtis with "Understanding the Syndemic Consequences of Intersectional Stigma on Substance Abuse: Appraising the Role of Traumatic Stress"; Jacob Gordon with "Technology Use of SGM Individuals: Implications for Digital Mental Health"; and Juan Pablo Zapata with "Using Implementation Science to Tailor HIV Intervention(s) for Latino Men in the U.S."

Stonewall Conference Room
625 N. Michigan Avenue, Suite 1400, Chicago
More information

Scott Lecture Series: The Chromosomal Basis of Sex Differences in Health and Disease

March 9, 3:30 to 4:30 p.m.

This presentation is a part of the Scott Lecture Series and is co-sponsored by the Driskill Graduate Program in Life Sciences at Northwestern University. Guest speaker David Page, MD, studies the genetic differences between males and females and the biological and medical ramifications of these differences. Ultimately, the grand opportunity awaits: To understand male-female differences in diseases by understanding male-female differences in healthy cells, tissues and organs, at a molecular level and across the body. A reception will follow the lecture at 4:30 p.m. in the Ryan Family Atrium.

Hughes Auditorium
Robert H. Lurie Medical Research Center
303 E. Superior St., Chicago
More information

CAN Seminar Series: Understanding the Social Brain

March 23, 2:00 to 3:00 p.m.

Social interactions between individuals and among groups are a hallmark of human society and are critical to the physical and mental health of a wide variety of species including humans. Weizhe Hong will discuss the central goal of the lab: to study the fundamental principles of how social behavior is regulated in the brain. They study how neural circuits and the underlying computation regulate social behavioral decisions within a single brain as well as how emergent inter-brain neural properties arise from social interactions between individuals.

Simpson Querrey Auditorium
Simpson Querrey Biomedical Research Center
303 E. Superior St., Chicago
More information

Northwestern's Women in Medicine Conference

March 24, 8:00 a.m. to 4:30 p.m.

Women in medicine face unique challenges and obstacles throughout their professional careers. These challenges may affect leadership development and opportunities for women in medicine resulting in a gender gap in the governance of academic medical centers. Women physicians and other healthcare workers currently lack a conference or forum for discussing strategies to achieve equality in the workplaces, wellness and work-life balance, mentorship and career development. The fifth annual Northwestern Women in Medicine conference will help to identify the obstacles that contribute to gender inequity and will start the discourse to bridge it by hosting an in-person conference.

Northwestern Memorial Hospital
Feinberg Pavilion, Feinberg 3 – Third Floor
251 E. Huron St., Chicago
More information

Research in the News

***TIME*, January 5**
The Daily Habits of Happiness Experts
Judith Moskowitz, PhD, MPH, was featured.

***WTTW*, January 7**
Make a Resolution: Get Screened for Hypertension in 2023
Pierre Blemur, Jr., MD, was featured.

***New York Times*, January 11**
Gas Stoves Are Tied to Health Concerns. Here's How to Lower Your Risk.
Ravi Kalhan, MD, MS, was featured.

***US News and World Report*, January 18**
Appendicitis Often Spotted Later in Black Patients
Anne Stey, MD, was featured.

***USA Today*, January 24**
Xylazine, an animal tranquilizer, is a new threat in the opioid epidemic: What we know
Maryann Mason, PhD, was featured.

***The Washington Post*, January 24**
How to prevent and treat chronic constipation
Christian Stevoff, MD, was featured.

Understanding and Improving Variant Interpretation in Minoritized and Underserved Populations

Adam Gordon, PhD, assistant professor of Pharmacology

Adam Gordon, PhD, is a member of the Center for Genetic Medicine. His laboratory investigates the implementation of genomic testing in medical and consumer contexts, and the process of variant interpretation that seeks to translate this testing into actionable clinical findings.

What are your research interests?

Our genomes are more accessible than ever before through commercial and clinical testing. However, the accumulation of this personal genomic data has significantly outpaced our ability to interpret it. My research focuses on how we decide what genetic variants mean, how we identify genetic variation that is clinically actionable and how to implement genomic medicine broadly and equitably without exacerbating the disparity, bias and scientific racism that's pervasive in medicine. As these questions are not unique to a specific clinical domain, I have active projects in oncology, cardiology, rheumatology, ophthalmology and other fields.

What is the ultimate goal of your research?

My research has three ultimate goals: 1) To refine our understanding of clinical actionability and penetrance in genomic medicine through data-driven approaches that integrate population and family-based cohorts of genomic and EHR data; 2) To broaden access and utility of genetic testing, especially in communities where such testing is beneficial but underutilized; and 3) To disrupt harmful notions about genetic determinism and scientific racism in medicine and the public at large through intersectional genomics education.

How did you become interested in this area of research?

In 2001, my biology teacher put up a poster of the map of the brand-new draft human genome. I was utterly fascinated at the idea that our genomes are what make us all fundamentally the same, but also fundamentally unique. That's when I knew I wanted to be a human geneticist.

My early work and interests were focused on population genetics and human evolution, thinking about the relationships between common and rare genetic variation, how these variants assort into different population groups, and how we decide which variants "do something." However, as I saw genomics expanding rapidly into medicine, I realized the extent to which concepts from human genetics have been misunderstood and misused in ways I believe are directly harmful to the public, and especially to minoritized communities. I believe those of us in medical research have a duty to acknowledge and repair these injustices, and I try to align my research with this intention.

What types of collaborations are you engaged in across campus (and beyond)?

As a team scientist, my goal is to partner with groups with deep expertise in specific clinical domains. Combining this expertise with emerging genomic technologies and data from large-scale population cohorts can lead to new insights into risk management, treatment and the biology of disease. Some current examples include studying the genetic architecture of sudden cardiac death with Greg Webster, MD, developing polygenic predictors of lupus risk with Theresa Walunas, PhD, and building a registry of individuals undergoing genetic testing for hereditary cancer risk with Mohammad Abbass, MD, PhD.

I have also for many years been a part of the national electronic Medical Records and Genomics (eMERGE) Network, which in its current iteration is studying the utility of polygenic risk testing in primary care: I am leading the prostate cancer arm of this study. Additionally, I serve on the American College of Medical Genetics secondary findings workgroup, using data to create policy about what genetic variation is actionable, and what sorts of incidental, actionable variation labs and providers have an ethical duty to report.

Finally, I'm very passionate about genomics education; I've worked with Nia Heard-Garris, MD, Susanna McColley, MD, and others to develop a course on anti-racist research strategies for current physicians, and recently completed a major revamp of the medical school genetics curriculum as a co-leader of the Foundations 1 module.

How is your research funded?

My research is primarily funded through the National Institutes of Health, especially the National Human Genome Research Institute, as well as the National Cancer Institute through Northwestern's Prostate Cancer SPORE. I also have some funding through foundations, particularly the American Heart Association.

Who are your mentors?

I am eternally grateful to those who have mentored me, and I carry their lessons with me every day. Specifically, my PhD advisor Debbie Nickerson and postdoc advisor Gail Jarvik; they taught me that the key to good science is teamwork, and that our responsibility as scientists is to be aspirational ...

Read more on page 8.

Investigating Endothelial Cytoskeletal Dynamics

Jocelynda Salvador, third-year PhD student in the Driskill Graduate Program

Jocelynda Salvador is a third-year PhD student in the Driskill Graduate Program. After graduating from University of California Irvine with a degree in biomedical engineering, she then worked as a post-baccalaureate fellow conducting research focused on microtubule dynamics during endothelial morphogenesis using 3D matrices.

In her work in the laboratory of Luisa Iruela-Arispe, PhD, the chair and Stephen Walter Ranson Professor of Cell and Developmental Biology, Salvador investigates endothelial cytoskeletal dynamics under different flow conditions in vitro and in vivo, as well as the effects of aging on the endothelium.

Where is your hometown?
I am from Los Angeles.

What sparked your interest in science or medicine?
I have always had an interest in innovations in science and medicine. Being involved in research as an undergraduate solidified my interest in research as a path that would allow me to contribute to scientific knowledge driving those innovations.

What are your research interests?
I am interested in the vasculature. Our organs rely on stable vessel networks to get nutrients delivered throughout our bodies in a regulated manner. I am interested in how blood vessel networks form during embryonic development and how heterogeneity of different vascular beds arises.

What are you currently working on?
The main project I am focused on is understanding how blood flow in the aging aorta affects nuclear and chromosomal integrity of endothelial cells (the cells that line the inside of all blood vessels). Loss of nuclear integrity in diseases like Hutchinson Gilford Progeria Syndrome leads to accelerated aging and cardiovascular phenotypes. I find that endothelial nuclear shape is compromised in areas of the aorta exposed to oscillatory flow that becomes progressively severe with age. I am working on understanding the consequences of loss of endothelial nuclear shape and if they contribute to accelerated vascular aging.

Please tell us about a defining moment in your education at Feinberg thus far.
When I first arrived at Feinberg, I felt a strong sense of community among the PhD students in my program, the Driskill Graduate Program and the research labs. The scientists at Northwestern are a community that openly collaborate, sharing ideas and reagents to fully support basic science advancement. As a trainee, I feel supported by my own peers and my department to succeed.

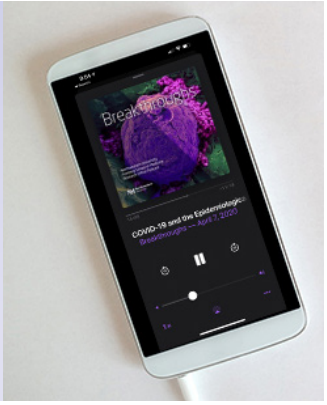
What do you hope to do with your degree?
I am still not set on a specific path but remain interested in research in government, industry or academic institutions.

Breakthroughs Podcast

A New Focus on Implementation Science with Sara Becker, PhD, and Rinad Beidas, PhD

To have the greatest impact on human health, biomedical research findings and evidence-based practices need to be implemented into routine healthcare. What is implementation science, and how can we ensure research successfully makes an impact? Rinad Beidas, PhD, and Sara Becker, PhD, discuss the field and its future as a research priority at Feinberg.

Listen to the episode.



Postdoctoral Investigator Pursues Research on Microbiome

Booker Davis IV, PhD, postdoctoral fellow, Division of Trauma and Critical Care

By Olivia Dimmer

As a young boy growing up on the southeast side of Chicago, Booker Davis IV, PhD, always had an interest in science. His budding knowledge and personality even earned him the nickname "professor."

After graduating high school and serving in the army, Davis completed his undergraduate degree at Chicago State University, where he had his first experience conducting research on metabolic diseases. After completing his PhD from Rush University in a laboratory led by gut specialist Ali Keshavarzian, MD, Davis joined Northwestern and currently works as postdoctoral fellow in the lab of Steven Schwulst, MD, FACS, FCCM, assistant professor of surgery in the Division of Trauma and Critical Care.

Davis' work focuses on the brain-gut axis, specifically how the gut microbiome and immune system can influence healing after a traumatic brain injury.

Early results have shown that mice with traumatic brain injuries benefit from receiving a dose of healthy gut bacteria, Davis said.

"The results were almost magical to look at," Davis said. "We saw almost no secondary effects. It was very protective to replace the gut bacteria of an injured mouse with that of a healthy mouse. Now, we're following up on that to see which specific organisms in the microbiome have this positive effect: could it be bacteria, fungus, a virus, something else? The brain is the most complex system we know of in the universe, and we're just beginning to understand the connection to the gut."

Davis recently received the National Institutes of Health Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) award, given by the National Institute of General Medical Sciences, designed to facilitate the transition of promising postdoctoral researchers from diverse backgrounds into independent, tenure-track or equivalent research-intensive faculty positions.

The next phase of his research will involve studying the effects of introducing specific short chain fatty acids to the gut microbiome of mice with traumatic injuries to see which fatty acids are most effective in supporting healing brains. Davis will study the effects in both very young and elderly mice.

"I hope to one day use this research to help aging populations who have neurological diseases and veterans who have suffered traumatic brain injuries on the battlefield," Davis said. "This work is my personal mission. I'm honored by the MOSAIC award and excited that I can really put my head down and focus on this work so that it might go on to help people."

New Faculty

Kenneth Carson, MD, PhD, joined Feinberg as associate professor of Medicine in the Division of Hematology and Oncology on January 1. His clinical interests include lymphomas and other hematologic malignancies. His research interests are in the areas of real-world evidence and understanding and predicting clinical outcomes. Previously, he was assistant professor at Washington University in St. Louis, where he was section chief of hematology/oncology at the St. Louis VA Medical Center. Before joining Feinberg, he spent time working in the technology industry at the start-up companies Flatiron Health and Tempus Labs. Carson received his medical degree from the University of Southern California, Keck School of Medicine and his PhD from the School of Public Health at the University of Illinois Chicago. He completed his residency at Duke University Medical Center and his fellowship at Northwestern University, McGaw Medical Center. Carson is a fellow of the American College of Physicians and a member of the American Society of Hematology and the American Society of Clinical Oncology.

NUCATS Corner
Clinical and Translational Sciences Institute

Translational Science Pilot Awards, Voucher Grants Available

The NUCATS Institute's Translational Science Pilot Awards program is seeking proposals for highly innovative, multi-disciplinary pilot projects that will advance Translational Science and are aligned with one of two priority areas: Clinical and Translational Research (CTR) or Dissemination and Implementation (D&I). This funding mechanism combines, replaces, and builds on the two prior NUCATS pilot funding mechanisms: Clinical and Translational Pilot Awards and Dissemination and Implementation Pilot Awards. Proposals may request funding for CTR, D&I, or hybrid effectiveness-implementation studies that encompass both CTR and D&I.

The NUCATS Voucher Award program is designed to assist investigators in developing resources and/or preliminary data to facilitate hypothesis-driven research initiatives. The fund is intended for projects involving critical steps in the device and drug development pathway and projects that address a critical need in translational science that are too small to be suitable for conventional internal or external funding mechanisms. Proposals that address a specific translational barrier and have a high probability of external federal funding if the barrier is addressed are most likely to receive funding.

Details about the Voucher Award program — including funding priorities, eligibility criteria, program expectations, and allowable expenses — are available on the NUCATS funding website. Funding decisions are typically communicated to applicants within five business days.

If you would like additional information on these or other NUCATS funding mechanisms, please email NUCATS-funding@northwestern.edu

Adam Gordon, PhD... *(continued from page 5)*

... and progressive "gate-openers" instead of gatekeepers.

I'm inspired by so much in history and culture, but two scientists stand out. Julia Bell, a pioneering statistical and medical geneticist who created the very first compendium of genetic diseases, and in 1937 was the first to describe X-linked traits in humans (colorblindness and hemophilia). Also, Arno Motulsky, who fled Nazi Germany on the SS St. Louis, famously turned away by the U.S. He eventually made his way to America where he went on to become a trailblazer in medical genetics and the field of pharmacogenetics.

NIH News

Lessons learned from the NIH-led research response to COVID-19
Leaders from the National Institutes of Health and partner organizations outline NIH's COVID-19 research response in a policy forum in the journal of *Science*. The authors also reflect on crucial lessons learned that will inform the public health research response to future pandemics. The authors emphasize that by building on decades of basic and applied research and convening all sectors in highly collaborative partnerships, the biomedical research community was able to quickly develop vaccines, therapeutics and diagnostics in response to the COVID-19 pandemic.

NIH launches intramural bioengineering center to foster technology collaboration across the agency
The National Institute of Biomedical Imaging and Bioengineering (NIBIB) has established the Center for Biomedical Engineering Technology Acceleration (BETA Center), a new intramural research program to solve a range of medicine's most pressing problems. The center will incorporate a focused engineering approach to accelerate cutting-edge technologies' development, validation and disseminations. A unique feature of the center will be its ability to rapidly assemble expert teams for purpose-driven technology development to address urgent national and global health needs. A fundamental objective of the BETA Center is to expand diversity, equity, inclusion and accessibility (DEIA) at NIBIB, building on the inherent interdisciplinary nature of biomedical engineering.

Changing long-term opioid prescribing behavior
America's opioid overdose epidemic now claims more than 100,000 lives each year. A 2018 study tested the use of a low-cost intervention to reduce new or inappropriate opioid prescriptions. They identified almost 170 people who died of overdoses in a single country in California during a one-year period. They also identified more than 800 clinicians who had written a prescription to one of the deceased within a year of their death. Half of these clinicians were then sent a letter from the county medical examiner informing them of the patient's overdose death. The group of clinicians who received a letter prescribed a 7 percent smaller quantity of opioids per week than those who did not receive a letter. These results suggest that the impact of the notification letters on prescribing behavior persisted for up to a year. The research has shown that one possible policy change could be to make such notifications from county medical examiners mandatory.

Sponsored Research

PI: Hongxin Dong, MD, PhD, **professor in the Departments of** Psychiatry and Behavioral Sciences (General Psychiatry) **and** Neurology - Ken and Ruth Davee Department**.**

Sponsor: National Institute on Aging

Title: Epigenetic Regulation in Aging and Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and neuropathological changes in the brain. Aging remains the single largest risk factor for sporadic AD, but the mechanisms underlying this risk are not well understood. Epigenetics has been implicated in both aging and the pathogenesis of AD. Promising results from our group and others have showed that epigenetic alterations occur during aging and thereby affect neuronal function, and contribute to memory deficits and the pathogenesis of AD.

In the proposed project, we will use mouse models of both aging and AD, as well as human postmortem tissues, to determine the histone modifications in the epigenome that occur during aging. We will also determine whether these changes promote the development of neuropathological changes that are associated with AD. Our hypothesis is that dysregulations of histone modification during aging promote AD by initiating the development of AD-related changes in neuronal networks at the molecular level. In turn, we also hypothesize that histonedeacetylase (HDAC) inhibitors can mitigate or even prevent the neuropathogenesis of AD. To test our hypotheses, we will first map histone modifications that occur at three critical life stages (three, 12 and 18 months of age) in both wild-type (WT) and APP/PS1 mice, as well as human postmortem tissues (AD patients, young, aged healthy controls), to determine whether differential histone acetylation and methylation contribute to memory deficits and neuropathological changes associated with AD. This will be achieved through CUT&RUN seq and RNA seq combined with pathway analysis to determine the functional consequence of significant genes that are regulated by epigenetics. We will also profile histone modifications at specific gene promoter regions that are related to memory, synaptic plasticity, and the typical elements of AD neuropathology. Second, given that HDACs are key factors in histone modification and in the regulation of gene transcription, we will determine whether dysfunction of any specific HDACs causes memory deficits in AD mouse models. For this purpose, we will utilize genetic editing tools including CRISPR/Cas9-mediated knock-down and AAV9-eGFP-mediated over-expression to identify critical HDACs (eg. HDAC2 and 3) that modulate histone acetylation and methylation marks at gene promoters specifically linked to memory and neuronal plasticity. Finally, we will determine whether HDAC inhibitors have beneficial effects on memory-like behaviors and AD-like neuropathological changes in APP/PS1 mice (3, 12 and 18 months of age) as well as in age-matched WT mice. More specifically, we will investigate whether non-selective (i.e., VPA) or selective HDAC inhibitors (i.e., MS-275 and CI-994) are effective in preventing and/or rescuing memory function and neuronal changes in aging and AD mouse models.

Overall, this project will significantly improve our understanding of the epigenetic mechanisms that link aging with the neuropathogenesis of AD. Identification of these mechanisms will lay the basis for developing novel therapeutic strategies for the prevention and treatment of AD. Read more about the project.

PI: Nicolae Valentin David, PhD, **Frank Krumlovsky, MD, Professor and associate professor of** Medicine **in the Division of** Nephrology and Hypertension**.**

Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases

Title: Role of FGF23 peptides in chronic kidney disease (CKD)

Iron deficiency and inflammation are major stimulators of fibroblast growth factor 23 (FGF23) production and FGF23 cleavage. In diseases associated with impaired FGF23 cleavage, such as chronic kidney disease (CKD), iron deficiency and inflammation contribute to disproportionately and extremely elevated levels of circulating intact FGF23 compared to the levels of FGF23 cleaved peptides, which directly leads to adverse cardiovascular outcomes. This project proposes to investigate the function of C and N terminal FGF23 peptides as key regulators of iron metabolism, erythropoiesis and cardiac remodeling, providing novel therapeutic targets to improve outcomes related to FGF23 perturbations in patients with CKD.

Intact fibroblast growth factor 23 (iFGF23) is a phosphate regulating hormone secreted by bone. In CKD, increased FGF23 transcription is associated with cardiovascular mortality, disturbed iron metabolism and anemia. FGF23 transcription is physiologically coupled to FGF23 cleavage by Furin resulting in secretion of iFGF23, carboxy terminal (Cter) and amino terminal (Nter) FGF23 peptides. The well-established function of iFGF23 is to maintain normal phosphate homeostasis by targeting the kidney but there is emerging evidence supporting extra-renal FGF23 targets which might be the result of increased Cter- and Nter-FGF23 signaling. Novel approaches to reduce FGF23-associated adverse outcomes in CKD are desperately needed but current therapies are suboptimal due to lack of understanding of the role of FGF23 peptides. In preliminary data we show that in addition to iFGF23, FGF23 peptides are secreted by bone and extraosseous sources, including erythroid cells, in CKD. We also show that these peptides display novel physiological functions. Cter-FGF23 peptides suppress the secretion of the hepatic iron regulatory hormone, hepcidin, leading to increased circulating iron. Nter-FGF23 peptides are not released in the circulation when FGF23 is expressed in bone, but in iron deficient animals and patients and mice with CKD, FGF23 production by erythroid cells contribute to increased circulating Nter-FGF23 levels. When elevated, Nter-FGF23 reduces the secretion of erythropoietin, inhibits erythropoiesis and induces left ventricular hypertrophy (LVH).

These observations support important new roles of FGF23 peptides, and a functional role for the coupled regulation of FGF23 transcription and iFGF23 cleavage. In Aim 1, we will establish the physiological and pathological role of Cter-FGF23 peptides in iron metabolism. Using multiple genetic mouse models, we will delete and overexpress FGF23 and Cter-FGF23 in bone, to test whether Cter-FGF23 peptides generated from increased FGF23 cleavage, protect mice against overt hypoferremia by uniquely limiting hepcidin secretion in models of high (inflammation and iron overload) or low (iron deficiency) endogenous hepcidin and compare these effects to exogenous hepcidin administration. We will further test the therapeutic potential of genetic and pharmacologic Cter-FGF23 supplementation in two mouse models of CKD and assess the onset and development of iron deficiency anemia. In Aim 2, we will use the genetic overexpression and pharmacologic administration of FGF23 and Nter-FGF23 in osteocytes and erythroid cells, *in vivo* and *in vitro*, to investigate the direct role of iFGF23, Nter-FGF23 and FGFR signaling in the inhibition of erythropoiesis, and their indirect role by regulating erythropoietin (EPO) production in kidney and liver. We will further investigate whether erythroid-produced Nter-FGF23 peptides contribute to LVH in mice with CKD and test the direct hypertrophic effects of Nter-FGF23 in cardiomyocytes cultures.

This project will contribute to new insights into the molecular functions of FGF23 and support our ultimate goal of developing novel therapeutic approaches to improve adverse outcomes associated with excess FGF23. Read more about this project.

Funding

The Feinberg School of Medicine has increased seed funding up to $50,000 for application preparation to initiate new multi-investigator program project or center grant applications involving Feinberg faculty. Learn more on the website here.

Healthy Eating Research: Addressing Supportive Family Policies and Programs So All Children and Adolescents in the U.S. Can Thrive

More information

Sponsor: Healthy Eating Research (Robert Wood Johnson Foundation)
Submission deadline: April 5
Upper amount: $275,000 over 2 years

HER, a national program of the Robert Wood Johnson Foundation, seeks research proposals to generate evidence on supportive family policies and programs that have strong potential to impact equitable access to nutritious food in communities, nutrition security, diet quality and improved nutrition and health outcomes. Programs that will be studied are in the areas of: federal nutrition assistance programs; hunger-relief programs; community-powered food systems efforts; and social and economic programs (non-food policies). HER is especially interested in strategies to improve health outcomes for children ages 0 to 18 at the highest risk for poor nutrition, specifically lower-income families, as well as the racially and ethnically diverse populations experiencing higher rates of health disparities.

Biomedical Research Fellowship

More information

Sponsor: Helen Hay Whitney Foundation
Submission deadline: June 15
Upper amount: $181,500 over three years

The Helen Hay Whitney Foundation supports early postdoctoral research training in all basic biomedical sciences. To attain its goal of increasing the number of imaginative, well-trained and dedicated medical scientists, the foundation grants financial support of sufficient duration to help further the careers of young men and women engaged in biological or medical research. Candidates who hold, or are in the final stages of obtaining, a PhD, MD, or equivalent degree and are seeking beginning postdoctoral training in basic biomedical research are eligible to apply for a fellowship. The foundation accepts applications from candidates who have no more than two years of postdoctoral research experience at the time of the deadline for submitting the application, and who have received a PhD (or DPhil or equivalent) degree no more than three years before the deadline, or an MD degree no more than four years before the deadline.

Pediatric Research Grants

More information

Sponsor: The Gerber Foundation
Submission deadline: May 15
Upper amount: $350,000

The Gerber Foundation is particularly interested in fresh approaches to solving common, everyday problems or emerging issues within our defined focus area. Projects should focus on issues faced by care providers that, when implemented, will improve the health, nutrition and/or developmental outcomes for infants and young children. The board is particularly looking for practical solutions that can be easily and rapidly implemented on a broad scale with a predictable time frame to clinical application.

Cancer Research Grants

More information

Sponsor: Elsa U. Pardee Foundation
Submission deadline: April 30
Upper amount: $300,000

The Elsa U. Pardee Foundation funds research to investigators in United States non-profit institutions proposing research directed toward identifying new treatments or cures for cancer. The foundation funds projects for a one-year period which will allow the establishment of capabilities of new cancer researchers or new cancer approaches by established cancer researchers. It is anticipated that this early-stage funding by the foundation may lead to subsequent and expanded support using government agency funding. Project relevance to cancer detection, treatment, or cure should be clearly identified. By design, there are no limits set on the grant amount that can be requested.

Read more about the highlights of our educational programs, innovative research and discoveries, and our outstanding students, faculty, and staff in the Feinberg News Center and the *Northwestern Medicine Magazine.*

Clarivate Analytics Announces 2022 Highly Cited Researchers

By Karen Gutzman, Head, Research Assessment and Communications Librarian

Each year, Clarivate Analytics releases a list of highly cited researchers, who have "demonstrated significant and broad influence, reflected in the publication of multiple papers frequently cited by their peers during the last decade."

Below is a list of the Feinberg researchers who made the list in 2022, their appointment at the medical school and the category they were identified in. Congratulations! (Please note that faculty may have more than one appointment.)

David Cella, PhD, Medical Social Sciences, in Social Sciences

Navdeep Chandel, PhD, Medicine (Pulmonary and Critical Care), in Molecular Biology and Genetics

Mark Hersam, PhD, Medicine (Pulmonary and Critical Care), in Materials Science

Shana Kelley, PhD, Biochemistry and Molecular Genetics, in Cross-Field

Donald Lloyd-Jones, MD, Preventive Medicine, in Clinical Medicine

Chad Mirkin, PhD, Medicine (Hematology and Oncology), in Cross-Field

Brian Mustanski, PhD, Medical Social Sciences, in Cross-Field

Amy Paller, MD, Dermatology, in Cross-Field

John Rogers, PhD, Neurological Surgery, in Materials Science

Sanjiv Shah, MD, Medicine (Cardiology), in Clinical Medicine

Jeffrey Sosman, MD, Medicine (Hematology and Oncology), in Clinical Medicine

Richard Wunderink, MD, Medicine (Pulmonary and Critical Care), in Cross-Field

Clyde Yancy, MD, Medicine (Cardiology) in Clinical Medicine

Clarivate evaluates papers that were published and cited from 2011 to 2021 and ranked in the top 1 percent by citations for the field and year. Approximately 6,938 highly-cited researchers were identified in 2022, with around 4,000 in specific fields and 3,200 for cross-field performance.

Thirty-two Northwestern researchers are included on this 2022 list and represent departments across the university. This year, Northwestern moved up to be ranked 33rd in the world for the number of highly-cited researchers, from 39th in 2021.
The specific fields that Clarivate Analytics utilizes for classification are the 21 fields that are delineated in the Essential Science Indicators (ESI), a database focused on emerging science trends that is updated every two months and contains a 10-year rolling file. They determine the number of researchers to be selected in each field by taking the square root of the authors that are listed in that field's highly cited papers.

The thresholds for fields related to Feinberg are noted in the table below:

Clarivate began identifying researchers with cross-field impact in 2018 in an effort to recognize individuals who demonstrate "exceptional performance across several fields." Their calculation methods for this distinction involves normalizing the highly-cited paper and citation counts through fractional counting according to the thresholds required for each field. There is detailed information on their methodology available on their website.

ESI Field	Number of Highly Cited Researchers
Social Sciences	270
Molecular Biology & Genetics	206
Materials Science	222
Cross-Field	3,244
Clinical Medicine	466

Clarivate reminds us that "although this list is updated and refreshed each year, a Highly Cited Researcher is always a Highly Cited Researcher — whether their name was included in 2014 or 2022."

Read the full report on Highly Cited Researchers for 2022.

Learn More
The Metrics and Impact Core housed in Galter Health Sciences Library can help you track your work and learn more about metrics.
Please contact Karen Gutzman (karen.gutzman@northwestern.edu) or Mao Soulakis (mao.soulakis@northwestern.edu) to learn more about using metrics to tell your science story.

High-Impact Factor Research

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High-Impact Factor Research

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Featured Core

Northwestern Memorial Hospital Clinical Research Unit

The Clinical Research Unit (CRU) and CRU Core Lab are part of the Northwestern University Clinical and Translational Sciences (NUCATS) Institute's Center for Clinical Research.

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To submit an initial request for CRU services, complete the revised NUCATS Center for Clinical Research Intake Form.

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