Breakthroughs

Feinberg School of Medicine Research Office

May 2020

Michael Jewett, PhD, Center for Synthetic Biology director and Walter P. Murphy Professor of Chemical and Biological Engineering

Propelling Synthetic Biology into the Future

By Melissa Rohman

In the past decade, synthetic biology — the reengineering of organisms and their genetic information so they can produce a new substance or gain a new ability — has rapidly emerged to the forefront of modern-day science. Northwestern's Center for Synthetic Biology has been leading the way.

"At Northwestern, we thrive on interdisciplinary excellence, and we've been on the leading edge of defining the first wave of synthetic biology activities — in large part because of the center," says Michael Jewett, PhD, center director and the Walter P. Murphy Professor of Chemical and Biological Engineering at McCormick.

The center was established in 2016 to enable scientists from Feinberg, the McCormick School of Engineering and the Weinberg College of Arts and Sciences to engage in collaborative research involving the emerging field.

This past fall, the center was relocated from Evanston to its new home on the 11th floor of the Simpson Querrey Biomedical Research Center. This move, says Jewett, has provided an opportunity for even more collaborations.

"One of the amazing things about the people here is that they're not only pushing paradigms on their own, but they all realize that some of the most exciting discoveries happen at the intersection between multiple disciplines," Jewett said. "We're all happy to play in that same sandbox and we recognize that by working together and trying to identify those areas of intersection, we're creating better science."

Defining the Field

"The idea that you can move beyond programming DNA information toward this space of building and controlling atoms and living matter is really what synthetic biology is all about," says Jewett. "It's exciting, and over the past decade, I think experts in the field have really made remarkable advances in being able to create, control and reprogram cellular behavior to do new things."

The quickly evolving field of synthetic biology is also starting to become a research priority on both a national and international level. Earlier this year, the U.S. Senate introduced the Industries of the Future Act of 2020, which would provide support for research and development initiatives in synthetic biology, along with other emerging industries in science and technology. According to Jewett, synthetic biology is well positioned to permanently transform society.

"If a university isn't focusing on synthetic biology within the next five years, they're going to miss it, and I think we at Northwestern have hit the sweet spot," says Jewett.

Jewett's lab at the center focuses on cell-free synthetic biology,

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Northwestern Medicine®

Synthetic Biology *(continued from cover page)*

which involves the extraction and repurposing of different parts of a cell to reprogram DNA and enable portable, on-demand biomanufacturing, as well as diagnostic and educational platforms. Currently, he and fellow investigators are using cell-free synthetic biology in order to accelerate drug development for COVID-19.

Specifically, these efforts have involved producing a promising molecule called valinomycin in a cell-free system. The method successfully increased production yield by more than 5,000 times in just a few rapid design cycles, resulting in higher concentrations of the molecule than previously achieved.

Additionally, Jewett's lab has pioneered the use of cell-free systems as easy-to-use, point-of-need diagnostics for infectious diseases, including COVID-19.

Recently, members of the center received funding from the National Science Foundation to develop a single-step test for COVID-19 and other infectious diseases, both in humans and the environment. The project is co-led by Jewett and center faculty member Julius B. Lucks, PhD, associate professor of Chemical and Biological Engineering, and was also devised with Josh Leonard, PhD, associate professor of Chemical and Biological Engineering, and Niall Mangan, PhD, assistant professor of Engineering Sciences and Applied Mathematics.

In collaboration with Jewett's laboratory, the lab of Milan Mrksich, PhD, founding director (with Jewett) of the center and vice president for Research at Northwestern, has been able to achieve accelerated measuring of biochemical reactions using cell-free synthetic biology and self-assembled monolayers for desorption ionization (SAMDI), mass spectrometry, which was developed by Mrksich's lab. The high throughput method has enabled his lab to perform tens of thousands of reactions each day, making transformative advances in the design and synthesis of glycosylated protein medicines.

Mrksich, who has held multiple leadership roles at the center and Northwestern, says the ability to make proteins with cell-free synthesis and then test their activities with SAMDI mass spectrometry, as well as machine learning, has been a game changer in the field.

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Gabriel Rocklin, PhD, assistant professor of Pharmacology, (left) and Milan Mrksich, PhD, founding director of the Northwestern's Center for Synthetic Biology and vice president for Research at Northwestern.

"Rapid protein synthesis, rapid protein testing and machine learning — when you put those together, it gives the capability to develop enzymes that can catalyze reactions that are important. We can do that at levels that a decade ago were just unimaginable," Mrksich said.

Collaboration at its Core

In an effort to expand the center's mission and increase collaborative research efforts, over the last few years synthetic biology faculty members have been recruited specifically for the center through a partnership with Feinberg. This growing network of synthetic biology faculty are addressing important societal medical challenges through partnerships across the entire university.

Gabriel Rocklin, PhD, assistant professor of Pharmacology, joined the center in March 2019. His lab focuses on computational protein design — both designing new protein structures and improving the tools used by protein designers around the world. With the help of large-scale DNA synthesis, Rockiln's lab has been computationally designing and testing tens of thousands of proteins to study protein folding stability and how proteins bind therapeutic targets.

In the future, Rocklin hopes to collaborate with Jewett's lab and use cell-free synthetic biology technology to enhance the process and enable experiments to be conducted faster. He has also begun to collaborate with Leonard, to combine protein engineering with cell engineering. In addition to having a designated space to conduct synthetic biology research, the center has also given Rocklin ample opportunities for mentorship and collaboration.

"Having come here a year ago, the faculty at the center have definitely been the most valuable in terms of expanding my own vision of what our lab can do and contribute to, in helping ideas materialize and connecting with other people," he says.

Similarly, Arthur Prindle, PhD, assistant professor of Biochemistry and Molecular Genetics and at the McCormick School of Engineering, has been a faculty member of the center for almost two years. Prindle's lab is focused on understanding and engineering collective behaviors in bacterial communities, as well as using synthetic biology to re-engineer these bacteria in an effort to overcome antibiotic resistance and figure out new ways to leverage the bacteria's microbiome to detect and treat disease.

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Faculty Weigh in on the COVID-19 Response

Recent editorials published by Feinberg faculty outline ways to improve care delivery, interpret new information and maintain ongoing clinical trials and experiments during a pandemic.

COVID-19 Demonstrates Need for Molecular Research

In the first weeks of the COVID-19 pandemic, scientists raced to sequence the genome of the SARS-CoV-2 genome. Using next-generation sequencing technology that was unfathomable just 15 years ago, investigators quickly developed a picture of the virus' genetic structure, providing a framework for developing vaccines, therapies and tests.

This is a reminder of the importance of basic molecular science, according to Ali Shilatifard, PhD, the Robert Francis Furchgott Professor, chair of Biochemistry and Molecular Genetics, and author of an editorial in Science Advances, where he also serves as editor.

"This catastrophe should be a reminder that a healthy investment in all institutes of the NIH, NCI and other federal science agencies will be lifesaving when future pandemics arise," said Shilatifard, also director of the Simpson Querrey Center for Epigenetics and a professor of Pediatrics.

Supporting the Healthcare Workforce

The delayed onset of COVID-19 symptoms and its high transmissibility requires healthcare workers to constantly self-monitor for symptoms, as they are at elevated risk for contracting the disease and spreading it, both at the workplace and at home, according to James Adams, MD, chair of Emergency Medicine and lead author of an editorial published in JAMA.

Long work hours and high stress among frontline care providers, combined with the possibility of spreading the disease to friends and family, will take a toll and conversations with care providers may help reduce anxiety.

"The protection of healthcare workers is an essential priority in order to assure a successful response to this epidemic," Adams said.

Association of COVID-19 with Cardiac Injury and Mortality

Not much is yet known about the risks for COVID-19 to people with underlying cardiovascular conditions. However, lessons learned from influenza combined with new information about COVID-19 can provide some guidance for clinicians, according to an editorial published in JAMA Cardiology.

The editorial was authored by Robert Bonow, MD, the Max and Lilly Goldberg Distinguished Professor of Cardiology and vice chair for Development and Innovation in the Department of Medicine, and Clyde Yancy, MD, the Magerstadt Professor, chief of Cardiology in the Department of Medicine and vice dean for Diversity and Inclusion.

COVID-19 has some characteristics not seen with other severe infections, according to Bonow. Unlike influenza, the SARS-Cov2 virus enters a patient's cells by attaching to receptors on the cell membrane that line blood vessels.

"These receptors also have a prominent role in regulating blood pressure and heart function," Bonow said. "This virus has the potential to cause thrombosis in blood vessels and to cause coronary plaques to become unstable, which could trigger a heart attack."

These patients should be advised to not only practice social distancing but social isolation, according to Yancy.

Rush to Judgment on Hydroxychloroquine

This pandemic has placed enormous pressure on the medical and scientific communities to find safe and effective treatments for COVID-19, but that pressure cannot result in relaxed standards of data generation and interpretation, according to Michael Putman, MD, '19 GME, instructor of Medicine in the Division of Rheumatology and co-author of an editorial published in Annals of Internal Medicine.

There is preliminary evidence that hydroxychloroquine, a drug used to treat malaria, lupus and other rheumatic conditions, could be effective in treating COVID-19. However, no large-scale randomized clinical trial has tested the drug.

While low-quality studies are a problem in and of themselves, Putman also points out, "This low-quality evidence may drive a hydroxychloroquine shortage for patients with rheumatic diseases, which could result in patients with lupus experiencing disease flares. Data are good, but bad data are dangerous."

Maintaining Integrity of Trials

COVID-19 has threatened the integrity of the more than 250,000 ongoing clinical trials in the United States, according to Mary McDermott, MD, '92 GME, the Jeremiah Stamler Professor and professor of General Medicine and Geriatrics.

"The COVID-19 crisis suddenly and dramatically threatened our ability to maintain the integrity and progress of each trial," said McDermott, who was lead author of an editorial published in JAMA. But, she urges investigators to keep going, despite social distancing and other obstacles. "Be persistent in finding creative ways to complete ongoing trials without compromising the integrity of the trial or the health of patients and investigators, and keep both participants and funding agencies well-informed," she said.

"Ongoing trials could help millions of people realize sustainable, durable health benefits," McDermott said. "After the COVID-19 crisis is over, the health problems my investigative team is focused on will still be there and people will need effective treatments to improve their health."

Investigating Rare Genetic Disorders

Nicholas Katsanis, PhD, professor of Pediatrics

Nicholas Katsanis, PhD, is a professor of Pediatrics at Feinberg. He is also the Valerie and George D. Kennedy Research Professor of Human Genetics, associate chief research officer for translational science and director of the Advanced Center for Translational and Genetic Medicine (ACT-GeM) at the Stanley Manne Children's Research Institute at Ann & Robert H. Lurie Children's Hospital of Chicago. As director of ACT-GeM, Katsanis oversees the center's collaborative research efforts which intersect genetics, genomics, cell biology and clinical investigation. Over the course of his career, he has published over 300 peer-reviewed papers; serves on several advisory, editorial, and organizational boards; and has given over 250 lectures in 40 countries.

Q&A

What are your research interests?
In a general sense, my interests revolve around rare genetic disorders, specifically the identification of novel genetic disorders and understanding their genetic architecture; using this type of knowledge to inform gene and protein function; and developing new paradigms for empowering and accelerating treatment discovery and implementation.

What is the ultimate goal of your research?
To become irrelevant. It sounds glib, but if we eventually are able to build a discovery engine that can accelerate diagnosis and treatment for rare genetic diseases, I will be able to put on the slippers and watch from my armchair as we eradicate this odious problem from the planet.

How did you become interested in this area of research?
The roots of my interest are personal. As a pre-teen, I watched as my first cousin perished from a rare genetic disease called San Filippo syndrome. Later on, I also began to understand the horrible impact this calamity had on the overall family (my uncle and aunt divorced a little after my cousin passed away). This was a priming event that pushed me into genetics. Once in it, I became enamored by the discipline.

How is your research funded?
We have been privileged to have extensive NIH funding for many years. We have also had support from private foundations, donors and corporate sponsors — a very diverse group who have shared our conviction that our goals are both laudable and pragmatic.

Where has your work been published?
Our group publishes a broad range of papers across the spectrum, from *Nature* to focused clinical journals. We celebrate all of them and do not subscribe to vanity "bean counting".

Who inspires you? Who are your mentors?
The list of my mentors is extensive, but the people who truly inspire me are the young people who are dipping their toes into the discovery enterprise. The challenges of the current generation in science, and their expectations, are very different than when I started out. I remain enthralled by the talent I see, and I consider it a true privilege to help polish so many of these "rough diamonds." Amid the histrionics of our society at present, and the cynicism, my message remains: Come on in — the water feels great!

Seriously, this is actually an extraordinary time to pursue discovery. Trust me when I say that it is possible to experience indescribable satisfaction by pursuing a dream while contributing to the spirit of the human race.

Synthetic Biology *(continued from page 2)*

"We may not have found our way to a medical center as new faculty if it wasn't for the Center for Synthetic Biology, so the hope of the center is that this is going to be a way to apply bioengineering to these biomedical challenges," Prindle said.

As the field of synthetic biology continues to evolve and expand, Jewett envisions the same for the center. In the next five years, he hopes to see the number of synthetic biology faculty increase and the center continue to act as a hub for those interested in using synthetic biology research to break new ground in their own respective disciplines and in the field of synthetic biology itself.

"The center is a place where, when you look around, every single person, you're proud to be their colleague because they're defining where the field is going," Jewett said. "I want people who are going to define the future of synthetic biology because we're going to transform how it contributes to the bio-economy, impacting our society and changing the way we interact with the living world."

Driven to Protect Healthcare Workers and Patients from Hospital- and Community-Acquired Infections

Margaret Schiffhauer, first-year student in the Physician Assistant (PA) Program.

Q&A

Where is your hometown?
I grew up in Buffalo, New York.

What are your research interests?
Before starting PA school, I received my Master of Health Science in infectious disease epidemiology at The Johns Hopkins Bloomberg School of Public Health. There, my research focus was on HIV in the aging population.

Data is just starting to come out about the unique health challenges associated with individuals who have been on long-term antiretroviral therapy. These epidemiologic data will likely have tremendous implications for healthcare providers taking care of this population in the future.

After completing my master's, I worked as an epidemiologist at The Johns Hopkins Hospital, where my primary interest was how to best protect healthcare workers and patients from hospital- and community-acquired infections. I had (and still have) a particular interest in multidrug-resistant organisms in immunocompromised patients. Having the opportunity to work with patients in this setting is what ultimately prompted me to pursue the PA profession.

What attracted you to your program?
Northwestern's PA program was my first choice from the start. The problem-based learning curriculum is what initially attracted me, as I have always felt that I learn best and retain the most information when working through real-life examples and situations with colleagues. After interviewing, it became apparent that the program environment was exceptionally warm, collaborative and supportive. The clinical rotation options are unparalleled, and the opportunity to pursue my education in the city of Chicago was so appealing to me. My expectations were quickly exceeded upon matriculation.

What has been your best experience at Feinberg?
Getting to know my classmates has been my best experience at Feinberg. Each of my classmates has a unique background and perspective that makes learning together so effective and rich. I feel extremely fortunate to have made so many lifelong friends, and I am constantly humbled by their intelligence and compassion.

How would you describe the faculty at Feinberg?
The faculty at Feinberg are exceptional. Everyone is clearly an expert in his or her field, which makes each lecture and discussion particularly engaging and valuable. Perhaps just as importantly, though, the faculty is approachable; I never feel hesitant to ask a question, set up a meeting, or inquire about further educational opportunities. Their passion for teaching and mentorship is apparent.

What do you do in your free time?
I love exploring Chicago with my family and friends. I have been so fortunate to make such close friends in PA school, and I spend most of my free time exploring the city's neighborhoods and restaurants with them. I am also quite happy to relax with my corgi and my husband at home when I am not studying!

What are your plans for after graduation?
I have found so many new clinical interests through didactic year in PA school, so I am eager to explore these interests during clinical year. After graduation, I hope to have the opportunity to work within my chosen specialty in Chicago — ideally, at Northwestern!

Research in the News

***National Public Radio*, April 22**
In New York Nursing Homes, Death Comes To Facilities With More People Of Color
Clyde Yancy, MD, was mentioned.
- This published work was also featured in *The New York Times*, MSNBC

***Crain's Chicago Business*, April 24**
Northwestern Memorial testing drug for severe COVID cases
Richard Wunderink, MD, was mentioned.
- This research was also featured in *Chicago Tribune*.

***ABC News*, April 28**
Upward mobility may be good for your wallet, but health problems may follow Gregory Miller, PhD, was mentioned.

***Heart Association News*, April 28**
Traumatic childhood increases lifelong risk for heart disease, early death Jacob Pierce, fourth-year medical student, was mentioned.
- This research was also featured in *HealthDay* and *U.S. News & World Report*.

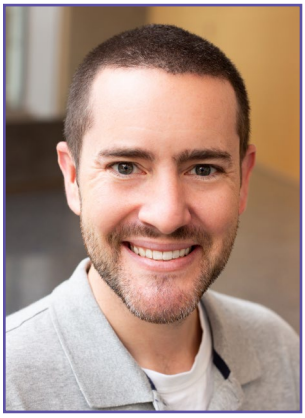
***San Francisco Chronicle*, April 29**
A First: U.S. study finds Gilead drug works against coronavirus
Babafemi Taiwo, MBBS, was mentioned.
- This research was also featured in *ABC News*.

***TIME*, April 30**
Are You Experiencing COVID-19 "Caution Fatigue"? Here's What It Is, and How to Fight It Jacqueline Gollan, PhD, was mentioned.

More media coverage

Translating Science for Multiple Audiences

Roger Anderson, director of Marketing and Communications at the Northwestern University Clinical and Translational Sciences Institute (NUCATS)



Q&A

Where are you originally from?
I was born and raised in Wisconsin and am a proud product of Milwaukee Public Schools.

What is your educational background?
I have bachelor degrees in journalism and political science from the University of Wisconsin-Madison and a master's degree in integrated marketing communications from Northwestern.

Please tell us about your professional background.
Following my undergraduate degree, I became a copy editor at *The Journal Times* in Racine, Wisconsin. Working at a newspaper was an amazing experience — from nearly having to spend the night during "Snowmageddon" to designing the front page the night Barack Obama accepted the Democratic Party nomination.

Wanting to write full time, I accepted a position at the Northwestern University Feinberg School of Medicine eight years ago. I spent the past six years as the publications editor at the Office for Research in Evanston, before recently returning to the Chicago campus to become director of communications for the NUCATS in November.

Why do you enjoy working at Northwestern?
As a science writer, I get to talk to world-class investigators, learn how their research may someday change the world and share that knowledge with the Northwestern community and beyond. I am continually amazed by those I work alongside. As prestigious as the faculty are, my peers are what continue to make my time at Northwestern memorable.

How do you help scientists and/or research students at the medical school?
My role, in part, is that of a translator. Scientific publications are a very specific type of content, and working with researchers — postdocs, graduate and medical students, and faculty — to make their work more relatable for the general public is both a challenge and greatly rewarding.

What exciting projects are you working on?
I am thrilled to be the first director of communications at NUCATS and am excited to have redesigned the News Center. I am looking forward to working on the annual report and continuing to build the case for grant renewal.

What do you like to do in your spare time?
I love to take photographs and travel. We're big proponents of bringing our girls (ages 4 and 1) along for the adventure. In the past two years we've been to Austin, DC, Phoenix, Portugal, Morocco, Italy, France, Grand Cayman, and, of course, Wisconsin.

Because of COVID-19, we've had to cancel trips to Canada and Iceland. A new hobby has become looking through our extensive collection of travel photo albums (and teaching preschool).

Anything else we should know about you?
We recently adopted a beautiful dog through Greyhounds Only, and have a cat and two turtles.

Welcome New Faculty

Feng Yue, PhD, joins as associate professor of Biochemistry and Molecular Genetics, the founding director of the Center for Cancer Genomics at the Robert H. Lurie Comprehensive Cancer Center and the Duane and Susan Burnham Professor of Molecular Medicine. He is also the director of the Center for Advanced Molecular Analysis at the Institute for Augmented Intelligence in Medicine. Previously, Yue was an associate professor at the Pennsylvania State University and director of Bioinformatics Division at the Penn State Institute for Personalized Medicine. The main research area for Dr. Yue's group is epigenomics and 3D genome organization in the context of human diseases. He completed his doctoral degree in computer science from University of South Carolina, and received his postdoctoral training at the University of California, San Diego. Yue has been an active member of several large National Institutes of Health funded consortia, including the ENCODE, Roadmap/ Epigenomics, and 4D Nucleome projects.

NUCATS Corner
Clinical and Translational Sciences Institute

NUCATS Stands Ready to Help

This is an unprecedented time for Northwestern, as we are in the midst of an ongoing pause in non-essential research and on-campus work. Even during this suspension of research projects, many activities supported by NUCATS, including grant planning and writing, regulatory work, research planning, data management and analysis, and more, will continue — although in a virtual setting.

The worldwide COVID-19 outbreak may have changed how we work, but the NUCATS Institute continues to stand ready to help our research community. Please refer to our COVID-19 funding opportunity and resource page for more information, including notices from the Feinberg School of Medicine as well as University Leadership.

Have You Considered eConsent in REDCap?

We know that our research community has been greatly affected by COVID-19. Given the impact of the pandemic on research studies, your research team may want to consider using eConsent in REDCap. This workflow can help you to deliver the consent process completely electronically. Contact the REDCap team at redcap@northwestern.edu for information. Please note that the IRB protocol would need to be amended to support online consent. Northwestern's IRB provides excellent templates and guidance to help with online consent. Also, stay tuned for a future Zoom info session about how to best take advantage of this tool.

NUCATS Members Continue to Make Research Impact

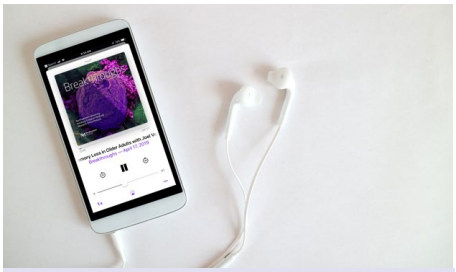
We want to thank the Northwestern research community for continuing to make critical discoveries every day. NUCATS members' efforts include:

- Babafemi Taiwo, MBBS: COVID-19 drug trial launches
- Ron Ackermann, MD, MPH, and Jen Brown, MPH: City-wide mobilization to protect community
- Nicholas Soulakis, PhD: Soulakis Joins IDPH to Fight COVID-19
- Karla Satchell, PhD: New drug target found for COVID-19

NUCATS Offers New Services as Centers, Programs Expand Resources

NUCATS remains committed to making sure our research community is aware of available COVID-19 resources, including:

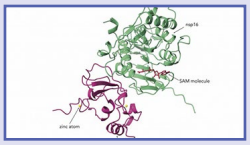
- Virtual studio consultations
- Online trainings
- Biosketch development
- Working with our community partners
- A wealth of digital information through the Galter Health Sciences Library
- Funding opportunities



Listen to the Latest Breakthroughs Podcasts

After listening to an episode, you will be able to identify the research interests and initiatives of Feinberg faculty and discuss updates in clinical and translational research. If you would like to claim CME credit for listening to Breakthroughs, visit the Continuing Medical Education website. If you have additional questions about processing CME credits, please contact the Office of Continuing Medical Education.

The Dangers of Unproven COVID-19 Therapies with Benjamin Singer, MD



Investigating the New Coronavirus with Karla Satchell, PhD, Part 2

High Risk Adults and COVID-19 with Michael Wolf, PhD, MPH

More Breakthroughs podcasts here.

Sponsored Research

PI: Yong Wan, PhD, professor of Obstetrics and Gynecology in the Division of Reproductive Science in Medicine and of Pharmacology

Sponsor: National Cancer Institute

Title: Targeting Posttranslational Modifications in Breast Carcinogenesis

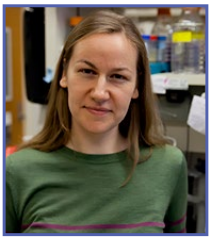
Triple negative breast cancers (TNBCs) have a poor prognosis and are not amenable to endocrine- or HER2-targeted therapies. While the newly approved PARP inhibitors (PARPi) such as olaparib and talazoparib provide a glimmer of hope to the 15-20% of TNBC patients with BRCA1-deficiency, the need for a novel strategy that could benefit the remaining 80-85% BRCA1-proficient TNBC patients is urgent and significant. The goal of this project is to determine the impact of interplay between Krüppel-like factor 4 (KLF4) and poly-ADP-ribose polymerase 1 (PARP1) in breast tumor progression and metastasis, and further develop a small molecule inhibitor of KLF4 that synergizes with PARPi for anti-TNBC treatment.

This research is based on our original discovery that KLF4 acts as a critical signaling node in mediating DNA damage response (DDR)/DNA repair, wherein the Poly-(ADP-ribosyl)ation (PARylation) of KLF4 by PARP1 dictates the chromatin recruitment for KLF4 that, in turn, governs KLF4 transcriptional function with respect to the maintenance of genome stability, tumor progression/metastasis and drug sensitivity in breast cancer. These findings led to our central hypothesis that dysregulation of KLF4 by PARP1 results in genome instability and tumor promotes progression/metastasis, and blockade of KLF4 by newly developed KLF4 inhibitor synergizes PARPi for efficient killing of TNBC cells.

Three specific aims are proposed to elucidate the importance and mechanisms regulating KLF4 by PARP1: (1) To determine the mechanism by which PARP1 regulates KLF4-mediated genome stability and carcinogenesis through orchestrating the recruitment of KLF4 to chromatin; (2) To determine the physiological and clinical relevance of KLF4 PARylation in breast tumor progression/metastasis; and (3) To validate the therapeutic intervention of KLF4 inhibitor in synergizing with olaparib/talazoparib in anti-TNBC treatment using human breast tumor organoid and patient-derived xenografts (PDXs).

Read more

PI: Eva Gottwein, PhD, assistant professor of Microbiology-Immunology



Sponsor: National Cancer Institute

Title: Transcriptional Control of Cellular Survival and Proliferation in KSHV-transformed B Cells

Kaposi's sarcoma-associated herpesvirus (KSHV) is a major cause of cancer in the context of HIV/AIDS. We recently showed that KSHV-transformed primary effusion lymphoma (PEL) cell lines exhibit a strong requirement for the cellular lymphoid transcription factor IRF4. This finding places PEL into an emerging group of blood cancers where IRF4 is a key oncogenic driver. A detailed understanding of the oncogenic roles of IRF4 has not been achieved in any of these cancers, but evidence suggests that IRF4 functions as a master transcription factor that induces extensive epigenetic and transcriptional reprogramming.

In PEL, IRF4 is required for overexpression of the MYC oncogene, but how KSHV controls IRF4, the molecular mechanism by which IRF4 regulates MYC, and whether IRF4 acts solely through MYC or has additional oncogenic roles, is unknown. The long-term objective of this proposal is to determine the downstream effects that underlie the oncogenic roles of IRF4 in PEL and to use our results to develop novel therapeutic strategies. The central hypothesis of this proposal is that KSHV-induced, IRF4-dependent oncogenic transcriptional reprogramming is required for tumor cell survival and proliferation in PEL. This hypothesis is premised on our extensive preliminary work, which has identified both KSHV-encoded and cellular transcription factors that control IRF4 expression and function in PEL.

Based on ChIP-Seq and mRNA-Seq experiments, we specifically hypothesize that IRF4, together with its viral and cellular co-factors, associates with promoters and distal cis-regulatory elements to drive an IRF4-dependent oncogenic transcription program, which involves both the silencing of "toxic" tumor suppressors and the overexpression of several essential survival genes, including MYC, but also others.

To test our hypothesis, we propose two Specific Aims, i.e. we will: (1) determine which toxic genes must be silenced by IRF4 to promote PEL cell viability and proliferation, and (2) determine which IRF4-stimulated genes are essential IRF4 effectors in PEL cells. Several of the already identified candidates for IRF4 effectors are high-confidence drug targets. We will therefore exploit our results in both aims to identify and test novel therapeutic strategies, in vitro and in vivo. This work uses a cutting-edge approach that integrates hypothesis-driven experiments with unbiased functional genomics approaches.

Read more

Funding

Congressionally-Directed Medical Research Programs (CDMRP) Peer Reviewed Medical Research Program (PRMRP) Clinical Trial Award for Emerging Viral Diseases and Respiratory Health

More information

Sponsor: U.S. Department of Defense
Letter of Intent: June 8
Submission Deadline: June 22
Amount: $30M

Synopsis: This funding opportunity supports the rapid implementation of clinical trials of novel interventions with the potential to have a significant impact on patient care, the topic areas of emerging viral diseases and respiratory health. Applications must address at least one of the focus areas published in the program announcement and may range from small proof-of-concept trials (e.g., pilot, first in human, Phase 0), to demonstrate feasibility or inform the design of more advanced trials, through large-scale trials to determine efficacy in relevant patient populations.

Clinical and Translational Science Award (CTSA) Program: Collaborative Innovation Award (U01 Clinical Trial Optional)

More information

Sponsors: National Center for Advancing Translational Sciences (NCATS)
Letters of Intent: Due 30 days prior to submission deadline
Submission Deadlines: July 10, November 9
Upper Amount: $750,000

Synopsis: The award supports collaborative research activities that develop innovative solutions that will improve the efficiency, quality and impact of turning laboratory, clinic and community observations into interventions that improve the health of individuals and the public. This funding opportunity will support investigators from three or more CTSA Program hub institutions to either:

1. Form new collaborations;
2. Significantly expand the scientific scope of existing collaborations; or
3. Engage new collaborators in pre-existing collaborations to solve a translational science problem no one hub can solve alone, or disseminate a solution to a translational science problem developed at one hub to other hubs, in so doing testing its robustness to different hub environments and structures and adapting it for further dissemination within/outside the CTSA program consortium.

Clinical Trials in Organ Transplantation in Children and Adults (CTOT-CA) (U01 Clinical Trial Optional)

More information

Sponsor: National Institute of Allergy and Infectious Diseases
Letter of Intent: September 9
Submission Deadline: October 9
Upper Amount: $3.4M

Synopsis: This funding opportunity seeks the participation of a clinical studies program to improve the long-term outcome of adult and pediatric transplant recipients (thoracic organ, abdominal organ, vascular composite tissue and cellular replacement). The CTOT-CA program will support cooperative, multi-institutional consortia for the conduct of interventional trials (Phase 1, 2, or 3) or observational clinical studies in organ, vascularized composite tissue or cellular replacement allotransplantation. Each applicant institution must represent a consortium of two or more clinical sites. Each clinical study must include associated mechanistic studies that focus on immune-mediated processes that are relevant to the proposed clinical study. The goals of this research will be to further understanding of and ultimately reduce immune- and infection-mediated morbidity and mortality of allotransplantation.

NIAID Emergency Awards: Rapid Investigation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) (R21 Clinical Trial Not Allowed)

More information

Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)
Submission Deadline: Applications are accepted on a rolling basis until April 30, 2021
Upper Amount: $275,000

NIAID is providing an expedited funding for research on SARS-CoV-2 and COVID-19 to improve understanding of fundamental virology, immunology, and the development of animal models, reagents, and medical countermeasures and to share findings quickly and broadly. Applications submitted should be exploratory and novel. These studies should break new ground or extend previous discoveries toward new directions or applications.

View COVID-19 funding opportunities

View more funding opportunities

Galter Library COVID-19 Resources and Research Support

The Galter Library team has developed and launched a number of resources and workflows to support COVID-19 efforts at Northwestern University:

COVID-19 Evidence Search & Synthesis Service

Fast-track COVID-19 searches on topics such as healthcare workforce safety, patient care, materials science, policy, supply chains, ethics, legal and regulatory issues, media, and more.

Requests are completed by expert searchers from Galter Library, Northwestern University Libraries, and Pritzker Legal Research Center through a strong cross-campus collaboration. Searches will be prioritized based on urgency. Results from completed searches are available.

Evidence synthesis briefs can be requested on this form and will be completed by a team of volunteers on campus with experience in these domains. We're grateful for their assistance.

Access the Literature

View the latest articles and research resources in Galter Library COVID-19 Resource Guide. If you know of a paper you'd like to add, please use our Suggest a Resource form.

Through the Public Health Emergency COVID-19 Initiative, COVID-19 and coronavirus-related publications, and the available data supporting them, will be made immediately accessible in PubMed Central (PMC) and other appropriate public repositories to support the ongoing public health emergency response efforts. Several publishers have responded to the call and are working with NLM to make their coronavirus-related articles discoverable and accessible through PMC and facilitate text mining and secondary analysis through machine-readable formats and licenses.

Find COVID-19 Resources

The Northwestern COVID-19 Resource Guide is now available, containing the latest COVID-19 content, tools, data, and relevant scholarly resources from a wide range of publishers and content providers curated by Galter Library. Use the Suggest a Resource form to suggest tools, data aggregators, dashboards, etc. to include on the guide.

Preserve and Share

Help facilitate sharing and information discovery through the Chicago COVID-19 Collection. This is a great way to share datasets, analyses, visualizations, white papers, slides, etc., relevant to COVID-19 activities and track access/use of your materials. All materials, regardless of collection, are discoverable through Zenodo.

Upload your research materials directly to the collection (first sign in or create a Zenodo account) or fill out the form for assistance with deposit.

If you have questions about these or any other Galter Library services and resources, please reach out. Right now, email is the best way to contact us. Stay safe and healthy!

High-Impact Factor Research

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Featured Core

Comprehensive Metabolic Core

The Comprehensive Metabolic Core aims to advance Northwestern research in diabetes, obesity and cardiovascular disease by establishing validated high-throughput hormone analyses and to create a consolidated reference center for efficient testing.

The core recognizes that the development of transgenic animal models across a wide range of laboratories at the university has increased the interest in studies of metabolism and cardiovascular physiology at multiple levels. The identification of novel gene pathways in diabetes and obesity is also a common area of interest among these laboratories and the core recognizes that these findings, which have various applications from biomedical engineering to transplantation, suggest an increasing interest in technologies for phenotyping mouse metabolic systems.

Assay services offered include:

- Immunoassays and Radioimmunoassays (RIA) for endocrine hormones
- Luminex: multiplex assays using a small volume of sample
- Roche Cobas e 411 analyzer (human samples including serum, plasma and urine)

Metabolic services offered include:

- TSE Labmaster/Phenomaster System
- Indirect calorimetry to assess energy expenditure
- Locomotor activity monitoring
- Feeding activity monitoring
- Pair feeding
- Restricted feeding

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NIH News

The COVID-19 Portfolio Tool

The National Library of Medicine (NLM) at NIH recently joined the White House and key industry and university leaders to release the COVID-19 Research Dataset (CORD-19) and called on the artificial intelligence (AI) community to develop text mining tools that help analyze and summarize the over 45,000 coronavirus articles. The CORD-19 dataset represents the most comprehensive, freely available library of machine-readable coronavirus scholarly literature to date, with hundreds of AI tools and technologies already created.

Building on this effort, the NIH Office of Portfolio Analysis has assembled a comprehensive listing of COVID-19 publications and preprints that is freely available to the public and coupled with a user-friendly portfolio analysis interface for querying the full text and supplemental data. The COVID-19 portfolio is updated daily with new literature selected for inclusion by subject matter experts. It draws upon NLM's PubMed resource for citations and abstracts of published biomedical literature. Learn more about the COVID-19 portfolio tool here.

NIH to Launch Public-Private Partnership to Speed COVID-19 Vaccine and Treatment Options

The National Institutes of Health and the Foundation for the NIH are bringing together more than a dozen leading biopharmaceutical companies, the Health and Human Services Office of the Assistant Secretary for Preparedness and Response, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration and the European Medicines Agency to develop an international strategy for a coordinated research response to the COVID-19 pandemic.

The planned Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership will develop a collaborative framework for prioritizing vaccine and drug candidates, streamlining clinical trials, coordinating regulatory processes and/or leveraging assets among all partners to rapidly respond to the COVID-19 and future pandemics. Read more here.

NIH Study Validates Decontamination Methods for Re-Use of N95 Respirators

Early findings show that vaporized hydrogen peroxide-treated N95 masks may be the best way to decontaminate masks while maintaining their integrity for up to three uses, according to a new NIH study. While not yet peer-reviewed, NIH is releasing preliminary results to help the COVID-19 response. Read more about the study here.