



Center for Clinical and Translational Science e-Newsletter

Center News

2023 Marguerite S. Lederberg Annual Lecture

By Editorial Staff

The second Marguerite S. Lederberg Annual Lecture was delivered by two world renowned bioethical experts, Jeffrey Kahn PhD, MPH and Michael Parker, BEd, MA, PhD on September 6, 2023. Dr. Lederberg was a leader in research on the challenging bioethical issues affecting the care of cancer patients and the medical and nursing staff caring

for cancer patients. The Marguerite S. Lederberg Annual Lecture is a tribute to Dr. Lederberg's pioneering bioethical research and her profound impact on countless trainees and colleagues.

Dr. Kahn is the Andreas C. Dracopoulos Director of the Johns Hopkins Berman Institute of Bioethics, and the Levi Professor of Bioethics and

Public Policy. He is also Professor in the Department of Health Policy and Management in the Johns Hopkins University Bloomberg School of Public Health. His research interests include the ethics of research, ethics and public health, and ethics and emerging biomedical technologies. Dr. Parker is the Professor of Bioethics and Director of



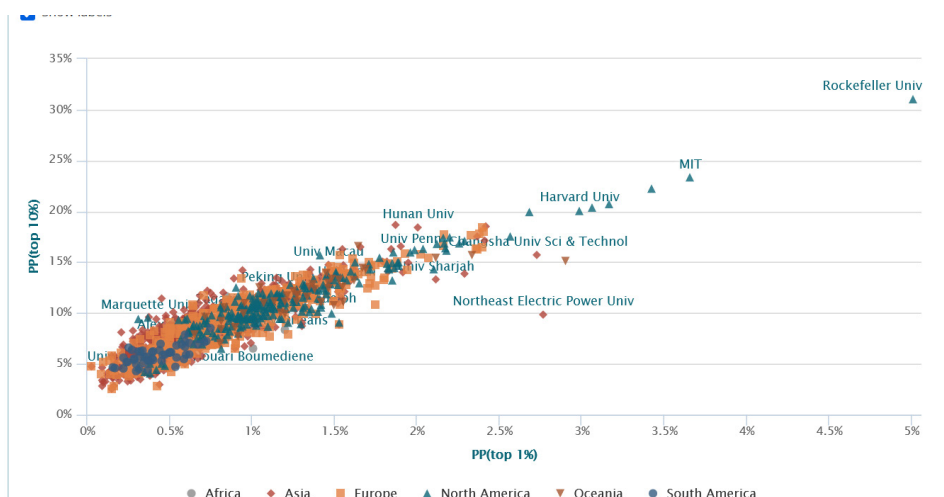
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Drs. Sarah Schlesinger, Barry Collier, Michael Parker, Jeffrey Kahn, Clinical Scholars, and members of the Lederberg Family

Rockefeller University Ranks Number 1 in The 2023 Centre for Science and Technology Leiden Rankings

By Editorial Staff

Rockefeller University ranked first among all universities in the world in the All Sciences and Biomedical and Health Sciences categories based on scientific papers published from 2018-2021. The figure below charts the percentage of papers published that were among the top 1% and 10% cited papers for the All Sciences category. Rockefeller has held the top ranking in this category since at least 2006. Note that ~6% of Rockefeller's papers were in the top 1% category (abscissa) and more than 30% were in the top 10% category (ordinate).



the Ethox Centre, University of Oxford, and Director, Wellcome Centre for Ethics and Humanities. He has chaired and served on many United Kingdom and International committees on regulation and governance of research ethics, ethical issues in global health research, and the ethical aspects of genomics.

Drs. Kahn and Parker's primary objective is to collaborate with scientists, health professionals, and

public health experts to identify, analyze, and endeavor to devise strategies for addressing the pragmatic ethical dilemmas that arise in their routine professional endeavors. Their presentation, Emerging Technologies, Emerging Infectious Diseases, and the Role of Bioethics, focused on the emergence of the profound ethical issues that arise in the course of research on global infectious diseases, most

importantly, the equitable distribution of crucial vaccines and medications. Together they lead the Oxford-Johns Hopkins Global Infectious Disease Ethics Collaborative (GLIDE), which aims to provide a flexible collaborative platform for identifying and analyzing ethical issues arising in infectious disease treatment, research, response, and preparedness, through the lens of global health ethics.

2023 – 2024 Stavros Niarchos Foundation Institute for Global Infectious Disease Research Pilot Grant Recipients

By Editorial Staff

The primary objective of the Stavros Niarchos Foundation Institute for Global Infectious Disease Research is to establish a comprehensive platform for facilitating worldwide scientific collaboration, with the aim of promoting novel research advancements and translating them into tangible improvements in public health. Pilot awards are solicited to investigators annually in April and July focused on this objective. This year the institute funded 8 pilots out of 42 applications submitted. There were 13 applications in round 1 and 29 applications in round 2. \$283,964 was allocated for the pilot awards listed below, with the aim of stimulating research and facilitating activities in the field of clinical and translational sciences.

Name of Investigator: Fahd Al Qureshah, PhD

Lab: St. Giles Laboratory of Human Genetics of Infectious Diseases

Title of Pilot Project: *Genetic Predisposition to Acute Severe Viral Infections*

Abstract: The role of type I interferons (IFNs) in susceptibility to viruses was revealed by the discoveries of autosomal recessive, loss-of-function IFNAR1/2 deficiencies, which lead to complete loss of response to type I IFNs. We aim to identify autosomal recessive and dominant variants in IFNAR1/2 in patients with severe viral infections, followed by studies to determine the causal role of the variants in response to all 17 types I IFNs. We showed that these missense variants impaired responses to IFN- α 2a and IFN- ω , but response to IFN- β was normal. This suggests that IFNAR1 variants affect response to particular IFN subtypes and can also lead to severe COVID-19 pneumonia, and treatment with IFN- β may be beneficial. We will uncover previously unknown roles of type I IFN subtypes.

Name of Investigator: Barbara Bosch, MD, PhD (Clinical Scholar)

Lab: Laboratory of Molecular Biophysics

Title of Pilot Project: *Assessing Novel Compounds Against Mycobacterial Pathogens Within Infected Human Macrophages: A Pilot Study on RNA Polymerase Inhibitors*

Abstract: Mycobacterial infections are notoriously hard to treat, and novel treatment regimens are urgently needed. This project aims to advance target-based drug discovery against 2 pathogenic mycobacteria. The proposed pilot project therefore aims to study these new RNA polymerase inhibitors in macrophages of healthy volunteers. If successful, we will expand the project to macrophages of patients with cystic fibrosis to model Mabs infections in a disease-relevant host context.

Name of Investigator: Jan Burian, PhD

Lab: Laboratory of Genetically Encoded Small Molecules

Title of Pilot Project: *New metagenomic Discovery Platform for Rapid Access to Previously Inaccessible Clinically Relevant Natural Products*

Abstract: Antibiotic resistance is a global health issue. Rising antibiotic resistance has decreased our antibiotic arsenal and required new ones. Most environmental microbes can't be cultured, yet they may create new antibiotics. Metagenomic DNA in large clone libraries permits microbial majority research for new medicines that culture-dependent methods cannot. Complex soil metagenomes are difficult to examine because an evolutionary arms race has developed many distinct antibiotics that culture-based discovery methods cannot detect. I want to generate scalable access to complex soil metagenome genetic biodiversity for culture-independent therapeutic discovery. Our approach leverages 'long-read' nanopore sequencing for bioinformatic metagenomic sequence access and two of our new CRISPR-based technologies for fast physical access and heterologous expression of newly found target sequences. We and the scientific community can address emerging clinical issues by developing and distributing a quick, cost-effective, and scalable metagenomic mining platform.

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Name of Investigator: Danyel Lee

Lab: St. Giles Laboratory of Human Genetics of Infectious Diseases

Title of Pilot Project: *The Genetic Dissection of the Cellular and Molecular Mechanisms of SARS-CoV-2 Related Multisystem Inflammatory Syndrome in Children (MIS-C)*

Abstract: Viruses can cause debilitating or fatal post-viral syndromes even after the initial replication has been suppressed. SARS-CoV-2 and its global spread have highlighted this burden. Multisystem inflammatory disease in children (MIS-C) is a rare disease occurring after an asymptomatic or mild SARS-CoV-2 infection, with up to 90% of patients requiring intensive care and rarely succumbing to the disease. Recent genetic studies found recessive monogenic deficits in OAS-RNase L pathway genes as causes of MIS-C, which inhibits RIGI/MDA5-MAVS pathway inflammation in mononuclear phagocytes. We now believe that mononuclear phagocytes' RIG-I/MDA5-MAVS pathway drives MIS-C inflammation. We seek patients with RIG-I, MDA5, MAVS, or regulator genetic deficits or enhancements. Immunological and experimental studies using genetically engineered human cell lines and patient blood cells will map the fine-tuned machinery of antiviral inflammation, allowing us to study MIS-C and other post-viral diseases, including SARS-CoV-2, develop targeted therapeutics, and develop precision medicine for infectious diseases.

Name of Investigator: Cindy Meyer, PhD

Lab: Laboratory of RNA Molecular Biology

Title of Pilot Project: *Expression and Biochemical Characterization of Tick-Borne Encephalitis Virus and Powassan Virus NS5 Methyltransferases for Small-Molecule Drug Discovery*

Abstract: Flaviviruses are a family of positive-sense, single-stranded, enveloped RNA viruses, which are found in arthropods (primarily ticks and mosquitoes) and occasionally transmitted to humans. Tick-borne encephalitis (TBE) virus and the closely related Powassan virus (POWV) are tick-borne flaviviruses (TBF) that can cause severe human disease, including infection of the brain (encephalitis) or the membranes around the brain and spinal cord (meningitis). Currently, there are no medications to treat TBF encephalitis or POWV disease. Recently, the Tuschl laboratory in collaboration with Dr. Fraser Glickman (Drug Discovery Resource Center, DDRRC), the laboratory of Dr. Charles Rice at the Rockefeller University (RU), and the Tri-Institutional Therapeutics Discovery Institute (TDI) identified and developed small-molecule antagonists of the RNA cap methyltransferase (MTase) NSP14 of SARS-CoV-2, which potently inhibit virus replication in cell culture models. Building on this expertise, we aim to initiate small molecule high-throughput screening (HTS) campaigns targeting the RNA cap MTases of TBEV and POWV.

Name of Investigator: Jonathan Tobin, PhD

Department: Hospital Clinical Research Office - Community-Engaged Research

Title of Pilot Project: *Chagas' disease as an Emerging Infectious Disease in the United States*

Abstract: The pilot project will build a full-spectrum translational research team of community-based primary care clinicians and laboratory scientists to study a potential US Chagas disease outbreak. The team will develop bi-directional workforce development and training activities for laboratory investigators and practicing clinicians that can be disseminated to CTSA community-engaged research cores, FQHC clinicians, practice-based research networks (PBRNs), and public health departments serving high-risk Latin American immigrants and migrants. A computable phenotype will be developed and tested to identify identified and possible/probable cases in FQHC electronic health records (EHRs) using diagnostic codes, laboratory tests, cardiac and gastrointestinal imaging reports, and prescribed medications. Follow-up studies may (1) examine how training and workforce development affect diagnostic and treatment at FQHCs, (2) implement the computable phenotype developed and tested across geographic areas where immigrants and migrant workers live in the US, and (3) identify opportunities for drug development and testing (Phase III clinical trials) for acute and chronic infections in collaboration with FQHCs serving high-risk, high prevalence populations.

Name of Investigator: Zijun Wang, MD, PhD (Clinical Scholar)

Lab: Laboratory of Molecular Immunology

Title of Pilot Project: *Impact of Anti-HBsAg Antibody Therapy on Adaptive Immune Responses in Human Chronic Hepatitis B Virus Infection*

Abstract: Chronic HBV (CHB) remains a global health challenge, primarily driving liver cirrhosis and hepatocellular carcinoma. Prolonged elevated HBsAg levels can overstimulate immune cells, leading to exhaustion and tolerance. Lowering serum HBsAg via antibody transfer shows promise for restoring immune control. HepBmAb19 (NCT05856890), a potent human anti-HBsAg monoclonal antibody, has shown robust antiviral efficacy in animal models. We hypothesize that HepB-mAb19 immunotherapy in human chronic HBV infection will provide crucial insights into fundamental immune mechanisms governing viral immunity, enhancing our understanding of immune responses to persistent infections.

The Rockefeller University Hospital and Center for Clinical and Translational Science celebrate Hispanic Heritage Month

By Maija Williams, COO, MPH

Americans observe National Hispanic Heritage Month from September 15 to October 15, by celebrating the histories, cultures, contributions, traditions, and cultural diversity of Hispanic/Latino/Latinx Americans whose heritage is rooted in 20 Latin American countries and territories across the world.

The national observation started in 1968 as Hispanic Heritage Week under President Lyndon Johnson and was expanded by President Ronald Reagan in 1988 to cover a 30-day period starting on September 15 and ending on October

15. It was enacted into law on August 17, 1988, on the approval of Public Law 100-402.

The national theme this year, “Todos Somos, Somos Uno: We Are All, We Are One,” reinforces the diversity inherent within the Hispanic community, as well as the power that comes from being a united community.

As part of this year’s celebration, Rockefeller University Hospital and the Center for Clinical and Translational Science celebrated the different Hispanic/Latino cultures that make up our staff

and research participant population and discussed population statistics and health disparities among Hispanics/Latinos that are prevalent today. According to the Center for Disease Control and Prevention Hispanics/Latinos are the largest racial and ethnic minority population in the United States, representing 18.8 percent of the total population in 2021. This group includes any person of Cuban, Mexican, Puerto Rican, South or Central American descent, or another Spanish speaking culture or origin, regardless of race.

The [U.S Department of Health and](#)



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The Hospital and Center for Clinical and Translational Science Staff Celebrates Hispanic Heritage Month

FDA on Artificial Intelligence in Drug Development

By Robert B. MacArthur, PharmD, MS, BCSCP

FDA has reported an increased use of artificial intelligence (AI) and machine learning (ML) in the drug development process, across a wide range of applications and therapeutic areas. For example, in 2021, there were more than 100 (NDA) new drugs and biologic (BLA) application submissions that incorporated either AI or ML.

As background, AI and ML can be described as a branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions, and making predictions. ML is considered a subset of AI that allows models to be developed by training algorithms through analysis of data, without models being explicitly programmed.

In a recent position paper, [Using Artificial Intelligence & Machine Learning in the Development of Drug](#)

[& Biological Products, Discussion Paper and Request for Feedback](#), FDA described 8 areas where AI and ML intersect with clinical research (Table 1).

Table 1: Areas Where Clinical Research Intersects with

- Artificial Intelligence and Machine Learning
- Recruitment
- Selection of Trial Participants
- Dose/Dosing Regimen Optimization
- Adherence
- Retention
- Site Selection
- Clinical Trial Data Collection,

Selection and Stratification of Trial Participants

Enrichment strategies can aid participant selection in clinical investigations designed to demonstrate the effectiveness of drug and biological products. AI/ML has been used as part of a clinical

investigation to predict individual participant’s clinical outcome based on baseline characteristics (e.g., demographic information, clinical data, vital signs, laboratory test results medical imaging data, and genomic data). Such predictive models can be used to enrich clinical trials (e.g., identifying high-risk participants or participants more likely to respond to the treatment). When these AI/ML algorithms are used for patient evaluation and selection before randomization, it may be possible to reduce variability and increase study power. In addition, such predictive models can also be used for participant stratification. For example, an AI/ML model may be able to predict the probability of a serious adverse event before an investigational treatment is administered. Based on their predicted risk for these serious adverse events, participants can be stratified into different groups and then monitored accordingly (or excluded depending on

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The Rockefeller University's Certificate in Clinical and Translational Science Program

By Editorial Staff

The Rockefeller University's Certificate in Clinical and Translational Science Program was developed to provide trainees with an introduction to the principles and practice of clinical and translational research. PhD students, MD-PhD students, postdoctoral trainees, investigators, research nurses, and university staff are all eligible to participate in the program. The 2022 – 2023 class was comprised of individuals with diverse experiences and from 8 different labs.

The program consists of two one-credit courses taken over one year. Trainees completing the courses receive a Certificate in Clinical and Translational Science. The first course, which begins in September, is titled Introduction to Clinical and Translational Research. This course consists of two 60–90-minute

weekly sessions, starting at noon on Mondays and Fridays. The first session of each week consists of a presentation and discussion of specific elements in the development of a human subject protocol, including the elements of informed consent, clinical trial design, biostatistics, and the bioethical basis of human studies. The second session each week consists of a presentation by a faculty member or guest lecturer on translational research, emphasizing the protocol element discussed earlier in the week. Students design a hypothetical clinical study and write it up as a formal protocol. Then as part of peer mentoring, the protocols are reviewed by a mock Institutional Review Board in which each student serves as a reviewer.

The other required course, offered in the spring, is titled Introduction to

Techniques in Clinical and Translational Science. The course meets once per week for three hours to review the principles and application of select techniques used in clinical and translational science. Rockefeller Resource Center Directors and staff play an important role in hosting visits by the students to the Resource Center.

Students spontaneously commented that the program enhanced their understanding of the complexity of clinical research and the need for rigor in developing a protocol. Both courses received positive student evaluations, with 100% of the students reporting that they would recommend to others participation in the Certificate Program.



Certificate Course students with Dr. Barry Coller - Zhiyong Liu, Lorena Buitrago, Zhaoyue Zhang, Tia Gareau, Christine Kim

Rockefeller University Hospital Chief Operating Officer Maija Neville-Williams selected as a Thomas C. Dolan Executive Diversity Scholar

By Editorial Staff



Rockefeller University Hospital Chief Operating Officer Maija Neville-Williams was selected as a Thomas C. Dolan Executive Diversity Scholar as part of the [American College of](#)

[Healthcare Executives](#) Senior Executive Program. The ACHE Senior Executive Program connects seasoned healthcare professionals over a 6-month period to learn about best practices and successful strategies. Executives tackle current industry topics in tailored professional development sessions, gain leadership skills through personalized coaching and mentoring, and make purposeful connections with fellow leaders. The in-person modules were held in Atlanta, Chicago, and Houston in June-October with interim virtual programming. Top health issues studied in the program include advancing health equity, working

effectively with boards and committees, mentorship, improving safety and quality, negotiation, resiliency, and workforce solutions. Ms. Neville-Williams was selected to receive a full scholarship to participate as a Dolan Scholar. Learning organizational strategies to advance health equity, and both connecting and collaborating with senior healthcare leaders across the United States will help Ms. Neville-Williams manage the complexities and challenges of the ever-changing health care environment and be responsive to the diverse research participants we serve

New Clinical Scholars Join the Center for Clinical and Translational Science

By Editorial Staff

We are pleased to announce that Drs. Nicole Cruz and Dennis Schaefer-Babajew will be the Chief Clinical Scholars for the academic year 2023 - 2024. Dr. Cruz is a member of the Roeder Laboratory, and her research focus is to elucidate the epigenetic basis of the oncogenic function of histone methyl transferase in a form of myeloid leukemia. Dr. Dennis Schaefer-Babajew is a member of the Nussenzweig Laboratory, and his research focuses on the concept of 'antibody feedback' and its impact on vaccine efficacy. To this end, he investigates how soluble antibodies impact subsequent adaptive immune reactions, both clinically and in terms of fundamental immunobiology.

We are also pleased to welcome five new Clinical Scholars who joined the Center for Clinical and Translational Science on July 1, 2023.



Juan Angulo-Lozano, MD

Mentor: Jeffrey V. Ravetch, MD, PhD

Leonard Wagner Laboratory of Molecular Genetics and Immunology

Research Interest: Dr. Angulo-Lozano's research interest is investigating the immunologic interactions and tumor microenvironment changes in prostate and bladder cancer and their response to different antibody-based therapies (ABT). His research project will focus on testing novel immunotherapies and combinations for the treatment of early-stage bladder cancers and how the Fc-domain of ABTs affect tumor immunity.

Biography: Dr. Angulo-Lozano received his MD from the Universidad Anahuac Norte in Mexico City. He previously was a postdoctoral research associate in the Leonard Wagner Laboratory of Molecular Genetics and Immunology.



Barbara Bosch, MD, PhD

Mentor: P Seth A. Darst, PhD and Elizabeth Campbell, PhD

Laboratory of Molecular Biophysics

Research Interest: Dr. Bosch's research interest is microbiology, particularly mycobacteria, focusing on microbial physiology and genetics. Her research project aims to visualize and understand the regulation of the transcriptional process using a combination of genetic, biochemical, and structural techniques.

Biography: Dr. Huang received both her MD and PhD from Washington University School of Medicine in St. Louis. She completed her Internal Medicine residency at Barnes-Jewish Hospital in St. Louis, and is currently a Radiation Oncology resident at Memorial Sloan Kettering Cancer Center.



Nicolás Gomez Banoy, MD

Mentor: Paul Cohen, MD, PhD

Laboratory of Molecular Metabolism

Research Interest: Research Interest: Dr. Gomez Banoy's research interest is focused on unraveling the mechanisms behind obesity, diabetes and cardiovascular disease. His current research project will focus on understanding the genetic and pharmacologic determinants of brown adipose tissue (BAT) in adult humans, with the ultimate goal of harnessing thermogenic adipocytes to treat cardiometabolic diseases.

Biography: Dr. Gomez Banoy received his MD from the Universidad Nacional de Colombia in Bogota, Colombia. He then did a postdoctoral fellowship with Dr James Lo at Weill Cornell Medicine studying pancreatic islet biology. Dr. Gomez Banoy completed his Internal Medicine residency at Weill Cornell Medicine/New York Presbyterian Hospital. He is currently an Endocrinology, Diabetes and Metabolism fellow at the joint Weill Cornell Medicine/Memorial Sloan Kettering program.

New Clinical Scholars Join the Center for Clinical and Translational Science



Mai Takahashi, MD, PhD

Mentor: Sohail Tavazoie, MD, PhD

Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology

Research Interest: Dr. Takahashi's Mai's research interest is the molecular mechanisms of cancer metastasis and exploring potential key genes associated with disease progression. Her research project will focus on the biological understanding of signaling pathways on pancreatic cancer and colon cancer metastasis and its therapeutic targeting.

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Shin-Rong (Julia) Wu, MD, PhD

Mentor: Sidney Strickland, PhD

Patricia and John Rosenwald Laboratory of Neurobiology and Genetics

Research Interest: Dr. Wu's research interest focuses on how the immune and blood clotting systems interact to maintain homeostasis in health and to affect organ damage in disease. Her research project seeks to understand how peripheral blood components, encompassing both cellular populations and plasma proteins, contribute to Alzheimer's disease.

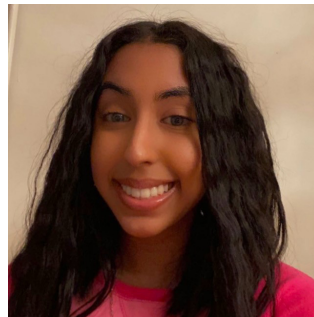
Biography: Dr. Wu received her MD and PhD from University of Michigan Medical School. Dr. Wu completed her internal medicine residency at New York-Presbyterian, Weill Cornell Medical Center. She is currently doing her Hematology/Oncology Fellowship at New York-Presbyterian, Weill Cornell Medical Center.

The Heilbrunn Undergraduate Nurse Externship Program

By Bernadette 'Candy' Capili, PhD, NP-C

The Heilbrunn Undergraduate Summer Externship completed its third year. The 8-week program is designed for undergraduate nursing students who want to learn more about clinical research. The Summer Externship is a collaboration among the Heilbrunn Family Center for Research Nursing, the Department of Nursing and Patient Care Services, the Department of BioNutrition, and Science Outreach. The participating mentors are Bernadette 'Candy' Capili (Director Heilbrunn Family Center), Rita Devine (Director Nursing & Patient Care), and Andrea Ronning (Director Bionutrition).

Two students were selected for 2023 program, Valentina Marin, from the New York University – Honors program, and Leah Misripersaud, from the Hunter College – Honors program. The selection process was highly competitive. To qualify as a nurse extern, students must have completed their Sophomore year with a grade point average of 3.0 or higher.



Valentina Marin

The externship introduced students to good clinical research practice by providing a curriculum on topics that included the informed consent process, research design, the roles and responsibilities of study team members, the roles/domains of a clinical research nurse, and elements of a clinical research protocol related to caring for participants. Students participated in class discussions, clinical research observations, and activities. For example, the students worked with members of the Department



Leah Misripersaud

of Bionutrition under Andrea Ronning's direction. They learned how to assess dietary intake (calories and nutrients) and developed a menu consistent with dietary and caloric intake targeted for their weight and activity. They also learned first-hand the process required to implement a clinical research study involving a controlled diet. The summer experience is a highlight for both mentors and students.

New Pilot Grants Awarded

By Editorial Staff

The Rockefeller University Center for Clinical and Translational Science (CCTS), The Shapiro-Silverberg Fund for the Advancement of Translational Research, and The Maurice R. and Corinne P. Greenberg Center for the Study of Inflammation, Microbiome, and Metabolism awarded 22 pilot projects in support of research initiatives at the institution. A total of 37 pilot projects received support this academic year. Clinical Scholars received 10 pilot awards. This academic year's total of \$847,193 awarded brings the grand total of pilot project funding to \$12,485,905 since the program began under the initial CTSA grant in 2006. A total of 595 different pilots have been funded in 51 different laboratories.

Clinical Translational Science Award Funding

Name of Investigator: Juan Angulo-Lozano, MD (Clinical Scholar)

Lab: Leonard Wagner Laboratory of Molecular Genetics and Immunology

Title of Pilot Project: *Understanding the Immunomodulatory Effects of Intravesical Enfortumab Vedotin in Combination with CD40 Agonism (2141-V11) In Non-Muscle Invasive Bladder Cancer.*

Abstract: Understanding the immunomodulatory effects of intravesical Enfortumab Vedotin (EV) in combination with CD40 agonism (2141-V11) in Non-Muscle Invasive Bladder Cancer. Based on compelling preliminary data and to further enhance antitumor immunity using rational therapeutic combinations for bladder cancer, this proposal aims to understand whether the immunomodulatory effects of 2141-V11 can be synergized by EV, which is a novel anti-nectin4 antibody-drug conjugate that has been recently approved for the management of metastatic urothelial carcinoma, We hypothesize that EV promotes upregulation of activation markers in human dendritic cells (DCs) including CD40, which will result in enhanced CD8+ T cell infiltration in the TME during treatment with CD40 agonism.

Name of Investigator: Rachel Kimani, DNP (Clinical Scholar)

Lab: Laboratory of Neurogenetics of Language

Title of Pilot Project: *Effects of Compassion-Based Resiliency Training Intervention on Racism-based Stress among African Americans: A Feasibility Pilot Study*

Abstract: The primary aim of this pilot study is to explore the feasibility, acceptability, and preliminary effectiveness of Compassion-Based Resiliency Training (CBRT) intervention among African Americans compared to a wait-list control group. By investigating the potential benefits of CBRT in alleviating racism-induced stress and associated health disparities, this research aims to contribute essential insights into mindfulness-based interventions to address racism-related stress and its broader implications for the well-being of Black, Indigenous, and People of Color communities.

Name of Investigator: Alon Millet

Lab: Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology

Title of Pilot Project: *Therapeutic Targeting of Cancer Metastasis-Promoting Pathways*

Abstract: Neuroinflammation driven by microglia is a prominent feature of Alzheimer's disease (AD). Our prior work used single-cell techniques to study microglia during AD progression, identifying a new functionally impaired microglial population co-expressing inflammatory and stress markers. We named these cells terminally inflammatory microglia (TIMs) and proposed that they represent an exhausted microglial state in the inflammatory AD milieu. Still, much is unknown about mechanisms governing the emergence of TIMs, and it remains to be seen whether TIMs are also present in non-AD neuroinflammation. Here, we propose a set of computational and experimental approaches addressing these questions.

The Maurice R. and Corinne P. Greenberg Center for the Study of Inflammation, Microbiome, and Metabolism Funding

Name of Investigator: Jan Burian, PhD

Lab: Laboratory of Genetically Encoded Small Molecules

Title of Pilot Project: *Transmembrane Proteome-Wide Analysis of Non-Canonical Janus Kinase Activation to Guide the Development of Inhibitors*

Abstract: Many cytokines and hormones signal via Janus kinases (JAKs). JAKs are protein tyrosine kinases that mediate signal transduction downstream of receptors. The mammalian JAK family consists of JAK1, JAK2, JAK3, and TYK2, all of which associate with the membrane-proximal regions of cytokine receptors through conserved intracellular domain motifs. Given the roles JAKs play in aberrant signaling in both cancer and rheumatoid arthritis, there has been significant pharmaceutical investment in the development of JAK inhibitors. Our aim is to gain an improved understanding of the complete physiological role of JAKs.

Name of Investigator: Nicolas Gomez Banoy, MD (Clinical Scholar)

Lab: Laboratory of Molecular Metabolism

Title of Pilot Project: *Repurposing of Pharmacologic Agents to Regulate Brown Adipose Tissue in Humans*

Abstract: Elevated body mass index (BMI) is associated with an increased risk of cardiometabolic diseases, which are major contributors to morbidity and mortality worldwide. Brown adipose tissue (BAT) plays a central role in systemic metabolism as it utilizes energy to produce heat via non-shivering thermogenesis. Recent studies from the Cohen Lab have shown that a significant proportion of adult humans have detectable BAT in FDG-PET scans, and this is associated with protection from type 2 diabetes, hyperlipidemia, coronary artery disease, and hypertension, even amongst obese individuals. Ultimately, the goal is to identify widely used, approved pharmacologic agents that can be repurposed to regulate BAT in patients with cardiometabolic diseases.

Shannon Gillespie, 2020 Heilbrunn Nurse Scholar awarded R01 from the National Institutes of Health

By Bernadette 'Candy' Capili, PhD, NP-C



Shannon Gillespie, PhD, RN, an assistant professor at The Ohio State University College of Nursing, was awarded a [\\$3.8 million grant by the National Institutes of](#)

[Health/National Institute of Nursing Research \(NIH/NINR\)](#). This five-year funding will support her research on the effects of various postpartum primary care models on maternal and infant health during their first year after

birth. The clinical trial, titled “The mom and infant outcomes study: A trial of perinatal outpatient delivery systems” or The MOMI Study, aims to gather crucial information about diseases and deaths related to pregnancy. Pregnancy-related deaths have doubled over the past 20 years, particularly among socioeconomically disadvantaged and marginalized groups.

Dr. Gillespie’s primary goal is to reduce the risk by offering superior care to mothers and infants through efficient, equitable, and scalable care models that will address the persistent socioeconomic, racial, and ethnic disparities in pregnancy-related illnesses and fatalities as well infant health outcomes. The research will compare two

distinct mother and infant care methods during the first year after birth that differ in patient scheduling, communication between healthcare providers, use of medical history in care, and referral procedures.

For Dr. Gillespie, this research is not just a professional undertaking. Rather, it’s a personal mission inspired by her experiences. Her decision to become a nurse 15 years ago was prompted by the loss of her mother at a young age. She sees this project as her opportunity to improve the care of every mother and baby.

Heilbrunn Nurse Scholar - Dr. Paule Joseph Receives NIH NINR Friends of Nursing Research 2023 The Protégé Award

By Bernadette 'Candy' Capili, PhD, NP-C



Paule Joseph, PhD, EMBA, MS, FNP-BC, FTCNS, FAAN, a 2016 Heilbrunn Nurse Scholar recipient, received the NIH National Institutes of

Nursing Research Friends of Nursing Research 2023, “The Protégé Award.” The Protégé Award is given to a nurse scientist who shows great promise in advancing science within the first six years of completing their PhD or Post-Doctoral studies

Dr. Joseph is a nurse scientist who has impacted chemosensory science, genomics, and precision health. She is a Lasker Clinical Scholar at the National Institutes of Health (NIH) and a Distinguished Scholar at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Nursing Research (NINR).

She is Chief of the Sensory Science and Metabolism Section (SenSMet) at the Division of Intramural Clinical and Biological Research. Dr. Joseph’s educational background encompasses both nursing and the biological sciences. She completed her PhD at the University of Pennsylvania and conducted her PhD work at the Monell Chemical Senses Center, where she focused on sensory biology and genomics. She then completed a Clinical and Translational Postdoctoral Fellowship at the NINR supported by the Office of Workforce Diversity. With over 100 publications, she is a recognized figure in sensory science research. Her insights have been highlighted in various media outlets, reflecting her role as a leading voice in her field. Her research explores how taste and smell influence health, especially those with chronic illnesses. Specifically, she investigates the neurological mechanisms of chemosensation and its relation to ingestive behaviors, especially in those with chemosensation and its relation to ingestive behaviors, especially in those with obesity and substance abuse disorders.

Notably, during the COVID-19 pandemic, she examined the effects of the virus on taste and smell and co-founded the Global Consortium for Chemosensory Research.

Dr. Joseph is a staunch advocate for diversity in science. She mentors and fosters inclusivity, especially for underrepresented individuals. She also leads initiatives such as the Amazing Grace Children’s Foundation in Ghana and the African Research Academy for Women. Honored with multiple awards, the National Minority Quality Forum has recognized her, the National Association of Hispanic Nurses, the Johnson& Johnson-American Association of Colleges of Nursing, and the Rockefeller University Heilbrunn Nurse Scholar. She has been recognized with the Ajinomoto Award for Young Investigators in Gustation. She is a fellow of the American Academy of Nursing, a Fellow of the New York Academy of Medicine, and a Fellow of the Transcultural Nursing Society. She is also the inaugural American Academy of Nursing Fellow at the National Academy of Medicine.

Meet the Scholar: Nicole Cruz, MD

By Editorial Staff



Dr. Nicole Cruz joined the Clinical Scholars program in July 2021 in the Laboratory of Biochemistry and Molecular Biology, led by Dr. Robert Roeder. Dr.

Cruz received her MD from the San Juan Bautista School of Medicine in Puerto Rico. Dr. Cruz completed her internal medicine residency and Hematology-Oncology Fellowship at New York Presbyterian Hospital -Weill Cornell Medicine. She was selected to be the Co-Chief Scholar for the 2023 – 2024 academic year.

How did you get interested in research?

My research interest evolved over time. In college, I didn't initially connect with the research that I was doing because I couldn't see its practical benefits to humanity. However, during a summer research experience between my first and second year of medical school, I started working with human cell lines. That experience changed everything for me. I fell in love with research because I could see how it could benefit people's health. This newfound passion has been a driving force in my academic and professional journey ever since.

How did you come to the Roeder Lab?

I became a member of the Roeder Lab through the Clinical Scholars program. My specific goal was to find a laboratory where I could explore and gain insights into the variations in the transcriptional programs among various types of acute myeloid leukemia. With the help and guidance of Dr. Barry Collier, I interviewed and considered different laboratories and ultimately found a perfect match in Dr. Roeder's laboratory.

What is your current research?

My current research focuses on understanding the mechanisms by which the KMT2D protein locates its target genes. I'm particularly interested in identifying the transcription factors or co-factors involved in this process. One of my hypothesis centers around the idea that the transcription factor PPAR-gamma may be responsible for recruiting KMT2D to genes associated with the metabolic program of some leukemias.

What were your expectations when you joined the Clinical Scholar program, and have they been met?

When I joined the Clinical Scholar program, my primary expectation was that it would help me carve out a distinctive role in the field of acute myeloid leukemia as a physician-scientist. I'm delighted to share that this expectation is well on its way to being fully realized with my ongoing training as a biochemist in the Roeder laboratory,

What are your expectations and goals as Chief Scholar?

As Chief Clinical Scholar, I aim to facilitate a seamless transition for the incoming Scholars as they navigate the pilot program, IRB submissions, and project timelines. Additionally, I aim to cultivate a sense of camaraderie among our Scholar community. To achieve this, I plan to arrange engaging events that allow us to build stronger connections and get to know one another.

What has been a learning opportunity or teaching moment as a Scholar?

Recognizing the unique challenges of being a physician collaborating within a non-physician scientific team, I have understood that my role brings a distinct set of skills to our research collective. It's essential to acknowledge that these skills are equally valuable as those of my non-physician colleagues. I've come to terms with the fact that, as a physician,

my approach to problem-solving centers around patient concerns. I prioritize addressing research questions from this perspective before delving into the underlying mechanisms rather than the other way around.

What has been the most educational, interesting, or surprising aspect of being in the Clinical Scholars program?

The most pleasantly surprising aspect of my journey was the many opportunities that have unfolded since I became part of the Clinical Scholars program. It's been a true blessing to have secured nearly all the grants I've applied for since joining the Clinical Scholars.

If someone asked you to describe the Clinical Scholars program in one sentence, what would it be?

It is a pivotal step in the journey from a mentored research experience as a physician-scientist to forging an independent career in research, providing the necessary support and guidance along the way.

What are your next steps/career goals when you graduate from the program?

Upon graduating from the program, my immediate career goal is to continue my research journey. There is a notable absence of physician-scientists in my field who conduct the type of biochemistry work we do in the Roeder lab. Therefore, I plan to remain at Rockefeller for a few more years, where I can further develop my expertise. Ultimately, I aspire to establish myself as an independent physician-scientist specializing in the comprehensive study of acute myeloid leukemia from a biochemical perspective.

Meet the Graduate: Teresa H. Evering, MD, MS

By Editorial Staff



Teresa H. Evering received her medical degree from Weill Cornell Medical College and master's degree from Rockefeller University. Dr. Evering completed her

Internal Medicine Residency at Columbia Presbyterian Hospital and her Infectious Diseases Clinical and Research Fellowship at Albert Einstein College of Medicine/Montefiore Medical Center. Dr. Evering joined Rockefeller University as a Clinical Scholar in the Aaron Diamond AIDS Research Center Laboratory of Dr. David Ho in July 2007. She was mentored by Dr. Martin Markowitz. Dr. Evering is currently an Assistant Professor of Medicine at Weill Cornell Medicine.

What sparked your research interest?

My passion for research grew in tandem with my decision to specialize in Infectious Diseases. This field captivated me from the moment it was introduced to me during medical school.

How did you come to the Markowitz laboratory?

During my research fellowship in Infectious Disease, a growing desire to build a translational research career that complemented my passion for HIV clinical care led me to apply for and ultimately accept a position in the Rockefeller University Clinical Scholars Program at the Aaron Diamond AIDS Research Center.

What is your current research, and how is your R21 grant going to assist with the research?

My NIH-funded, translational HIV-pathogenesis research program focuses

on the use of phylogenetic, molecular, and systems biology approaches to study HIV-1 infection of the Central Nervous System and HIV-Associated Neurocognitive Disorders (HAND). Since the height of the COVID pandemic, I have also been privileged to collaborate on several important clinical studies on COVID-19 therapeutics and post-COVID complications. My two NIH R21 translational research proposals is centered around the generation and immunologic, transcriptional, and functional characterization of induced neurons from people living with HIV (PLWH). Ongoing work under these grants allows us to study the impact of aging (National Institute on Aging) and neurocognitive impairment (National Institute of Neurological Disorders and Stroke) on neuronal health.

What were your expectations when you joined the Clinical Scholars program, and were they met?

My primary aspiration upon entering the program was to acquire the expertise needed to conduct translational research, with a specific focus on advancing my knowledge in the field of HIV-pathogenesis research. I aimed to develop the ability to formulate impactful research questions, acquire advanced laboratory skills, navigate the journey from conceptualizing a research question to achieving a published outcome, and compete successfully for grant funding. I'm delighted to report that my expectations have been not only met but exceeded.

What has been a learning opportunity or teaching moment as a Scholar?

I have gained invaluable insights into the art of capitalizing on opportunities to advance one's research, especially when it

leads you to uncharted territories. In my case, this entailed a dedicated investment in exploring advanced coursework in molecular evolution, a decision that has proven exceptionally advantageous for my work on HAND.

What has been the most educational, interesting, or surprising aspect of being in the Clinical Scholars program?

One of the most interesting aspects of the program was undoubtedly the privilege of collaborating with and gaining knowledge from an exceptionally diverse and highly talented group of individuals.

If someone asked you to describe the Clinical Scholars program in one sentence, what would it be?

The Clinical Scholars program is a unique platform for fostering learning, collaboration, and innovative research in a supportive and stimulating environment.

What are the takeaways you would share with a junior Scholar?

I encourage junior Scholars to seek mentorship and guidance from experienced researchers as well as colleagues, network and collaborate, and be open to learning and adapting as their research and technology evolve.

Clinical Scholars Program Celebrates New Graduates

By Editorial Staff

On June 8, 2023, the Center for Clinical and Translational Science celebrated the graduation of five Clinical Scholars with a dinner celebration in the Kellen BioLink. The celebration is the highlight of the year, and it was a wonderfully warm and inspiring event, with friends, and family members. Mentors spoke about their Scholars and Scholars shared their experiences in the program. Dr. Sarah Schlesinger, Director of the Clinical Scholars program, welcomed the participants with inspiring words about the Scholars' achievements and the pride that the entire CCTS leadership has in the Scholars. Dr. Barry Collier, Co-Director of the program, concluded the festivities by congratulating the Scholars and their families.

Dr. Yelina Alvarez's research focused on the interactions among the intestinal microbiota, its products, and the enteric nervous system and how this can contribute to the development of disorders of gut-brain interactions. She has employed animal models and human studies to address these questions. Dr. Alvarez will continue her research as Instructor in Clinical Investigation at Rockefeller University in the Mucida Lab as she is considering positions in industry.

Dr. Charlie Buffie's research focused on bioactive metabolites derived from the intestinal microbiota and their impact on gastrointestinal disorders, including inflammatory bowel disease. Dr. Buffie will continue his research as Instructor in Clinical Investigation at Rockefeller University in the Brady Lab as he is considering positions in academia.

Dr. Katherine Knorr's research has defined patterns of known and novel therapeutic antibody targets on the surface of malignant myeloid cells, including the spliceosome protein U5 snRNP200. Expression of this protein has been demonstrated to correlate with durable responses after allogeneic stem cell transplant in acute myeloid leukemia patients where the proposed mechanism of response involves the formation of antibodies against the U5 snRNP200 protein. Dr. Knorr has generated therapeutic antibodies against this protein and others that have shown activity in preclinical models and is now moving forward toward clinical development. Dr. Knorr is joining the biotechnology company Regeneron as Clinical Director of Hematologic Malignancies/Bi-specific Antibody Therapy Division.

Dr. Mira Patel's research focused on the mechanisms of immune modulation by human Apolipoprotein E (APOE) protein variants, specifically how APOE expression in immune cells either promotes cancer targeting, as in the case of APOE4, or cancer cell survival, as in the case of APOE2. With a better understanding of how the APOE gene affects the body's response to cancer, she hopes to improve cancer therapy by tailoring treatment to the form of APOE each patient possesses. Dr. Patel received the Damon Runyon Cancer Research Foundation 2022 Physician-Scientist Training Award. She will continue her research as Instructor in Clinical Investigation at Rockefeller University in the Tavazoie Lab while considering academic physician-scientist and industry positions in the New York City area.

Dr. Kareem Rashid Rumah's research investigates the potential role of the gut bacterium, *Clostridium perfringens*, and its epsilon neurotoxin in triggering brain lesions in multiple sclerosis. Dr. Rumah is actively considering positions in academia in the New York City area.



Clinical Scholars program graduates, Drs. Yelina Alvarez, Mira Patel, Katherine Knorr, Charlie Buffie with Drs. James Krueger, Barry Collier, Sarah Schlesinger, and Ms. Maija Williams.

New Pilot Grants Awarded

Name of Investigator: Timothy Kenny, PhD

Lab: Laboratory of Metabolic Regulation and Genetics

Title of Pilot Project: *The Impact of FLVCR1 Mediated Choline Transport on Organismal Metabolism and Non-Alcoholic Steatohepatitis (NASH)*

Abstract: Dysfunctional lipid accumulation is characteristic of numerous metabolic diseases and pathologies including insulin resistance, heart failure, and hepatic steatosis. Enhanced understanding of the molecular mechanisms controlling affecting lipid metabolism holds great promise for the treatment of these diseases. This proposal seeks to understand the mechanism by which FLVCR1 mediated choline transport influences organismal physiology and to investigate the therapeutic importance of choline metabolism in NASH.

Name of Investigator: Luke Olsen, PhD

Lab: Laboratory of Molecular Metabolism

Title of Pilot Project: *Mouse Models of The Complications of Obesity*

Abstract: Obesity is a major public health concern affecting ~42% of adults in the United States and is associated with the leading causes of morbidity and mortality such as cardiovascular disease, type 2 diabetes, and muscle wasting. A growing body of research has indicated exercise is a promising intervention to ameliorate obesity-linked pathologies through remodeling adipose metabolism. This adipose remodeling phenomenon is thought to occur via exercise-mediated secretion of skeletal muscle-derived proteins – a class of hormones termed myokines. This proposal will provide fundamental insights into interorgan and intercellular crosstalk and, more specifically, a critical perspective into the mammalian muscle-adipose signaling axis

Name of Investigator: Marina Schernthanner

Lab: Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development

Title of Pilot Project: *Dissecting the Roles of Lymphatic-derived IL-33 During Intestinal Regeneration*

Abstract: Intestinal stem cells (ISCs) maintain epithelial turnover, barrier integrity and mediate tissue repair. To do so they depend on coordinated signaling cues from cells in their microenvironment (niche). I have uncovered lymphatic capillaries as a new component of the ISC niche, able to directly crosstalk with crypt-based stem cells through spatially concentrated expression of molecular factors. This work holds great therapeutic promise by clarifying the pleiotropic function of IL-33 in IBD and revealing additional modes of ISC modulation in health and disease.

Name of Investigator: Yue Yu, PhD

Lab: Laboratory of Molecular Genetics

Title of Pilot Project: *Neural Circuits Underlying Energy and Nutrition Homeostatic Behaviors*

Abstract: Essential amino acids (EAAs), which are not synthesized by mammals including humans, and are therefore dietary essential, are indispensable for vital processes that regulate body homeostasis and brain functions. Studies in rodents and humans show that dietary EAA deficiency leads to decreased appetite, fatigue, depression, and anxiety. However, how dietary EAA is sensed, and the adaptive feeding in response to EAA-deficient diet are largely unknown.

This study will support to uncover the biological mechanism of specific dietary nutrition sensing and the neural and molecular regulation of feeding by dietary nutrition content. Moreover, this study will shed light on the right guidance to the public on how to eat a balanced diet and how to prevent diseases caused by nutrition imbalance.

The Shapiro-Silverberg Fund for the Advancement of Translational Research Funding

Name of Investigator: Tamar Berger, MD (Clinical Scholar)

Lab: Laboratory of Genome Maintenance

Title of Pilot Project: *Detection of Pre-Malignant Changes in Fanconi Anemia Mucosa*

Abstract: Fanconi anemia (FA) is a hereditary genomic instability syndrome due to inability to repair DNA interstrand crosslinks. FA patients have a very high predisposition to head and neck squamous cell carcinoma (HNSCC). FAHNSCC is distinct from sporadic HNSCC, presenting earlier in life, often at a late-stage disease. Since FA-HNSCC have a high level of genome instability driven by structural variants and display p53 mutations, in this study, we aim to map somatic mutation changes in normal-appearing oral mucosa cells and lesions. This will shed light on the pathogenesis of oral SCC, allow for earlier cancer detection and facilitate effect measurement of potential prophylactic therapies. Finally, we will evaluate the differential expression of a serum cancer biomarker from FA patients and healthy volunteers to facilitate early diagnosis and disease monitoring.

Name of Investigator: Kristina Hedbacker, PhD

Lab: Laboratory of Molecular Genetics

Title of Pilot Project: *Mapping cell-type-specific mTOR Interactomes That Regulate Energy Balance*

Abstract: Obesity is associated by mTOR hyperactivity. Our recent research demonstrates that rapamycin, an mTOR inhibitor, reduces obesity by restoring leptin sensitivity in diet-induced-obese (DIO) mice. These findings suggest that mTOR hyperactivity in specific hypothalamic cell types causes leptin resistance and energy imbalance. These studies will establish an atlas of cell types exhibiting mTOR hyperactivity in DIO mice, and potentially uncover novel, cell-type-specific mTOR binding partners for obesity treatment.

Name of Investigator: Thomas Kartika, MD

Lab: Allen and Frances Adler Laboratory of Blood and Vascular Biology

Title of Pilot Project: *Studies of Genetic Disorders of Blood Cells and Coagulation Factors, and Transforming Growth Factor- β 1 In Health And Disease.*

Abstract: Bruton's tyrosine kinase inhibitors (BTKi) have transformed the landscape of B-cell lymphoproliferative disease treatment by acting on key maturation pathways. A toxicity of bleeding, however, emerged with use of these drugs and may be associated with morbidity, mortality and interruption of life prolonging therapy. While BTK within platelets is targeted by these drugs, patients with a congenital deficiency, X-linked agammaglobulinemia (XLA), do not exhibit a bleeding diathesis. We hypothesize that the effects on platelets are due to off-target effects of the BTKi on related kinases within platelets. In this pilot project, we aim to elucidate the effects of BTKi of varying target specificity on platelet function with regards to aggregation and clot retraction by utilizing and comparing BTKi treated platelets from healthy donors and persons with XLA.

Name of Investigator: Matthew Kudelka, MD, PhD (Clinical Scholar)

Lab: Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development

Title of Pilot Project: *Harnessing Anti-Glycan Immunity for Cancer Immunotherapy in Human Melanoma*

Abstract: Checkpoint inhibitors have revolutionized the treatment of cancer. Checkpoint inhibitors are thought to work by activating the immune system against altered proteins/peptides. However, tumor mutational burden, a surrogate of protein/peptide alteration, fails to predict patient outcomes in many cases, suggesting that other molecules, such as carbohydrates may be targeted following treatment. I hypothesize that checkpoint inhibition induces anti-glycan immunity that can predict treatment response and/or toxicity. This study will advance our understanding of anti-glycan immunity and the treatment of human cancer.

Name of Investigator: Shanshan Liu, PhD

Lab: Laboratory of Metabolic Regulation and Genetics

Title of Pilot Project: *Understanding the Role of Mitochondrial Redox Sensing in Cancer*

Abstract: Cells need to maintain metabolic homeostasis to survive and proliferate. Many biochemical systems have evolved to coordinate levels of cellular metabolites in response to changes in extracellular cues. Recent studies from the host lab discovered SLC25A39 as a mitochondrial transporter for glutathione (GSH), the major antioxidant thiol in mammalian cells. Remarkably, SLC25A39 protein levels are negatively regulated specifically by mitochondrial GSH availability. This observation raises the possibility that mitochondria harbor a sensing system for GSH availability. Building upon these observations, I will identify the mechanism by which mitochondria sense GSH availability and test whether it is required for tumor formation.

Name of Investigator: Carly Rosemore, MD

Lab: Laboratory of Cellular Biophysics

Title of Pilot Project: *Profiling of Fibrolamellar Hepatocellular Carcinoma Genome and Transcriptome*

Abstract: Fibrolamellar hepatocellular carcinoma (FLC) is a rare primary liver tumor that affects primarily adolescents and young adults without underlying liver disease. Our proposed study will use long read sequencing of patient tumor samples to assess for the specific breakpoint in each patient's tumor, and then will design individualized primers that we will use in targeting analysis of circulating tumor DNA in a patient's blood samples. This can be used for either monitoring of a patient's disease throughout treatment, or it can assess for residual or recurrent disease. This study will address the critical unmet need for development of sensitive diagnostic tools for the detection of recurrent disease and tumor burden throughout treatment in patients with fibrolamellar hepatocellular carcinoma.

Name of Investigator: Leon Seifert, MD (Clinical Scholar)

Lab: Laboratory of Virology and Infectious Disease

Title of Pilot Project: *In Vivo Hepatitis B Virus Launch from Patient-Derived HBV DNA: A Novel Method to Study Patient-Specific Virus Diversity*

Abstract: Although vaccines and antiviral treatments are available, HBV currently affects over 260 million people globally. Chronic HBV can cause cirrhosis and liver damage. HBV causes nearly 50% of hepatocellular carcinoma and lacks curative treatment. Modern in vitro and in vivo models use single HBV clones, whereas HBV is a heterogeneous virus with several genotypes and a swarm of variants in infected persons. The virus can develop immune-escape and drug-resistant mutants that dominate under selection pressure using these polymorphisms. Current research models cannot replicate HBV diversity, a key limitation. We propose a novel technique to infect severely immunodeficient human liver chimeric mice (huFNRG mice) with patient-derived HBV DNA to study more viral variants from HBV-infected persons. We will use HBV DNA from HBV-infected study participants to examine virus variety in our model after enhancing our unique in vivo launching approach. This will show us how much patient-specific variety this new approach can capture. Reducing selective immune pressure on HBV may also help identify genomic regions under severe immunological pressure.

Name of Investigator: Mai Takahashi, MD (Clinical Scholar)

Lab: Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology

Title of Pilot Project: *Utilizing Circulating MicRNAs for Breast Cancer Risk Stratification*

Abstract: The Tavazoie Lab identified specific circulating micro RNAs that are present in breast cancer patients' blood and can be used as molecular markers to predict which patients have breast cancer or benign tumor. The potential application is to guide clinical decision making by informing clinicians as to the likelihood of whether a lesion found on mammography represents breast cancer. It also could tell the probability of a malignant cancer to metastasize or to respond to chemotherapeutic and targeted agents. The goal is to extend this project and include a general healthy population to identify the optimal machine learning algorithm and provide proof of concept.

Name of Investigator: Lu Wang, PhD

Lab: Allen and Frances Adler Laboratory of Blood and Vascular Biology

Title of Pilot Project: *Studies of Protein Disulfide Isomerase (PDI) Binding to Platelet α Ib β 3 and Production of the Murine Monoclonal Antibody (mAb) that Inhibits PDI Binding and Platelet Aggregation*

Abstract: The platelet integrin α Ib β 3 plays a key role in hemostasis and thrombosis and is a validated target for antiplatelet therapy. It undergoes a conformational change from a low affinity, bent-closed conformation to a high-affinity, extended- open conformation upon activation, resulting in ligand binding and platelet aggregation. The activation of α Ib β 3 is regulated by protein disulfide isomerase (PDI). PDI is shown to bind to activated α Ib β 3, but the conformation(s) and domain(s) of α Ib β 3 to which PDI binds is unknown. The project aims to reveal the conformation(s) and domain(s) of α Ib β 3 for PDI binding by production of new anti- α Ib β 3 monoclonal antibody (mAb) that inhibits PDI binding and characterization of the antibody with biochemical and structural approaches.

Name of Investigator: Shin-Rong Wu, MD, PhD (Clinical Scholar)

Lab: Patricia and John Rosenwald Laboratory of Neurobiology and Genetics

Title of Pilot Project: *Investigating the Impact of Inflammation on Amyloid Precursor Protein (APP) Expression in the Hematopoietic Compartment*

Abstract: Approximately 30 million people worldwide have Alzheimer's disease (AD), an irreversible memory disorder. Current medications barely slow disease progression or reduce symptoms. Understanding AD development will influence new preventative and treatment methods. Many studies have discovered amyloid precursor protein (APP) and its harmful breakdown products in the blood, despite AD being a brain disease. Also, blood-based proteins can reach the brain more easily with age. No one has researched how blood cells regulate APP synthesis. Inflammation from infection, autoimmune illness, obesity, and air pollution increases AD risk. Our preliminary mouse experiments show that inflammation enhances blood cell App expression. We want to see if chronic inflammatory illness or experimental acute inflammatory triggers boost APP expression in human blood cells. We also suggest directly comparing blood cell expression levels. This study will shed light on how inflammation influences AD risk and how to lower risk or slow disease development.

Name of Investigator: Sicong Zhang, PhD

Lab: Laboratory of Biochemistry and Molecular Biology

Title of Pilot Project: *Developing a Better Approach to target Bromodomain and Extraterminal (BET) Proteins*

Abstract: Transcription of proliferative regulators by estrogen receptor- α (ER) promotes tumor development.1. In ER+/HER2- breast cancer patients, endocrine treatment suppresses ER-mediated transcription. However, endocrine resistance is widespread. Endocrine resistance may be treated using BETi. BETi and bromodomains compete to remove BET proteins from chromatin and limit oncogene transcription. Recent ER+/HER2- breast cancer BETi clinical trials failed due to ineffectiveness. Initial BETi therapy did not repress numerous oncogenic ER targets, including MYC, according to our preliminary data. BRD4's bromodomain-independent recruitment by the Mediator complex and function by the PAF1 complex mediate intrinsic BETi-resistant transcription. A successful BETi treatment must also disrupt the molecular links that recruit and activate bromodomain-independent BRD4 in ER+ breast cancer. Understanding these interactions' architecture will help us create new inhibitors. Disrupting these interactions may improve BETi's ER+ breast cancer and inflammatory disease treatment.

Name of Investigator: Edmondo Campisi, PhD

Lab: Laboratory of Bacterial Pathogenesis and Immunology

Title of Pilot Project: *Identifying the Initial Triggers of Multiple Sclerosis (MS)*

Abstract: Multiple Sclerosis (MS) is a terrible neurological illness that affects young individuals and their families. Despite intensive research, its cause is unknown. Our team linked gut-derived bacterial neurotoxin Epsilon Toxin (ETX) to relapsing-remitting MS after a decade of study at Weill Cornell Medical Center. ETX from *Clostridium perfringens* strains may cause many MS cases. A recent study found that 61% of MS patients had ETX-producing *C. perfringens* in their intestines, compared to 13% of healthy people. These findings strongly support the ETX-MS hypothesis, but we need to find ETX in MS patients' blood to prove it. Our newly found high-affinity anti-ETX nanobodies can be used to create an ultra-sensitive immunoassay that can detect minuscule ETX levels in human plasma. This novel approach may prove ETX's role in MS, enabling new paths for MS treatment and control.

Name of Investigator: Aris Mourelatos

Lab: St. Giles Laboratory of Human Genetics of Infectious Diseases

Title of Pilot Project: *Genetic Dissection of Congenital Asplenia*

Abstract: Isolated Congenital Asplenia (ICA) is a developmental disorder defined by the absence of a spleen at birth without any other birth defects. It is a life-threatening disorder, as it renders children susceptible to invasive *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* infections. An understanding of how mutations in the 5'UTR leads to ICA, and why some RPSA mutations lead to ICA with incomplete penetrance, will prove useful in our understanding of a life-threatening immunodeficiency, will inform genetic counseling for families carrying RPSA mutations, and will provide a roadmap for the study of reduced penetrance in genetic diseases caused by haploinsufficiency.

The Rockefeller University Hospital and Center for Clinical and Translational Science celebrate Hispanic Heritage Month

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Human Services Office of Minority Health reported:

Hispanic/Latino Americans have the highest uninsured rates of any racial or ethnic group within the U.S. In 2022, the estimated uninsured rate for Hispanic/Latino adults was 27.6 percent compared to 7.1 percent for non-Hispanic Asian, 7.4 percent for non-Hispanic white, and 13.3 percent for non-Hispanic Black adults.

Hispanics/Latinos have higher rates of obesity than non-Hispanic whites and are also significantly affected by chronic lower respiratory diseases (including asthma and chronic obstructive pulmonary disease), liver disease, influenza and pneumonia, suicide, and kidney disease.

Leading causes of death among Hispanics/Latinos include cancer, heart disease, unintentional injuries (accidents), stroke and other cerebrovascular diseases, diabetes, and Alzheimer disease.

In 2022, more than 10 percent of Hispanic/Latino adults reported not getting needed medical care in the past 12 months due to cost, compared to 5.2 percent of non-Hispanic white adults.

While the celebration is important, it is also important that we reflect on the Hispanic/Latino Health Disparities that exist in our healthcare system today and identify ways we can work together to eliminate these disparities and achieve better health outcomes.

Hispanic Heritage Month serves as a reminder to honor the rich cultures of the Latino community and make sure that we implement Culturally and Linguistically Appropriate Services (CLAS) practices that include self-awareness, and effective communication.

Understanding, respecting, and responding to our research participant's needs and preferences is an important way to honor and celebrate our diversity and ensure the provision of the highest quality of care to all.



Maritza Sanchez, Jill McCabe, Tia Gareau, and Rita Devine



Zhen Lin, Lucy Apicello, and Sharon Adams



Reshma Kapadnis, Ummey Johra, Melecia Lee, Luz Damarys Alequin, Kelly Ann Turner, and Cameron Coffran

predicted severity of the adverse event).

Recruitment

AI/ML is increasingly being developed and used to connect individuals to trials for investigational treatments from which participants may benefit. Specifically, AI/ML is being used to mine vast amounts of data, such as data from clinical trial databases, trial announcements, social media, medical literature, registries, and structured and unstructured data in electronic health records (EHRs), which can be used to match individuals to trials. While these algorithms are trained on high volumes of patient data and enrollment criteria from past trials, it is important to ensure adequate representation of populations that are likely to use the drug (e.g., gender, race, and ethnicity) as matching algorithms are created and, when used, to confirm that equitable inclusion was achieved during the recruitment process.

Dose/Dosing Regimen Optimization

AI/ML can be used to characterize and predict pharmacokinetic (PK) profiles. It can also be used to study the relationship between drug exposure and response, taking into consideration confounding factors. These kinds of models can be used to optimize the dose/dosing regimen selection for a study. This could potentially include aiding in dose optimization in special populations where there may be limited data (e.g., rare disease studies, and pediatric and pregnant populations).

Adherence

AI/ML can be used to monitor and improve adherence during a clinical trial through tools such as smartphone alerts and reminders, eTracking of medication (e.g., smart pillboxes and tools for visual confirmation), and eTracking of missed clinical visits, which trigger non-adherence alerts. Examples of AI/ML used in clinical research to improve medication adherence include using digital biomarkers, such as facial and vocal expressivity, to monitor adherence remotely.

Retention

AI/ML has the potential to improve the participants' access to relevant trial information by enabling tools, such as AI chatbots, voice assistance, and intelligent search. AI/ML can also be used to reduce the burden for participants by using passive data collection techniques and by extracting more information from available data generated during

clinical practice or by study activities. Additionally, data from digital health technologies (DHTs) and other systems can be used to develop patient profiles to potentially predict dropouts and adverse events to ensure participant retention.

Site Selection

Trial operational conduct can be optimized by utilizing AI/ML to help identify which sites have the greatest potential for a successful trial and to aid sites in identifying process gaps. For example, algorithms can be used to evaluate site performance and to help determine which sites may have a higher risk of running behind schedule based on data from other trials at that site.

Clinical Trial Data Collection, Management, and Analysis

DHTs such as wireless and smartphone-connected products, wearables, implantables, and ingestibles, are increasingly being used in clinical trials to collect objective, quantifiable, longitudinal, and continuous physiological data. In addition, many of these DHTs enable the use of AI/ML, either as embedded algorithms within the DHT or employed upon the data generated after the data are collected from the DHT and have been used to predict the status of a chronic disease and its response to treatment or to identify novel characteristics of an underlying condition. AI/ML can be utilized to analyze the large and diverse data generated from the continuous monitoring of persons using these technologies. This could include using AI/ML to aid in the evaluation of multimodal data and composite measures that may combine individual measures collected through multiple DHTs.

Data Management

AI/ML can be used for a range of data cleaning and curation purposes, including duplicate participant detection and imputation of missing data values as well as the ability to harmonize controlled terminology across drug development programs. Use of AI/ML could also significantly enhance data integration efforts by using supervised and unsupervised learning to help integrate data submitted in various formats and perform data quality assessments. Additionally, AI/ML can be used for data curation via masking and de-identification of personal identifiable information, metadata creation, and search and retrieval of stored data. These applications can potentially increase

data accuracy and improve the speed at which data are prepared for analyses.

Data Analysis

AI/ML has been used to analyze high volumes of diverse and complex real world data (RWD) extracted from EHRs, medical claims, and disease registries, among other sources. Additionally, the use of AI/ML in predictive modeling and complex simulation to inform clinical trial designs is being actively explored. For example, in silico clinical trials utilize computational modeling and simulation to evaluate drug candidates using a virtual cohort of simulated participants with realistic variability of traits representing the desired participant population. AI/ML could be employed in these situations to aid in evaluating a vast number of counterfactual simulations and to predict trial outcomes before human trials. At an even more personalized level, AI/ML can also be used in the context of digital twins of patients. To create digital twins of patients, AI/ML can be utilized to build in silico representations of an individual that dynamically reflect molecular and physiological status over time. In comparison to a participant in a clinical trial that received an investigational treatment, the digital twin could potentially provide a comprehensive, longitudinal, and computationally generated clinical record that describes what may have happened to that specific participant if they had received a placebo.

Clinical Endpoint Assessment

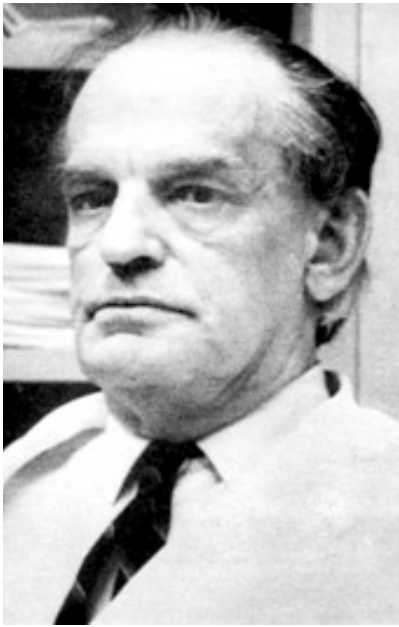
Clinical endpoint assessment is a key part of evaluating safety and efficacy of medical interventions in clinical trials. AI/ML-enabled algorithms can detect clusters of signs and symptoms to identify a potential safety signal, as well as help detect cases with safety issues in real time. AI/ML could be used to assist in the assessment of outcomes captured from diverse sources (e.g., DHTs, social media) during a clinical trial, including those consisting of large amounts of data for which manual review may be impractical.

Next Steps for FDA

FDA will continue to solicit feedback and engage a broad group of stakeholders to further discuss considerations for utilizing AI/ML throughout the drug development life cycle. These discussions and future collaborations with stakeholders will provide a foundation for a future framework or guidance.

Developing a Novel Vaccine Against Yellow Fever That Remains Important 86 Years Later

By Elizabeth (Betsy) Hanson

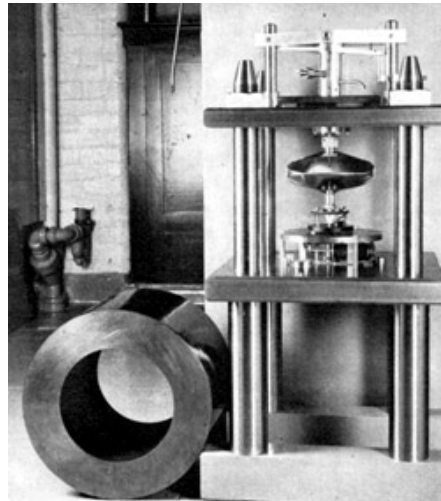


By 1930, the year that Max Theiler (1899-1972) arrived at the Rockefeller Foundation's International Health Division laboratories on the Rockefeller Institute campus, yellow fever was known to be a viral disease transmitted by *Aedes aegypti* mosquitoes. Controlling these mosquitoes reduced outbreaks of the disease, but a vaccine was needed to eliminate it. Theiler already was at the forefront of yellow fever research. He had disproved the claim of Rockefeller's Hideyo Noguchi that a spirochete was responsible for the disease, and he had shown that the West African and South American strains produce the same immunological response. In addition, just before moving to the Rockefeller campus, Theiler had made an important advance: he demonstrated that yellow fever could be propagated in mice. Previously researchers had used rhesus monkeys as animal models of the disease,

but with mice—inexpensive and prolific—Theiler was poised to make rapid progress toward a vaccine.

The Rockefeller Institute was a world-renowned center for virus research in the 1930s. Theiler continued his mouse studies in the Rockefeller Foundation laboratories, finding that the yellow fever virus became less virulent in monkeys after many passages through mouse brain. He also cultivated the virus in tissue culture, working with Eugen Haagen. Tom Rivers, an eminent virologist at the Rockefeller Hospital, had with Haagen developed an attenuated strain of vaccinia virus a few years before, for use as a smallpox vaccine, and in informal conversations

tissue culture and testing them for the ability to attack the nervous system—a property of the virus that needed to be eliminated to make a safe vaccine. In 1937 these studies succeeded when a strain known as the Asibi strain underwent a change that rendered it harmless. This became the basis of a live vaccine of attenuated virus, known as the 17D strain, that was field tested in Brazil the next year. Since then hundreds of millions of doses of the yellow fever vaccine have been given, and the methods for producing it have remained essentially the same as those Theiler developed. For his discoveries concerning yellow fever and how to combat it, Theiler was awarded the Nobel Prize in 1951.



The ultracentrifuge used in recent studies on yellow fever. From *Yellow Fever* by Strode, G., 1951

Rivers had suggested this as a research path toward the yellow fever vaccine

Theiler experimented with several strains of the yellow fever virus, passing them hundreds of times in different kinds of

Max Theiler studied at the University of Capetown Medical School, and later at the London School of Tropical Medicine, where he was awarded a diploma of tropical medicine and hygiene in 1922. That year he became a Licentiate of the Royal College of Physicians and a member of the Royal College of Surgeons, and joined the department of tropical medicine at Harvard Medical School. In 1930 he moved to the International Health Division of the Rockefeller Foundation, to a laboratory on the campus of the Rockefeller Institute. He remained with the Rockefeller Foundation, becoming in 1951 the director of laboratories of the foundation's Division of Medicine and Public Health, New York. In addition to the Nobel Prize (1951), Theiler's work was recognized by the Chalmer's Medal of the Royal Society of Tropical Medicine and Hygiene (London, 1939), the Flattery Medal (Harvard, 1945), and the Lasker Award (1949).