THE ROCKEFELLER UNIVERSITY HOSPITAL
CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

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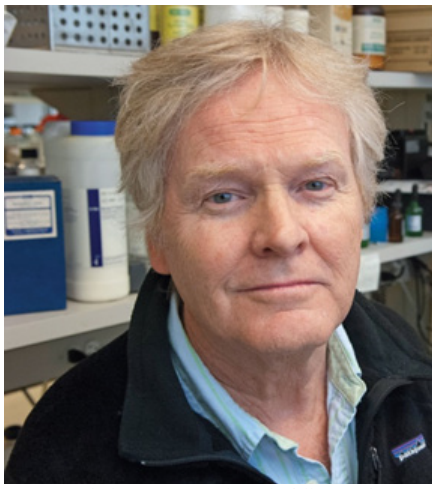
Center for Clinical and Translational Science
e-NEWSLETTER

Center News

Rockefeller University Biologist Michael W. Young Honored With Nobel Prize for Pioneering Studies on Circadian Rhythm

The Rockefeller University website



2017 Nobel Laureate and Rockefeller professor Michael W. Young, Ph.D.

Rockefeller University biologist Michael W. Young is this year's recipient of the Nobel Prize in Physiology or Medicine for his discovery of the molecular mechanism of circadian rhythm, which governs biological clocks that regulate sleep, eating behavior, and metabolism. He shares the prize with Jeffrey C. Hall and Michael Rosbash of Brandeis University.

Dr. Young used genetics to identify gene mutations that disrupt the ability of the fruit fly Drosophila melanogaster to appropriately modulate its internal clock in response to a changing environment, and went on to define their biochemical mechanisms. This clock found in fruit flies proves to be conserved throughout the animal kingdom, and provides insight into how the brain translates environmental cues into altered behavior. His work has direct implications for understanding human sleep disorders, the mechanisms of jet lag, and the challenges of working on the night shift.

Dr. Young's lab is currently working to assess how rhythmic gene and protein activities are established in cells derived from patients with sleep and depressive disorders. Among other discoveries, this work recently identified a common mutation that slows the human biological clock. People with the "night owl" variant of this gene have a long circadian cycle, making it challenging for them to stay on a normal 24-hour cycle.

"I am delighted that the Nobel Foundation has chosen to honor Mike for his pioneering work on circadian rhythm," says Richard P. Lifton, Rockefeller University's president. "The discoveries made by Mike and his colleagues have provided fundamental insight into the molecular mechanisms by which the brain responds to environmental cues, a profound advance. The Nobel Prize is the pinnacle of scientific recognition, and I can think of no one more deserving than Mike to receive this award."

Dr. Barry Coller, Physician-in-Chief of the Rockefeller University Hospital and Director of the Center for Clinical and Translational Science (CCTS), noted "We are thrilled that the Nobel Prize Committee is recognizing Mike for his landmark studies with this singular honor, and delighted that the CCTS, with support from an NCATS CTSA grant, has helped support Mike's translation of his basic findings in Drosophila to new insights into human diseases."

Dr. Young, Richard and Jeanne Fisher Professor and head of the Laboratory of Genetics, is the 25th scientist associated with Rockefeller University to be honored with the Nobel Prize. In addition to

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Roger Vaughan, MS, DrPH, Joins the Center for Clinical and Translational Science as Director of Biostatistics

By Dr. Barry Coller

Roger Vaughan

We welcome Dr. Roger Vaughan to The Rockefeller University as Director of Biostatistics in the Center for Clinical and Translational Science (CCTS). Dr. Vaughan comes to us from Columbia University where he held several leadership positions, including Professor and Chairman of the Department of Biostatistics, Vice Dean for Academic Advancement, and Director of the Biostatistics, Epidemiology and Research Design Core for Columbia's Clinical and Translational Science Award (CTSA). Dr. Vaughan received his MS in Mathematical Statistics and his doctorate in Biostatistics from Columbia University. He has won numerous awards for outstanding teaching, including awards from the American Statistical Association, the American Public Health Association, and The Mailman School of Public Health, as well as Columbia University's Presidential Teaching Award. He is an active member in many professional organizations, including the New York Academy of Medicine, the American Statistical Association, and the Association for Clinical and Translational Science. He has been a leader in the American Public Health Association and currently serves as Associate Editor and Editor for Statistics and Evaluation for their flagship journal, the American Journal of Public Health. Dr. Vaughan's biostatistical expertise lies in methods for the analysis of clustered and

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Albany Medical Center Prize awarded to Luciano Marraffini

The Rockefeller University website

Luciano Marraffini

Luciano Marraffini has been named a recipient of the 2017 Albany Medical Center Prize in Medicine and Biomedical Research, one of the country's most prestigious science prizes. Marraffini and four other scientists will share the prize for development of the genome-editing system known as CRISPR-Cas9, which in recent years has revolutionized biomedical research and provided new hope for the treatment of genetic diseases.

In 2008, Marraffini published the pathbreaking observation that CRISPR-Cas systems, first discovered in bacteria and archaea, can target DNA. Building on this observation, he suggested that these systems could be used for editing genome sequences outside of their native contexts. Then, in 2013, Marraffini reported the first successful in vivo genome-editing projects in both prokaryotes and eukaryotes, work done in collaboration with colleagues at the Broad Institute.

In the relatively brief period since those landmark findings were published, biomedical science has seen the usefulness of the new technology expand dramatically. CRISPR has now been used to create cell lines and organisms with targeted mutations, as well as to perform genetic screens for novel phenotypes by systematically turning genes on or off. CRISPR has the potential to revolutionize agriculture by introducing desired mutations into crops, and its ability to correct specific disease-causing genetic errors in humans has clear implications for improving human health.

Today, Marraffini continues to elucidate the molecular mechanisms by which CRISPR-Cas operates in bacteria. For example, his lab recently showed during what stage of infection this bacterial immune system kicks in, and discovered a way to ramp up its ability to form immunologic memories.

Established in 2000, the $500,000 Albany Prize honors scientists who have altered the course of medical research. Marraffini will receive this year's award on September 27 together with Emmanuelle Charpentier of the Max Planck Institute in Germany; Jennifer Doudna of the University of California, Berkeley; Francisco Mojica of University of Alicante, in Spain; and Feng Zhang of the Broad Institute.

Previous Rockefeller recipients of the prize include James E. Darnell and Robert G. Roeder in 2012, Elaine Fuchs in 2011, Ralph Steinman in 2009, and Arnold J. Levine in 2001.

Rockefeller Nurses Lead NYC Pilot Chapter of International Association of Clinical Research Nurses

By Rita Devine, RN, MPA

The International Association of Clinical Research Nurses (IACRN) is a professional nursing organization whose mission is to define, validate and advance clinical research nursing as a specialty practice and to support the professional development of registered nurses who directly or indirectly impact the care of clinical research participants. Its vision is to enhance clinical research quality and safety through specialized nursing practice. IACRN was established in 2009 and Rockefeller University Clinical Research Nurses under the leadership of Kelly McClary played a vital role in the founding of the organization.

More recently, Rockefeller University Hospital clinical research nurses spearheaded an application to the IACRN Board of Directors to create a pilot chapter of IACRN for the hundreds of clinical research nurses and nurse practitioners in the NYC area. This chapter will provide representation, education and support for their professional development as well as recognition in the international clinical research nurse community.

Led by Rita Devine, CRN, President, Regina Butler, CRN, Vice-President and Vedanta Sharma, CRN, Treasurer, and with the support of Dr. Barry Coller, Physician in Chief, Rockefeller has already hosted three successful meetings. The last meeting was attended by 35 Clinical Research Nurses and Clinical Research Nurse Practitioners representing five New York hospitals, Rockefeller University Hospital, Memorial Sloan Kettering, Hospital for Special Surgery, New York University Langone Health, and Weill Cornell Medical Center. These meetings provide a mechanism for exchange of ideas, opportunities for education and collaboration, and dissemination of best practices.

There are only four IACRN Chapters in the USA: Boston, Ohio Valley, Rocky Mountain and Oklahoma. Ireland, United Kingdom and Japan are the current International Chapters and a China Chapter is in pilot status. At the 2017 Annual International Conference in October, the New York City Pilot Chapter hopes to attain full chapter status, keeping the long Rockefeller University Hospital traditional started by Nancy Ellicott, CRN, of leading the advancement and support of clinical research nursing.

Clinical Research Nurses and Clinical Research Nurse Practitioners Representives

Clinical Scholar Graduate Louis Cohen Identifies Novel Human Microbiome-Produced Small Molecules That Affect Blood Glucose

By Louis Cohen, MD

It is increasingly understood that the microbiome has an important role in human health. Little is known, however, about the mechanisms that human microbiota use to interact with their human host. At Rockefeller University Drs. Sean Brady and Louis Cohen have worked to advance our understanding of how bacteria interact with human physiology through the study of bacterial small molecules. While little is known about small molecules made by human microbiota, in other microbiomes small molecules mediate environmental interactions and are a resource for therapeutic discovery. A major barrier to the isolation of small molecules from bacteria is the inability to culture many bacterial species. One method to circumvent the culture barrier is the use of functional metagenomics, wherein pieces of bacterial DNA are isolated from an environment and expressed in a heterologous host. The Brady Laboratory at Rockefeller University is a pioneer in the field of functional metagenomics and when Dr. Cohen joined the laboratory as a Clinical Scholar they aimed to apply functional metagenomics methods to the study of human microbiota.

In their first study published in the Proceedings of the National Academy of Sciences (USA), Drs. Cohen and Brady coupled functional metagenomics and high-content imaging of a human cells to identify bacterial biosynthetic genes and small molecules whose functions activate inflammatory pathways. This study was made possible in part by the Clinical Scholars program at Rockefeller. As a Clinical Scholar Dr. Cohen was guided through the clinical trial design process, applied for pilot funding from the

Louis Cohen

Helmsley Charitable Trust, and was able to access the resources of both Rockefeller Hospital and the Center for Clinical and Translational Science. With the support of the Clinical Scholars program, Dr. Cohen collected stool samples from phenotypically diverse patients, isolated high molecular weight bacterial DNA, and cloned this DNA into a cosmid vector for transduction into E. coli. E. coli clones were then arrayed in microplates and sterile supernatant transferred to a human NF-κB reporter cell line that was imaged by high content microscopy at the High Throughput Screening Core. This study led to the identification of over 20 novel bacterial biosynthetic genes and the isolation of an N-acyl amide small molecule, commendamide.

In a follow-up study published recently in Nature, Drs. Cohen and Brady explored in depth the family of N-acyl amide small molecules produced by human microbiota. In humans N-acyl amides such as the endocannabinoids are signaling molecules with diverse functions often mediated by G protein-coupled receptors (GPCRs). Using publically available sequencing datasets from the human microbiome, 43 phylogenetically diverse N-acyl synthase genes were identified, synthesized, cloned into an inducible expression vector, and transformed into E. coli. Using this system 6 N-acyl amide small molecule families were identified. Each family was screened against a panel of 240 human GPCRs and specific molecule/receptor interactions were identified for GPCRs important to inflammation, immunity, metabolism, and wound healing. Interestingly, the bacterial and human GPCR ligands were structurally similar, suggesting a form of mimicry, and in the case of human and bacterial GPR119, ligands were nearly identical. It was then demonstrated in vitro and in vivo that bacterial GPR119 ligands are able to regulate GLP-1 secretion and blood glucose similar to endogenous GPR119 ligands, suggesting the targeted manipulation of commensal bacterial biosynthetic genes as a potential therapeutic strategy (microbiome-biosynthetic-gene-therapy) for modifying blood glucose, with potential implications for the treatment of diabetes.

Based on the success of this research program and his time as clinical scholar at Rockefeller University, Dr. Cohen was able to transition to the Icahn School of Medicine in the Division of Gastroenterology as an assistant professor. Drs. Cohen and Brady continue to collaborate to further elucidate mechanisms through which human microbiota affect host physiology as a way to understand disease pathogenesis and identify novel therapeutic strategies.

Rockefeller University Biologist Michael W. Young Honored With Nobel Prize

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Young, five other Nobel Prize winners are current members of the Rockefeller faculty: Roderick MacKinnon (2003), Paul Nurse (2001), Paul Greengard (2000), Günter Blobel (1999), and Torsten Wiesel (1981).

Dr. Young received his undergraduate degree in biology in 1971 and his Ph.D. in genetics in 1975, both from The University of Texas at Austin. Following postdoctoral work in biochemistry at the Stanford University School of Medicine, he was appointed assistant professor at Rockefeller in 1978 as part of The Rockefeller University Fellows Program. Dr. Young was named associate professor in 1984 and professor in 1988, and in 2004 he was appointed the university's vice president for academic affairs and Richard and Jeanne Fisher Professor.

Dr. Young was an investigator at the Howard Hughes Medical Institute from 1987 to 1996. He is a member of the National Academy of Sciences and a fellow of the American Academy of Microbiology. Young is a recipient of the 2013 Shaw Prize in Life Science and Medicine, the 2013 Wiley Prize in Biomedical Sciences, the 2012 Massry Prize, the 2012 Canada Gairdner International Award, the 2011 Louisa Gross Horwitz Prize, and the 2009 Peter and Patricia Gruber Foundation Neuroscience Prize.

Meet the Scholar: Yehuda Cohen, M.D.

By Michelle Romanick

Dr. Yehuda Cohen joined the Clinical Scholars Program at the Rockefeller University in 2015. Dr. Cohen received his M.D. from Stony Brook University School of Medicine, and he joined Dr. Michel C. Nussenzweig's Laboratory of Molecular Immunology as an Instructor in Clinical Investigation after completing his residency in internal medicine at Montefiore Medical Center in New York and his fellowship in Infectious Diseases at Beth Israel Deaconess Medical Center in Boston.

Dr. Cohen's interest in clinical and translational research began when he was an undergraduate at Columbia University, where he spent 2 years working in a laboratory studying the response to carcinogenesis in genetically obese and fatless mice. The study found that obese mice developed malignancies at a rate similar to controls, while fatless mice were more susceptible to carcinogenesis than both obese and control mice. This experience led to a co-first author publication in Cancer Research and inspired Dr. Cohen to pursue a career as a physician-scientist.

Dr. Cohen developed an interest in HIV through his training in infectious disease and he was referred by one of his mentors, Dr. Lindsey Baden, to Dr. Marina Caskey, Associate Professor of Clinical Investigation at Rockefeller University and graduate of the Clinical Scholars Program and Dr. Sarah Schlesinger, Program Director for the Clinical Scholars Program, as a Clinical Scholar candidate in the Nussenzweig Laboratory. Dr. Cohen thought the program was a great opportunity to further his goals as a physician-scientist. His expectation upon joining the program was to gain both laboratory and clinical research skills to enable him to conduct clinical trials and at the same time perform related bench research in the lab. Dr. Cohen states, "I've been very fortunate to be surrounded by people who are experts in both of these areas who have been able to teach me a great deal." Dr. Cohen has focused his research on better understanding the hidden "reservoir" of HIV in patients, since eradicating this source of virus is key to curing the disease. He has made major advances in improving the assay used to detect the viruses in the reservoir and has shown that the reservoir contains a greater diversity of viral subtypes than previously appreciated.

When asked about his experience as a Clinical Scholar, Dr. Cohen replied, "I have found that it is always a good idea to be open to learning new skills in order to broaden your horizons and not put all of your efforts into a single project. You never know which experiment is going to fail or which clinical trial will be delayed. One of the most unique and educational aspects of the program

Yehuda Cohen

has been lunch with the Seminar in Clinical Research speakers. These have included chief scientific officers of biotechology companies and renown clinician researchers who had fascinating anecdotes about their research and career paths and thought-provoking advice to share. The Clinical Scholars Program provides a unique opportunity to focus on science— whether your interest is in the clinic or at the bench, you have the opportunity to engage in both among world-class scientists."

Dr. Cohen is currently applying for an NIH Mentored Patient-Oriented Research Career Development Award (K23). His expectation is to use the award to continue his research at Rockefeller University with a future plan to transitition to a faculty position at one of New York City's academic medical centers.

Remembrance: John Barrea Zabriskie, M.D.

By Dr. Emil C. Gotschlich

John Barrea Zabriskie, a colleague of ours died in his sleep August 16th this year. He was born July 5, 1929 in Montreux Switzerland. John studied medicine and thus became a fourth generation physician in his family. His great grandfather, also named John Barrea was the first appointed physician at Kings's County Hospital in 1841. The Zabriskies were a prominent Brooklyn family and for generations many of them were members of the Holland Society of New York that is still active. A prerequisite for membership is that you have to be a direct descendent on the patrilineal side of a person residing here before 1675.

John went to boarding school at Hotchkiss School, College at Princeton, and Medical School at Columbia P&S. House staff training in pediatrics was two years at Bellevue. He then completed 2 years of military service in the Air Force and was stationed in France near Paris. He returned for an additional year of clinical training at Babies Hospital at Columbia. In 1960, he joined Dr. McCarty's laboratory with already a firm interest in streptococcal diseases and their sequella. A major attraction was that Dr. McCarty had started in the late forties the Rheumatic fever service in this hospital, which remained active until Mac's retirement in 1981 and over this period admitted and followed about 150 young patients with rheumatic fever.

The first project Dr. Zabriskie worked on was to decipher why some strains of streptococci produced a toxin that was the cause of scarlet fever while others did not have this property. He discovered that the property of being toxigenic was due to the presence of a bacterial virus or phage. Before this work, only diphtheria toxin had been demonstrated to be phage mediated and since John's demonstration, this has been shown to be true for many bacterial toxins. Group A streptococcal disease has had a particular importance not only for the acute disease caused by the actual infection, but for it ability to set in motion chronic inflammatory diseases that continue long after the streptococcal infection has been eliminated. At the time that John started his work the leading cause of death in people between the age of 40 and 50 was still rheumatic heart disease. He became a major contributor to demonstrating that rheumatic fever and glomerulonephritis were autoimmune diseases by identifying the presence of antibodies in patients afflicted with these diseases. In 1969, John took a mini-sabbatical at the Karolinska Institute in Sweden to learn techniques of measuring cellular immunology to complex antigens, a field that was opening up at that time. Over the next decade he demonstrated the existence of cellular immunity not only in the post-streptococcal diseases, but also in multiple sclerosis. Since post-streptococcal diseases were getting to be quite infrequent in the US John established international collaborations

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New Clinical Scholars Join the Center for Clinical and Translational Science (CCTS)

By Michelle Romanick

On July 1, 2017, seven New Clinical Scholars joined the Rockefeller University Clinical Scholars Program. They are Drs. Tobias Becher, Scott Drutman, Krithi Irmady, Chin-Lan Lu, Ethan Ravetch, and Tukisa Smith. Additionally, Bernice Yan, a 3rd year medical student from Weill Cornell Medical College joined the CCTS Year-Off Medical Student Training Program in the Clinical and Translational Science in the Laboratory for Investigative Dermatology of Dr. James Krueger. Below are the new Scholars' descriptions of their research interests.

Tobias Becher

Tobias Becher, MD
Mentor: Dr. Paul Cohen
Laboratory: Laboratory of Molecular Metabolism

Dr. Tobias Becher received his MD from the Friedrich-Wilhelms University Bonn, Germany. He completed his internal medicine residency and invasive cardiology and intensive care medicine fellowship at the University Medical Center Mannheim, Germany. As a Clinical Scholar, Dr. Becher is studying the genetic factors that influence brown fat activity in adults.

Scott Drutman

Scott Drutman, MD, PhD
Mentor: Dr. Jean-Laurent Casanova
Laboratory: St. Giles Laboratory of Human Genetics of Infectious Diseases

Dr. Scott Drutman received his MD and PhD from the New York University School of Medicine. He completed his internal medicine residency/medical research track at New York Presbyterian-Weill Cornell Medical Center and medical oncology fellowship at Memorial Sloan Kettering Cancer Center. As a Clinical Scholar, Dr. Drutman is studying the immunologic failure that underlies the development of oncovirus driven malignancies.

Krithi Irmady

Krithi Irmady, MD, PhD
Mentor: Dr. Robert Darnell
Laboratory: Laboratory of Molecular Neuro-oncology

Dr. Krithi Irmady received her MBBS from the Mysore Medical College, Rajiv Gandhi University of Health Sciences, Mysore, India and her PhD from the University of Heidelberg, Germany. She did her post-doctoral training in neuroscience at Griffin Hospital, Derby, Connecticut. Dr. Irmady completed her neurology residency at Yale New Haven Hospital. As a Clinical Scholar, Dr. Irmady will study the role of microRNAs in the pathogenesis of Parkinson's disease.

Ching-Lang Lu

Ching-Lan Lu, MD, PhD
Mentor: Dr. Michel Nussenzweig
Laboratory: Laboratory of Molecular Immunology

Dr. Ching-Lan Lu received her MD from the Chang Gung University, Taiwan and PhD from Weill Cornell Graduate School of Medical Sciences. She completed her internal medicine residency and her infectious disease fellowship at the National Taiwan University Hospital. As a Clinical Scholar, Dr. Lu is studying the role of immunotherapy in HIV infection.

Ethan Ravetch

Ethan Ravetch, MD
Mentor: Sohail Tavazoie
Laboratory: Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology

Dr. Ethan Ravetch received his MD from the State University of New York Downstate College of Medicine. He completed his surgical residency at Einstein/Montefiore Medical Center. As a Clinical Scholar, Dr. Ravetch is studying the molecular mechanism of cancer metastasis and the role of pentraxin proteins in cancer progression.

New Clinical Scholars Join the Center for Clinical and Translational Science

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Franck Rapaport

Franck Rapaport, PhD
Mentor: Dr. Jean-Laurent Casanova
Laboratory: St. Giles Laboratory of Human Genetics of Infectious Diseases

Dr. Franck Rapaport received his PhD from the Pierre-and-Marie-Curie University, France. He completed his post-doctoral training in bioinformatics at Memorial Sloan Kettering Cancer Center. As a Clinical Scholar, Dr. Rapaport is studying the genetic factors contributing to pediatric appendicitis.


Tukisa Smith

Tukisa Smith, MD
Mentors: Drs. Jan Breslow and Manish Ponda
Laboratory: Laboratory of Biochemical Genetics and Metabolism

Dr. Tukisa Smith received her MD from Saint Louis University School of Medicine. She completed her internal medicine residency at the State University of New York Downstate College of Medicine and her clinical allergy and immunology fellowship at the Icahn School of Medicine at Mount Sinai. Dr Smith is studying the coagulation contact-activation system, in particularly the role of factor XII, in immune-mediated diseases and inflammation in primary immunodeficiencies.


Bernice Yan

Bernice Yan
Mentor: Dr. James Krueger
Laboratory: Laboratory of Investigative Dermatology

Research Project: Ms. Yan's project revolves around the molecular characterization of dysplastic nevi and melanoma using differential gene expression analysis.

Remembrance: John Barrea Zabriskie, M.D.

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and a particularly fruitful one was with investigators in Trinidad. Somehow, the trips to further these collaborations seemed to occur during the winter months of the year and also proved very popular with other members of the laboratory that came along to help with the work. In the last dozen years of his active career John became increasingly interested in autoimmune diseases of the central nervous system particularly multiple sclerosis and choreaform disorders. In addition, he identified a genetic marker that appears to be predictive of susceptibility to rheumatic fever following a streptococcal infection.

During his career, John played a major role in the hospital. In 1962 Dr. McCarty, then the physician in chief, appointed John to be chief resident. This position was demanding involving daily rounds on all of the patients in the hospital and other administrative duties. This required that he hire a laboratory assistant and he chose a recent graduate of Wagner College, Vincent Fischetti, who is still with us as a professor. John also served for many years as the Chair of the Pharmacy and Therapeutics Committee at the Hospital.

John is survived by his wife, Paulette La Vigne, an extraordinarily attractive and warm person of French origin, born in Casablanca. She worked for many years until her retirement in the office of the Journal of Experimental Medicine. John and Paulette had two sons, John and Christopher and a daughter Valerie.

John was a very gregarious and charming person who, in addition to science, loved his country retreat in West Cornwall, tennis, skiing, arts and music, and entertaining a wide and diverse circle of friends. In the 1960s John was quite interested in playing the cello and had regular lessons from a music teacher named Dr. Ma. He would play his exercises while Dr. Ma's children, both musically talented, looked on. The younger was the boy, playing at that time a pint-sized cello rather well, and he would shake his head in disapproval about John's playing. With John's increasing scientific commitments, he gave up the cello and the boy grew up to be Yo-Yo Ma.

John was a gentleman, a caring physician who in addition to research fulfilled one of the missions of our hospital that used to be more prominent in the past, that is the direct medical care of patients afflicted with disease. Although he retired 17 years ago, many of us still miss him very much.

Clinical Scholars Program Celebrates New Graduates

By Michelle Romanick

Six graduating Clinical Scholars received Masters' of Clinical and Translational Science degrees at a dinner celebrating them and their mentors on June 8, 2017.

Dr. Kemal Akat studied RNA molecular mechanisms in the cardiovascular system in Dr. Thomas Tuschl's Laboratory of RNA Molecular Biology. His research included aortic valvular disease, as well as circulating RNA molecules using next-generation sequencing with the goal of improving the diagnosis of patients with heart disease and other disorders. Dr. Akat is a resident in Internal Medicine at New York Presbyterian/Weill Cornell Medicine and will continue his research as a Visiting Fellow in the Tuschl Lab.

Dr. Julien Hsieh's research focused on improving smell testing in healthcare and the development of an ontology-based smell and taste phenotyping system in Dr. Leslie Vosshall's Laboratory of Neurogenetics and Behavior. Dr. Hsieh's research focuses on improving smell testing in healthcare and the development of an ontology-based smell and taste phenotyping system. His research may benefit the 19.4 million U.S. citizen that experience smell and/or taste abnormalities. Dr. Hsieh has resumed his ENT residency at the Geneva University Hospital in Switzerland in the Department of Ear Nose and Throat-Head and Neck Surgery. He is continuing his research on clinical olfaction at the Geneva University Hospital.

Dr. Gadi Lalazar's research focuses on liver carcinogenesis and specifically on a rare liver cancer called Fibrolamellar Hepatocellular Carcinoma in Dr. Sanford Simon's Laboratory of Cellular Biophysics. There is currently no approved therapy for this cancer and the overall survival is poor. Dr. Lalazar is using patient derived xenografts to understand the oncogenic dependence of this cancer and as a tool for pre-clinical drug development. Dr. Lalazar will continue his research in Dr. Simon's laboratory.

Dr. Shinji Noda studied Asian atopic dermatitis phenotype with combined features of atopic dermatitis and psoriasis with increased Th17 polarization in Dr. James Krueger's Laboratory of Investigative Dermatology. Dr. Noda found that Asian patients with atopic dermatitis have a distinct skin phenotype characterized by epidermal hyperplasia and Th17 activation. The precise stratification of disease phenotypes will contribute to building strategies for a future personalized approach with targeted therapies. Dr. Noda is Assistant Professor in the Department of Dermatology at the University of Tokyo.

Dr. Christina Pressl's research focuses on face perception deficits in pharmaco-resistant temporal lobe epilepsy in Dr. Winrich Freiwald's Laboratory of Neural Systems. Dr. Pressl's research investigates the functions and malfunctions of face perception and face memory to gain a deeper understanding on how the brain memorizes, recognizes, and perceives socially important cues. Her aim is to understand how malfunctions of neural networks can lead to behavioral changes, how these can results in conditions like face blindness (prosopagnosia), and lead to psychological or social disabilities. Her research combines advanced neuroimaging with behavioral and genetic measures. Dr. Pressl is now in the Rockefeller University PhD graduate program and will continue her research in to collaborate with the Epilepsy Center at NYU Langone Medical Center.

Dr. Lotta von Boehmer's research focused on induced host immune response to HIV-1 after antibody therapy in Dr. Michel Nussenzweig's Laboratory of Molecular Immunology. Dr. Von Boehmer systematically induced broadly neutralizing antibodies to HIV-1 in mice, a daunting task given the complicated features of HIV-1 immunity. She also identified a broadly neutralizing antibody that may help define strategies for developing a vaccine for HIV-1. Dr. von Boehmer was awarded a K99 (Pathway to Independence Award) grant from NIH and is a Senior Academic Researcher in the Mark M. Davis Laboratory at Stanford University, California.

Drs. Barry Coller, Gadi Lalazar, Christina Pressl, Shinji Noda, Kemal Akat, Julien Hsieh, Lotta von Boehmer, Sarah Schlesinger, and James Krueger

New Pilot Grants Awarded

By Editorial Staff

The Rockefeller University Center for Clinical and Translational Science (CCTS), along with the Center for Basic and Translational Research on Disorders of the Digestive System (CDDS), the Sackler Center for Biomedicine and Nutrition and the Shapiro-Silverberg Fund for the Advancement of Translational Research supported 46 pilot projects this year. CCTS Clinical Scholars received 14 pilot awards and Rockefeller Early Phase Physician Scientists (REPPS) received 5 pilot awards. A total of 66 applications were submitted. This year's total of $933,200 awarded brings the grand total of pilot project funding to $7,880,837 since the program began under the initial CTSA grant in 2006.

Support from the Center for Clinical and Translational Science

Pilots Projects Led by CCTS Clinical Scholars

Patrick Brunner, MD (Krueger Lab): *Impact of Narrow-Band UVB Phototherapy on Systemic Inflammation in Patients with Atopic Dermatitis.* This project will use an established, skin-only treatment for Atopic Dermatitis, namely narrow-band UVB phototherapy to assess whether resolution of skin inflammation will change levels of inflammatory and cardiovascular risk biomarkers in the peripheral blood of moderate-to-severe Atopic Dermatitis patients. This information might guide future treatment approaches for this patient population.

Yehuda Cohen, MD (Nussenzweig Lab): *Origins of HIV Viral Rebound After Treatment with a Broadly Neutralizing Anti-HIV Antibody.* Our lab has developed a novel technique to measure the latent reservoir of HIV-1 virus in cells of infected patients. The assay markedly amplifies the number of unique replication-competent sequences that can be isolated from the reservoir. This pilot project will help to employ this assay in a clinical trial to determine the origin of viral rebound after stopping therapy.

Jason Hawkes, MD, (Krueger Lab): *Investigating the Molecular Phenotype of Guttate and New-Onset Plaque Psoriasis.* This pilot project will offer insight into the natural history of psoriasis and its disease variants and may ultimately lead to the development of new treatments or therapeutic strategies.

Moonjung Jung, MD (Smogorzewska Lab): *Identifying Disease Modifying Genes in Fanconi Anemia.* This pilot project will help identify Fanconi Anemia disease modifying genes by targeted gene sequencing of metabolism-related genes in patients with Fanconi Anemia and by forward genetic screening using metabolism-focused CRISPR/Cas9 library. This approach may identify novel metabolism genes that interact with defective Fanconi Anemia DNA repair pathway and reveal novel therapeutic targets in Fanconi Anemia and other bone marrow failure syndromes.

Isaac Marin-Valencia, MD (Hatten Lab): *Uncovering Mechanisms of Cerebral Maldevelopment in the Context of Defective Mitochondrial Metabolism.* This pilot project aims to discover the molecular underpinnings of altered brain development in one of the most common mitochondrial disorders, pyruvate dehydrogenase deficiency with the ultimate goal of developing molecular-based therapies that change the natural course of the disease.

Kathrine Meyers, DrPH (ADARC/Markowitz Lab): *Supportive Behavioral and Social Science Research: Perceptions, Beliefs, and Experiences of Novel HIV Prevention and Treatment Modalities among Clinical Trial Participants.* This project intends to generate data that can strengthen the design and outcomes of clinical trials of novel HIV prevention and treatment modalities, with a specific focus on informing future trials of broadly-neutralizing antibodies (bNABs) to be conducted by clinical investigators at The Rockefeller University in the next few years.

Pilots Projects Led by Rockefeller Early Phase Physician Scientists and Staff

Teresa Evering, MD (ADARC/Ho Lab): *A Single-Cell Transcriptomics Approach for Biomarker Discovery in HIV-Associated Neurocognitive Disorders.* This pilot project will help identify cell-type clusters and determine the most highly expressed genes specific to each computationally-derived cell cluster and differentially expressed genes between cohorts who are neurocognitively normal or have HIV-associated neurocognitive disorders.

Rhonda Kost, MD (Center for Clinical Translational Science): *Engaging Carter Burden Network in a Community-Academic Partnership to Understand the Biological, Environmental and Person-level Correlates of Successful Aging in Place.* A community-academic partnership was formed among The Rockefeller University-Center for Clinical and Translational Science, Clinical Directors Network, and the Carter Burden Network (CBN), a multisite senior services organization serving East Harlem including many seniors from racial and ethnic minority groups. Many of those served live in poverty and suffer from multiple chronic conditions, depression, and food insecurity. The pilot project has two aims – Aim 1: Engage seniors, CBN leadership, staff and stakeholders in research priority-setting, and joint protocol design, study conduct, and analysis and dissemination, so as to align patient-centered and scientific research aims. Aim 2: Characterize the health of CBN senior populations by collecting validated cardio-metabolic, musculoskeletal, quality of life, psychosocial, and nutritional assessments.

Manish Ponda, MD (Breslow Lab): *Biomarkers of Contact System Activation in Immune-mediated and Inflammatory Diseases.* Immune cell trafficking is a fundamental aspect of immunity and abnormalities in cell migration contribute to a plethora of human diseases. We have discovered a novel immune signaling pathway by identifying a peptide fragment of high molecular-weight kininogen (HK) as an accelerant of lymphocyte and monocyte chemotaxis. Further, we have determined that generation of this active peptide is dependent upon coagulation factor XII (FXII), a plasma protease. As proof-of-concept, we have demonstrated that pharmacologic inhibition of FXII can ameliorate disease in an animal model of multiple sclerosis. Because many diseases have an immune or inflammatory component, a rational step towards understanding where FXII inhibition may be applied clinically would be to study biomarkers of HK and FXII activation patients. Therefore, the purpose of this study is to quantitatively determine the degree of HK and FXII activation in patients with immune-mediated and inflammatory diseases.

New Pilot Grants Awarded

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Support from Center for Basic and Translational Research on Disorders of the Digestive System

Pilots Projects Led by CCTS Clinical Scholars

Tukisa Smith, MD (Breslow Lab): *Contact System Activation in Common Variable Immunodeficiency.* The contact system consists of a plasma protease cascade that has been suggested to contribute to the pathophysiology of various inflammatory disease states. Of the primary immunodeficiency diseases, common variable immunodeficiency (CVID) is the most symptomatic antibody deficiency. The purpose of this pilot project is to characterize these biomarkers in affected human subjects so as to elucidate the contact system's role in pathogenesis and its potential contribution to the clinical variability of CVID. This biomarker may also guide the development of novel therapeutic approaches.

Pilots Projects Led by Rockefeller Early Phase Physician Scientists and Staff

Ana Emiliano, MD (Friedman Lab): *The Effects of Sleeve Gastrectomy on the Celiac Ganglia.* The celiac superior mesenteric ganglia (CSMG) play a role in the stress response to hypoglycemia glucose counterregulation by stimulating the release of glucagon, cortisol and catecholamines, as well as by mobilizing hepatic glucose. Based on preliminary data, our hypothesis is that sleeve gastrectomy is associated with impaired glucose counterregulation because it alters CSMG function. This pilot project will provide support for the development of a reproducible CSM ganglionectomy mouse model and assessing changes in liver and pancreatic sympathetic innervation associated with the procedure by measuring norepinephrine content in those tissues. This work may benefit other lines of research linked to metabolism and the autonomic nerve system as the CSMG is involved in immune and inflammatory responses in the gut, with possible bidirectional interactions with the microbiome.

Gadi Lalazar, MD (Simon Lab): *High Throughput Identification of Apoptosis Sensitizing Compounds in Fibrolamellar Hepatocellular Carcinoma.* Fibrolamellar hepatocellular carcinoma (FLC) is a liver cancer with no effective systemic therapy. Patients have a poor 5-year survival and are in urgent need of new therapeutic options. We have developed several patient-derived xenograft (PDX) models that retain expression of the genetic driver mutation, histology, transcriptome, and proteome of the original human tumor. This pilot project will assist in performing unbiased chemical screens to identify compounds that induce tumor regression in PDXs of FLC. As this is a rare disease with an unmet need for systemic therapy, this study has the potential for clinical translation and may offer the first effective treatment for these young patients.

Support from the Sackler Center for Biomedicine and Nutrition

Pilots Projects Led by CCTS Clinical Scholars

Tobias Becher, MD (Cohen Lab): *Genetic Determinants of Brown Adipose Tissue Activity.* Brown Adipose Tissue (BAT) possesses the ability to generate heat by uncoupling cellular respiration from adenosine triphosphate generation. The combustion of glucose and lipids leads to favorable metabolic effects and renders BAT an attractive target for battling obesity. Considerable interpersonal differences in BAT activity have been demonstrated in 18F-FDG-PET/CT (PET) studies, pointing to variable underlying genetic predisposition. Elucidating the genetic determinants of BAT activity may therefore improve our understanding of BAT regulation. This pilot project, with collaboration with Memorial Sloan Kettering Cancer Center, will retrospectively review PET scans to identify patients with extreme BAT variants as a prelude to whole exome sequencing to identify candidate genes involved in the regulation of BAT. The role of these candidate genes in BAT activity will be further elucidated using CRISPR-Cas9 gene editing in a cellular model.

Pilots Projects Led by Faculty

Peter Holt MD (Breslow Laboratory): *Effects of Dietary Fructose on Gut Microbiota and Fecal Metabolites in Obese Postmenopausal Women*. Elevated fructose consumption contributes to non-alcoholic fatty liver disease (NAFLD), a condition, which occurs in about 30% of the U.S. adult population. NAFLD has rapidly become the most common cause of chronic liver disease in the U.S. Current mechanistic hypotheses for fructose-induced liver disease focus on altered hepatic lipid metabolism. This pilot project study's goal is to provide new insights into the potential effects of dietary fructose on the colonic microbiota, findings that could in turn, be important for understanding human disease.

Support from the Shapiro–Silverberg Fund for the Advancement of Translational Research

Pilots Projects Led by CCTS Clinical Scholars

Scott Drutman (Casanova Laboratory): *Role of the Inflammasome sensor NLRP1 in Human Papilloma Virus Infection.* Human Papilloma Virus (HPV) is an oncovirus implicated in the development of multiple human cancers. Infection by oncogenic HPV is common and usually self-limited, but in rare individuals, a failure of host anti-HPV immunity permits chronic infection, leading in some cases to cancer. This pilot project proposes that detection of HPV by NLRP1 is a novel host-pathogen interaction, and offers a model whereby inflammasome activation by HPV triggers innate immunity, but during chronic infection leads to tissue inflammation and hyperplasia, a phenotype exaggerated in patients with gain-of-function NLRP1 mutations.

Krithi Irmady (Darnell Lab): *Role of microRNAs in Parkinson's disease Pathogenesis*. Parkinson's disease (PD) is the second most common neurodegenerative disease for which currently no therapeutic options exist. This pilot project will study the combination of high-throughput RNA profiling techniques such as Argonaute High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation (Ago-HITS CLIP), miRNA-Seq, RNA-Seq and ribosomal profiling to develop an unbiased and comprehensive view of miRNA:mRNA functional interactions in induced pluripotent stem cells (iPSCs) derived from PD patients and PD patient brain autopsy samples. Using integrative analysis to determine pathways disrupted in early and late neurodegeneration may identify a potential therapeutic target and biomarker of disease.

New Pilot Grants Awarded

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Support from the Shapiro–Silverberg Fund for the Advancement of Translational Research

Pilots Projects Led by CCTS Clinical Scholars

Ching-Lan Lu (Nussenzweig Lab): High Throughput Characterization of HIV-1 Latent Reservoir in Antiretroviral Therapy (ART)-Suppressed Patients. The major barrier to curing HIV-1 infection is latently infected CD4+ T cells containing intact integrated viral genome. This viral reservoir is seeded early after infection and remains stable despite years of highly effective antiretroviral therapy (ART). Accurate measurement of the viral reservoir is crucial for evaluating eradication interventions. This pilot project will characterize the latent reservoir by reconstructing full-length HIV-1 genome from DNA of CD4+ T cells in ART-suppressed patients. This method can rapidly evaluate the quality and quantity of the HIV-1 reservoir in ART-suppressed patients and the impact of HIV-1 broadly neutralizing antibodies (bNAbs) on the reservoir.

Franck Rapaport (Casanova lab): Understanding the Genetic Susceptibility to Appendicitis. 7.5% of the American population develops acute appendicitis, making it the most common source of acute abdominal pain requiring surgery in the United States. However, the causes of the disease are still largely unknown. A positive family history for acute appendicitis confers an increased risk for contracting the disease. In this pilot project we will recruit families with multiple occurrences of acute appendicitis and use whole exome sequencing and monogenic and polygenic models to uncover the genetic events that are the basis of the hereditary transmission of the disease. As appendicitis is infectious in its nature in the majority of cases, we hypothesize that some patients suffer from inborn errors of immunity. The findings from this project have the potential therefore to not only improve our understanding of appendicitis, but also will contribute to better understanding of the immune system.

Ethan Ravetch (Tavazoie Lab): NPTX1 as a Biomarker of Pancreatic Cancer. This pilot project seeks to assess NPTX1 as a biomarker for pancreatic cancer and analyze its utility as a screening tool. Pancreatic cancer is the 7th leading cause of cancer deaths globally, often diagnosed at a late stage in which curative surgical resection is not possible. NPTX1, a member of the pentraxin family, is a secreted protein identified by the Tavazoie Lab as a promoter of pancreatic cancer metastasis.

Norihiro Yamaguchi (Tavazoie Lab): Targeting Aberrant Metabolic Pathway in Metastatic Liver Colonization of Colorectal Cancer. Despite the progress being made in treating colorectal cancer (CRC), metastatic progression of cancer remains a leading cause of cancer related mortality. Among all distant organs where CRC metastasizes, liver metastasis accounts for 70% as the first target organ. Thus, elucidating the mechanism of liver metastasis can potentially provide a therapeutic option for patients suffering from otherwise incurable metastatic disease. In this study we will assess whether our previous findings of an abnormal metabolic pathway in patients with CRC is generalizable to a larger cohort of patients.

Pilots Projects Led by Rockefeller Early Phase Physician Scientists and Staff

Daniel Gareau (Krueger Laboratory): *Augmented Mobile Phone Technology for Dermatology.* An imaging biomarker (IB) is a characteristic extracted from quantitative imaging as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention. This project accelerates the development and translation of a computer program created by the principal investigator into useful applications (Apps) that execute image processing and produce diagnostic IBs. Spanning the full spectrum from clinical care to basic research, these apps each provide a quantitative diagnostic to increase precision in disease diagnosis.

Uri Sela (Fischetti Lab): *Various Staphylococcus aureus Strains Differ in IgE Induction: Elucidating the Mechanism.* Atopic conditions and food allergy are a major cause of morbidity, with increasing prevalence in the last decades, and mediated by IgE. The results from this pilot study will enable us to identify S. aureus strains that are more pathogenic in relation to atopy and food allergy and to define the "responsible" phage/gene. This is necessary for future design of new strains that are potentially less pathogenic that may be used for "replacement" therapy.

Roger Vaughan, MS, DrPH, Director of Biostatistics

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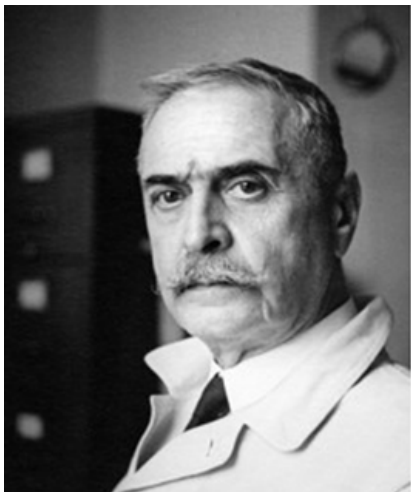
Group- or Cluster-randomized trials. He is an author of more than 150 peer-reviewed articles in both Biostatistical methodological development and the application of statistical methods in medicine and public health.

Dr. Coller commented, "Dr. Vaughan has joined the CCTS in this very important leadership position. As an award winning educator, he has led the biostatistics education of Clinical Scholars on a part-time basis for nearly a decade, and now we will benefit greatly on a full-time basis from his vast senior leadership experience and deep Biostatistical expertise. When asked about future developments he envisions for the Biostatistics department, Dr. Vaughan replied, "It is a pleasure and privilege to join the Rockefeller research community, and I am thrilled to help create and lead the next generation Biostatistics at the University. The Biostatistical needs here are enormous, and the level of research and science is clearly outstanding, so the challenge is to build capacity across the collaboration, service, education, and methods reserch arms, while supporting that level of excellence. With the terrific support of collegues across the University, I'm looking forward to getting started, and meeting those goals."

Please join me in welcoming Dr. Vaughn to Rockefeller.

Rockefeller Historical Vignette: The Rh Factor: Enhancing the Safety of Blood Transfusion and Setting the Stage for Preventing Hemolytic Disease of the Newborn

By Elizabeth (Betsy) Hanson



Karl Landsteiner (1868-1943) discovered the Rh factor—a type of protein, or antigen, on the surface of red blood cells—in 1940. Most people are Rh positive. But if a pregnant woman is Rh negative and her fetus is Rh positive, her body may mount an immune response against the fetus's blood and cause harm. With the description of the Rh factor, screening tests to predict such problems, and means of preventing injury to the fetus, were developed.

Landsteiner was a pioneer in the young field of immunology. His interest in unraveling the nature and origin of antibodies led him, in 1900, to discover the major A, B, and O blood groups. For this achievement, Landsteiner was awarded the Nobel Prize in 1930. In the 1920s and 1930s, while at Rockefeller, he focused on the chemical analysis of immune reactions. He synthesized artificial antigens by joining small organic molecules, which he called haptens, to proteins of known structure, and showed that small alterations in haptens could produce major changes in antibody production. The underlying idea that antibodies could be directed toward molecules of known chemical structure is a founding principle of immunochemistry. This work provided Landsteiner the basis for discovering the Rh factor with Alexander Wiener.

Landsteiner's research had a broad impact on both clinical practice and medical research. Understanding blood groups made possible safe blood transfusions, and laid the foundation for the blood banking technique developed by Rockefeller's Peyton Rous during World War I. Blood typing dried blood also allowed the identification of criminal evidence and paternity testing. At Rockefeller, Landsteiner's fundamental contributions to immunology informed the work of many researchers, including Oswald Avery, Walter Goebel, and Michael Heidelberger. Landsteiner also made a major contribution to understanding polio, reporting in 1909 that the disease was a caused by a virus that could be transmitted to monkeys. This finding inspired early studies of polio at the Rockefeller Hospital, led by Simon Flexner.

Karl Landsteiner was born near Vienna, Austria in 1868. He received his MD from the University of Vienna in 1891, and for the next five years studied in the laboratories of prominent chemists, including Emil Fischer. From 1897 to 1919 Landsteiner held positions at the Pathological Anatomical Institute in Vienna, the Wilhelminen Hospital, and the University of Vienna, including professor of pathological anatomy. Anti-Semitism in Austria after World War I made it difficult for Landsteiner to advance his career, and he left for a post at a hospital in The Hague. Then, late in 1921, Simon Flexner invited him to become a member of the Rockefeller Institute. Landsteiner remained at Rockefeller until his death in 1943. In addition to the Nobel Prize (1930), Landsteiner's achievements were recognized with election to the U.S. National Academy of Sciences and with the Lasker Award (1946).