Center News

The Rockefeller University Center for Clinical and Translational Science Applies for Clinical and Translational Science Award (CTSA)

By Editorial Staff

The Rockefeller University Center for Clinical and Translational Science (CCTS) submitted a Clinical and Translational Science Award application on September 25, 2015 to the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). CCTS has been continuously funded by the Clinical and Translational Science Award (CTSA) program since the inception of the program in 2006, including a successful renewal application in 2011. The grant supports the University's high quality translational and clinical research infrastructure that facilitates research locally, regionally and nationally and fosters innovation in research methods, training, and career development.

NCATS has set the goal of catalyzing the development of methods and technologies that lead to more efficient translation of biomedical discoveries into interventions shown to improve health. To that end, the CTSA program is focused on developing into a fully integrated research and training environment for clinical and translational sciences that aims to dramatically improve efficiency and quality across the translational research spectrum.

The overall vision of the Rockefeller University Center for Clinical and Translational Science (CCTS), supported by the CTSA program, is to develop, demonstrate, and disseminate innovative programs to achieve translational success and to integrate these into a seamless "Learning Clinical Research Enterprise" that uses outcome data to drive quality improvement for the benefit of human health. To achieve this vision CCTS proposed to enhance our existing programs and add new ones.

The Specific Aims of the proposal define the future direction of CCTS. 1. To integrate our existing and new programs into a Translational Research Navigation (TRN) Program that encourages, facilitates, and insures the integrity of all human subjects research from conception to conclusion, and that will expedite our participation in the CTSA network of multi-center studies. 2. To integrate our existing and new programs into a Translational Workforce Educational Program that insures that all members of the translational workforce have the knowledge and skills required for them to perform their functions individually and as members of diverse scientific teams. 3. To integrate our existing and new programs into a From Discovery to Health-Enhancing Product Program to insure that investigators have the resources to maximize the likelihood that they can translate their novel discoveries into products that improve human health.

The Rockefeller Investigators Collaborate with other New York City CTSAs and Clinical Directors Network to Build and Use the New York City Clinical Data Research Network (NYC- CDRN)

By Rhonda G. Kost and Jonathan N. Tobin

The Rockefeller University and Clinical Directors Network (CDN) are both participating in an exciting novel program to create an accessible, sustainable, scalable clinical data network that will enable patient-centered research, support a national patient-centered outcomes research network, and facilitate the development of learning healthcare systems.

The New York City Clinical Data Research Network (NYC-CDRN), funded by the Patient-Centered Outcomes Research Institute (PCORI) as part of PCORnet, is designed to link the approximately 4.4 million electronic health records (EHR) of all patients cared for at the major New York academic medical centers, and in Federally Qualified Community Health Centers affiliated with CDN to form a searchable clinical data resource.

The collaboration, led by Dr. Rainu Kaushal of Weill Cornell Medical Center, is made up of over 22 organizations, including seven independent health systems (CDN, Columbia, Einstein/Montefiore, Mount Sinai, New York-Presbyterian, NYU Langone, and Weill Cornell), as well as the New York Genome Center, The Rockefeller University, and other partners. The NYC-CDRN aligns patient, researcher and institutional requirements within a rigorous regulatory context that includes: 1. a central IRB, Biomedical Research Alliance of New York (BRANY), 2. robust organization and governance, and 3. patient privacy and data security protections. The NYC-CDRN seeks to engage patients and front-line clinicians in all phases of research protocols and to embed research into practice at the point of care.

A description of the progress made under Phase I of the NYC-CDRN was recently published, including a focus on two common conditions, diabetes and overweight/obesity, and one rare disease, cystic fibrosis.

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CCTS Inaugurates New Training Program on Using Big Data and Electronic Health Records to Advance Translational Research

By Editorial Staff

One of the new initiatives the Rockefeller University Center for Clinical and Translational Science (CCTS) is implementing a training program to use data from electronic health records (EHRs) as a research tool to advance translational science across the entire spectrum from basic science discoveries to epidemiology. The training program will enable bench to bedside (T1) researchers to utilize EHR databases to answer basic science research questions using clinical data by analyzing large data sets to test basic and translational science hypotheses. Traditionally, querying such databases has been the exclusive province of epidemiologists and health services investigators (T3-T4) and the primary goals have been to identify key information for improving health care delivery systems. The CCTS leadership believes that one of the key new skills that will advantage the translational workforce throughout the entire T0-T4 spectrum is the ability to obtain valid information from the new large clinical data sets.

In 2010 Dr. Barry Coller, CTSA PI, developed an agreement with QUEST Diagnostics to collaborate on projects joining an investigator at Rockefeller with investigators at QUEST. This agreement led to the collaboration between Dr. Manish Ponda, a Clinical Scholar graduate from Dr. Jan Breslow's laboratory, and information technology experts at QUEST to assess the impact of oral vitamin D repletion on serum cholesterol levels. Dr. Ponda was able to confirm from data cleverly extracted from the QUEST database the previous finding by others of an inverse epidemiologic association between vitamin D levels and serum cholesterol levels. He was also able to confirm the paradoxical results from his small size mechanistic study that oral vitamin D repletion in patients deficient in vitamin D does not lower cholesterol levels. To reconcile these findings, he conducted a subsequent study to compare the impact on cholesterol levels of oral vitamin D repletion versus controlled exposure to UV light.

Preliminary data indicate that UV light may have a disparate effect on cholesterol metabolism pathways, and this finding can potentially not only reconcile the epidemiologic and clinical study findings, but point to new therapeutic measures.

This experience and the emerging availability of large clinical data sets encouraged the CCTS to expand this initiative by developing a course focused on T0-T1 translational investigators to assist them in gaining the skills of querying population-based large databases to extract data that can help them test their basic and translational hypotheses at the population level.

Dr. Ponda, Dr. Coller and Dr. Jonathan Tobin, a PhD epidemiologist, President of Clinical Directors Network (a practice-based research network), and Co-Director of the Community Engagement program, who has extensive experience querying large databases, developed a draft curriculum. This was then reviewed by Dr. Richard Platt of Harvard, who leads FDA Sentinel

Clinical Scholar Taia Wang and Colleague Jad Maamary Discover That Anti-HA Fc Glycoforms Determines Influenza Vaccine Efficacy through Type II Fc Receptor Signaling

By Editorial Staff

Studies conducted by Clinical Scholar Taia Wang, Postdoctoral Associate Jad Maamary and mentor Jeffrey V. Ravetch, which were recently published in *Cell,* provide exciting new information on the mechanism by which the antibody response leads to the selection of more potent antibodies over time, and open up important new translational opportunities to improve influenza vaccination. As the 2015-6 influenza season is now reaching its peak, this is welcome news!

Interactions between immune complexes and Fc receptors mediate a wide array of cellular processes that are required for maturation of protective vaccine responses. This project was designed to dissect the role of immune complex – Fc receptor interactions in the production of neutralizing anti-hemagglutinin (HA) antibodies after seasonal flu vaccination. Because B cells are selected, in part, on immune complexes that are fixed on specialized cells within the germinal center, the team hypothesized that the composition of those immune complexes might change over time after vaccination, thus providing a mechanism for directing progressive selection of B cells. In the flu system, this meant that seasonal flu vaccination might
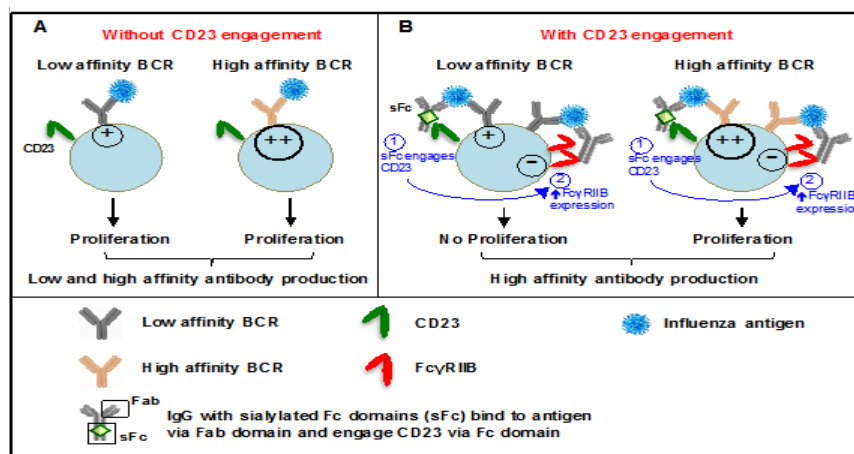
High affinity antibody production through B cell CD23 engagement. (A) Signaling through B cell receptor (BCR) triggers proliferation of low and high affinity B cells. (B) Co-engagement of CD23 with BCR induces increased expression of the inhibitory FcγRIIB, which, in turn, results in apoptosis/anergy of low affinity B cells and proliferation of high affinity B cells.

induce modulations in the composition of Fc domains on anti-HA IgGs within germinal center immune complexes; those Fc domain changes would, in turn, have a role in directing selection of B cells producing neutralizing antibodies.

To study this, they characterized changes in the structural determinants of IgG Fc domains (subclass and Fc glycan composition) on anti-HA IgGs elicited by the seasonal flu vaccine. This

analysis showed something intriguing: that influenza vaccine efficacy, measured by production of neutralizing antibodies, could be predicted by the early abundance of a specific type of Fc glycoform on anti-HA IgGs. The glycoforms that correlated with influenza vaccine efficacy contained a terminal sialic acid residue, which are known to confer binding to Type II FcRs. This finding suggested that sialylated Fc domains within

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Clinical Scholar Graduate Dr. Shen-Ying Zhang is Studying the Genetics of Immune Deficiences with the Support of Two NIH RO1 Grants

By Editorial Staff
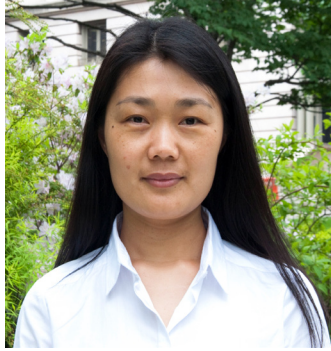
Shen-Ying Zhang

Dr. Shen-Ying Zhang, Assistant Professor of Clinical Investigation at Rockefeller University is Co-PI with Dr. Jean-Laurent Casanova, Head of the St. Giles Laboratory of Human Genetics of Infectious Diseases, on two NIH (R01) research project grants. R01 grants are prestigious awards that provide support for health-related research and development aligned withthe mission of the NIH. Dr. Zhang is a graduate of the Clinical Scholars Program and a member of the Rockefeller Early Phase Physician Scientists (REPPS) group.

The first R01 is titled Cellular Dissection of Herpes Simplex Encephalitis with iPS Cells. It focuses on analyzing Herpes simplex virus 1 (HSV-1) encephalitis (HSE), the most common form of sporadic viral encephalitis in Western countries. The St. Giles Laboratory of Human Genetics of Infectious Diseases discovered that childhood HSE may result from inborn errors of Toll-like receptor 3 (TLR3)-dependent, interferon (IFN)-α/β-mediated immunity against primary infection by HSV-1. The lab has identified mutations in the TLR3-pathway molecules UNC-93B, TRIF, TRAF3 and TBK1 that are important in a cell's ability to sense the presence of viral double-stranded RNA (ds-RNA) molecules. Children with mutations in STAT1 or NEMO have also been identified and they have broader impairment in immunity and are predisposed to both HSE and other infections.

Dr. Zhang's research has shown that forebrain neurons and pro-oligodendrocytes derived from TLR3- and UNC93B-deficient induced pluripotent stem cells (iPSCs) have markedly abnormal cellular responses to poly(I:C), a TLR3 mimic of dsRNA, and are highly susceptible to HSV-1 infection, unlike other central nervous system (CNS)-resident cells tested. These data suggest that childhood HSE results from
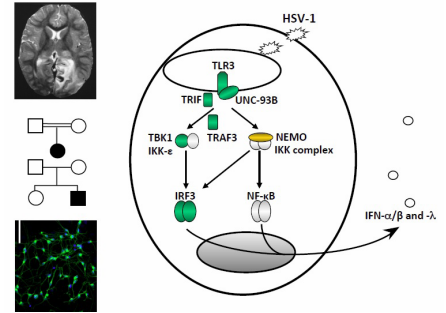
Left: Brain, Family Trees, Neurons
**Right:** TLR3-IFN signaling pathway controls HSV-1 infection in the brain.

inborn errors of non-hematopoietic, CNS-specific, "intrinsic" immunity, affecting neurons and oligodendrocytes in particular. This novel finding changes the paradigm of immune compromise form impaired immune blood cell function to tissue-specific defects in combating viral infection.

The goal of her current research is to dissect in greater depth, and from three complementary angles, the neuron-intrinsic pathogenesis of HSE. First, a faster protocol will be devised to differentiate and test iPSC-derived forebrain neurons

Dr. Yupu Liang, Leader of CCTS Research Bioinformatics Wins Amazon Research Grant to Enhance Use of Cloud Services to Support Rockefeller Investigators

By Editorial Staff
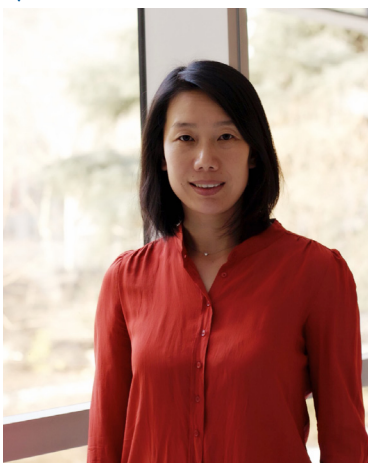
Yupu Liang

Dr. Yupu Liang, Director of Center for Clinical and Translational Science (CCTS) Research Bioinformatics Program was awarded $10K Amazon Web Services (AWS) credit to facilitate translational bioinformatics research projects conducted by Rockefeller investigators. AWS provides a full line of products to solve complex scientific problems across the domains of scientific computing, web applications, data storage, and data backup. The projects that will benefit from this voucher program include one on detecting subtelometric chromosomal fusion events from direct sequencing project, and another on predicting the clinical impact of de novo mutations. The subtelometric sequencing is a collaboration between the Research Bioinformatics group led by Dr. Liang and Dr. John Maciejowski from the De Lange lab and the mutation effect prediction project is in a collaboration with Dr. Lorena Buitrago in the Coller lab and Dr. Yuval Itan in the Casanova Lab. The bioinformatics goal of the subtelometric project is to scale up the current analytical method to be able to analyze hundreds of samples in a timely manner. The goal for the mutation effect prediction project is to create a wide web-based application that will allow the entire scientific community to access the tools we have developed to analyze the likelihood that variants in an increasing number of genes will be deleterious. The latter builds on a recent study by Drs. Buitrago, Liang, and Coller along with colleagues from the Icahn School of Medicine and members of ThromboGenomics Consortium in the United Kingdom analyzing the platelet integrin receptor αIIbβ3 (Buitrago, et. al., PNAS. 2015 Apr 14;112(15):E1898-907)

The grant will also make it possible for Dr. Liang to analyze the benefits and drawbacks of utilizing cloud-based computing resource vs. local computing resource. This information will inform how best to conduct future bioinformatics projects that require intense computing and data storage support.

Meet the Scholar: José O. Alemán, MD, PhD

By Michelle Romanick
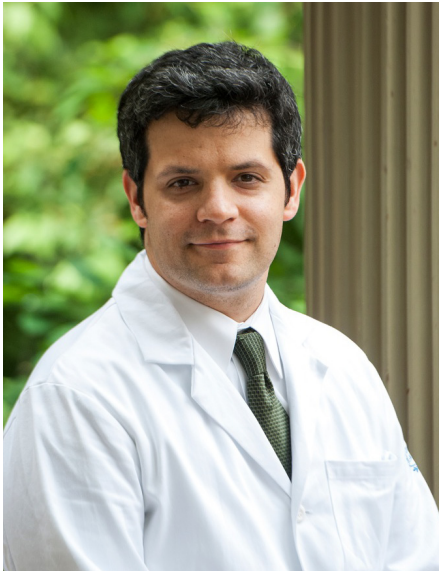
José O. Alemán, MD, PhD

Dr. José O. Alemán joined the Rockefeller University Clinical Scholars Program as an Instructor in Clinical Investigation in Dr. Jan Breslow's Laboratory of Biochemical Genetics and Metabolism in 2013. Born and raised in Puerto Rico, Dr. Alemán completed his undergraduate studies in Chemical Engineering at Cornell University. Following a Fulbright grant in Spain, he pursued combined MD-PhD training at Harvard Medical School. During his PhD in Medical Engineering at the Massachusetts Institute of Technology, Dr. Alemán developed metabolomic and flux analysis techniques to elucidate insulin resistant metabolism in transgenic mice in collaboration with investigators at the Joslin Diabetes Center

Dr. Alemán's interest in research started through a high school research program at the University of Puerto Rico Medical Sciences Campus. His mentor at the time was an ocular biochemist who was studying cataract formation as a complication of diabetes. Foreshadowing his research career, he and his mentor developed a model to test compounds that may impact cataract formation in diabetes.

Upon finishing his MD-PhD degrees, Dr. Alemán moved to New York with his wife; she was appointed Assistant Professorship in Art History at Hunter College and he entered the Medical Research Residency program at New York-Presbyterian-Weill Cornell Medical Center. Dr. Alemán met Dr. Breslow during his residency interviews in 2009, and three years later he joined

his lab to study metabolic disease in a translational research project. Dr. Breslow recently trained other Clinical Scholars with medical subspecialty training thus, making his laboratory an ideal setting for Dr. Alemán's next stage of postdoctoral research.

Dr. Alemán's current research focuses on how the complications of obesity occur. In collaboration with scientists at Weill Cornell Medical College and Memorial Sloan Kettering cancer Center, they concentrate on immune cells in adipose tissue in a phenomenon called crown like-structures (CLS) as a potential risk factor for obesity complications. In the first study, Dr. Alemán teamed with 2 other engineers from the Tri-I area to apply noninvasive light detection of CLS in patients undergoing fat biopsies at Rockefeller Hospital. In a second study, Dr Aleman and the clinical team at Rockefeller administered a Very Low Calorie Diet to a cohort of obese postmenopausal women to examine the metabolic consequences of weight loss on immune cells in adipose tissue.

Dr. Alemán was introduced to the Clinical Scholars program by mentors at Cornell who knew of Dr. Coller's initiative to train physician-scientists in translational science. In joining the program, Dr. Alemán's Endocrinology fellowship research was consolidated into a meaningful translational research experience. Dr. Alemán was eager to take advantage of the research focus of the Rockefeller University Hospital to execute one or more clinical studies, and focus on the central component of his transition to independence. Dr. Alemán stated, "In this respect my expectations have been met thoroughly!" Dr. Alemán was selected to serve as the Chief Clinical

Scholar for the 2015-6 academic year. In this leadership role he insures that the program runs smoothly and that the experience for Scholars is optimized for their educational goals.

When asked to about his experience as a Clinical Scholar and Chief Scholar, Dr. Alemán stated,

"The most important learning opportunity as a Scholar came during my general presentation on obesity to my fellow Scholars as part of the tutorial. I had a chance to step back from the details of my research and think about obesity throughout time and the public health impact it will have on our society, and place my research efforts within this context. This tutorial served as a phenomenal opportunity to present my work to the general scientific population.

As a Chief Scholar, the most important teaching moment has been realizing the amount of behind the scenes work it takes to run this program. I gained further appreciation of prior Chief Scholars, and the leadership in maximizing the educational opportunities of the program. In requesting help for the various activities, I learned to seize the unique talents of each Scholar.

The most interesting aspect of the Clinical Scholars program has been the diversity of perspectives among Scholars who conduct translational research. The predominant specialties in recent years include gastroenterology, dermatology and infectious disease, but our current Scholars represent disciplines that include neuroscience, endocrinology, and pediatrics, among others.

The Clinical Scholars program is a unique three year immersion experience into translational research anchored by the basic science of a laboratory at Rockefeller University."
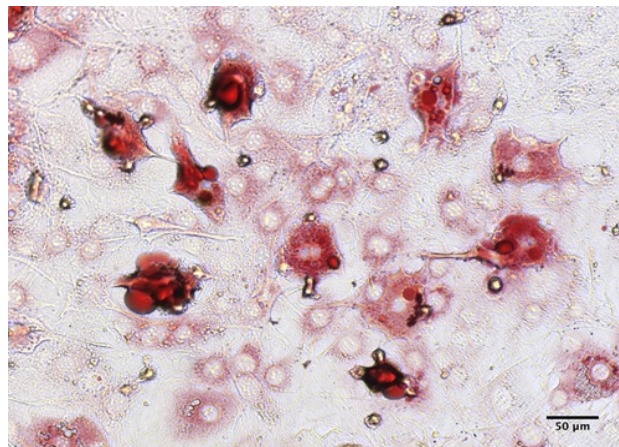
Image is a recreation of a crown like structure using mouse cells lines for adipose tissue and macrophages. Adipose cells are stained red, and macrophages are small, clear cells surrounding the adipose cells.

Accrual Index, A Novel Way of Measuring the Timeliness of Clinical Study Enrollment

By Rhonda G. Kost

Investigator-initiated studies that enroll (accrue) research participants more slowly than expected delay scientific discovery. Recent studies documenting the failure of many clinical trials at the national level to accrue participants on time, or to ever reach study endpoints, led to calls for accountability in study accrual from the Institutes of Medicine and funding agencies such as NIH/NCATS/CTSA. These agencies would like to standardize the evaluation of accrual success across the CTSAs nationally, but no validated measure of this success has yet been developed.

To speed study accrual in protocols conducted by investigators in the Rockefeller Center for Clinical and Translational Science (CCTS), Dr. Rhonda Kost, Clinical Research Officer, andmembers of Clinical Research Recruitment and Outreach Support Service (CRROSS), Lauren Corregano MSW, and Katelyn Bastert MS, have developed data-driven recruitment practices and documented the positive impact of focused data capture and analysis on recruitment success. They have demonstrated the benefits of incorporating recruitment planning early in the Protocol Navigation process to optimize the many factors that impact on the ability to recruit participants into a study.

Estimating the availability of the target population is a core element of assessing recruitment feasibility estimated through review of prevalence data, prior recruitment experience, and the presence of eligible volunteers registered in the Research Volunteer Repository. The recruitment staff initially focused on reducing the time from activation of recruitment to the first participant screening visit which in 2014 was a median of just 10 days. More recently, they devised a new measure, the Accrual Index (AI) to provide near real-time assessment of whether study enrollment proceeding in alignment with the recruitment plan predictions. A paper describing the AI was recently published in the Journal Clinical and Translational Science (8:655, 2015).

Summary of the steps in the development of the AI:

Formulating a Measure I– Participants: The Accrual Target is the number of evaluable participants needed to complete the study, captured as the sample size from the calculation in the IRB approved protocol performed to judge how many individuals need to be studied to have a good chance of obtaining a statistically valid result. A coarse measure of enrollment progress toward the completion goal can be expressed as

Percent Accrual=Evaluable Patients/ Accrual Target

Percent Accrual is useful to illustrate how study enrollment fared at the end of the study, but the absence of a time indicator limits its use in judging the status of studies that are still open to enrollment.

Formulating a Measure II – Adding Time: Since the inception of the CCTS, the CRROSS team has increasingly refined its approach to estimating how long it will take to complete accrual into a study, assuming the availability of the population has been properly assessed. From 2007-2010 CRROSS estimated burdens and incentives for participants as key factors in accrual success; in 2011-2012 it began to incorporate specific investigator availability information; and in 2013-2014 it delved deeper to incorporate predictable lags on recruitment timelines such as leaves of absence, vacations, delays for assay refinement, predictable months of recruitment doldrums, and required FDA review periods, as well as other factors. To obtain a measure of the impact of these improvements in enrollment prediction, CRROSS developed a simple measure to compare its recruitment performance across studies spanning a broad range of accrual targets and anticipated durations.

The measure: The AI places the progress of accrual in the context of the anticipated time frame at any moment during study conduct and is calculated from the equation:

Progress toward Accrual Target/ Time Elapsed Relative to Total Target Time = AI

When accrual progress is on-time the AI =1. When accrual lags, AI is less than 1, and when accrual is ahead of schedule, AI is great than 1. The simplicity of the Index makes it possible to rapidly assess the effectiveness of recruitment strategies across studies and across time. Thus, every study can be immediately evaluated throughout the life of the study rather than having to wait for its completion. The full equation is below:

(Evaluable Subjects Enrolled/Accrual Target)/((Days since Recruitment Start)/ (Predicted Number of Days to Accrual Completion))

Using data captured in the IRB approval protocols, iRIS study management data, and the recruitment core's database, CRROSS has evaluated AI for every study in which recruitment was initiated at the CCTS between 2007-2014. The major trend in the past two years has been toward a narrower range of AIs for open and completed protocols centered around an AI of 1, which indicates both the increasing precision the CRROSS group has achieved in predicting how long it will take to accrue research participants and the success of the recruitment strategies developed by investigators in collaboration with CRROSS staff. For example, more than 50% of studies actively enrolling, or completing/closing enrollment in the year 2014 had AIs between 0.65 and 1.2.

We also created a dashboard (below) to assess accrual in real time for studies active at the CCTS.

Study Name	Status	AI past month	AI current month	AI Trend (slope)	Percent PTAC elapsed
Protocol M	Open	↓0.33	↓0.22	↓-0.11	7%
Protocol X	Open		→0.94		8%
Protocol S	Open		↑1.22		8%
Protocol R	Open	↑2.40	↑2.00	↓-0.40	25%
Protocol N	Open	↑1.88	↑2.11	↑0.23	26%
Protocol T	Open	↑1.60	↑1.12	↓-0.48	42%
Protocol L	Open	↑1.07	↑1.04	↓-0.03	46%
Protocol Q	Open	↓0.50	↓0.70	↑0.19	46%
Protocol K	Open	↑1.89	↑1.57	↓-0.31	50%
Protocol G	Open	↓0.36	↓0.30	↓-0.06	75%
Protocol V	Open	↓0.80	↓0.86	→0.06	117%
Protocol W	Open	↓0.64	↓0.53	↓-0.12	133%
Protocol H	Open	↓0.70	↓0.70	→0.00	133%
Protocol Z	Open	↓0.64	↓0.64	→0.00	133%

Clinical Scholars Program Celebrates New Graduates

By Michelle Romanick

Seven graduating Clinical Scholars received Masters' of Clinical and Translational Science degrees at a dinner celebrating them and their mentors on June 4, 2015.

Dr. Nathalie Burg studied the role of platelets and leukocytes in scleroderma in Dr. Barry Coller's laboratory. Dr. Burg will continue her research on the vascular biology of inflammatory disorders, focusing on systemic lupus erythematosus in Dr. Timothy Hla's laboratory at Weill Cornell Medical College under a grant from the New York State Empire Clinical Research Investigator Program. Dr. Burg is also an Instructor at the Hospital for Special Surgery.

Dr. Louis Cohen studied the metagenomics of natural product pathways as they relate to inflammatory bowel disease in Dr. Sean Brady's laboratory. After graduation, Dr. Cohen was appointed Instructor in the Division of Gastroenterology in the Department of Medicine at the Icahn School of Medicine at Mount Sinai. He will continue to conduct research at Rockefeller as an adjunct member of the Brady Laboratory.

Dr. Tali Czarnowicki studied the pathophysiology of atopic dermatitis in Dr. James Krueger's laboratory. She will continue her research in Dr. Krueger's laboratory, performing studies on the immunologic basis of atopic dermatitis and its relationship to food allergies.

Dr. Peter Forgac studied patients with disorders of consciousness in the laboratories of Drs. Donald Pfaff and Nicholas Schiff. Upon graduation, Dr. Forgacs was appointed Instructor in Neuroscience at Weill Cornell Medical College. He will continue as a member of the Schiff and Pfaff laboratories and continue his research on patients in the minimally conscious state at the Rockefeller University Hospital.

Dr. Xiao-Fei Kong's research focused on the genetics of defects in interferon production associated with increased susceptibility to microbial diseases in Dr. Jean-Laurent Casanova's laboratory. After graduating, Dr. Kong entered an Internal Medicine Residency Program at Queens Hospital Center. He is also continuing his research in the Casanova laboratory.

Dr. Uri Sela's research focused on the development of a vaccine against Staphylococcus aureus infection in Dr. Vincent Fischetti's laboratory. Dr. Sela is continuing his research on the development of a vaccine to Staphylococcus aureus in Dr. Fischetti's laboratory.

Dr. Amir Shlomai's research focused on the pathophysiology of hepatitis C and hepatitis B infections in Dr. Charles Rice's laboratory. Dr. Shlomai is the Head of the Hepatitis Service at the Institute of Liver Disease in the Rabin Medical Center, Beilinson Hospital in Petah-Tikva, Israel where he is continuing his studies of hepatitis C and B.

Drs. Barry Coller, Uri Sela, Sarah Schlesinger, Peter Forgacs, Nathalie Burg, Louis Cohen, Xiao-Fei Kong, Tali Czarnowicki, and James Krueger

Jean-Laurent Casanova honored with the Korsmeyer Award

By Katherine Fenz

Jean-Laurent Casanova, professor and head of the St. Giles Laboratory of Human Genetics of Infectious Diseases, is the recipient of the 2016 Stanley J. Korsmeyer Award for his work investigating the genetic basis of pediatric infectious diseases. The award, given by the American Society for Clinical Investigation, recognizes Casanova for discovering that vulnerability to life-threatening infectious diseases in otherwise healthy children and young adults can arise from single-gene inborn errors.

Dr. Casanova, who is also senior attending physician at The Rockefeller University Hospital and an investigator with the Howard Hughes Medical Institute, will receive a $20,000 grant and present an award lecture at the society's annual meeting in April.

Founded in 1908, the American Society for Clinical Investigation is a nonprofit honor society of physician-scientists who have made major contributions to the understanding of human disease. The award is named after its first recipient, oncologist Stanley J. Korsmeyer, whose findings shed light on the significant role that the dysregulation

of apoptosis, or cell death, plays in disease. The annual Korsmeyer Award is given to members of the society who have advanced knowledge in a specific field and who have mentored young life science researchers. Dr. Casanova was elected to the society in 2008.

Dr. Casanova and his colleagues discovered "holes" in the immune systems of otherwise healthy children that make them susceptible to certain infectious diseases. These holes are caused by congenital mutations in a single gene and are responsible for severe and selective vulnerability to illnesses including tuberculosis, pneumococcal disease, herpes simplex, encephalitis, and Candida infection.

This discovery has far-reaching clinical implications for patients, such as the possibility for genetic counseling as well as the creation of targeted therapies to restore the deficient immune response.

Dr. Casanova received his M.D. from Paris Descartes University and his Ph.D. in immunology from Pierre and Marie Curie University in Paris. While a professor of pediatrics at the Necker Hospital in Paris, he cofounded

Jean-Laurent Casanova

the Laboratory of Human Genetics of Infectious Diseases with his colleague Laurent Abel. Dr. Casanova joined Rockefeller in 2008 and is the recipient of numerous awards, including the E. Mead Johnson Award from the Society for Pediatric Research in 2010 and the Robert Koch Award in 2014. In 2015, he was elected both as a foreign associate of the National Academy of Sciences and to the U.S. National Academy of Medicine.

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Automating data capture with touch screen technology

By Antonia Martinez
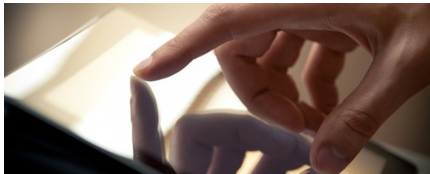
An interactive kiosk with a touch screen provides an easy way to capture research, survey or other data, and to automate simple processes such as registrations or obtaining consent. The Outpatient Unit of the Rockefeller University Hospital (RUH) uses a touch screen kiosk as a convenient self-service option for registering new and returning patients. The system, developed in collaboration with IT, is able to populate the iRIS and ADT databases used by the Hospital, allowing vital information to be available to a variety of stakeholders in real-time.

"New patients enter their demographic information and electronically sign the hospital and patient survey consent

forms," says Riva Gottesman, Director of Regulatory Affairs and HIS. "Returning patients…have the ability to update their demographic information. We are able to track on a daily basis how many new and returning patients came, for which protocols and what time they arrived. Kiosk reports are monitored daily by the nurses in the Outpatient Unit to verify their acuity levels." The system also automatically fills out pdf forms containing the patients' registration data, including a superimposed image of the captured signatures.

The patient registration kiosk system includes two desktops and one laptop kiosk on the Outpatient Unit, and one laptop kiosk on the 3rd floor inpatient unit. Patients can enter their information on the desktop via touchscreen or mouse/keyboard; they can sign their names via stylus pen or finger.

Work on the kiosk system began in

July 2014. It was launched in January 2015. "When I arrived at RUH in December 2013," Riva explains, "it became apparent that the kiosk program in place then, [which was provided by an outside vendor], needed to be revised and expanded to meet the needs of our outpatients." Having programmers here on campus was an advantage. "I began to meet with George Lee (IT's lead Web programmer and the university's webmaster) and Ummey Johra (Hospital IT) to map out the revisions and discuss a go live date." The project also included discussions with IT's security team to ensure that the capture of information would be secure. The design of the system provides "one of the most vibrant patient registration experiences one can have."

New Pilot Grants Awarded

By Michelle Romanick

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), and the Sackler Center for Biomedicine and Nutrition, supported 48 pilot projects this year. CCTS Clinical Scholars received16 pilot awards, and the Rockefeller Early Phase Physician Scientists (REPPS) received 5 pilot awards. A total of 66 applications were submitted, the highest number received to date. This year's total of $887,700 awarded brings the grand total of pilot project funding to $5,775,240 since the program began under the initial CTSA grant in 2006.

Support from the Center for Clinical and Translational SciencePilots Projects Led by CCTS Clinical Scholars

Kemal Akat, MD, PhD (Tuschl Lab): *Dissecting Pro-Calcific Pathways in Calcific Aortic Valve Disease.* Calcific aortic valve disease is the most common valvular heart disease in developed countries. The 5-year survival for symptomatic CAVD is 20%, with surgical or interventional valve replacement being the only therapeutic options. The goal of the pilot project is to discover new opportunities for pharmacological intervention.

Patrick Brunner, MD (Krueger Lab): *Characterization of Circulating Microparticles in Adult Atopic Dermatitis Patients.* While an increased risk of cardiovascular disease is now widely recognized in other chronic inflammatory skin conditions such as psoriasis, atopic dermatitis has also been associated with increased cardiovascular risk. However, it is currently unknown whether it is the disease itself or associated comorbidities (and particularly obesity, which was recently shown to be associated with atopic dermatitis) that are responsible for increased CV risk. Thus, we would like to characterize various circulating blood microparticles, which are markers of CV risk. Results might have an immediate impact on future treatment strategies of atopic dermatitis.

Yehuda Cohen, MD, (Nussenzweig Lab): *Characterization of the Replication Competent Latent HIV Reservoir in HIV-Infected Individuals Controlled on Antiretroviral Therapy (ART)*. This project will perform a detailed genetic characterization of the replication competent latent reservoir in individuals chronically infected with HIV and controlled on ART and will provide important data to advance HIV cure research.

Julien Hsieh, MD (Vosshall Lab): *Olfactory Resolution and General Olfactory Threshold Assessment in Culturally Diverse Populations and Patients with Nasal Polyps.* This pilot project will help to accelerate the development of a new generation of smell tests, namely the "olfactory resolution test" and the "general olfactory threshold test." There is a need to have more accurate smell tests that are: (a) independent of odor-specific sensitivity and (b) generalizable to different populations. This study will allow us to establish a proof-of-concept for further improvement in smell testing.

Jaehwan Kim, MD, PhD (Krueger Lab): *Molecular Phenotyping Acral Melanoma in The Asian Population.* Acral melanoma is a rare but invasive subtype of melanoma that occurs on the hands and feet. Compared with other subtypes, acral melanoma carries a worse prognosis. However, it is challenging to study acral melanoma, because it is the least common subtype in the United States. Since UV exposure, the most important risk factor of melanoma, is not associated with this subtype, understanding the pathogenesis of acral melanoma will enable the discovery of potential therapeutic targets beyond the current paradigm of melanoma treatments.

Shinji Noda, MD, PhD (Krueger Lab): *Defining Phenotypes of Atopic Dermatitis in East Asians Living in the United States.* Atopic dermatitis has a very high prevalence (7-10% of adults) in Asia, with a large unmet need for effective therapeutics. Earlier studies suggest that East Asian atopic dermatitis is characterized by increased epidermal abnormalities together with an activation of a specific immune axis (Th17), arguing for a "psoriasis-like phenotype." However, since the samples of Asian atopic dermatitis leading to these conclusions were obtained from Japanese and Korean patients living in these countries, it could not be determine whether these phenotypic differences are stable in East Asian patients living in the US. To address this question, East Asian patients (Japanese and Korean) living in the US for more than 1 year will be recruited and their skin phenotypes will be compared to those of European Americans.

Djin-Ye Oh, MD, PhD (Ho Lab): *Developing a Novel Assay for Measurement of the Latent HIV-1 Reservoir.* This project will employ flow cytometry to detect single HIV-infected cells, with the ultimate goal of establishing a reliable diagnostic assay that directly measures the latent HIV reservoir. This may result in a standardized assay for the detection of HIV-infected cells that have been reactivated from latency, leading directly to clinical validation studies.

Taia Wang, MD, PhD (Ravetch Lab): *Co-Engaging BCR and CD23 in Respiratory Syncytial Virus Vaccination.* Respiratory infections are a leading cause of global morbidity and are predominantly caused by influenza and respiratory syncytial viruses (RSV). The main barrier to prevention against RSV infections is the absence of an approved vaccine. Our lab recently showed that immunizing mice with the influenza virus hemagglutinin (HA) in complex with IgG containing sialylated Fc domains leads to an antibody response with increased potency and breadth of protective activity. We established that the mechanism for the enhanced antibody response involves co-engagement of CD23 by sialylated Fc domains with the B cell receptor (BCR), leading to upregulation of the inhibitory FcγRIIb, which in turn suppresses the activation/proliferation signal triggered by HA interaction with low affinity, but not high affinity, BCR. As a result, there is selection for the higher affinity B cells that generate antibodies with enhanced neutralizing activity against influenza viruses. We will now use this discovery to determine whether the CD23/BCR co-engagement mechanism can be exploited to elicit potent, protective antibodies against RSV.

New Pilot Grants Awarded

Pilots Projects Led by Rockefeller Early Phase Physician Scientists and Staff

Peter Forgacs, MD, (Pfaff Lab): *Exploratory Study of Melatonin Induced Sleep Regularization in Severe Brain Injury.* This project will investigate causal relationship between normalization of sleep and improvement in behavior in patients with disorders of consciousness (DOC). The effects of melatonin administration will be assessed in patients with severe brain injuries and test its effect on the brain sleep and wakeful activity. We will collect subjective and objective assessments of sleep quality and correlate the findings with changes in behavioral level.

Dana Orange, MD, (Darnell Lab): *Characterizing Rheumatoid Arthritis Related Morning Stiffness.* We will study rheumatoid arthritis patients with severe morning symptoms as well as controls and document fluctuations in their level of pain, stiffness, and swelling over the course of three days. We will then compare circadian symptoms to ultrasound assessments of synovial thickness and vascularity as well as peripheral blood RNA expression profiles. We hypothesize that exaggerated circadian changes in innate immune cells correlate with morning stiffness and delineation of these will provide insight into effector mechanisms of disease activity and novel treatment strategies for this frustrating problem.

Yupu Liang, PhD, (Hospital Informatics): *Development of an Ontology-Based Human Phenotyping System for Smell and Taste Disorders.* This pilot project will lay the groundwork for the development of an Ontology-Based Human Phenotyping System for smell and taste disorders. This collaborative and standardized system will answer the need to: (a) assist physician in diagnosing smell and taste disorders, and (b) collect, manage, store and share smelling disorder phenotypes. The potential application of this system are broad (e.g., studies of genotype-phenotype-environment interactions, optimization of diagnostic criteria, and diagnostic prediction based on patient's history and physical examination) and will tremendously advance translational science in the field of clinical chemosensory disorders.

Ana Pereira, MD, (McEwen Lab): *Glutamate Transporter EAAT2 as a Drug Target for Age-Related Cognitive Decline and Alzheimer's Disease.* The projects tests the hypothesis that the glutamate transporter EAAT2 is critical for maintenance of synaptic health in the aging brain and its dysregulation is an important pathophysiological mechanism for cognitive decline. It delineates the biology of the glutamate transporter EAAT2 in the aging brain at the structural, molecular, and functional levels and it may identify EAAT2 as a drug target for development of novel and more effective treatments for age-related cognitive decline and AD, great unmet medical needs.

Uri Sela, MD, PhD (Fischetti Lab): *Induction of protective Skin Immune Cellular Memory Following Infection or T Cell Based Immunization Against Staphylococcus aureus.* Bacterial skin and soft tissue infections are a major cause of morbidity, and a port of entry to fatal infections by Staphylococcus aureus. CD8+ non-recirculating tissue resident memory T cells (TRM) were shown recently to persist long term in barrier tissues to provide rapid onsite protection against virus, and achieve superior protection compared to circulating memory T cells. However, little is known about whether CD4+ TRM induction has a protective role in skin following either bacterial infection or immunization. This project will compare CD4+ TRM induction in the skin following Staphylococcus aureus infection or immunization with either dendritic cell targeting (T cell based immunity) or a conventional vaccine approach. The findings may elucidate the protective role of skin TRM in Staphylococcus aureus skin infection, and the advantage of dendritic cell targeting in skin protection.

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

Pilots Projects Led by CCTS Clinical Scholars

José Alemán, MD, PhD (Breslow Lab): *Mechanisms of Accelerated Atherosclerosis in Brown Adipose Tissue Expansion.* Brown adipose tissue is found in rodents and infant humans, and only recently has it been demonstrated to be present in adult humans. Characterized by the presence of uncoupling proteins, this tissue has the ability to short-circuit electron transport in order to generate heat for core-body temperature maintenance. There is considerable research interest in the recruitment of white adipose tissue into brown adipose tissue as a means to combat the obesity epidemic affecting the United Stated and developed world. However, preclinical models of brown adipose tissue activation suggest possible acceleration of atherosclerosis through release of free fatty acids and worsening lipid profiles in susceptible subjects. This project will begin the examination of the molecular mechanisms connecting BAT expansion, insulin resistance, and atherosclerosis.

Tali Czarnowicki, MD (Krueger Lab): *Phenotype, Regulation and Development of the Immune System in Adult Atopic Dermatitis Patients. Atopic Dermatitis is the most common inflammatory skin disease. Trigger factors are numerous, including ones that* are environmental and nutritional. Different patterns of skin reactions to food have been described in atopic dermatitis. This project will evaluate several kinds of food allergies, including immediate (e.g., hives) and delayed (e.g., atopic dermatitis) hypersensitivity (DTH) reactions. It is hypothesized that adults with AD will have frequent food allergies, as determined by testing for immediate and DTH, and in those with positive reactions to foods, AD will be exacerbated by ingestion of these food allergens. The phenotype/skewing of T-cells, B-cells and cytokines in the circulation as a result of the immune activation in AD patients will also be evaluated.

Oyebisi Jegede, MBBS, PhD (Rice Lab): *Effects of Chronic Viral Infection on Immune Response to Zoster Vaccination.* Zoster vaccine (Zostavax®, Merck) is recommended for the prevention of Varicella zoster reactivation (shingles). The FDA licensed the vaccine for individuals 50 years without underlying immunodeficiencies. Chronic bystander infections such as chronic Hepatitis C virus (HCV) have been associated with persistent inflammation and immune dysfunction. Zoster vaccine is routinely recommended for individuals with chronic HCV infection. However, no study to date has documented the immune response elicited by Zoster vaccination in this population. This pilot study aims to identify the innate and adaptive immune signatures elicited by zoster vaccination in individuals with chronic HCV and healthy volunteers.

New Pilot Grants Awarded

Gadi Lalazar, MD (Simon Lab): *Phosphoproteomics of Fibrolamellar Hepatocellular Carcinoma.* Fibrolamellar hepatocellular carcinoma is a primary liver tumor affecting adolescents and young adults. It is associated with poor survival despite surgical resection and has no approved systemic therapy. This project will analyze the phosphoproteomic landscape of fibrolamellar hepatocellular carcinoma in patient tissue samples compared with paired normal liver. Human liver cells will be transduce with the DNAJB1-PRKACA chimeric transcript and then we will temporally study downstream phosphorylation targets with the goal of identifying key signaling pathways involved in the pathogenesis of the disease. This approach may shed light on the mechanism of a dysregulated Serine/Threonine kinase in cancer and allow us to identify potential therapeutic targets for the treatment of fibrolamellar hepatocellular carcinoma.

Avi Levin, MD (Steller Lab): *Colon Cancer-Associated Proteasomal Assembly is a Potential Novel Therapeutic Target.* Protein degradation by the ubiquitin-proteasome system is central to cell homeostasis and survival. The 26S proteasome is a large protease complex that degrades ubiquitinated proteins. 26S proteasomal assembly is enormously increased as a result of tumorigenic transformation of the gut epithelium. This project intends to elucidate the molecular mechanism of enhanced tumor-specific 26S proteasomal assembly, and to develop in-vivo assays to track 26S proteasome assembly in the normal and transformed gut epithelium cells. We hypothesize that targeting factors that increase assembly of the 26S proteasome will selectively inhibit rapidly growing cancer cells, but not affect other important proteasome-dependent processes on which normal cells rely.

Isaac Marin-Valencia (Gleeson Lab): *Expanding Diagnostic and Therapeutic Approaches for Inherited Brain Metabolic Disorders by Exome Analysis.* Inherited disorders of metabolism are mostly recessive conditions in which specific proteins cannot properly break down metabolites. As a result, toxic compounds accumulate primarily in blood and brain, or products may become deficient, resulting in deleterious effects on health. This project will apply exome analysis to children affected with inherited metabolism disorders of unknown origin. The ultimate goal is to identify new genes and to study their role in metabolism in order to improve patient care.

Ethan Weinberg (Tavazoie Lab): *Phosphoenolpyruvate Carboxykinase 1 (PCK1) is a Potential Therapeutic Target for Metastatic Colorectal Cancer Liver Colonization.* Colorectal cancer (CRC) remains a leading cause of cancer-related death. Patients diagnosed with early-stage CRC have an excellent prognosis. However, those with extensive liver metastases have a grim prognosis with limited therapeutic options, accounting for 50,000 deaths in the United States annually. The genes governing metastatic CRC (mCRC) liver colonization remains largely unknown. In this vein, we created an in vivo model of mCRC liver colonization using immunodeficient mice and patient-derived primary and metastatic colorectal cancer tissue to discover genes associated with mCRC liver growth. Using this model, we identified phosphoenolpyruvate carboxykinase 1 (PCK1) as a necessary enzyme for mCRC liver colonization. In this project, we will explore the mechanism by which PCK1 dictates mCRC liver colonization and the feasibility of a PCK1 inhibitor in mCRC in vivo models.

Pilots Projects Led by Rockefeller Early Phase Physician Scientists

Ype de Jong (Rice Lab): *Programmed Bacteria to Coordinately Deliver Antitumor Therapeutics in Hepatocellular Carcinoma Xenografts.* This project will explore the safe and widely used probiotic Escherichia coli Nissle 1917 to deliver therapeutics for hepatocellular carcinoma (HCC). Our previous work demonstrated that this probiotic resulted in specific colonization of liver metastases in mice without significant health effects, but its application has yet to be demonstrated in more clinically relevant patient derived xenografts (PDX). This project will accelerate development of engineered probiotics that can safely and selectively deliver therapeutics to human HCC PDX.

Support from the Sackler Center for Biomedicine and Nutrition

Pilots Projects Led by Rockefeller Early Phase Physician Scientists

Ana Emiliano, MD (Friedman Lab): *Tracing the Origins of Sleeve Gastrectomy's Glycemic Effects.* It is unclear how vertical sleeve gastrectomy (VSG) leads to the rapid clinical amelioration of type 2 diabetes. This knowledge gap prevents the potential development of novel pharmacological therapies for diabetes. Our data on diet-induced obesity (DIO) mice indicate that they have a similar glycemic response to humans with type 2 diabetes that undergo VSG, characterized by a rapid reduction in glycemic levels that is unrelated to weight loss and acute surgical stress. In spite of becoming hypoglycemic in the first few days after VSG, DIO mice do not present the normal hormonal response to low blood glucose. This suggests disruption of brain mechanisms that protect against hypoglycemia. Our hypothesis is that VSG alters gastric neural input to the brain, leading to an inhibition of central glucose counter-regulatory mechanisms that prevent and reverse hypoglycemia. We will use nerve-tracing techniques to determine the contribution of gastric denervation to glucose homeostasis. This project may advance the current understanding of how gastric-brain interactions contribute to the regulation of glucose metabolism.

Community Engagement Projects

Pilots Projects Led by CCTS Clinical Scholars

Christina Pressl, MD (Freiwald Lab): *Utilization of an ICD-Coded Big Database to Characterize the Epidemiology of Prosopagnosia.* Individuals affected by prosopagnosia experience great difficulty to perceive, recognize, or memorize faces. Living with prosopagnosia greatly impacts the affected individuals' quality of life (QOL). The number of individuals affected is currently unknown. In this project, we will use an existing large electronic health records dataset to examine the prevalence and correlates of prosopagnosia. Furthermore, we aim to enhance the populations' QOL by engaging with clinicians, patients, and family members to learn about their needs and expectations and to disseminate current educational information about the disorder. This project is expected to reveal novel epidemiological insights and bridge a gap between patients, physicians, and researchers, while building the infrastructure to identify, reach, enroll and consent patients with prosopagnosia for more detailed observational studies that will elucidate the associated neural mechanisms and to eventually lead to interventional trials.

The Rockefeller University Center for Clinical and Translational Applies for Clinical and Translational Science Award (CTSA)

To achieve the vision embodied in these Specific Aims, CCTS will:

1. Integrate our Community Engaged Navigation, Protocol Navigation, Research Participant Engagement in Protocol Priorities and Design, Basic Scientist Outreach, Mutually Aligned Community Engaged/ Mechanistic Science, Centralized Recruitment and Research Volunteer Repository, Ontology-Backed Phenotyping, and Research Participant Perception programs with a new Protocol Implementation Navigation program into an overarching TRN program under a new administrative structure with senior leadership. TRN will be supported by an integrated Informatics infrastructure adopting best practices and NIH and CTSA data standards. TRN will support both local protocols and CTSA network protocols with TRN leadership serving on the Liaisons to the Trial and Recruitment Innovation Centers.

2. Integrate our extensive current educational programs, including the KL2 Clinical Scholars program, with new educational initiatives to: prepare community clinicians to participate in research teams, enhance Clinical Research Nursing training, provide a full range of educational experiences in translating scientific discoveries into health-enhancing products, develop ontology-backed phenotyping instruments, and query large electronic health record databases to test scientific hypotheses at the population level.

3. Integrate the new Tri-Institutional Therapeutic Development Institute, which provides access to medicinal chemists and drug project management, with the CCTS Pilot program, the Rockefeller scientific resource centers, the New York Genome Center, the new Robertson Therapeutic Development Fund, the TRN program, and the CCTS Hospital to enable investigators to traverse the Valley of Death through Phase 1/2 studies. Outcome metrics will drive performance improvement throughout. The three diagrams below provide a pictorial summary of these initiatives.

Translational Navigation Program

Protocol Development	Protocol Implementation	Protocol Conduct	Protocol Completion
Community Engaged Navigation Program			

Protocol Navigation Program	Protocol Implementation Navigation Program	Centralized Recruitment Program and Research Volunteer Repository	Research Participant Perception Survey Program
Research Participant Engagement in Protocol Priorities and Design Program			
Basic Scientist Outreach Program			
Mutually Aligned Community Engaged/Mechanistic Science Program		Ontology-Backed Phenotyping Program	

Novel Informatics Platforms to Support Protocol Development, Conduct, Analysis, Dissemination, and CTSA Network Interoperability

Metrics to Drive Process Improvement in the Learning Clinical Research Enterprise

Translational Work Force Training

	PhD Students Post-Doctoral Fellows	Clinical Scholars	Multi-Disciplinary Research Teams		
			Other Team Members	Research Nurses	Community Clinicians
Broad Scientific Education	Weekly Seminar in Clinical Research				Webcasts
	Symposia, Retreats, Poster Presentation Sessions, Interdisciplinary Rounds Presentations				
Focused Training and Certification	Good Clinical Practice (GCP) CITI Program Certification				
	Human Subjects Protections Certification				
	From Discovery to Health-Enhancing Products Curriculum				IT and Protocol-Specific Training
	Translational Navigation: Community Engagement Training, Protocol Design, Recruitment, IND Preparation, Biostatistics, Bioinformatics, REDCap Database Design and Management, Investigational Drug Management, Research Documentation, Study Implementation, Monitoring and Auditing Reviews				Scientific writing and presentation training

Certificate Program in Clinical and Translational Science	Tutorial in Clinical and Translational Science	Rockefeller Early Phase Physician Scientist Curriculum	Heilbrunn Nursing Programs
	Epidemiology, Biostatistics, Bioinformatics, Big Data Courses		GCP Boot Camp
	GCP Boot Camp		
Responsible Conduct of Research			Community Health Worker Training

From Discovery to Health-Enhancing Product Educational Programs

Target Identification	Compound Selection		Pre-IND Meeting		IND Generation	IND Clinical Development			
Basic and Animal Studies	HTS	Medicinal Chemistry	Pharmacology	Formulation	IND Enabling Studies	IND Submission	Phase I	Phase II	Phase III
CCTS Pilot Support	RU HTS								
Robertson TDF		Tri-I TDI		Robertson TDF					
RU Animal Center			RU Animal						
NYGC			CCTS Research Pharmacy						
Resource Centers			CCTS Regulatory Support						
				Translational Navigation					
				Rockefeller Hospital					

The Rockefeller Investigators Collaborate with other New York City CTSAs and Clinical Directors Network to Build and Use the PCORI-funded New York City Clinical Data Research Network (NYC- CDRN)

The NYC-CDRN recently received Phase II funding to complete the integration of the health records of approximately 4.5 million unique individuals (many of whom receive care across multiple institutions) from the NYC area and is poised to provide a platform for city-wide and nation-wide population health research, patient-centered clinical trials, observational studies, and precision medicine.

The Rockefeller University has been part of the NYC-CDRN collaboration since its inception. Dr. Jonathan N. Tobin, Community Engagement Core Co-Director of the Rockefeller University Center for Clinical and Translational Science (CCTS) and President/CEO of CDN, a primary care practice-based research network (PBRN) of Federally Qualified Health Centers (FQHCs) co-chairs the Research Committee of the NYC-CDRN. Dr. Rhonda G. Kost, Co-Director of the Community Engagement Core, is an active member of the Privacy and Security and Patient Engagement Committees of the NYC-CDRN Dr. Kost also serves as liaison to The Rockefeller University IRB and the Advisory Committee for Clinical and Translational Science in providing updates regarding NYC-CDRN policy, procedures and protocols. Dr. Barry Coller, Rockefeller Physician-in-Chief, serves along with Dr. Tobin on the NYC-CDRN Senior Advisory Council, which is charged with setting the vision and mission of the NYC-CDRN.

As part of its Phase II initiatives, the NYC-CDRN recently began to accept research requests from investigators and to host demonstration projects to query the health record database.

Currently, NYC-CDRN conducts two main types of data queries: 1. De-identified queries of the database using a "computable phenotype" to identify potentially eligible patients for analysis, thus providing individual level data that cannot be connected back to a specific patient; 2. Distributed queries, which have the potential to use de-identifiable data to characterize a cohort, and then to connect to the patients' physicians to explore the possibility of contacting the patients to obtain their participation in prospective observational and experimental research, including clinical trials.

Rockefeller investigators are on the forefront of testing these algorithms and taking advantage of the wealth of opportunities represented by the database, and several "early adopters" have already begun to work with the NYC-CDRN. These include the PCORI-funded patient-centered comparative effectiveness research study of Home-Based Interventions to Prevent CA-MRSA Infection Recurrence study ("CAMP2"). The project, which is being conducted by Drs. Tobin, Kost and Tomasz is designed to define the patterns of MRSA drug resistant infections and infection recurrence in NYC in parallel with a clinical trial of home visits for decolonization and decontamination to prevent recurrence of the MRSA infection. In addition,

Dr. Ana Emiliano, a former Rockefeller University Clinical Scholar and current member of Rockefeller Early Phase Physician Scientist Program leadstwo NYC-CDRN research projects related to obesity, which is a priority condition for all CDRNs. In one CCTS-funded pilot project grant, she

is querying the NYC-CDRN related to her work with bariatric surgery patients cared for by collaborating community physicians in Brooklyn at the NYU Lutheran Family Health Center, one of the CDN member Community Health Centers. The second is a nation-wide PCORI-funded project that is engaging five other CDRNs, in addition to the NYC-CDRN, to examine the impact of bariatric surgery on patient metabolism. Dr. Emiliano is the NYC-CDRN scientific lead investigator in conjunction with a community-based bariatric surgeon, Dr. Rabih Nemr, who practices at the NYU Lutheran Family Health Center. Other investigators are also starting to explore the potential of the NYC-CDRN, including Clinical Scholar Dr. Christina Pressl who plans to query the NYC-CDRN for neurologic diagnoses that might serve as surrogate markers of unrecognized facial prosopagnosia, a disorder characterized by the inability to recognize faces, which will help to build the capacity to identify rare disorders that may be under-diagnosed in practice.

The studies cited above will establish an initial approach to conducting "Big Data" analysis of de-identified EHR data to characterize the prevalence and correlates of the conditions under study. Subsequent studies will build on these efforts by engaging clinicians and their patients in designing and carrying out prospective observational and intervention studies to improve clinical outcomes for patients with these conditions, while increasing our knowledge about the biological mechanisms underlying the conditions and the therapeutic interventions.

Varun Ramprasad, New Manager of Hospital Informatics

By Editorial Staff

Varun Ramprasad

Varun Ramprasad, MS in Biomedical Informatics, joined Rockefeller University Hospital in July 2015 as Manager of Hospital Informatics. In this role, Mr. Ramprasad works closely with the Hospital Senior Staff and Leadership to ensure the proper functioning of all information technology applications related to the use of information for clinical research,

take the necessary measures to ensure the security of electronic patient information, work with University Information Technology (IT) to perform upgrades and maintenance, and manage the activities and staff of the Medical Informatics Core.

Prior to joining the Rockefeller University, Mr. Ramprasad served as a consultant in Healthcare IT and Analytics, working for hospitals, academic medical centers, government, and industry in the applications of data from Electronic Medical Records (EMRs). In his current position he will evaluate potential novel

uses of EMR technology at Rockefeller University Hospital for the unique purposes of managing inpatient and outpatient care information for clinical research studies.

In his current leadership role, Mr. Ramprasad oversees the services of the Medical Informatics Group of the Center for Clinical and Translational Science (CCTS), which includes Ross Gillman, Senior IT Project Manager; Ummey Johra, Senior Technical Programmer; and Cameron Coffran, Senior Scientific Programmer. Together, they provide valuable support and

CCTS Inaugurates New Training Program on Using Big Data and Electronic Health Records to Advance Translational Research

large data program and the PCORnet coordinating center, and has a lead role in the NIH Collaboratory program that focuses on large pragmatic clinical trials, and Dr. Leslie Curtis the Co-Director of the Collaboratory coordinating center. After incorporating their suggestions, the draft curriculum was distributed to the New York City CTSA leaders for their input and participation. Representatives from Columbia (Siqin Kye Ye, MD, MS), NYU (Yindalon Aphinyanaphongs, MD, PhD), and Cornell (Elizabeth Wood, MS) then joined the course leadership. An X02 application was submitted to the National Center for Advancing Translational Science (NCATS) that proposes both an EHR didactic course and a "hands-on" module where investigators can query EHR data in various formats.

These laboratory-based modules will be designed to teach discrete querying skills so that investigators gain familiarity with various data models that may be relevant to their research (e.g., structured, unstructured, or enterprise databases). To further facilitate utilization of big datasets, a third aim of the X02 is to form a working group to share experiences, standardize query development processes, and identify new opportunities to enhance cross-CTSA collaboration.

Faculty with appropriate expertise will be drawn from participating CTSA institutions to teach and facilitate discussions among course participants. In addition, external experts will be invited to incorporate niche knowledge outside of the CTSA network. Classes will be rotated among participating institutions, but all classes will be broadcast live to remote sites, as well as archived in an online repository.

Teaching faculty will determine the appropriate resource materials to prepare for each class, and participants will supplement their learning by accessing the wealth of information available from online resources, including the NIH Collaboratory Knowledge Repository.

The topics to be covered include: 1. Understanding how and why electronic data are captured and what it means for research; 2. Defining a query: translating a basic science discovery into a tractable clinical question; 3. Utilizing and incorporating existing knowledge through effective literature searches; 4. Understanding human subjects protection and HIPAA regulations; 5. The NIH Collaboratory, PCORNet, FDA Mini-Sentinel and NYC-CDRN; 6. The structure of EHR databases; 7. Principles

and practice of distributed research data networks; 8. Identifying a database: parameters available; representative population; data quality; 9. Constructing a query: working with clinicians and other stakeholders, epidemiologists and data specialists; inclusion/exclusion criteria; 10. Choosing the appropriate descriptive and inferential statistical methods; 11. Data Integrity: sources of error/threats to validity; importance of data refresh; internal measures of validity; longitudinal completeness; 12. Teamwork and Leadership: collaborating with external data managers to design, develop and execute studies; 13. Bioethical considerations in searching patient databases; 14. Effective ways to communicate results and study output: tables; graphics; presentation formats; 15. Case studies using topics proposed by the trainees. Readings were selected for each topic from a variety of sources, most notably the government's HealthIT.gov site; the 2014 Institute of Medicine report on integrating research and practice; the NIH Collaboratory, PCORnet, and FDA Sentinel web sites; and the Collaboratory on-line Living Textbook. The first tutorial was conducted with the Clinical Scholars on July 29 and the immediate feedback was extremely positive!

Clinical Scholar Taia Wang and Colleague Jad Maamary Discover That Anti-HA Fc Glycoforms Determines Influenza Vaccine Efficacy through Type II Fc Receptor Signaling

germinal center immune complexes might signal through B cell CD23, the only type II FcR expressed by B cells.

Next, they performed a series of experiments to determine what role, if any, CD23 signaling on B cells might play in B cell selection. The results showed that sialylated Fc glycans, which were elevated on anti-HA IgG following flu vaccination, signaled through CD23 to trigger upregulation of an inhibitory Type I FcR called FcγRIIb. Increased FcγRIIb expression, in turn, elevates the

threshold of selection of B cells based on affinity of the B cell receptor (Figure 1). They found that the higher affinity anti-HA IgGs were more potent and, interestingly, provided greater breadth of protection against different influenza viruses. These results on the natural regulation of Fc domain structure during the evolution of protective vaccine responses led to identification of a mechanism driving selection of B cells within the germinal center that is dependent on CD23 signaling.

In addition, the results suggest immunization strategies involving administration of immune complexes containing sialylated Fc glycans to elicit broadly protective antibodies against influenza viruses.

Varun Ramprasad, New Manager of Hospital Informatics

services for iRIS, the comprehensive IT program used for protocol development, review, and conduct, as well as several other applications used for Hospital Operations. In addition, the Medical Informatics team works closely with the Research Bioinformatics group under the leadership of Dr. Yupu Liang on initiatives to build tools that support

research for the greater University scientific investigator community.

When asked about future developments he envisions for the Medical Informatics program, Mr. Ramprasad replied, "The next big project for the group is the development of an online platform and portal that will enable Rockefeller investigators to communicate

with research participants. This will enhance both patient care and the design and conduct of clinical research. We also strive to enhance our existing Hospital electronic infrastructure with tools that promote the aims and goals of the CCTS."

Clinical Scholar Graduate Dr. Shen-Ying Zhang is Studying the Genetics of Immune Deficiences with the Support of Two NIH RO1 Grants

from healthy controls and four groups of patients, including those with mutations in (i) HSE-predisposing TLR3-pathway genes (TRIF, TBK1, TRAF3, NEMO), (ii) HSE-predisposing IFN-α/β- and -λ-pathway genes (STAT1 and newly discovered IFIT2), (iii) other IFN-pathway genes not related to HSE (IL10RB, TYK2, IRF7), and (iv) novel HSE-causing genes that cause immune defects by unknown mechanisms (DBR1, SNORA31). Second, a novel protocol will be devised to differentiate iPSCs into trigeminal neurons in which HSV-1 establishes latency in children without HSE, and compare control cells and cells with mutations in TLR3, STAT1, IL10RB, DBR1, and SNORA31 for their response to poly(I:C), IFNs, and HSV-1. Third, she will study the entry, retrograde axonal transport, gene delivery and replication of HSV-1 in forebrain and trigeminal neurons from patients with defects in TLR3 function. To demonstrate the disease-causing role of any genetic defect, isogenic iPSC lines will be tested in which the mutation has been corrected or introduced by CRISPR-Cas9 gene editing. Exciting preliminary data have already been obtained, including: (i) novel genetic etiologies of childhood HSE (IFIT2, DBR1, SNORA31), (ii) novel Sendai virus (SeV)-based generation of iPSCs, (iii) novel protocols to differentiate HSV-1-permissive forebrain and trigeminal neurons, and (iv) novel imaging of HSV-1 infection in neurons.

While studies of HSE have traditionally been limited to animal models, the pursuit of this human iPSC-based study will enable Dr. Zhang and her colleagues to dissect in-depth the molecular and cellular basis of HSE in children with inborn errors of CNS-intrinsic immunity to HSV-1. This path-breaking collaborative study has far-reaching medical and biological implications.

The second R01 grant is titled Mendelian Genetic Predisposition to Herpes Simplex Encephalitis in Childhood. It focuses on childhood herpes simplex encephalitis (HSE), which is a life-threatening complication of primary infection by herpes simplex virus 1 (HSV-1), a common virus that is typically innocuous. HSE is the most common sporadic viral encephalitis in Western countries and even with treatment with the antiviral drug acyclovir, survivors often suffer from severe neurological sequelae. The pathogenesis of HSE remained unclear until the research conducted by St. Giles Laboratory of Human Genetics of Infectious Diseases showed that the disease results, in some children, from single-gene mutations impairing TLR3- and IFN-α/β-mediated immunity to HSV-1 in the central nervous system (CNS).

Following a candidate gene approach, 13 patients were reported with rare mutations in one of the TLR3 pathway gene (TLR3, UNC93B1, TRIF, TRAF3, TBK1). In parallel, a hypothesis-generating search was initiated for novel gene defects that may predispose a patient to HSE by studying well characterized HSE kindreds by genome-wide (GW) linkage (GWL). Using this method, DBR1 was discovered as a novel HSE-causing gene in two relatives. However, no genetic etiology has yet been identified for 235 of the 250 HSE patients under study. The research team hypothesizes that HSE in some of these children is a consequence of a collection of CNS-intrinsic inborn errors of immunity to HSV-1, possibly but not necessarily related to the TLR3-IFN-α/β circuit. The goal of this research is to extend the GW approach by taking advantage of whole-exome sequencing (WES) to both the 28 patients consanguineous and 207 non-consanguineous patients (trio design). The WES data will be analized in two ways: 1) hypothesis-based, searching for mutations in TLR3-IFN-α/β pathway genes; 2) hypothesis-generating, searching for mutations in other genes.

The research will benefit from GWL and human gene connectome analysis. Whole-genome sequencing (WGS) will be performed in patients for whom WES fails to reveal candidate mutation. Patients' fibroblasts will be used to investigate the impact of the new candidate genetic etiologies on anti-HSV-1 immunity.

This grant is strengthened by the investigators developing an international cohort of 230 children with HSE, their finding rare mutations in 18 key genes of the TLR3-IFN pathway in up to 52 patients and their identifying by unbiased GW analysis rare heterozygous mutations in the IFN-inducible gene IFIT2 in 4 patient and in a small non-coding RNA gene SNORA31 in 6 other patients. The research will decipher the pathogenesis of a devastating pediatric illness, paving the way for new therapeutic approaches. The genetic analysis of HSE will also provide proof-of-principle that sporadic, life-threatening infectious diseases in otherwise healthy children may result from single-gene inborn errors of immunity.

Accrual Index, A Novel Way of Measuring the Timeliness of Clinical Study Enrollment

The dashboard displays the AI for the prior month, the AI for current month, the trend in AI (change over time), and uses conditional formatting to create a visual alert for studies that are on-time or ahead of schedule (green), on the border of timeliness (yellow), or behind schedule (red) for timely accrual.

Although the PTAC is incorporated into the AI, staff finds it useful to include the percent PTAC elapsed on the dashboard for sorting studies according to how far along they are in the study life cycle. This type of dashboard is reviewed by the Clinical Research Office's recruitment team monthly, Investigators can anticipate reviewing the dashboard and AI data for their studies regularly with the recruitment team. The dashboard is reviewed at intervals by the Senior Staff as part of the review of hospital operations. Starting in 2016, the ACCTS will review the dashboard as part of its accountability and charge to oversee the use of resources and services provided to investigators in alignment with the CCTS mission to accelerate the completion of translational research.

Meet the Scholar: José O. Alemán, MD, PhD

In addition to being a Clinical Scholar, Dr. Alemán is also a Clinical Instructor in Endocrinology at Weill Cornell Medical College, where he focuses on caring for patients with Type 2 Diabetes and Obesity. Following the Clinical Scholars Program, Dr. Alemán will pursue a tenure-track academic endocrinology position in the New York area that will allow him to continue executing translational research, caring for patients with diabetes and obesity and teaching fellows and medical students. At some point in his career Dr. Alemán wishes to interact with the pharmaceutical/ biotechnology industry research as part of the process of bringing medications to patients. Dr. Alemán looks forward to a career in patient-oriented research in obesity and to pursue science that benefits human health!

Learning From Viruses: Phage Lysins as Novel Alternatives to Antibiotics - Centennial Vignette

By Elizabeth (Betsy) Hanson

Pathogenic bacteria are increasingly becoming resistant to antibiotics. But they do have natural enemies: they can be killed by viruses that infect only bacteria, called bacteriophages, or phages. For nearly a century scientists have attempted to treat bacterial infections with whole phages. Rockefeller's Vincent Fischetti (1940-) is the first, however, to focus on the deadly weapons produced by these viruses-potent and specific enzymes called lysins that chew lethal holes in bacterial cell walls. Fischetti and coworkers have identified lysins that can kill a wide range of Gram-positive pathogenic bacteria, and have proven their effectiveness in both preventing and treating infections in mice, an important step toward their potential application to human disease.

Phages infect bacteria in order to reproduce. For a virus's progeny to get out of the cell, the phage directs the synthesis of an enzyme, lysin, that weakens the bacterial cell wall from the inside. Because of the high internal pressure of the bacterial cell (3-5 atm) it essentially explodes once the cell wall is eroded, releasing the new viruses to begin the cycle again. Unlike most antibiotics, which often kill a range of beneficial bacteria along with pathogens, lysins are specific to a bacterial species or subspecies: lysins from streptococcal phage kill certain streptococci, lysins from pneumococcal phage kill pneumococci, and so on. Lysins only are effective against Gram-positive bacteria, which have an exposed cell wall. Gram-negative bacteria have an outer membrane that protects them from lysins. Fischetti's laboratory has used recombinant techniques to artificially produce lysins that specifically attack some of the most widespread and deadly human pathogens-S. pyogenes, S. aureus, S. pneumoniae, E. fecalis, E. faecium, and group B streptococci-as well as a feared agent of biological warfare, B. anthracis.

In a test tube, a few drops of lysin can kill tens of millions of bacteria within a few seconds. In mice, Fischetti and coworkers have shown, for example, that the appropriate lysin can quickly clear group A streptococci from the respiratory mucous membranes. Most human bacterial infections begin in the nose and throat from organisms that are carried there. If proven in clinical trials, lysins could be used not only to treat such infections, but also to remove disease bacteria in people who are carriers, and prevent or reduce serious infections among people in hospitals and nursing homes where antibiotic-resistant Gram-positive pathogens are common.

Dr. Fischetti's group also has used lysins to successfully treat pneumococcal pneumonia, meningitis, endocarditis, and anthrax in mice, and to prevent secondary ear infections. Other studies in Fischetti's laboratory have shown that lysins can work synergistically in combination with other lysins or with antibiotics. Lysins in combination with antibiotics can kill bacteria that antibiotics cannot kill on their own. Ongoing research is designed to assess the safety and effectiveness of lysins in treating human infections.

Vincent A. Fischetti received the BS in bacteriology from Wagner College (1962), the MS in microbiology from Long Island University (1967), and the PhD in microbiology from New York University (1970). He came to Rockefeller University as a postdoctoral fellow in 1970 and became assistant professor in 1973, associate professor in 1978, and professor in 1990. In 1987, Fischetti
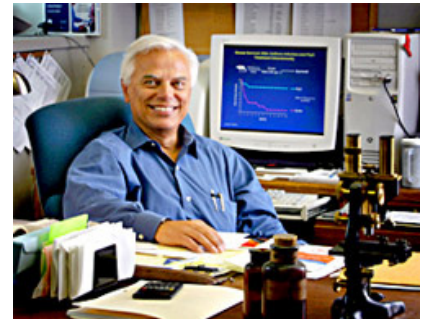
Vincent Fischetti

received a 10-year National Institutes of Health MERIT Award that was renewed in 1997. He was editor-in-chief of Infection and Immunity for 10 years and he is an editor of the authoritative text Gram-Positive Pathogens. Fischetti holds nearly 50 patents on the control of infections by Gram-positive bacteria.