



## Center for Clinical and Translational Science

### Center News

## Rockefeller Leads Largest Survey of Clinical Research Participants: New England Journal of Medicine Report Documents Mostly Positive Experiences

By Zach Veilleux

A multi-center survey of close to 5,000 volunteers who enrolled in clinical research studies, the largest of its kind, shows that by and large participants feel valued and respected by investigators. But although many gave high marks to the research teams' trustworthiness and ability to explain their protocols, the survey also revealed that a sizable minority did not feel completely prepared for the study, and that participants wanted researchers to inform them of the results of the studies.

The study, which was led by researchers in The Rockefeller University Hospital's Center for Clinical and Translational Science, and collaborators at the National Institutes of Health Clinical Center and the

Propel Center for Population Health, included responses from participants at 15 clinical research centers including 13 funded by Clinical and Translational Science Awards from the NIH. It was published in the New England Journal of Medicine. (<http://www.nejm.org/doi/full/10.1056/NEJMp1311461>)

"We depend on research participants as our partners to advance science and medicine," says study author Rhonda Kost, clinical research officer at The Rockefeller University Hospital. "But their experiences have never been widely measured in a scientific way. The survey we have developed gives us, for the first time, a robust method to begin understanding how effective our current processes are and provides

data we can use to improve those experiences for every participant."

The researchers distributed their 77-question survey — similar to those used by physicians' groups and hospitals to incorporate patient feedback into quality improvement efforts — to a total of 18,890 clinical trial participants. Overall, 73 percent of those who returned the surveys rated their overall experience very highly (marking 9 or 10 on a 10-point scale), and 66 percent said they would either probably or definitely recommend research participation to friends or family. Almost all participants also said they did not feel pressure to participate.

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## Rockefeller University Hospital and Chinese Clinical Research Nurses Meet for a Day of Collaboration

By Rita Devine, Rhonda Kost, and Donna Brassil

On October 30, 2013, Rockefeller University Hospital was honored to host five clinical research nurses from China for a day of education in the principles and practice of clinical research as well as the evidence-based practice of clinical research nursing. The group was led by Dr. Xiaokun Liang RN, PhD, project coordinator for Global MD China. The Global MD Organization has jointly initiated special training programs for selected Chinese clinical research nurses since 2009.



Rockefeller University medical staff and Clinical Research Nurses from China

Dr. Liang was among the first five awarded PhD nurses in China trained jointly with the John Hopkins University School of Nursing and Peking Union Medical Center. The nurses' visit is one part of a larger Chinese initiative to build translational research expertise throughout China,

building on the translational research university begun by Dr. Tim Shi.

Dr. Liang was accompanied by Ms. Dandan Yang CRN, a clinical research coordinator in metabolic disorders at Zhejiang University School of Medicine; Ms Qiu Yu CRN in the Department

of Nephrology at Xiyuan Hospital of China in Beijing; Ms. Xiuya Xing CRN, a nurse educator at Beijing Medical University; and Ms. Qiaoya Wang CRN, Chief Nurse for the Clinical Research Department at Beijing YouAn Hospital and Beijing Capital Medical University.

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# Large-scale Survey of Clinical Research Participants Shows Mostly Positive Experiences

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About one-third of participants, however, felt that the “informed consent” process, during which investigators explain the study’s goals, risks and procedures, did not completely prepare them for participation, a figure the researchers say should be improved.

The responses to more detailed questions provided insight into the factors contributing to positive or negative experiences. The survey also identified a gap in communication that could serve as an opportunity to acknowledge the partnership between researchers and participants and encourage future

engagement with clinical research.

Only 23 percent of participants received a summary of the results of the study, yet 85 percent indicated they would have liked to receive one.

“Participants who rated their experience highly were the ones who felt most respected, who felt they could trust the research team and who felt valued as a partner in the research process. They also wanted to be able to make contact with the research team readily when they had a question or problem. A large majority wanted to receive some feedback about the results of the study.

What did the researchers learn?

The survey instrument is a powerful tool with which researchers can work to address these and other aspects of the participant experience,” says Kost. It is now available to researchers throughout the U.S. via a public-private partnership between Rockefeller, the NIH, and NRC/Picker, Inc. The research was funded, in part, by The Rockefeller University’s Clinical and Translational Science Award from the National Institutes of Health.

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## Dr. Shen-Ying Zhang awarded R21 Grant, co-funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

By Michelle Romanick



Shen-Ying Zhang, M.D., Ph.D.

Dr. Shen-Ying Zhang, Clinical Scholars Master’s graduate and a member of the Rockefeller Early Phase Physician Scientist was awarded an R21 grant co-funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The title of the project is Human DBR1 Defines a New Pathway of Intrinsic Antiviral Immunity in the CNS.

Childhood herpes simplex virus 1 (HSV-1) encephalitis (HSE) is a life-threatening

complication of primary infection by HSV-1, a common virus that usually causes innocuous infections in children. The pathogenesis of HSE remained unclear until Dr. Zhang and her colleagues recently showed that the disease may result from single-gene mutations in some children that impair Toll-like receptor 3 (TLR3)-dependent, interferon (IFN)- $\alpha/\beta$ -mediated immunity to HSV-1 in the central nervous system (CNS).

Both DBR1 and XRN1 have particular CNS expression patterns. Although yeast Xrn1 is known as an essential antiviral molecule, it is completely unknown how DBR1 and XRN1 can control anti-HSV-1 immunity in the human CNS. The research team hypothesized that human DBR1 and XRN1 define a new, CNS-specific mechanism of intrinsic anti-HSV-1 immunity.

The goal of the present application is to test this hypothesis at the molecular and cellular levels. The proposed work will be focused on the exploration of the specific role of DBR1 and its related genes (mainly XRN1) in CNS-intrinsic

anti-viral immunity. Preliminary data using the dermal fibroblasts from one patient homozygous for a DBR1 missense mutation express only very low levels of DBR1 protein and enhanced HSV-1 susceptibility, as compared to the healthy controls tested.

Dr. Zhang and her team will test fibroblasts from all patients carrying mutations in DBR1 or XRN1. They will also use in vitro assays to investigate the antiviral activity of DBR1 and XRN1, indirectly via TLR3- or IFN-mediated immunity, or directly via the suppression of viral RNA recombination by DBR1 or XRN1. Anti-HSV-1 immune responses and HSV-1 susceptibility, both IFN-dependent or not, in patients’ fibroblasts and induced pluripotent stem cell (iPSC)-derived neurons will be investigated, in comparison with those with impaired TLR3-, IFN-mediated immunity. This research will shed light on a novel molecule and cellular mechanism of HSE pathogenesis, which will likely open new therapeutic avenues.

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### Cite the Grant

Please remember to cite the CTSA grant. The following manuscript citation is suggested: “Supported in part by grant # UL1 TR000043 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program.”

## New Pilot Grants Awarded

By Michelle Romanick

In October 2013, a total of 42 pilot grants—providing \$950,000 in funding—were awarded to investigators to advance their translational research projects. Support for these awards was provided by the Rockefeller University Center for Clinical and Translational Science (CCTS) and the Center for Basic and Translational Research on Disorders of the Digestive System (CDDS), as well as a grant from The Iris and Junming Le Foundation. CCTS Clinical Scholars were awarded 14 of the pilot grants, and Rockefeller Early Phase Physician Scientists (REPPS) were awarded 3 pilots. With the addition of this year's grants, pilot project funding awarded since the program began in 2006, under the initial CTSA grant, now totals more than \$3,250,000.

### Support from the Center for Clinical and Translational Science

#### Pilot Projects Led by CCTS Clinical Scholars

**Natalie Burg, MD (Coller):** *A Proposal to Search for Evidence of Active Platelet-Derived TGF- $\beta$ 1 and Its Impact on Leukocytes in Systemic Sclerosis.* This project will test the hypothesis that if targeted early, anti-platelet agents may help diminish inflammation and forestall the pro-fibrotic program in Systemic Sclerosis that leads to end-stage organ damage.

**Tali Czwarnowski, MD (Krueger):** *Phenotype, Regulation and Development of the Immune System in Adult Atopic Dermatitis (AD) Patients.* This project will test the hypothesis that cutaneous reaction to a food allergen may produce an inflammatory condition that simulates AD or induces AD in susceptible patients. This study is expected to develop new basic knowledge on T-cell and B-cell activation/differentiation in the context of adult atopic individuals and will shed light on the questionable relationship between food allergy and eczema. These data might be used in the future for disease characterization, follow up and development of targeted medical and/or dietary therapies.

**Daniel Gareau, PhD (Krueger):** *Clinical Translation of the Melanoma Advanced Imaging Dermatoscope.* The initial project created a prototype novel camera, the melanoma Advanced Imaging Dermatoscope (mAID) that images beyond humanly visible wavelengths. Independently, an algorithm was developed to transform raw image data into diagnostic metrics that train a neural-network classifier, which quantifies the likelihood that an imaged lesion is melanoma. This project will support hardware and software refinement and integration in a durable, independent second-generation prototype, for clinical trials.

#### Pilot Projects Led by CCTS Departments/Staff

**Sergio Botero, MSc (Simon):** *A Diagnostic Platform Derived From Olfactory Receptors.* Olfactory receptors allow the chemical characterization of samples, even when their particular composition is unknown. This quality would be of great use as a diagnostic tool when coupled to pattern recognition algorithms to classify samples as healthy or diseased. Yeast offer a unique opportunity to achieve this, but only a few olfactory receptors have been functionally expressed in them. This project intends to optimize the best strain of yeast available, and transfer a very complete library of mammalian olfactory receptors already available for mammalian expression into this yeast system.

**Sarah Jill de Jong, PhD (Casanova):** *Characterization of Inherited CIB1 Deficiency in Patients with Epidermodysplasia Verruciformis.* Mendelian predisposition to persistent human beta-papillomavirus (EV-HPV) infections in otherwise healthy patients is known as epidermodysplasia verruciformis (EV). The aim of this project is to characterize a novel genetic etiology of EV. From a clinical standpoint, the dissection of the pathogenesis of EV will provide molecular diagnoses for patients as well as genetic counseling for families and will pave the way for the study of other, more common HPV-driven pathologies.

**Judilyn Fuentes, MD, PhD (Krueger):** *Exploratory Approach to Study Keloid Formation in Human Skin.* This project will study the genomics of keloid formation, as well as the biological pathways that drive the disease process. The outcome of the study can potentially lead to development of innovative and more effective treatments.

**Jacob Oppenheim, PhD (Magnasco):** *Charting the Vasculome: Understanding the Principles of Vascular Organization in Mammalian Tissues and Organs.* This project proposes the development of a custom optical system, based on the principles of a documentation microscope, to allow sharp resolution of micron-scale structures in the vasculature.

**Francesca Ortenzio BA; Medical Student (Krueger):** *Development of a Psoriasis Patient Decision Aid.* This project will generate data for development of an evidence-based, patient-oriented and interactive Patient Decision Aid to help patients decide on optimal, personalized therapy of their disease.

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## Meet the Scholar: Ana Pereria, MD

By Michelle Romanick



Ana Pereria, M.D.

Dr. Ana Pereria joined the Clinical Scholars Program at the Rockefeller University in 2011. Dr. Pereria received her M.D. from the Universidade Federal de São Paulo in Brazil, and she joined Dr. Bruce McEwen's Laboratory of Neuroendocrinology as a post-doctoral fellow after completing her residency in Neurology at Harvard Medical School. Dr. Pereria was selected as Chief Clinical Scholar in 2013.

Dr. Pereria's research investigates the susceptibility of glutamatergic neural circuits for age-related cognitive decline and for neurodegeneration, with a view toward developing methods to better regulate those neural circuits to prevent and treat cognitive decline. Her mechanistic projects in rodents focus on understanding the neuroplastic changes that occur with aging in those glutamatergic circuits, as well as interventions designed to modulate those circuits pharmacologically.

Dr. Pereria also leads a project to treat patients with mild Alzheimer's disease with a glutamate modulator in a pilot clinical trial, using neuroimaging biomarkers along with cognitive measures to assess the drug's effectiveness. In addition, she leads a project to assess whether hypoxia due to sleep-disordered breathing, which is common in the elderly, contributes to dysregulation of glutamatergic neural circuits. Sleep-disordered hypoxia can be treated and may partially prevent some forms of cognitive decline.

Dr. Pereria's long term goal is to study risk factors and mechanisms of cognitive aging disorders and develop effective therapies to address this crucial medical need that is growing rapidly as

the population ages. She said, "As life appears to me to involve a progressive refinement of one's knowledge and taste, my goal is to do the same with my career as a physician-scientist in neuroscience and clinical neurology."

Dr. Pereria's interest in science and research began in medical school in Brazil where she read "Principles of Neural Science", by Kandel, Schwartz and Jessell, and translated a few chapters from English to Portuguese. She appreciated the brain's complexity and precise neural circuitry and so neuroscience research appealed to her. Dr. Pereria also aspires to understand emotions, thoughts, memories, and insights, and ultimately to have a grasp on creativity by studying the biology of cognition. Neuroscience seemed to her to be an important bridge between sciences and humanities, as has been pointed out by Dr. Eric Kandel, providing a novel modern framework for connecting the "two cultures" described by C.P. Snow.

After medical school, Dr. Pereria joined the laboratory of Dr. Scott Small at Columbia University who works on the aging brain. The environment in the lab was very exciting, leading her to decide on a career in neuroscience research. She thus went on to train as a neurologist at Harvard University under the leadership of the chairman, Dr. Clifford Saper, a renowned physician-scientist. He was a great educator, describing the structural and functional organization of the brain and intertwining this knowledge with descriptions of different neurological disorders.

Dr. Pereria joined the Clinical Scholars Program to develop a foundation as a physician-scientist. The program provides strong basic science knowledge and opportunities to translate this knowledge into novel treatments for human disorders, form crucial collaborative networks, and navigate the complex aspects of human regulatory research.

When asked about her experience as Chief Clinical Scholar and the Clinical Scholars Program, Dr. Pereria responded, "It has been in many ways an exciting learning experience for me to bring colleagues together in common interests, develop novel ideas for

important educational activities, form stronger bonds with other scientists such as the Rockefeller Early Phase Physician Scientists, and cultivate new collaborative opportunities that can advance the Scholar's careers.

Our regular interactions with Dr. Barry Collier are, in my view, one of the most educational aspects of how to develop in yourself your own ideal of a physician-scientist. At every opportunity he passes on his deep wisdom of his long and intense experience in co-habiting the worlds of medicine and science, his passion and creativity for how to make important scientific discoveries and also to translate them to useful applications in human diseases in an effective manner, which is very difficult with the complexity of the divided research spheres we live in.

The program is unique in that you not only have the opportunity to interact with intelligent, enthusiastic, and focused individuals, but you also feel their genuine interest in helping you develop your career. Drs. Barry Collier and Sarah Schlesinger are always available for advice and to help you as much as possible in obtaining your goals. This aspect I feel is a major part of the culture of the Clinical Scholars Program. You also closely interact with fellow Clinical Scholars who come from different medical and scientific fields and so you can learn from their experiences and generate interdisciplinary collaborations; cross-disciplinary discoveries are especially exciting and rewarding.

The Clinical Scholars Program provides a unique infrastructure and intellectual framework to nurture physician-scientists who will make meaningful scientific discoveries to improve human health."

# The Rockefeller University Center for Basic and Translational Research on Disorders of the Digestive Systems (CDDS) hosts its First Retreat and Second Annual Research in Progress Poster Session

By Maija Williams and Luciano Marraffini

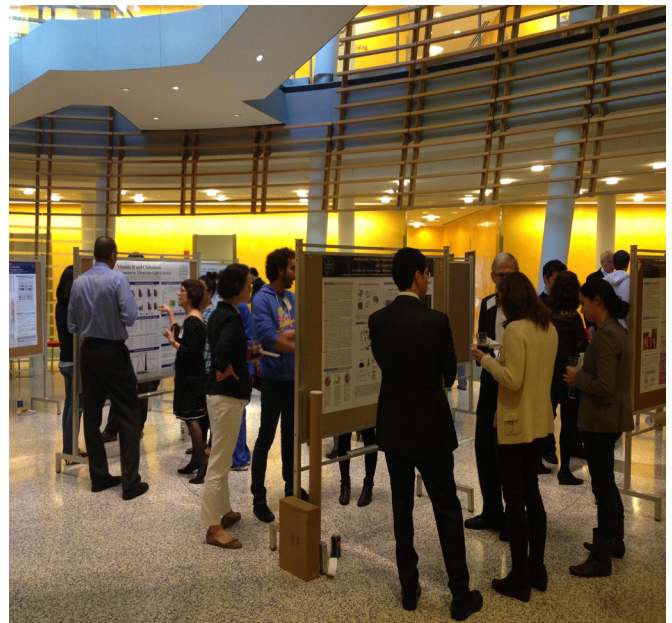
The Rockefeller University Center for Basic and Translational Research on Disorders of the Digestive Systems (CDDS) hosted its first retreat on September 20-21, 2013. More than 60 members of the University gathered at the Edith Macy Conference Center in Briarcliff Manor, New York. Postdoctoral fellows, graduate fellows, and Clinical Scholars presented ongoing research in the fields of immunology, microbiology and disorders of the digestive system. The presentations promoted relations among scientists of different disciplines and spurred the development of new collaborations. Attendees also

enjoyed two “social hours” with refreshments and games that fostered and strengthened the relationships and camaraderie of our scientific community.

CDDS also hosted its 2nd Research in Progress poster session on October 18, 2013, attended by basic and translational scientists from the Rockefeller campus, Weill Cornell Medical Center, and other neighboring institutions. Twenty-two posters were presented highlighting research in hepatitis C, colorectal cancer, metabolic syndrome, metagenomics, gastrointestinal infections, CRISPR technology, dermatology, obesity, vitamin

D, mucosal vaccines, and hepatitis. The 3rd annual research in progress poster session will be held October 24, 2014.

CDDS was established in 2012 with a \$15 million grant from the Leona M. and Harry B. Helmsley Charitable Trust to fund research in digestive disorders, including metabolic diseases, cancers and infections. The Center supports interdisciplinary basic research and fosters collaborations among some 20 Rockefeller labs that study biological processes related to the digestive system.



## Clinical Scholars visit The New York Genome Center

By Ana Pereira

The Clinical Scholars at the Rockefeller University visited the New York Genome Center on January 17, 2014. The Center’s President, Dr. Bob Darnell gave them a guided tour of the facilities and discussed the latest genome sequencing techniques. The Scholars also met many outstanding experts who Dr. Darnell has recruited to the Center and discussed with Dr. Darnell the current genomic approaches to personalizing therapy of an important brain tumor, glioblastoma.

Dr. Darnell’s ability to synthesize both the basic and clinical information was especially educational for the physician scientists in the Clinical Scholars Program. The New York Genome Center provides a state-of-the-art infrastructure to face the challenges of the Genomic era and fosters collaborations within and across New York academic and research institutions. The visit opened the doors for future collaborations with the scientists at the New York Genome Center.

# Rockefeller University Hospital and Chinese Clinical Research Nurses Meet for a Day of Collaboration

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The day began with a welcome by Dr. Barry Collier, Physician in Chief and Vice President for Medical Affairs, who then presented a brief history of Rockefeller University Hospital and its many scientific accomplishments. Donna Brassil RN, MA, CURN, CCRN, Clinical and Translational Research Facilitator, shared her knowledge and experience in research protocol development and navigation.

Dr. Rhonda Kost, Clinical Research Officer, Director of the Clinical Research Support Office and Director of Community Engagement Core explained the importance of research education and training and the principles of good clinical practice.

The nursing department was represented by Rita Devine RN, MPA, Acting Director of Nursing and Clinical Operations Manager, and Ms. Wei Yue CRN. Ms. Yue, a night nurse on the inpatient unit, who is a native of Sichuan, China, acted as liaison and at times as interpreter for both groups.

In the afternoon, Dr. Liang, Ms. Xing, and Ms. Wang had the opportunity to observe the mosquito center in the Vossall Lab while Ms. Yang and Ms. Yu toured the Bionutrition Department. Andrea Ronning MA, RD, Director of the Bionutrition Department prepared a “hands-on” demonstration of creating a metabolic diet. The day concluded

with an animated round table discussion chaired by Dr. Collier. It was interesting to note the differences of our programs while appreciating the similarities. This training program day provided an excellent opportunity for the exchange of ideas about advancing clinical research nursing and created a solid foundation for future collaborations on clinical research and beyond.

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## Riva Gottesman, New Manager, Hospital Information Systems

By Michelle Romanick

Riva Gottesman, MPA, RHIA (Registered Health Information Administrator) joined Rockefeller University Hospital in December 2013 as the Manager of the Hospital Information Systems (HIS). In this role, Ms. Gottesman works closely with the Medical Director and medical staff to ensure the management of patient information, including medical record compliance with Hospital policies and state medical record retention laws. She also works closely with members of senior staff to provide timely access to medical records, and responds to the requests from University officials on patient information in accordance with regulatory requirements for handling sensitive and confidential information.

The HIS department is the repository for all medical records at Rockefeller University Hospital. Records date back to the founding of the Hospital in 1910 and provide valuable information about the treatment of patients at different times since then. The carefully maintained records are also a rich resource for retrospective chart analysis for research purposes. The latter requires multiple steps to insure that the integrity of the archived records is strictly maintained.

Currently Ms. Gottesman is leading HIS projects designed to streamline the participant registration process and increase the value of the patient kiosks both the inpatient and outpatient units, in which allow patients to input their own data.

Prior to joining Rockefeller University Hospital, Ms. Gottesman was the Director of Clinical Resources at the Jewish Home Lifecare, and oversaw the Health Information Department, Clinic, Phlebotomy and Radiology services. Ms. Gottesman holds a BA in Studio Art/ Art History from Hunter College and earned her MPA in Health Care Policy from Baruch College. She has more than 20 years’ experience in compliance and regulatory oversight of health information.

Ms. Gottesman stated, “I look forward to working with my team on modernizing the HIS process to improve efficiency for the medical staff and providing a positive experience for research participants. I am happy to be part of the rich environment of medical history and culture at Rockefeller.”



Riva Gottesman, MPA, RHIA

**Sidney Strickland, PhD (Strickland):** *A $\beta$  Accelerates Clotting Which Can Contribute to a Prothrombotic State in Alzheimer's Disease.* This project will investigate whether the interaction of the Alzheimer's disease-associated peptide A $\beta$  with components of the coagulation cascade contributes to vascular abnormalities and dementia in Alzheimer's Disease. Understanding the details of A $\beta$ 's role in thrombosis and vascular dysfunction may lead to the identification of new biomarkers for disease diagnosis and to therapeutic strategies for preventing or slowing disease progression

**Jonathan N. Tobin, PhD (Clinical Directors Network):** *Hospital-Acquired Methicillin-Resistant Staphylococcus aureus Pilot Project: Expanding the CA-MRSA Surveillance Network.* This project aims to build upon the existing Community-Acquired Methicillin-Resistant Staphylococcus aureus (CA-MRSA) Surveillance Network to extend the surveillance network by studying the clinical and microbiological characteristics of hospital-acquired MRSA in the same communities as the participating community health centers in order to allow for simultaneous examinations and comparisons of both hospital-acquired and community-acquired MRSA.

**Jonathan N. Tobin, PhD (Clinical Directors Network):** *Hepatitis C Pilot Project: Surveillance and Community Outreach, Engagement, and Education.* The goals of this project are: (1) to determine current prevalence and practices associated with identifying and managing HCV in Community Health Centers (CHCs) and to establish levels of knowledge and awareness of HCV by CHC Clinicians, (2) ascertain diagnosis and treatment rates in CHCs, and (3) to provide community HCV health education and outreach emphasizing prevention as well as timely diagnosis and treatment.

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

#### Pilot Projects Led by CCTS Clinical Scholars

**Jose Aleman, MD, PhD (Breslow):** *The OWL Skin Study.* This project will test the hypothesis that weight loss will result in decreased numbers of crown-like structures and inflammatory cytokines in adipose tissue with decreased signs of inflammation by immunohistochemistry and gene expression in skin biopsies, providing evidence for crosstalk between adipose and skin immune cell compartments in fostering obesity-associated inflammation.

**Ethan Weinberg, MD (Tavazoie):** *Development of A Reproducible In Vivo Murine Model of Metastatic Colorectal Cancer (CRC) Liver Colonization Using Patient-Derived CRC Grafts and Identification of Genes Implicated In Colorectal Cancer Liver Metastasis.* This project will create an in vivo model of mCRC liver colonization utilizing immunodeficient mice and patient-derived primary and metastatic colorectal cancer tissue to identify genes associated with mCRC liver growth. The identification of genes responsible for liver colonization has clear clinical implications. Tumor profiling at diagnosis could alert the physician to those patients with limited disease at higher risk for metastatic disease. Therapeutics targeting the genes responsible for mCRC liver colonization could improve both the quality of life and survival among this group.

**Ana Emiliano, MD, (Friedman):** *Missing Links: Brain and Gut Adaptations in Sleeve Gastrectomy-Induce Weight Loss.* This project will utilize a mouse model of sleeve gastrectomy to determine the effects of this type of surgery on brain centers regulating food intake and energy balance and on gut-hormone producing cells. Novel immunoprecipitation techniques will be used to probe molecular brain and gut changes that may occur after sleeve gastrectomy. The results of these studies may lead to the development of drugs to treat obesity.

**Amir Shlomai, MD, PhD (Rice):** *Identifying Essential Host Factors in Hepatitis B Virus Life Cycle and Persistence by Novel Infection Systems.* This project will define the differentiation stage at which the human induced pluripotent stem cells (iHLCs) become permissive to HBV infection, and will also generate iHLCs from stem cells of individuals harboring different genetic backgrounds. As a complementary approach, we plan to use the CRISPR system to target candidate genes in HBV infected micro-patterned cocultures, and to test their effect on HBV life cycle and its DNA maintenance. Our work is expected to significantly expand the scientific knowledge of HBV and its interactions with its host cell and may also lead to the development of effective anti-viral agents that have the potential not only to suppress the virus but also to eliminate it and cure the patients.

#### Pilot Projects Led by REPPS

**Manish Ponda, MD (Breslow):** *The Effect of Oral Vitamin D vs. Ultraviolet Light on Cholesterol.* This project will study the difference between oral supplementation and a more physiologic method of raising vitamin D levels, i.e. ultraviolet light exposure. This information will increase our understanding of the role vitamin D therapy. The high prevalence of vitamin D deficiency, the failure of oral vitamin D to improve cholesterol levels, and the possibility that oral vitamin D may be harmful, make this study a high priority.

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**Support from the Center for Basic and Translational Research on Disorders of the Digestive System (continued)**Pilot Projects Led by CCTS Departments/Staff

**Juana Gonzalez, PhD (CCTS):** *A Pilot Study to Characterize Adipose Tissue Leukocytes by Flow Cytometry and Microscopy In Lean, Obese And Psoriatic Subjects.* This project will identify inflammatory cells in adipose (fat) tissue, which may help to understand the causes and consequences of obesity. Specifically, we hope to determine how these cells might be implicated in the initiation and/or progression of obesity and psoriasis.

**Zeynep Gumus, PhD (Cornell) (Tavazoie):** *Functional Impact Characterization of Mutations in Colon Cancer Genomes.* This project will provide preliminary data towards the characterization of previously uncharacterized mutations, which will generate a set of actionable therapy targets and may enhance our current understanding of colon cancer progression. Results will enable follow-up in vitro and animal model experiments on the precise cellular effects of these mutations. We anticipate that the model we develop will assist clinicians in identifying colon cancer patients who are at highest risk for future metastasis so that more aggressive and experimental therapies can be offered to them.

**Jai Min Loo, BA (Tavazoie):** *Colorectal Cancer.* Colorectal cancer is a highly prevalent cancer type affecting roughly 200,000 Americans a year and killing approximately 50,000 annually. We have identified two clinically relevant microRNAs and their downstream target that suppress colorectal cancer metastasis and have developed adeno-associated viral vectors for the delivery of these microRNAs. Preliminary studies involving xenograft models have demonstrated the efficacy and safety of these vectors in preventing metastasis demonstrating a potential new avenue for the prevention and treatment of metastatic colorectal cancer. This project will further test these vectors in the setting of metastatic progression. The result of this investigation is expected to lead to the development of novel therapeutics in the treatment of metastatic colorectal cancer.

**Jane Markle, PhD (Casanova):** *Intestinal Infections in Patients with Mutations in T-bet.* This project studies will contribute to the knowledge of the role of T-bet (TBX21) in the intestinal immune response against pathogens, characterize novel human mutations of TBX21 at the molecular genetic and biochemical level, and elucidate the mechanistic roles of these mutations in severe tuberculosis and Whipple's disease infections.

**Alexander Nguyen, MD, PhD (Tavazoie):** *Therapeutic Inhibition of Autocrine Signaling Pathways Involved in Colorectal Cancer Metastasis.* Metastatic colorectal cancer is a deadly disease with no effective preventative or curative therapy. Our identification of the secreted factor thrombopoietin (THPO) and its cognate cell-surface receptor (MPL) as promoters of colorectal cancer metastasis allows for the development of novel antibody-based therapies. This project will genetically engineer a chimeric protein consisting of MPL fused to the Fc region of human IgG1, serving to bind and inhibit THPO while possessing the beneficial structural characteristics of an antibody.

**Brad Rosenberg, MD, PhD (Rice):** *Gene Expression Profiling of Immune Response to Hepatitis B Virus Vaccination in Healthy Volunteers.* Chronic infection by hepatitis C virus (HCV) causes constitutive interferon stimulation. Although not considered immunocompromised, chronic HCV patients demonstrate high failure rates to vaccination against hepatitis B virus (HBV). This project will test the hypothesis that this poor response is due to immunomodulatory effects of persistent interferon activation by chronic HCV infection, and to evaluate the feasibility of characterizing the response to HBV vaccination in healthy volunteers by RNA-Seq.

**Sanford Simon, PhD & Constantin Takacs, PhD (Simon):** *Imaging of Early Steps of Hepatitis C Virus and Lipoprotein Release from Live Cells.* Hepatitis C virus (HCV) is peculiar in that it associates with liver-produced lipoproteins. This association is essential for HCV infectivity. This project will offer a live cell microscopy approach focused on single transport events to further understand the phenomena involved in HCV-lipoprotein association, and their secretion from infected cells. We hope to identify new therapeutic targets and develop a live cell microscopy approach focused on single transport events.

**Jeanne Walker, RN (CCTS/Hospital):** *The Effects of Trans-Resveratrol on Insulin Resistance, Inflammation, and the Metabolic Syndrome: A Placebo Controlled, Double Blind Study.* This project will investigate the effects of resveratrol, a natural plant-derived compound, on the metabolic syndrome (insulin resistance, hypertension and hyperlipidemia) in a double blind, placebo-controlled inpatient study.

***Support from the Iris and Junming Le Foundation***Pilot Projects Led by CCTS Clinical Scholars

**Thalia Farazi, MD, PhD (Tuschl):** *Sequence-Based Methodology for Non-Coding RNA Detection for Breast Cancer Diagnosis and Prognosis.* This project will pave the way for a large survey of ncRNA expression during breast tumor progression by examining benign, preneoplastic and Ductal Carcinoma in situ (DCIS), lesions imparting a varying risk of developing invasive cancer. We hope that defining these signatures can help patients with low risk of developing invasive cancer avoid unnecessary treatment.

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### Support from the Iris and Junming Le Foundation (continued)

#### Pilot Projects Led by CCTS Clinical Scholars

**Julien Hsieh, MD, PhD (Vosshall):** *Evaluation of Sodium Citrate Nasal Buffer as a Treatment for Post Viral Hyposmia.* A preliminary study showed that application of sodium citrate buffer to the olfactory epithelium improved olfactory function in hyposmic patients, that is, patients with a defect in the ability to smell. This treatment is thought to lower calcium ion concentrations in the nasal mucus, leading to increased excitability of olfactory sensory neurons. This project will provide pilot data to establish a larger study to assess whether sodium citrate nasal buffer could become the first effective treatment for post viral hyposmia.

**Avi Levin, MD (Steller):** *Role of TNKS-PI31 Mediated Proteasome Regulation in the Development and Treatment of Colorectal Cancer (CRC).* This project will examine and track TNKS activity by using an antibody specific for the ADPribosylated form of PI31. This project will also test the hypothesis that a subgroup of patients will benefit from tankyrase and proteasome inhibition by investigating the sensitivity of colorectal cancer cells with highly poly-ribosylated PI31 to proteasome inhibitors. Collectively, this work will provide proof-of-concept for treating specific CRC patients with available small-molecule TNKS- and proteasome inhibitors.

**Ana Pereira, MD (McEwen):** *Glutamatergic Dysregulation, Inflammation and Cerebral Damage in Sleep-Disordered Breathing.* This project will study potential mechanisms through which Sleep-disordered Breathing increase cognitive impairment in the elderly population by investigating the phenomenon of glutamate-mediated excitotoxicity in susceptible brain regions. It will also study the relationship between inflammatory markers and cortisol in sleep-disordered breathing with in vivo markers of glutamatergic dysregulation and brain damage.

**Lotta von Boehmer, MD (Nussenzweig):** *Endogenous Anti-HER Antibodies.* Using single B cell sorting technology, this project will identify and clone anti-HER autoantibodies from breast cancer patients and determine their characteristics. It will also analyze the in vivo anti-tumor activity of the newly identified anti-HER antibodies.

**Taia Wang, MD, PhD (Ravetch/Schlesinger):** *Role of IgG Fc Glycan Composition in Vaccination.* This project will conduct the first systematic study of vaccine-elicited Fc glycan modifications and the biological activities associated with those modifications during formation of an antibody response. The experiments proposed here are designed to investigate two basic hypotheses, both of which are relevant in the development of novel immunotherapeutics and vaccines, and may therefore directly impact public health: 1) that the composition of Fc glycans is actively regulated, and 2) that Fc glycan composition, either in the pre-existing IgG pool or on newly elicited IgGs, directs the maturation of a humoral immune response, thereby functioning as a host determinant of vaccine efficacy.

#### Pilot Projects Led by REPPS

**Jennifer Belasco, MD (Krueger):** *Establishing Pathogenic Links between Juvenile Dermatomyositis and Psoriasis in Pediatric Patients.* This project will analyze tissue repository samples for changes in immune products over time. This will potentially allow the identification of the initial pathomechanisms of disease in psoriasis. In addition, this study may lead to a better understanding of the process of how one autoimmune or inflammatory disease becomes superimposed on another autoimmune or inflammatory disease. Currently the standard treatments for juvenile dermatomyositis target the immune system broadly and have significant side effects.

**Dana Orange, MD (Darnell):** *Next-Generation Analysis of RNA Fluctuations as a Measure of Rheumatoid Arthritis (RA) Disease Activity.* This project will develop a better understanding of the molecular phenotype of RA disease activity by coupling meticulous clinical assessments with blood mRNA sequencing data gathered longitudinally at unprecedented frequency. Samples harvested prior to and during disease flares will be compared to establish which pathways fluctuate most during disease worsening as well as just prior to worsening.

#### Pilot Projects Led by CCTS Departments/Staff

**Gaelle Breton, PhD (Steinman):** *Modulation of Human Dendritic Cell Development by Adjuvants.* This project will test the hypothesis that human dendritic cell development, subset distribution, and state of activation are altered by administration of adjuvants.

**Chad Euler, PhD and Vincent Fischetti, PhD (Fischetti):** *Treatment of Clostridium difficile Colitis by the Secretion of Bacteriophage Lysins from Probiotic Bacteria and Yeast.* This project will use recombinant C. difficile bacteriophage endolysins (lysins) as novel agents for the prophylactic and therapeutic treatment of C. difficile infection and colitis. Established bacterial and yeast probiotics will be modified to express and secrete the C. difficile lysin protein to deliver it, without being degraded, to the lower gastrointestinal tract where C. difficile infection and colitis takes place. This would be the first time a genetically modified organism combines the positive effects of a bacterial or yeast probiotic with the killing power and specificity of bacteriophage lysins.

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### Support from The Iris and Junming Le Foundation (continued)

#### Pilot Projects Led by CCTS Departments/Staff (continued)

**Mary Hatten, PhD and David Buchholz, PhD (Hatten):** *Using Induced Pluripotent Stem Cells to Model the Role of Cerebellar Circuits in Autism.* This project will use induced pluripotent stem cells (iPSCs) to model the role of cerebellar circuits in autism. This research has the potential to provide a critical new model for autism and other developmental disorders that involve defects in cerebellar circuits and will accelerate development of small molecule and cell-based therapies.

**Aniek Ivens, PhD (Kronauer):** *The Role of Gut Microbes in a Nutritional Mutualism Between Aphids and Ants.* This project will explore a nutritional mutualism between ants, aphids, and gut microbes as a potentially powerful new model system to study the role of gut microbes in nutrition. Gut microbiomes strongly impact human health, for example by influencing an individual's metabolism. The two greatest challenges to gut microbiome studies are the high complexity of mammalian microbiomes and the high variability of human diets. Using insect models substantially reduces both challenges since insect gut structure, microbiomes, and diets are much simpler

**Fabien Lafaille, PhD (Casanova):** *Dissecting the Molecular and Cellular Mechanism of SNORA31 Mutations Underlying Herpes Simplex Encephalitis.* This project aims to decipher the molecular and cellular mechanism by which rare genetic variations in a non-coding RNA gene predispose children to herpes simplex virus 1 (HSV-1) encephalitis (HSE). The findings of the study would for the first time illustrate how mutations in a non-coding RNA gene underlie the disease pathogenesis of childhood HSE.

**Michael Rout, PhD, Braian T. Chait, PhD, and Hans-Guido Wendel, MD (Rout):** *A Revolutionary New Approach for Producing Better Cancer Diagnostics and Therapeutics.* Nano bodies, single domain antibodies (~15kDa) derived from camelids, are showing tremendous promise as anti-tumor reagents because of their high specificity, small size, and robustness. To date, however, their implementation has been thwarted by significant problems with efficiently identifying repertoires of suitable nano bodies. We have recently perfected a new method that completely overcomes these problems, enabling us to produce large repertoires of readily expressible recombinant Nano bodies against any given antigen with very high affinities and specificities. This project will pilot the application of our method for the generation of anti-tumor reagents.

**Agata Smogorzewska, MD, PhD (Smogorzewska):** *The International Fanconi Anemia Registry (IFAR) Patient Perspective.* This project will test the hypothesis that families will benefit from increased knowledge about the rare condition affecting their children. The proposed project has two stages; 1) an anonymous survey of families to gauge their goals of participating in the IFAR, their experienced frustrations, and ways in which we might enhance the benefits to their participation. Specifically we will also ask for families' thoughts about contributing medical and family history directly to the Registry, logistical details that might ease the burden, and any obstacles that might prohibit participation. 2) Using this information, we will distribute a medical history questionnaire that families can complete. This information will be compared to the more traditional data sources, including physician notes and medical records. If we can demonstrate that patient-reported data is both reliable and obtainable, we can begin to shift our study methods to empower families and strengthen the data we collect.

### Other Pilot Project Grants

#### Pilot Project Led by CCTS Clinical Scholars

**Jaehwan Kim, MD, PhD (Krueger):** *Comparative Analysis of Small and Large Plaque Psoriasis.* This project is expected to provide new understandings of the mechanisms involved in spreading of psoriatic plaques and provide new insights into psoriasis development. The study of a genetically homogeneous cohort, characterized by the relatively high prevalence of small plaque psoriasis in the Korean population, may filter out spurious signals while allowing for significant associations to emerge from a relatively low number of participants.

#### Pilot Projects Led by CCTS Departments/Staff

**Nicolas Gulati, MD, PhD (Krueger):** *Use of the Topical Immunomodulator Diphenylcyclopropenone (Dpccp) To Treat Cutaneous Metastases.* This project aims to employ topical immunotherapy to regress cutaneous metastases and to investigate the molecular and cellular mechanisms of such regression. Successful completion of these experiments will improve our understanding of immune-mediated tumor regression, and may provide a novel therapeutic strategy for metastatic cancer.

**Masahi Yamaji, PhD (Tuschl):** *Mechanisms Underlying the Stem Cell Function in Human Testis.* This project will identify molecules sufficient to proliferate functional, self-renewing human sperm stem cells (SSC) in vitro with three specific aims: (1) Characterize developmental-stage-specific gene expression dynamics during spermatogenesis in humans, (2) Identify evolutionarily conserved SSC-self-renewal genes and validate their functions using a murine SSC culture model, and (3) Identify the genes capable of sustaining the long-term cultivation of human SSCs as well as their genetic interactions in the SSC-self-renewal in humans. This research will create a research infrastructure in human reproductive biology: a gene expression database providing information on the molecular principles mediating SSC-self-renewal, and a human SSC culture model. Given adult stem cells replenish differentiated cells throughout life, the mechanisms regulating adult stem cells are crucial to understand. We hope to apply the potential of stem cells to regenerative medicine, as well as understand the principles of tumorigenesis.

# Rockefeller Medical Research History: Pioneering the Genome-Wide Association Study and Identifying a Cause of Age-Related Macular Degeneration

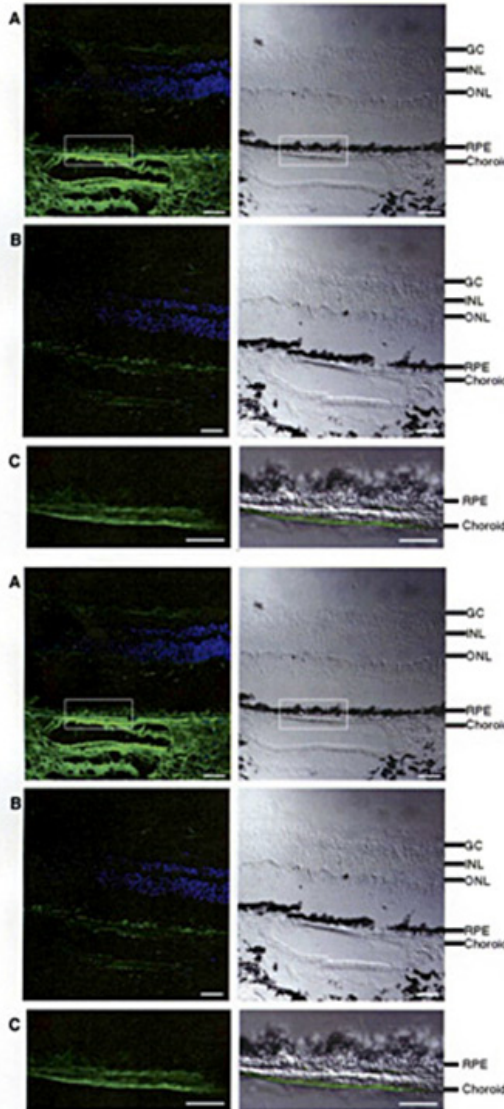
By Elizabeth (Betsy) Hanson



Ott, Jürg

Finding the many genetic mutations that contribute to common, complex diseases like diabetes and heart disease once seemed like a needle-in-a-haystack proposition. But Rockefeller's Jürg Ott (1939 - ) has led researchers in developing a new technique called a genome-wide association study (GWAS) for finding genetic differences between people with such complex diseases and in healthy individuals. In a landmark proof-of-concept study in 2005 he and colleagues identified a genetic variation strongly associated with age-related macular degeneration (AMD), the most common cause of irreversible vision loss in the developed world, which affects some 10 million Americans. This research opened the door to hundreds of subsequent studies by scientists who have since used GWAS to find genomic variations that underlie disease, and that also explain differences in how people respond to drug therapies.

This method scans the three billion nucleotides in an individual's genome sequence for the single-nucleotide polymorphisms (SNPs), or substitutions, that occur about once in every 1,000 nucleotides. Most of these small changes have no effect on health. So scientists must analyze hundreds of thousands of variations among a large group of people to find changes that occur in people with a disease but not in healthy people. Ott's laboratory has led the field in developing statistical and computational techniques for such analysis. In addition, scientists once thought it would be necessary to scan the genomes of thousands of people in order to find associations—a daunting prospect that would severely limit the utility of the technique. But by choosing well-matched



Immunofluorescence localization of CFH protein in human retina. From *Science*, 2005, 308: 385-389

cases and controls Ott, former research assistant professor Josephine Hoh, and colleagues showed that a case-control GWAS could be performed successfully with only 96 people with severe cases of AMD and 50 people matched for age, gender, and many environmental factors. They discovered that the so-called dry form of AMD is associated with a genetic variation on chromosome 1 that changes the sequence of an immune system protein involved in inflammation called human complement factor H. Prior to this study, no one had suggested that a complement factor was associated with the disease. Hoh is now an associate professor at Yale University.

Before turning to case-control association analysis, Ott was a founder of the field

of genetic linkage, another approach to locating genes on chromosomes and ultimately identifying those that contribute to disease. He authored the first publicly accessible computer program on human linkage analysis (dubbed LIPED). His work led to some of the first methods for computer simulation in family pedigrees and provided the statistical framework underlying the newer approaches to haplotype relative risk methods that have become important tools in the search for disease-marker associations. He has analyzed gene linkages for a number of other disorders, including hypertension, Creutzfeldt-Jacob disease, multiple sclerosis, and retinitis pigmentosa.

Ott's laboratory continues to focus on the interpretation of genomic data by developing new mathematical-statistical methods for human gene mapping and building computer programs to implement them. He uses the resulting information to study the interactions among multiple disease loci that underlie complex traits, as well as to study how environmental risk factors modify disease loci effects. Ott collaborates with other researchers on the analysis of their genetic data and maintains a web/ftp site for disseminating information and computer programs.

Ott received the PhD from the University of Zürich (1967), taught physics at a state college in Switzerland, and then worked as a biostatistician until 1970. He earned his master's degree in biomathematics from the University of Washington, Seattle (1972), then stayed on at the university, advancing to associate professor. Ott returned to Zürich in 1979 as the assistant director for the city's statistics office. In 1986 he accepted two positions in New York City: professor of genetics and development at Columbia University and research scientist and director of the department of statistics at the New York State Psychiatric Institute. Ott joined Rockefeller in 1996 as professor and head of the Laboratory of Statistical Genetics. He maintains an office at the Beijing Institute of Genomics, Chinese Academy of Sciences. His achievements have been recognized with the Medal of Honor from the German Society for Human Genetics (2007), and the Ming Tsuang Lifetime Achievement Award from the International Society of Psychiatric Genetics (2008). He received a MERIT award from the National Institutes of Mental Health (2001) and is a member of the American Association for the Advancement of Science and the Human Genome Organization.