Center News

Jean-Laurent Casanova, World Leader in Studying Genetic Immunodeficiencies, to Join Rockefeller University and the Center for Clinical and Translational Science

Dr. Jean-Laurent Casanova, an internationally recognized leader in the genetics of human immunodeficiency, has accepted the University's offer of appointment, and will join the faculty as Professor in Medicine in September. Dr. Casanova and his colleagues in Paris at Hospital Necker for Sick Children, including Dr. Laurent Abel, have made landmark discoveries of genetic mutations that predispose individuals to specific pathogens, including both bacteria and viruses. These studies have fundamentally changed the paradigm of the genetics of immunodeficiency, which previously focused on genetic alterations that result in predisposition to multiple pathogens. His group has also identified multiple genetic abnormalities in a single pathway that results in a predisposition to mycobacterial infections, reinforcing the biological insights that can be obtained from these studies. Dr. Casanova will establish his human subjects program in the Rockefeller University Hospital and the Center for Clinical and Translational Science.

Center Faculty Share Scientific Highlights from Past Year

This year, Center faculty made important discoveries ranging from the genetics of human odor perception to improved methods to enhance the immune response to vaccines. Below are the brief excerpts describing some of these discoveries and the papers that provide fuller descriptions.

Dr. Arleen Auerbach discovered that among 944 carriers of Fanconi anemia (a disorder that confers a dramatic increase in cancer risk in the homozygous state), there was no overall increased risk of cancer. Carriers of the FANCC gene were, however, at increased risk of developing breast cancer. (Berwick M, Sagatopan J, Ben-Porat L, Carlson A, Mah K, Henry R, Diotti R, Milton K, Pujara K, Landers, T, Batish SD, Morales J, Schindler D, Hanenberg H, Romas H, Levrano O, Auerbach AD. Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer. Cancer Res 67: 9591-9596, 2007)

Dr. Christian Münz and his colleagues characterized a novel immunoregulatory synapse between human dendritic cells and natural killer cells that transmits activating signals for natural killer cells and inhibitory signals that protect dendritic cells from natural killer cell lysis. They also demonstrated that tonsillar natural killer cells produce 5-fold higher concentrations of the anti-viral cytokine IFN-gamma after dendritic cell stimulation and are 100-fold more efficient in restricting B cell

CCTS Informatics Update

iRIS Study Management Rollout is Providing Investigators and Staff with New Functions to Facilitate the Conduct of Protocols

By Donna Brassil

The new Integrated Research Information System (iRIS) has been introduced in the Center for Clinical and Translational Science over the past several months and it currently manages more than 20 research protocols for Rockefeller University investigators. The system

Honors and Awards

Dr. Ralph Steinman received an honorary degree from the Mount Sinai School of Medicine.

Dr. Leslie Vosshall was named an Investigator of the Howard Hughes Medical Institute. Dr. Vosshall is internationally recognized as a leader in understanding the molecular and genetic basis of odor perception in humans.

Dr. Mary Jeanne Kreek was honored with a full day symposium on campus on May 16, 2008 led by many of her trainees who have gone on to become leaders in the field of substance abuse. Dr. Kreek joined the laboratory of Dr. Vincent Dole at Rockefeller in 1964 and was a member of the group, along with Drs. Dole and Nyswander that developed methadone maintenance therapy. Dr. Kreek’s laboratory has pioneered in establishing the neurobiologic and genetic contributors to substance abuse. She has received innumerable honors and has advised the U.S. and many foreign countries on public policy related to substance abuse.

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External Advisory Board Report on the Rockefeller University CTSA Program Highlights Center’s Progress

The External Advisory Board (EAB) for the Rockefeller University Clinical and Translational Science Award met on March 12, 2008. Additionally, Dr. Dan Rosenblum, Medical Officer for the Division for Clinical Research Resources at the National Institutes of Health, visited the Rockefeller campus in late March 2008. Both of these visits were designed to review and discuss the progress of the Center for Clinical and Translational Sciences (CCTS) initiatives and endeavors.

The EAB noted that the Rockefeller University CCTS has demonstrated “excellent progress in further implementing the key governance elements in the CTSA proposal” during the past year. The Advisory Committee on Clinical and Translational Science (ACCTS), along with its subcommittees, were singled out for providing valuable and “effective scientific review and strategic planning,” as well as assuring that resources are used “efficiently and effectively.”

The review cited marked progress in hiring new personnel to aid in recruitment, community outreach, auditing of studies, and regulatory interactions with federal agencies. Additionally, the accessibility of advanced training for research nursing staff and clinical research coordinators has demonstrated the Center’s commitment to excellence in the conduct of research.

The EAB expressed approval for the Center’s ability to facilitate research translation by: 1) initiating 10 pilot projects in one year’s time; 2) further developing educational programs for Clinical Scholars, nurses and coordinators; 3) introducing the iRIS system; 4) creating a Data Analysis Core; 5) continuing to make progress with the Center’s Participant Perception Survey; 6) supporting Clinical Scholar transitions to individual K (career development) awards; and 7) supporting and facilitating landmark studies, such as Dr. Leslie Vosshall’s research on the genetics of human odor perception. Dr. Rosenblum, in his review, emphasized that the interactions among the disciplines and programs are having the “desired synergistic effect.”

The Board recognized that the CCTS faces some serious challenges. As a result of NIH budget cuts, funding to implement all of the projects and hire all of the personnel outlined in the Rockefeller University CTSA application is inadequate. This has been an issue for all CTSA institutions, most particularly, those CTSSs funded in 2007 and thereafter. Implementation of the Good Clinical Practice, Community Engagement and Outreach, and Information Technology strategic plans will, therefore, need to be modified by the ACCTS and senior leadership of the Center.

• Dr. Nina Papavisiliou has shown that microRNA-155 is a direct, negative regulator of a cytidine deaminase that initiates hypermutation and class switch recombination of antibody genes. This enzyme (AIDCA) has been implicated directly in the generation of the majority of mature B cell lymphomas; hence its proper downregulation is a significant component of the mechanism that limits its mutagenic potential in the cell. (Teng G, Hakimpour P, Landgraf P, Rice A, Tuschi T, Casellas R, Nina Papavisiliou N. microRNA-155 is a negative regulator of activation induced cytidine deaminase. Immunity, In Press)

• Dr. Bruce McEwen and his colleagues provided important new information on the role of ionotropic glutamate receptors in aging and demonstrated that modifying one of the receptors could preserve neurologic function and protect against age-related neuron loss in an animal model. With Dr. Greengard, he also studied the actions of a novel antidepressant and their data suggest that antidepressants can have converging effects on the same molecular target via different signaling pathways and even different phosphorylation sites. (1. McEwen BS. Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol Rev 87:873-904, 2007. 2. Bloss EB, Hunter RG, Waters EM, Munoz C, Bernard K, McEwen BS. Behavioral and biological effects of chronic S18986, a positive AMPA receptor modulator, during aging. Exp Neurol 210:109-117, 2008)


• Dr. Jon Blumenfeld and his colleagues developed and validated a novel endonuclease-based method for detecting the PKD1 and PKD2 DNA mutations responsible for autosomal dominant polycystic kidney disease that is less expensive and more efficient than direct sequencing. They also identified novel mutations causing the disease.

• Dr. Barry Coller and his colleagues used the Rockefeller University High Throughput Screening facility to identify a novel low molecular weight organic molecule inhibitor of the platelet alphaIIbß3 receptor. This compound also has antithrombotic activity and may act as a precursor for improved orally active antiplatelet agents (Blue R, Murcia M, Karan C, Jirouskova M, Coller BS. Application of high throughput screening to identify a novel alphaIIb-specific small molecule inhibitor of alphaIIbß3-mediated platelet Interaction with fibrinogen. Blood 111:1248-1256, 2007)

• Dr. Leslie Vosshall and her colleagues identified both gain of function and loss of function mutations that affect human olfaction. She is now studying the neurobiologic effects of these mutations in humans. (Keller A, Zhuang H, Chi Q, Vosshall LB, Matsunami H. Genetic variation in a human odorant receptor alters odour perception. Nature 449:468-472, 2007)

• Dr. Robert Darnell and his colleagues identified T cells specific for the breast and ovarian tumor antigen cdr2. It is believed that these T cells mediate naturally occurring immunity to these tumors in rare individuals, but also have the potential to trigger autoimmune brain disease. (Santamasso BD, Roberts WK, Thomas A, Williams T, Blanchere NE, Dudley ME, Houghton AN, Posner JB, Darnell RB. A T cell receptor associated with naturally occurring human tumor immunity. Proc Natl Acad Sci U.S.A. 2007 Nov 19)

Sean Brady Joins the Faculty of the Center for Clinical and Translational Science

Dr. Sean Brady, Head of the Laboratory of Genetically Encoded Small Molecules, joined the faculty of the Center for Clinical and Translational Science. Dr. Brady's research focuses on the discovery, biosynthesis and characterization of new, genetically encoded small molecules from microbial sources. Dr. Brady has particular interest in small molecules produced by uncultured soil bacteria. Uncultured bacteria are one of the largest remaining pools of genetic diversity that have not yet been examined for the production of potentially useful natural products. Dr. Brady's research also investigates the role of small molecules in pathogenic bacteria. By studying the complex collections of small molecules that bacterial pathogens use, he hopes to gain new insight into the molecules used during infection and, in turn, determine how to best disrupt key steps in the establishment and propagation of bacterial infections. Additionally, Dr. Brady's research focuses on developing molecular tools that can be used to observe small molecules in vivo. The ability to detect small molecules in vivo would be useful for studying the roles they play in complex biological processes. Dr. Brady joined Rockefeller from the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School in 2006.

Rockefeller University Bionutrition Department Prepares New Diets to Support Novel Metabolic Studies

We've had a busy year in our department. We celebrated the retirement of two long-time employees of Bionutrition. Verline Barrett retired in May 2007 after 34 years of service, and Veronica Whiteman retired in Jan 2008 after 38 years! We were sad to say goodbye, but wish them well in their retirement! We have hired two wonderful new employees to fill those spots: Luz Alequin and Gladys Negron both joined the Bionutrition Department in 2007.

Early in 2007, the installation of our new walk-in refrigerator and freezer was completed. We survived the construction, and are very happy with the results! Our newest metabolic diet study was opened for enrollment in the summer of 2007. “Dietary Interventions for Insulin Resistance and the Metabolic Syndrome” involved the development of three 5-day rotating diets: an American-Style Diet, a DASH (Dietary Approaches to Stop Hypertension) diet, and a Low Glycemic Diet. The American-Style Diet has a macronutrient composition is 52% carbohydrates, 32% fat and 16% protein, simulating the average intakes of Americans as identified by the NHANES surveys. The DASH diet is rich in fruits, vegetables, whole grains, and low-fat dairy products, with moderate amounts of nuts, legumes, fish, and poultry; consumption of red meat, sweets, and sugary beverages is limited. The macronutrient composition of the DASH diet is 55% carbohydrate, 18% protein, 27% total fat, and 6% saturated fat.

Subjects with metabolic syndrome are admitted for a 19-day inpatient stay where they are kept weight stable. All subjects consume 4 days of the American Style diet, and then are randomized to one of the three diets for weight stability for the remaining 15 days. Indirect calorimetry measurement, body fat measurements by Bod Pod, measures of insulin resistance using the euglycemic insulin clamp, and dietary / lifestyle questionnaires are conducted during the last days of the inpatient stay.

Upon discharge, subjects move into a weight-loss phase for 8 weeks, where outpatient meals are provided by our department. Subjects consume the study diet at 50% calorie reduction from weight stability energy requirements. After the 8-week outpatient phase, the subjects are re-admitted for 14 days and fed the study diet for weight re-stabilization and repeat testing of the measures mentioned above.

This has been quite a challenging study for us to design and produce research meals for, but we are happy to report the successful completion of 5 subjects at this time. We are currently recruiting for the remaining seven subjects needed to complete this study.

At the beginning of 2008, we opened the protocol “The Natural History of Obesity and Associated Conditions Before, During, and After Treatment with Conventional Therapies”. This is an outpatient study offering treatment and support for weight management. There is a multidisciplinary team consisting of a physician, nurse practitioner, bionutritionist, psychologist, and an exercise physiologist that provide care to obese individuals. The Bionutrition Department offers nutrition counseling to subjects, and performs testing with the BodPod and the indirect calorimeter.

We look forward to an exciting year here at the Rockefeller University Center for Clinical and Translational Science!

iRIS Study Management Rollout is Providing Investigators and Staff with New Functions to Facilitate the Conduct of Protocols

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allows investigators and staff to manage clinical and administrative tasks for research studies by tracking patient data, accessing information about screening and individual clinical visits, generating reports regarding subject and study progress, and enabling investigators and study staff to quickly find other important information. Research personnel can make use of iRIS to set target dates for all protocol activities, schedule and view participants’ study visits, and create order sheets and nurses’ worksheets for the research staff. Additionally, iRIS can produce a Good Clinical Practice (GCP)-compliant database for each principal investigator that contains all study participant information. For more information regarding iRIS for study management, please contact Ms. Donna Brassil in the Research Facilitation Office or Ms. Ummey Johra in the Hospital Informatics department. Ms. Brassil’s contact information is: dbrassil@mail.rockefeller.edu; (212) 327-7886. Ms. Johra’s contact information is: ujohra@rockefeller.edu; (212) 327-7877.
CTSA Resources from an Investigator’s Point of View (continued from page 2)

When asked what could be improved upon, Dr. Hudgins commented that centralizing the participant data would have made rescheduling of study visits and troubleshooting data collection easier. She also wished that she had been given the opportunity to talk with the nursing staff and others involved for an informal presentation of her study. A research staff meeting before enrollment began would have given staff a chance to ask questions about the protocol and learn more about the research topic. Dr. Hudgins also suggested the CCTS look for ways to better familiarize all faculty and staff with protocols in progress to give a greater “sense of importance” to our campus and to “generate more appreciation” for the scientific endeavors that are underway at the Rockefeller University.

Finally, Dr. Hudgins offered some advice to young investigators still working to establish themselves, “the most important thing you can do is identify the area of research that you are truly passionate about. It can be a minute detail to the broadest perspective. Turn to people who are experts in that area… get advice from and communicate with them.” Throughout her career, Dr. Hudgins felt that she was inspired by the people around her and was drawn to the power that research has to answer questions and generate knowledge. “Be adventurous!” she said with a smile, “because the end results are so important.”

New Staff Biographies

Ms. Teresa Grant joined Rockefeller as a Clinical Research Nurse in the Center for Clinical and Translational Science on March 10, 2008. Ms. Grant has more than 12 years experience as a Registered Nurse, working primarily in Intensive Care Units, and is currently enrolled in the Nurse Practitioner program at the University of Medicine and Dentistry, New Jersey. Ms. Grant will be responsible for coordinating and carrying out clinical research studies, including developing and updating protocols and collaborating with investigators to create standards for clinical studies. She will teach patients protocol-specific information, reinforce compliance with protocol procedures, collect research data, and provide direct nursing care. Additionally, Ms. Grant will coordinate and instruct other research team members on protocol-specific issues. Her contact information is: tgrant@rockefeller.edu; (212) 327-8448.

Ms. Angie Slattery joined the Rockefeller University staff on March 17, 2008. She will be working as the Communications Specialist for the Center for Clinical and Translational Science. Ms. Slattery previous worked at the University of Wisconsin-Madison as a research study coordinator, educational specialist and research program manager before moving to New York in March 2008. Her responsibilities for the Center include: assisting in the development of a new Certificate in Clinical and Translational Research educational program for PhD and and MD/PhD students and postdoctoral fellows, as well as providing administrative support of new courses in Clinical and Translational Research as components of the Certificate Program. Additionally, Ms. Slattery will provide editorial support of the Center for Clinical and Translational Research e-Newsletter, and will help to ensure the accuracy and timeliness of information on the Center for Clinical and Translational Science webpage. Her contact information is:aslattery@rockefeller.edu; (212) 327-7316.

External Advisory Board Report on the Rockefeller University CTSA Program Highlights Center’s Progress (continued from page 2)

The recruitment of new faculty members to the campus has been slower than anticipated, but this is being addressed by a concentrated effort of current faculty to identify potential new recruits.

Both the EAB and Dr. Rosenblum concluded that they were very impressed with the excellent progress made by the Center within the past year. Each discussed the impact that the Rockefeller University CTSA is having both locally and nationally, and emphasized the need for the CCTS to continue to advance clinical and translational science through the Center’s initiatives.

Meet the Clinical Scholar: Edgar Charles, M.D.

Chief Clinical Scholar, Dr. Edgar Charles first became interested in Hepatitis C virus (HCV) during his fellowship years at NYU where he encountered many patients suffering from HIV/HCV co-infection. He became intrigued by the clinical presentation of his patients, and wanted to further understand the immune response to HCV. Dr. Charles realized that an intensive laboratory experience would be the best way to develop his clinical research skills. Once he learned of the Clinical Scholars program at Rockefeller University, he quickly determined that this was the perfect opportunity to gain the experience and skills needed to become an independent clinical investigator.

His interest in viral pathogenesis and immunology led him to work with Drs. Charles Rice and Lynn Dustin in the Laboratory of Virology and Infectious Disease. Here, Dr. Charles and other lab members work to characterize B-cells response to HCV infection; these discoveries could lend valuable insight into the development of HCV therapeutics and vaccines.

Dr. Charles stated that the Clinical Scholars program has helped him to focus his clinical questions and has led him to think more analytically about symptom/disease relationships. “I now think more precisely about clinical questions that can be answered at the bench.” Dr. Charles also noted that the Clinical Research Support Office (CRSO) has been very helpful with recruitment of study participants into his studies. Additionally, Drs. Rice and Dustin have been “extraordinarily helpful and generous. I am very grateful for their support.”

Dr. Charles recently received a K08 award from the National Institute of Allergy and Infectious Disease (NIAID). This K08 award provides support to individuals with a clinical doctoral degree for an intensive, supervised research career development experience, as a crucial stepping stone to scientific independence.