

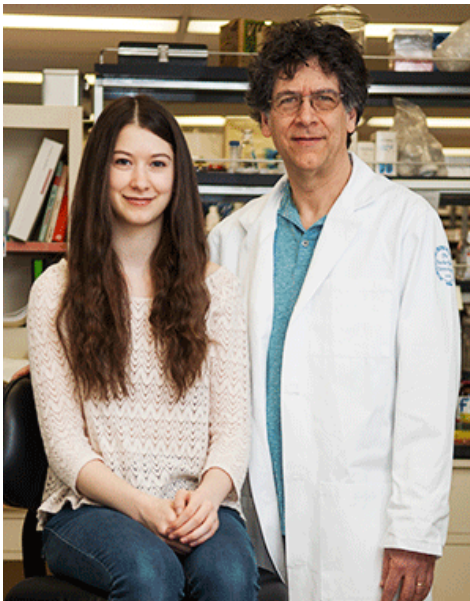


Center for Clinical and Translational Science

Center News

Candidate Driving Mutation in Fibrolamellar Hepatocellular Carcinoma Identified in 15 of 15 Cases by Patient Elana Simon, Her Father, Head of Laboratory, Dr. Sanford Simon, and Collaborators at New York Genome Center

By Zach Veilleux



Elana and Sandy Simon at Rockefeller

Elana Simon, the daughter of Rockefeller University professor Sanford Simon, received a devastating cancer diagnosis at age 12 — a rare and often deadly type of liver cancer called fibrolamellar hepatocellular carcinoma. Like many that affect rare adolescents cancers, it is not well understood because research funding typically goes to more common cancers. But four years after her surgery, in which most of her liver was removed, she began interning in a biology lab, and came up with a new idea for understanding the genetics behind her own tumor.

“I reasoned that it would be easier to identify genetic mutations in the tumors of young patients than it is in older ones, because in older people, their genomes have been altered by years of aging and environmental factors,” says Elana Simon,

an 18-year-old senior at the Dalton School who will attend Harvard this fall. “Also, in an adolescent, a tumor has not been around for very long, so the tumor itself will have less time to accumulate mutations. When we identify a possible mutation in an adolescent, it is much more likely that it’s driving the cancer.” Elana wanted to sequence the entire genome, 3 billion base pairs long, rather than just the shorter exome, which is the more manageable section that is often tackled. Her comfort with computer science and her drive to unlock the mystery of her own cancer compelled her to take on the challenge.

Meanwhile, to obtain as large a collection of tissue as possible, Elana reached out to other patients, asking them to contribute their tissues obtained during surgery, to a

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Rockefeller Ranks First in Both Scientific and Medical Science Publications Impact Among Global Institutions

By Zach Veilleux

Rank	University	Publications	Proportion in Top 10% Most Cited
1	Rockefeller University	1033	29.1%
2	MIT	9149	25.2%
3	Harvard University	29693	23.0%
4	University of California – Berkeley	11384	22.5%
5	Stanford University	13399	22.3%
6	Caltech	5072	22.2%
7	Princeton University	5017	21.9%
8	University of California – Santa Barbara	4246	21.2%
9	University of California – San Francisco	9990	20.2%
10	Yale University	9775	20.0%

Scientific Publications

Rank	University	Publications	Proportion in Top 10% Most Cited
1	Rockefeller University	305	33.0%
2	MIT	561	24.2%
3	Caltech	123	22.4%
4	University of Technology Sydney	115	22.0%
5	Harvard University	11598	21.1%
6	University of Oxford	2606	19.8%
7	University of Cambridge	1695	19.5%
8	University of California – Berkeley	713	19.5%
9	University of California – San Francisco	4963	18.5%
10	Queen Mary University of London	727	18.3%

Medical Science Publications

The Rockefeller University has the highest percentages of frequently cited scientific publications and medical science publications of 750 top universities worldwide, according to the CWTS Leiden Ranking, which measures citation impact and scientific collaboration. The ranking, conducted by the Center for Science and Technology Studies of Leiden

University in The Netherlands, is based on publications indexed in a Thompson Reuters database between 2009 and 2012. Although the ranking has been conducted annually since 2011, Rockefeller was not included in previous surveys. This year the number of institutions covered was expanded from 500 to 750, and smaller institutions, Rockefeller among them, were added.

Rockefeller is ranked above MIT, Harvard, UC Berkeley and Stanford in scientific publications, and above MIT, Caltech, U of Technology Sydney, and Harvard in medical science publications.

The top 50 universities with the highest percentage of frequently cited scientific and medical science publications is strongly dominated by U.S. institutions,

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Translational Research Awards made available through the Robertson Therapeutic Development Fund

By Bruce Conway



Bruce Conway, Ph.D.

A new funding initiative at the Rockefeller University was created earlier this year to help bridge critical gaps in drug discovery and translational science. The grants, totaling \$25 million over 5 years, are from the Robertson Therapeutic Development Fund (RTDF), which was established by noted investment manager Julian Robertson and his family. The RTDF has enabled the University to award grants ranging from \$30,000 to \$1 million to provide Rockefeller scientists

with the resources required to take exceptionally promising basic research initiatives through the steps that lead to breakthrough medications, new diagnostic tests or other clinical innovations.

To accomplish these objectives, two types of awards have been established through the RTDF. The first set of awards are for proof-of-concept projects aimed at identifying and validating potential therapeutic targets and diagnostics. In the first round of applications submitted in January, pilot funding was awarded to 12 early stage projects, two novel diagnostics, one vaccine and one stem cell therapy approach. Funding was also provided for several advanced projects: one for development of a vaccine and three for novel cancer therapeutics.

In a second round of applications completed in August, pilot funding was provided for 11 early stage projects and four advanced projects. Awards for the advanced projects were provided to identify biomarkers, screen for potential therapeutics and to develop novel technology platforms. A second type of award is for early clinical development

projects. These awards are intended to fund drug design and manufacturing, toxicology testing, and, in some cases, Phase I clinical trials. Funding for two early clinical development projects has been provided to date; one for a novel anti-cancer therapeutic and one for the prevention of HIV infection. The RTDF has had a promising launch, with ~ \$6 million in awards granted to Rockefeller scientists in the initial phases. In total, 37 proposals submitted by researchers in 25 Rockefeller labs have received funding.

All Rockefeller research faculty, Clinical Scholars and postdoctoral researchers are eligible for the awards. Requests are reviewed by an independent committee of experts drawn from the pharmaceutical, biotechnology and life sciences investment industries, and awards are distributed according to a schedule based upon the successful completion of agreed-upon milestones.

One exciting aspect of the Robertson Therapeutic Development Fund is that it provides the necessary resources to enable Rockefeller researchers to pursue important studies that are rarely

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Dr. Marina Caskey Conducting First in Human Study of a New Human Monoclonal Antibody to HIV Discovered and Developed at Rockefeller

By Michelle Romanick

Dr. Marina Caskey, Assistant Professor of Clinical Investigation in the Nussenzweig Laboratory of Molecular Immunology is conducting a phase I, open label, dose-escalation study of the safety, pharmacokinetics and antiretroviral activity of a monoclonal antibody (3BNC117) in HIV-infected and HIV-uninfected volunteer with Drs. Sarah Schlesinger, Michel Nussenzweig, and Trip Gulick.

This study is intended to support the development of 3BNC117 mAb for two potential indications (1) Therapeutic application in HIV-infected individuals, and (2) Prophylactic application in healthy HIV-uninfected individuals at risk for HIV infection.

A fraction of HIV-infected individuals (10 – 30%) mount a broad neutralizing

serologic response 2-3 years after infection. Accumulating evidence supports the idea that broadly neutralizing antibodies might play an important role in protection from acquisition of HIV infection because they can protect macaques from infection, and the presence of anti-HIV antibodies was the only positive correlate of protection in the recent phase III HIV vaccine trial (RV144 trial). HIV neutralizing antibodies also have the potential to alter the course of HIV infection in humans. These antibodies might be useful to both prevent and treat HIV-1 infection. However, clinical studies to date have shown rather limited effects when anti-HIV antibodies were administered to HIV-infected individuals during interruption of antiretroviral treatment. Therefore, antibodies fell out of favor as a therapeutic modality in acute or chronic HIV infection. More

recently identified anti-HIV antibodies have a broader spectrum of activity and are orders of magnitude more potent than the neutralizing antibodies previously used in human studies.

3BNC117 is a highly neutralizing anti-HIV antibody isolated and cloned in Dr. Nussenzweig's laboratory. In preclinical studies carried out in humanized mice and non-human primates, 3BNC117 alone or in combination with other neutralizing antibodies not only led to protection from contracting HIV or SHIV infection, but also to sustained suppression of HIV plasma viremia in already infected animals. The aims of the current protocol are to evaluate the safety, tolerability and pharmacokinetic profile of 3BNC117 in both HIV-infected and HIV-uninfected subjects, and its antiretroviral activity in HIV-infected

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

By Michelle Romanick

On July 1, 2014, five new Clinical Scholars joined the Rockefeller University Clinical Scholars Program. They are: Drs. Oyebisi Jegede, Gadi Lalazar, Shinji Noda, Christina Pressl, and Johannes Scheid. Additionally, with support from the CCTS, Benjamin Ungar, a 3rd year medical student from the Ichan School of Medicine at Mount Sinai joined Dr. James Krueger's laboratory under the Center's Year-Off Training Program for Graduate or Medical Students in Clinical and Translational Science. Below are brief biographies and descriptions of research interests of the new scholars.



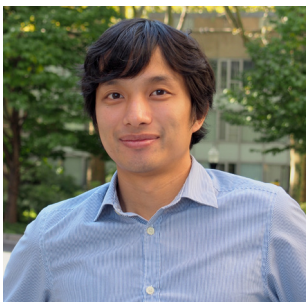
Oyebisi Jegede, MD, PhD
Mentor: Dr. Charles Rice

Dr. Oyebisi Jegede received her MBBS from the University of Ilorin, Kwara-State in Nigeria and her PhD from the Cleveland Clinical Foundation/Kent State University. She completed her Internal Medicine Residency at Western Reserve Care System, Northeast Ohio Medical University, and is currently completing her Infectious Diseases and Immunology Fellowship at New York University Medical Center. As a Clinical Scholar in Dr. Rice's lab, Dr. Jegede is studying the immunomodulatory effects of hepatitis C virus in the chronically infected host, and the impact of hepatitis C virus on the immune system in health and disease.



Gadi Lalazar, MD
Mentor: Dr. Sanford Simon

Dr. Lalazar received his MD from Hebrew University Hadassah Medical School in Israel. He completed his Internal Medicine Residency and Gastroenterology and Hepatology Fellowship at Hadassah Hebrew University Medical Center. As a Clinical Scholar in Dr. Simon's lab, Dr. Cohen is studying the genomics of fibrolamellar hepatocellular carcinoma.



Shinji Noda, MD, PhD
Mentor: Dr. James Krueger

Dr. Shinji Noda received his MD from the Faculty of Medicine, University of Tokyo and his PhD from the Graduate School of Medicine, University of Tokyo. He completed his internal medicine Internship at the Japanese Red Cross Medical Center and the University of Tokyo Hospital, and his dermatology residency at the Faculty of Medicine, University of Tokyo. As a Clinical Scholar in Dr. Krueger's lab, Dr. Noda is Identifying immune and barrier differences between Asian, African-American and European-American patients with atopic dermatitis.



Christina Pressl, MD
Mentor: Dr. Winrich Freiwald

Dr. Christina Pressl received her MD from the Medical University Graz in Austria. She went on to clinical training in internal medicine and radiology in Graz and Vienna, Austria, as well as advanced research training in radiology at the Medical University in Vienna. As a Clinical Scholar in Dr. Freiwald's lab, Dr. Pressl's research will focus on understanding the neural basis of face recognition and its impairments



Johannes Scheid, MD, PhD
Mentor: Dr. Michel Nussenzweig

Dr. Johannes Scheid received his MD from Charité - Universitätsmedizin Berlin, and his PhD from the Rockefeller University. He completed his clinical studies in Germany at the Charité - Universitätsmedizin Berlin. As a Clinical Scholar in Dr. Nussenzweig's lab, Dr. Scheid's research will focus on the use of broadly neutralizing antibodies in HIV therapy.

Sniff Study Suggests Humans Can Distinguish More Than 1 Trillion Scents

By Zach Veilleux



Andreas Keller, PhD

In an experiment led by Andreas Keller, of Rockefeller's Laboratory of Neurogenetics and Behavior, researchers tested volunteers' ability to distinguish between complex mixtures of scents. Based on the sensitivity of these people's noses and brains, the team calculated the human sense of smell can detect more than 1 trillion odor mixtures, far more discrete stimuli than previous smell studies have estimated.

The nose knows. Dr. Andreas Keller and colleagues had volunteers sniff vials of odors that held different combinations of 128 odor molecules responsible for scents

such as orange, anise and spearmint.

The existing generally accepted number is just 10,000, says Leslie Vosshall, Robin Chemers Neustein Professor and head of the laboratory. "Everyone in the field had the general sense that this number was ludicrously small, but Andreas was the first to put the number to a real scientific test," Vosshall says.

The quality of an odor has multiple dimensions, because the odors we encounter in real life are composed of complex mixes of molecules. For instance, the characteristic scent of rose has 275 components, but only a small percentage of those dominate the perceived smell. That makes odor much more difficult to study than vision and hearing, which require us to detect variations in a single dimension. For comparison, researchers estimate the number of colors we can distinguish at between 2.3 and 7.5 million and audible tones at about 340,000. To overcome this complexity, Keller combined odors and asked volunteers whether they could distinguish between mixtures with some components in common. "Our trick is we use mixtures of odor molecules, and we use the percentage of overlap between two mixtures to measure the sensitivity of a person's sense of smell," Keller says. To

create his mixtures, Keller drew upon 128 odor molecules responsible for scents such as orange, anise and spearmint. He mixed these in combinations of 10, 20 and 30 with different proportions of components in common. The volunteers received three vials, two of which contained identical mixes, and they were asked to pick out the odd one.

This approach was inspired by previous work at the Weizmann Institute in Israel, in which researchers combined odors at similar intensities to create neutral smelling "olfactory white." In that experiment and in Keller's study, the researchers were interested in the perception of odor qualities, such as fishy, floral or musky — not their intensity. But since intensity can interfere with the perceived qualities, both had to be accounted for. The results, published in *Science*, show that while individual volunteers' performance varied greatly, on average they could tell the difference between mixtures containing as much as 51 percent of the same components. Once the mixes shared more than half of their components, fewer volunteers could tell the difference between them. This was true for mixes of 10, 20 and 30 odors.

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New Sackler Center for Biomedicine and Nutrition Research and Rockefeller University Hospital Department of Bionutrition Join to Provide State-of-the-Art Support for Nutrient Control Studies

By Andrea Ronning

The Rockefeller University Sackler Center for Biomedicine and Nutrition Research (SCBN) was recently created to increase nutrition-related investigations by Rockefeller University laboratories. SCBN will support pilot project grants in three areas: laboratory research, patient-based research, and community-based research.

One goal of the SCBN is to encourage more Rockefeller laboratories to extend their usual fields of inquiry by considering the role of nutrition. This could include investigations of various nutrients, the physiology and neurobiology of appetite control, and the effects of over-nutrition and under-nutrition on normal growth and development, as well as the risk of nutrition-related diseases. The scientifically sophisticated Department of Bionutrition, located in The Rockefeller University Hospital,

will be a key participant in research studies supported by the Sackler Center.

The Department of Bionutrition has a long and distinguished history of providing customized research diets to accommodate the diverse needs of Rockefeller University investigators by designing and producing precisely controlled diets that can be manipulated in macro- and micronutrients. The highly experienced bionutritionists are trained to design well-controlled human studies that provide participants with food or formula diets that meet the specifications of the nutrients being studied, as well as enhancing participant compliance. Computer software programs such as ProNutra and Food Processor are used to aid in diet design by integrating information from nutrient databases, including USDA data, manufacturer's

data, and other reference data.

The following is a list of some diets that were designed by bionutritionists at Rockefeller to support different diet studies:

- Insulin resistance study- Timed meals with a specific nutrient composition:
 - Caloric intake designed to achieve weight maintenance: 65% of total from carbohydrates, 20% from fat, and 15% from protein;
 - Carbohydrate composition: 52% monosaccharides, 42% polysaccharides, and remaining from disaccharides.
- Colon Inflammation study - Western-style diet: caloric intake for weight maintenance: 40% from carbohydrates, 40% from fat, 20% from protein; cholesterol – 380 mg; polyunsaturated to saturated fat ratio = 0.33, fiber = 12.5 g.

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Clinical Scholars Program Celebrates New Graduates

By Michelle Romanick

Five graduating Clinical Scholars received Masters' of Clinical and Translational Science degrees at a dinner celebrating them and their mentors on June 10, 2014.

Dr. Ana Emiliano's research is on the central nervous systems mechanisms leading to obesity, including the search for new monogenic causative mutations of human obesity in Dr. Jeffrey Friedman's laboratory. Dr. Emiliano will continue her research in Dr. Friedman's laboratory to investigate how one form of bariatric surgery, sleeve gastrectomy, leads to weight loss and improvement of blood sugar (glycemic) control and to identify neuronal populations controlling glucose regulation and energy balance that are specifically recruited by sleeve gastrectomy.

Dr. Thalia Farazi's research is on RNA molecular biology in breast cancer cell lines in Dr. Thomas Tuschl's laboratory. She analyzed coordinated miRNA/mRNA data from patients to clarify the targets of miRNAs that mediate their critical molecular functions in breast tumorigenesis and thus identify patients who may benefit from therapeutic manipulation of miRNA levels. She delineated miRNA/mRNA prognostic signatures and is testing them in additional patient cohorts. Dr. Farazi will continue her research in Dr. Tuschl's laboratory to elucidate the role of post-transcriptional gene regulation in solid tumors; to learn how RNA binding proteins, miRNAs, and other non-coding RNAs (ncRNAs) exert control over many cancer genes; and to establish new diagnostic methods that could allow for patient stratification based on likely prognosis.

Dr. Daniel Gareau developed optical technologies to diagnose skin cancers, using novel imaging hardware and software algorithms to find the cancers faster, more effectively, and less painfully in Dr. James Krueger's laboratory. Dr. Gareau will continue his research in Dr. Krueger's laboratory, applying new imaging technology and software algorithms to enable rapid, noninvasive, quantitative melanoma screening of pigmented skin lesions.

Dr. Sharon Karmon's research in Dr. Martin Markowitz's laboratory is on the possible correlation between timing of antiretroviral therapy initiation and markers of inflammation in people with HIV who have been successfully treated with antiretroviral therapy, she compared indices of immune activation and aging in those who initiated therapy in early infection versus those who deferred the start of therapy. Dr. Karmon will continue her research in Dr. Markowitz's laboratory using microarray-defined transcriptional profiling to probe for differences in gene expression in immune cells between groups of patients who initiated treatment early and late in the course of the illness.

Dr. Ana Pereira's research focused on sleep-disorder breathing (SDB) as a risk factor that may contribute to pathological brain aging in Dr. Bruce McEwen's laboratory. SDB is commonly used to describe the range of breathing problems during sleep in which not enough air reaches the lungs (hypopnea and apnea). Advancing age is accompanied by physiological changes in respiratory functions during sleep, resulting in a significant increase of SDB. She also investigated the synaptic susceptibilities of the glutamatergic neurocircuits to aging, along with potential interventions with the use of glutamate modulators in animal models of aging. Dr. Pereira will continue her research with Dr. McEwen and is currently conducting a clinical trial with a glutamate modulator in patients with mild Alzheimer's disease in the Heilbrunn Outpatient Research Center of The Rockefeller University Hospital.



Drs. Barry Collier, Delivette Castor, James Krueger, Ana Pereira, Daniel Gareau, Ana Emiliano, Thalia Farazi, Sharon Karmon, and Sarah Schlesinger

Yale/Rockefeller University CTSA Collaborative Research Day

By Michelle Romanick

On June 19, 2014, 21 members of the Yale Center for Clinical Investigation (YCCI) visited the Rockefeller University Center for Clinical and Translational Science (CCTS), continuing the tradition of annual Collaborative Research Day meetings between Yale and Rockefeller that began in 2008. Dr. Carol Merchant, Program Director of the Common Fund Career Development Programs at the National Center for Advancing Translational Sciences (NCATS) and the NIH Program Officer for both the Rockefeller University and Yale University Clinical and Translational (CTSA) programs also attended the event.

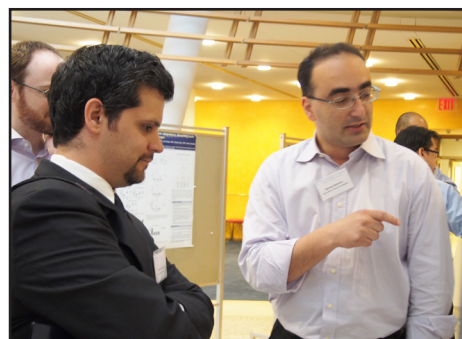
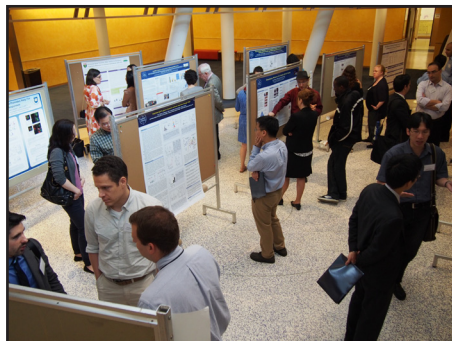
The mission of the day is to create an atmosphere of collegial research interaction for the trainees from both institutions to discuss their current research studies, develop collaborations, and discuss topics of mutual interest. The event was opened this year to the Rockefeller campus community. Dr. Robert Sherwin, Director of YCCI and Dr. Barry Collier, Director of CCTS warmly welcomed the attendees. The first event of the day was a well-attended poster session in which 25 posters were

presented and discussed. This was followed by a lively lunch-time discussion.

The afternoon was dedicated to presentations from Yale and Rockefeller trainees and faculty members. Dr. Jose Aleman, a Rockefeller Clinical Scholar and Instructor in Clinical Investigation in the Laboratory of Biochemical Genetics and Metabolism presented “The Obesity Weight Loss Study.” Dr. Aleman’s research addresses the impact of acute diet-induced weight loss in obese postmenopausal women on adipose tissue-associated inflammation in the form of crown-like structures. Dr. Alan Anticevic, Assistant Professor of Psychiatry and of Psychology at Yale then presented “Refining Neuroimaging Biomarkers for Schizophrenia via Pharmacology and Computation.” Dr. Anticevic’s lab focuses on cognitive neuroscience of psychiatric illness, functional connectivity, as well as functional neuroimaging analysis methodology. Dr. Marina Caskey, Assistant Professor of Clinical Investigation in the Laboratory of Molecular Immunology presented, “Clinical Development of the anti-

HIV Neutralizing mAb, 3BNC117.” Dr. Caskey’s research is focused on the therapeutic and prophylactic potential of broadly neutralizing antibodies to the HIV virus and the development and clinical testing of HIV vaccines and vaccine adjuvants, particularly vaccines that work by directly targeting infectious antigens to dendritic cells. To round out the session, Dr. James Yu, Assistant Professor of Therapeutic Radiology at Yale presented, “Investigating the Comparative Effectiveness of Prostate Cancer Radiotherapies.” Dr. Yu’s research interests are assessing the relative benefits and costs of novel therapies to treat genitourinary cancers and cancers of the central nervous system.

Drs. Collier and Sherwin closed the event by thanking everyone for their participation in creating another successful collaborative event. Yale will host the next Research Collaboration Day in 2015.



Candidate Driving Mutation in Fibrolamellar Hepatocellular Carcinoma

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repository set up at Rockefeller. Together with other patients and their family members she started a website to serve as repository for what little knowledge there was about fibrolamellar cancer. Though they lacked federal funding, the father-daughter team sought and received support in the form of private gifts from the Fibrolamellar Cancer Foundation and several individual donors whose lives have been touched by the disease, in addition to support from the Howard Hughes Medical Institute, the New York Genome Center, The Rockefeller University Center for Clinical and Translational Science and a gift to The Rockefeller University by an anonymous donor.

Elana worked in her father's lab after school and during breaks. In a collaboration involving the Simon Laboratory at The Rockefeller University, the Memorial Sloan Kettering Center surgeon who originally treated her, Dr. Michael P. LaQuaglia, and a team of computational biologists at the New York Genome Center (NYGC), the genetic data from 15 patients' tumors was analyzed and one abnormality was discovered that really stood out. All 15 patients had a DNA translocation that created a new chimeric gene that potentially coded for an abnormal protein. "We discovered chimeric RNAs in the tumor samples — made when DNA deletions create unnatural products that can drive cancer," says Nicolas Robine, co-first author and NYGC Computational Biologist. "This chimera had never been seen before, so we believe it will help drive the work of our Rockefeller colleagues and Elana's future. It is the NYGC's mission to undertake such collaborative genomic studies that will accelerate medical advances."

"If you tell a twelve year old that they have to leave school and their friends to go to the hospital and get most of

their liver removed, their first question is going to be why?" says Elana.

"Being raised by a scientist my first instinct was to try to understand as much of it as my young brain could handle. However, I was disappointed to find that nobody was really able to answer my question. Fibrolamellar was a mystery to me, and, as I soon realized, a mystery to doctors and scientists as well. What was even worse was that nobody seemed to be making progress on it, as the cancer didn't affect enough people for it to get significant attention. Someone had to do something about this disease, and since nobody else was going to, I decided to take it upon myself."

"These results were extremely encouraging," says Sanford Simon, head of the Laboratory of Cellular Biophysics and the study's senior author. "It is uncommon for a genetic screen for a cancer to turn up such a strong candidate mutation, and for the mutation to be present in every single patient tested." The lab is now working on testing the effects of the chimera on human liver cells and in mouse livers, to further elucidate its role in the disease.

"The hope is that we'd be able to screen the blood for the presence of this chimera, and patients wouldn't have to wait until the tumors are present, until it might be too late to do something about it," says Sanford Simon. "Also, often with these types of discoveries, the genetic mutation turns out to be connected to other rare cancers. Many of the molecular changes we are observing are much more reminiscent of specific forms of breast cancer than liver cancer."

"NYGC is thrilled to have this work be our first published example of the explosive power of collaborations between deeply invested biologists like those in the Simon lab including Elana Simon, and

thoughtful bioinformatics scientists like Nicolas Robine and NYGC team, who worked together so effectively with the tools of genomic sequencing and analysis to discover this new chimeric protein and cancer target," says Robert Darnell, head of Rockefeller's Laboratory of Molecular Neuro-Oncology, HHMI Investigator, and President and Scientific Director of NYGC. "The work done serves as an exemplar for how the power of interdisciplinary and inter-institutional genomic science has the potential to save people's lives in New York and beyond."

"I've never understood why I was so lucky in my experience with cancer while so many others have it much worse than I did," says Elana. "But I happened to get diagnosed in a time when these new sequencing technologies were really starting to flourish. I was in the perfect environment, at the right time, with the right motivation to take advantage of these technologies. All of the pieces fit together and it seemed inevitable that this was a field I was going to explore — a mystery I had to solve."

"I want everyone out there with rare diseases to know that it's really up to the patients to motivate progress and now we actually can do so. When I was first diagnosed with fibrolamellar, it seemed like no one cared about the disease," Elana says. "No one knew anything about it or what to do with it. That's what compelled me to take the science into my own hands. There are amazing advances in biomedical science being made every day. Further, new technologies are making it possible for us to share our information to help identify and understand our diseases. Through these, there is hope for cures that previously would have been considered miracles."

Recognition of Faculty and Staff

Dr. Mary Jeanne Kreek, Patrick E. and Beatrice M. Haggerty Professor and head of the Laboratory of the Biology of Addictive Disease, was the inaugural recipient of the Lifetime Service Award from the NIH's National Institute on Drug Abuse, in recognition of outstanding contribution to the field of drug addiction research.

Maija Neville-Williams, Hospital and CCTS Administrator, was selected to serve on the American College of Healthcare Executives Early Careerist Committee. The Early Careerist Committee provides feedback as needed regarding existing ACHE programs, products and services designed for Early Careerists, Evaluates and offers suggestions for enhancing the value of the Early Careerist Network on ache.org, suggests new programs, products or services for Early Careerists, recommends methods for expanding contact with young healthcare executives, recommend ways to enhance ACHE's Early Careerists marketing efforts for recruitment, retention and advancement, and provide an annual report of activities to the Board of Governors.

The Columbia University School of Nursing presented a plaque to the Rockefeller University nurse practitioners in recognition of teaching high quality clinical education to Columbia University nurse practitioner students who rotate at Rockefeller University.

Rockefeller Ranks First in Both Scientific and Medical Science Publications Impact Among Global Institutions continued from Page 1

with a few international institutions — from the United Kingdom, Switzerland and Israel — also achieving top 50 ranks.

The 750 institutions on the full scientific publications list represent 49 countries. The CWTS Leiden Ranking differs from other university rankings in its strict focus on citation impact and its advanced bibliometric methodology: publications that have been withdrawn, for instance because of scientific misconduct, are excluded and differences between scientific fields in citation and collaboration practices are accounted for.

“The Leiden ranking is evidence of something that our friends and colleagues already know — that the research Rockefeller scientists conduct has an impact that echoes internationally,” says Marc Tessier-Lavigne, the university’s president. “Despite our small size, our faculty are global leaders in their fields and their work underlies revolutionary advances in biology and medicine that are being made every day throughout the world.”

Rockefeller University Physician-in-Chief, Dr. Barry Collier noted that,

“It is very gratifying that Rockefeller faculty publications in the medical sciences are recognized by the scientific community for their importance in advancing our knowledge of disease and its prevention and treatment.”

Translational Research Awards made available through the Robertson Therapeutic Development Fund continued from Page 2

supported by conventional funding mechanisms. A second important aspect is the educational component for the applicants. The application process affords the researchers the opportunity to learn the best practices and considerations for drug discovery and development programs. Moreover, the external peer review process provides valuable insights and constructive suggestions relevant to the specific therapeutic area. The Fund

is also an important complement to the Tri-Institutional Therapeutics Discovery Institute (Tri-I TDI), a joint program with Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College designed to advance small molecule drug discovery programs. The Robertson Therapeutic Development Fund supports projects in the early and late stages of the drug development process that are not covered by Tri-I TDI, as well as biological

products and diagnostics that are not part of Tri-I TDI’s current mission. In this way, the Fund helps to develop basic research discoveries into new medical therapies and diagnostics, while ensuring that a range of promising findings made in the University’s labs have the best chance of impacting patients. For more information, please contact Dr. Bruce Conway at 212-327-8376.

Dr. Marina Caskey Conducting First in Human Study of a New Human Monoclonal Antibody to HIV Discovered and Developed at Rockefeller continued from Page 2

subjects. It is a phase 1, open label, dose-escalation study of 3BNC117 mAb alone in 3 target populations: HIV-uninfected subjects, HIV-infected subjects not on antiretroviral therapy (ART), and HIV-infected subjects on ART.

Since 3BNC117 is being developed for potential use in both HIV prevention and HIV therapy, the proposed study aims to evaluate its safety and tolerability in HIV-uninfected and infected individuals. Testing in both groups is important because HIV-uninfected individuals would be the target population for prevention, whereas infected individuals would be the target population for therapy.

To begin to explore the antiretroviral effects of 3BNC117, the proposed clinical study will evaluate its antiretroviral activity in HIV-infected individuals who have reached their viral load set points but have not yet been initiated on ART. 3BNC117 infusion in this group will

enable the evaluation of its potential as a new therapeutic modality or as an adjunct to conventional ART. When 3BNC117 was administered to humanized mice, the emergence of viral escape mutations was observed in residues that map to the antibody target sites, which do not overlap with target sites of currently approved antiretroviral drugs. In non-human primates chronically infected with SHIV (Ad8 and SF162P3), 3BNC117 led to suppression of viremia after a single administration of 3BNC117. Viremia rebound correlated with decreasing antibody levels, but escape mutations were not identified during follow up. In this proposed study subjects will be offered to initiate combination ART six weeks after 3BNC117 infusion, which we anticipate will lead to suppression of viral escape mutants that might arise following 3BNC117 administration.

HIV-infected individuals who are on ART but have detectable HIV-1 RNA

levels will also be studied. Data from this population will allow the evaluation of the antiretroviral activity of 3BNC117 in combination with ART and its potential as an adjunct to conventional HIV therapy. Current antiretroviral regimens are effective in lowering plasma viremia to levels below 20 copies/ml, but in approximately 50% of individuals persistent low-level viremia can be detected despite years of suppressive ART. To date, adding more antiretroviral drugs to conventional ART regimens has been ineffective in further lowering viral RNA levels. In contrast, experiments in humanized mice show that antibodies can be synergistic with conventional ART in lowering plasma viremia. In addition to valuable safety and PK assessments, monitoring the HIV-1 RNA level in this group of individuals will provide important information on whether this antibody can further decrease viremia. This would be an important measure of antibody activity against HIV-1 in vivo.

Sniff Study Suggests Humans Can Distinguish More Than 1 Trillion Scents

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By analyzing the data, the researchers could calculate the total number of distinguishable mixtures. “It turns out that the resolution of the olfactory system is not extraordinary, you need to change a fair fraction of the components before the change can be reliably detected by more than 50 percent of the subjects,” says collaborator Marcelo O. Magnasco, head of the Laboratory of Mathematical Physics at Rockefeller. “However, because the number of combinations is quite literally astronomical, even after accounting for this limitation the total number of

distinguishable odor combinations is quite large.” The 1 trillion estimate is almost certainly too low, the researchers say, because there are many, many more odor molecules in the real world that can be mixed in many more ways.

Keller theorizes that our ancestors had much more use and appreciation for our sense of smell than we do. Humans’ upright posture lifted our noses far from the ground where most smells originate, and more recently, conveniences such as refrigerators and daily showers, have effectively limited odors in the

modern world. “This could explain our attitude that smell is unimportant, compared to hearing and vision,” he says.

Nevertheless, the sense of smell remains closely linked to human behavior, and studying it can tell us a lot about how our brains process complex information. The results of this study are a step toward an elusive quantitative science of odor perception that can help drive further research, Keller says.

New Sackler Center for Biomedicine and Nutrition Research and Rockefeller University Hospital Department of Bionutrition Join to Provide State-of-the-Art Support for Nutrient Control Studies

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- Metabolic Syndrome Diet Study- All participants start on Western-style and then are randomized to three study diets.
 - o Western-style diet: Caloric intake designed for weight maintenance: 48% from carbohydrates, 36% from fat, and 16% from protein; 380 mg cholesterol; 542 mg Ca⁺⁺, 202 mg Mg⁺⁺, 1834 mg K⁺, 3650 mg Na⁺, and 14 g fiber.
 - o The three experimental diets: low-glycemic index diet, Western-style diet, and DASH (Dietary Approach to Stopping Hypertension) diet. Calories in all diets designed to maintain weight.
- Low Ca⁺⁺ and Low Vitamin D diet- 450 mg Ca⁺⁺ and 140 IU Vitamin D.

The diets can be designed so that they are appropriate for an in-patient or out-patient population and can repeat according to a 2 day, 3 day, or even 5 day cycle.

Bionutritionists also can perform anthropometric measurements to ascertain body composition. One method used to measure body composition is the BodPod, a device that uses electrical impedance to determine body composition. Measurements obtained from this device are based on Archimedes’ Principle, the physical law of buoyancy, discovered by the ancient Greek mathematician and inventor who determined that a body

completely or partially submerged in a fluid (gas or liquid) at rest is acted upon by an upward, or buoyant, force of a magnitude equal to the weight of the fluid displaced by the body.

There are many other resources available in the Department of Bionutrition. The Bionutrition staff is eager to assist new investigators in getting started. To arrange for a tour of the facility and/or to discuss a potential protocol with the research staff, please contact Andrea Ronning at aronning@rockefeller.edu.



Hospital Department of Bionutrition

Cancer Genetics: Susceptibility to Both Spontaneous and Induced Tumors Is Inherited

By Elizabeth (Betty Hanson)



Lynch, Clara
Courtesy of the Rockefeller Archive Center

In the early 20th century, scientists were beginning to understand the causes of cancer. They recognized that tumors could be induced in laboratory animals by rubbing coal tar on the skin. And they knew that some strains of mice tended to develop tumors spontaneously in particular organs. In the 1920s Clara J. Lynch (1882-1985) made important contributions to the young field of cancer genetics. Her careful mouse breeding studies proved that susceptibility to lung and mammary tumors, both spontaneous and experimentally induced, can be inherited.

Lynch worked in the laboratory of James B. Murphy (1884-1950) at the

Rockefeller Institute. Her early studies took advantage of the fact that some strains of laboratory mice were known to develop mammary tumors frequently and spontaneously, whereas others did not. Experiments crossing females from strains prone to tumors with males from other strains led her to conclude that the tendency to develop tumors was inherited in a dominant fashion. Her study took issue with the widely known view of another mouse geneticist, Maud Slye at the University of Chicago, that spontaneous tumors were inherited in a strictly recessive Mendelian pattern, and it helped keep open the question of the complexity of cancer genetics.

Lynch also was the first to study the genetics of spontaneous lung tumors in mice, breeding her own strains of animals for her experiments. Later she performed comparative studies of mice with induced tumors.

Lynch's legacy lives on not only in her research, but also in the stocks and strains of mice she introduced to science. Most famously, in 1926 she brought two male and seven female mice from a laboratory in Lausanne to Rockefeller. She called these outbred, albino mice her Swiss mice, and bred them and distributed them to other researchers. Some of the mice went to commercial breeders as well. In Lynch's lifetime Swiss mice were used in large-scale studies of yellow fever. Today many commercially available mouse stocks are derived from the Swiss mice.

Clara J. Lynch received the BA (1902) from Smith College and the PhD (1919) from Columbia University, where

she worked under geneticist Thomas Hunt Morgan. She taught mammalian anatomy and physiology at Smith College from 1913 to 1916. In 1918 Lynch joined the Rockefeller Institute as an assistant, and was promoted to associate in 1926. She remained at Rockefeller until her retirement in 1971.



Murphy, James
Courtesy of the Rockefeller Archive Center