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Digitizing and Preserving Medical History

BY JEFFREY S. REZNICK, NLM

Libraries around the world are digitizing their historical treasures and making them more accessible via the Internet than ever before. Leading the way is the National Library of Medicine (NLM), the world's largest biomedical library, located on the NIH campus in Bethesda, Maryland.

The NLM traces its origins to 1836, when it consisted of a few dozen books in what was then the Library of the Office of the Surgeon General of the United States Army. Since then, its vast collections have been built over multiple generations, literally passed down from one generation to the next, and they contain material from antiquity to the present and nearly every part of the world: from books, journals, photographs, and films and videos to artwork, postcards, pamphlets, and much, much more.

The library opened its doors on the NIH Bethesda campus in 1962, and it has served the world ever since in translating biomedical research into practice, in leading in information innovation, and, every day via the Internet, in serving millions of scientists, health professionals, and members of the public.

The NLM holds one of the world's largest and most treasured collections that includes both historical and contemporary items in a variety of media. One of the oldest items dates from the year 1094. It is an Arabic manuscript entitled *The*

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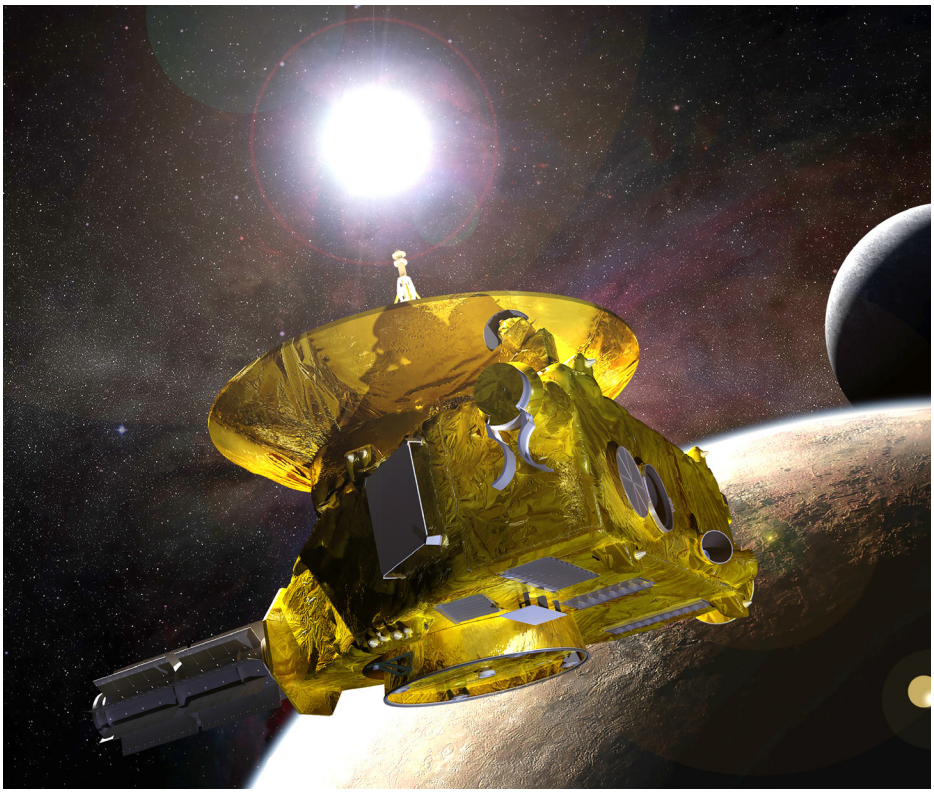
Demysifying Medicine

Bridging the Gap Between Basic Research and Clinical Medicine

BY LAURA STEPHENSON CARTER



JOHNS HOPKINS UNIVERSITY APPLIED PHYSICS LABORATORY/SOUTHWEST RESEARCH INSTITUTE

One of the Demystifying Medicine sessions featured a space scientist who talked about the importance of biomedical research that addresses the medical needs of future space travelers. Shown: Artist's concept of the New Horizons spacecraft encountering Pluto and its largest moon, Charon, in July 2015.

What do you get when you combine a clinician, a Ph.D. scientist, and a patient? A course called "Demystifying Medicine" that bridges the gap between basic research and clinical medicine and covers a range of topics from genetics to infectious disease to the effect of spaceflight on humans. The course is the brainchild of **Irwin "Win" Arias**, who started it at NIH in 2002 after having run a similar

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Making a Great Institution Even Greater

Red Team Report Update

BY MICHAEL GOTTESMAN, DDIR

The NIH Clinical Center is one of the most distinctive and influential research hospitals in the world. Many of its patients have rare and difficult-to-treat conditions, and the Clinical Center—with its numerous first-in-human studies, a dedicated staff of unique talent, and a backbone of hundreds of NIH principal investigators conducting research in surrounding NIH institutes and centers (ICs)—is often the last hope for these patients. Despite often insurmountable odds, this extraordinary staff seeks to cure patients, extend lives, and reduce suffering. Indeed, in 2011, the Clinical Center won the prestigious Lasker-Bloomberg Public Service Award. Bricks and steel and pretty sunlit atriums don't win such awards. People do. And the Lasker-Bloomberg award went to the entire Clinical Center staff.

Making Something Great Even Greater

The challenge before us now is how to make something great even greater. Recently, the "Red Team" (a working group of the Advisory Committee to the Director, ACD) was asked to review multiple aspects of the Clinical Center. The sentinel event that led to the need for this review occurred in May 2015 when the FDA identified significant deficiencies in the Clinical Center pharmacy, leading to the closure of the Pharmaceutical Development Section. An internal review then revealed several other areas of concern in the Clinical Center. The Red Team was established to obtain expert outside advice about possible remedies. In the course of its four-month-long review, the Red Team raised questions about whether the distributed organizational structure of the Clinical Center, and the absence of certain fail-safe systems and appropriate oversight, could lead to risks to patient safety and quality of care.

> The Clinical Center lies at the physical and emotional heart of the NIH Bethesda campus. We intend to keep it there, for no living and dynamic entity can survive without its heart.

New Research Hospital Board

One of the Red Team's major recommendations was to establish a new Clinical Center Research Hospital Board. That group met for the first time on Friday, July 15, 2016, in an open meeting. All NIHers were invited to attend in person or listen in on the presentations and discussions that dealt with how to improve systems that improve patient safety and governance of the Clinical Center (https://videocast.nih.gov/launch.asp?19791).

The board, chaired by Laura Forese, a pediatric orthopedist and chief operating officer of the New York–Presbyterian hospital system, was introduced to the Clinical Center by NIH Director **Francis Collins**, who described the current structure of the Clinical Center and some of its many contributions to modern medicine. Dr. Collins related that the press coverage of the Red Team report had delivered a significant blow to staff morale because it seemed to imply that the quality of patient care is routinely compromised at the Clinical Center, which is simply incorrect. He stated unequivocally that the vast majority of physicians, nurses, and other staff who work at the Clinical Center are highly capable and compassionate health-care providers, deeply dedicated to patient care.

In addition, Dr. Forese indicated that every member of the Red Team made it clear that they would not hesitate to be a patient in the Clinical Center themselves. And in a remarkable series of testimonials, each of the members of the new Hospital Board (including two representatives of the Patient Care Advisory Group) reiterated their confidence in the dedication of the Clinical Center staff.

One of the new board members is Paul O'Neill, former Alcoa CEO and United States Secretary of the Treasury, who has dedicated much of his career to improving employee safety and more recently to patient-safety issues. He was eloquent in his description of the importance of engaging the entire community in efforts to improve safety for both patients and employees, noting that health-care workers have the highest incidence of on-the-job injuries of any U.S. industry. **Laura Lee**, director of Patient Safety in the Clinical

Center, noted that for standard metrics, the Clinical Center has a strong track record of patient safety—but the goal, as articulated by Mr. O'Neill, is "the pursuit of perfect."

Changes

In reaching for this goal, the Red Team identified some aspects of the Clinical Center that needed work. **John Gallin,** director of the NIH Clinical Center, **Avindra Nath**, chair of the Medical Executive Committee, and **Henry Masur**, representing the chairs of the Clinical Center departments, presented constructive ideas for how to make needed improvements. Many of the changes that have to be made will need to originate from the professional and support staff at the Clinical Center, especially those who have direct and intensive patient-care responsibilities.

Steven Holland has already moderated a series of six open meetings with staff at all levels in the Clinical Center, and these meetings have given NIH leadership an opportunity to hear directly about the concerns and ideas of our colleagues. Additional meetings and focus groups are being planned to get into more detail about changes that can be made.

Dr. Collins and NIH Principal Deputy Director **Lawrence Tabak** summarized some of the changes that have already taken place to date including:

• New Office of Research Support and Compliance (ORSC)

Establishment of a new ORSC in the Office of Intramural Research, under the supervision of the Deputy Director for Intramural Research. **Kathryn Zoon**, former scientific director of NIAID, ably served as inaugural acting director of ORSC for the first couple of months but retired on June 23. **Andrew Griffith** has generously agreed to become acting Deputy Director for Intramural Clinical Research and will be the formal leader of ORSC while a national search is underway. To assist Dr. Griffith, **Valerie Bonham**, previously legal counsel with NIH's Office of General Counsel, has stepped in as Deputy Director of ORSC and will provide regulatory knowledge and management skill. Furthermore, **Bruce Burnett**, an experienced manager of Current Good Manufacturing Practice facilities and clinical activities at Duke University School of Medicine (Durham, North Carolina), will be a major contributor to the leadership of this office. (He arrived at NIH on July 18). He will begin by meeting our clinical directors and scientific directors and acquainting himself with current practices while we devise better support mechanisms for clinical research in all of our ICs. If you hear from any of these people, trust that they are here to help our clinical programs function with the highest possible safety and efficiency.

• Search for chief executive officer

A search committee has been established and an advertisement has been placed for a new chief executive officer to manage the operations of the Clinical Center. Discussion of the characteristics of a new Clinical Center CEO emphasized hospital-management skills, because it is expected that there will also be a chief scientific officer responsible for the clinical research conducted by the Clinical Center staff and the principal investigators in the ICs.

• Governance structure

One model for a possible new governance structure for the Clinical Center was proposed by Dr. Tabak. He stressed that this model was only a starting point for discussion, and he hopes and expects there to be modifications with input from all of the stakeholders across and outside NIH. Although the details of this structure are therefore not yet established (many decisions must await the arrival of a new CEO), some features have been endorsed by the IC directors, including the direct reporting of all clinical directors to their IC directors. This reporting relationship will establish that each IC director is providing oversight for quality of patient care and clinical research. The Red Team also strongly advocated for the formation of a Clinical Practice Committee consisting of clinical experts at different levels and in different areas of patient care, to establish the highest possible standards of practice in the Clinical Center. The precise makeup, scope of responsibility, reporting arrangements, and interactions with the Medical Executive Committee will be important areas for future discussions with staff and among leadership.

Helping the Clinical Center address the Red Team's recommendations will be one of the most important tasks of my tenure as Deputy Director for Intramural Research, and we are only beginning this process. The Clinical Center lies at the physical and emotional heart of the NIH Bethesda campus. We intend to keep it there, for no living and dynamic entity can survive without its heart. ●

For further reading (and viewing), see Michael Gottesman's editorial in the May–June 2016 issue of the *NIH Catalyst* (http://irp.nih.gov/catalyst/v24i3/from-the-deputy-director-for-intramural-research) and the presentation that he and Clinical Center Director John Gallin made at the April 22 town hall meeting (NIH only, at http://videocast.nih.gov/launch.asp?19639). The NIH response to the Red Team's report was approved by the ACD on June 9. You can download the response (http://acd.od.nih.gov/Red_Team_final_report_4262016.pdf) and slides from the ACD presentation (http://acd.od.nih.gov/presentations/062016_RedTeam.pdf).

SPECIAL FROM THE NIAID FELLOWS WORKSHOP

Collaborating for Success

BY OMOZUSI ANDREWS, NIAID

"If you want to walk fast, walk alone. If you want to walk far, walk together," observes an old African proverb that symbolizes the value of collaboration, said National Institute of Allergy and Infectious Diseases (NIAID) Training Director **Wendy J. Fibison** at the 10th annual NIAID Fellows Workshop. Postdocs and graduate students, some of whom had come from as far as NIAID's labs in Hamilton, Montana, had gathered on April 11 for a day of activities that promised to help them learn how to begin "navigating collaborative avenues for career success."

To get things started, NIAID Deputy Director **Hugh Auchincloss** presented a review of the institute's research achievements, including studies on antiretroviral therapies for patients with human immunodeficiency virus (HIV); the development of vaccines; and the importance of continuing basic-science research.

Trainees were then provided a variety of career options beyond the bench during the "Career Options" panel discussion. Panel members—whose jobs ranged from senior lead reviewer at the FDA to the China Media Project manager for the American Institute of Physics—advised the trainees to build their communication, teamwork, and networking skills.

Gaia Vasiliver-Shamis (Director of Career Development at Emory University School of Medicine in Atlanta), who said she got her job through networking, urged trainees to "play well with others in the sandbox" and learn how to interact with their managers. She also encouraged trainees to think about the workplace culture when accepting a job. Other panelists spoke about the importance of time management, conducting informational interviews, prioritizing work, and enrolling in networking and other classes for self-improvement.

The panelists also described successful experiences during their job search as well as useful lessons they had learned throughout their careers. In response to the question, "What things would you have done differently as a postdoc?" some shared that they wished they had explored opportunities away from the bench, tried new things so they could break out of their comfort zone, and networked more. It was refreshing to hear the similarities and differences among the panelists' experiences. Given the challenges of the job market, trainees were inspired by the words from FDA's Cynthia Chang, who commented, "Your career and your job do not define you."

> Advice for pursuing career options after postdoctoral training: Be committed to your goals; know the difference between needs and wants; understand the requirements for success; do your best; and never give up.

The trainees enjoyed a networking lunch with invited guests and former NIH postdocs and afterwards attended a "Research Management" panel discussion that also echoed the theme of collaboration. The three panelists—a medical science liaison at AstraZeneca, an assistant professor of medicine at the Indiana University School of Medicine (Indianapolis), and an investigator at the National Cancer Institute (NCI)—shared their strategies for landing bench-specific jobs including formulating e-mails, assessing career websites, maintaining a visible LinkedIn profile, and relying on word of mouth.

NCI investigator **Joe Ziegelbauer** advised trainees to "learn how to quickly immerse" themselves in their new environments. The "Research Management" panelists also encouraged trainees to master and merge more than one field such as bioinformatics with their research, improve their time-management and grant-writing skills, and actively build their own niche.

In his keynote address, Keith Micoli (Director of the Postdoctoral Program at New York School of Medicine in New York) urged trainees to take purposeful steps towards their future goals. He likened the journey after postdoctoral training to a challenging solo 125-mile hike that he completed in roughly 10 days. His hike taught him valuable lessons including the importance of being committed to your goals, knowing the difference between needs and wants, understanding the requirements of success, doing your best, and never giving up. ●

The workshop was sponsored by the NIAID Office of Training and Diversity. The theme, speaker selection, and program were almost entirely executed by the NIAID Fellows Workshop Planning Committee, which was led by NIAID postdoctoral fellow **Caleb McKinney** and NIAID graduate student **Jessica Hostetler**.

Patricia Flatley Brennan

Patricia Flatley Brennan to Lead NLM

Patricia Flatley Brennan has been named the director of the National Library of Medicine (NLM), succeeding **Donald Lindberg**, who retired in 2015. Brennan is expected to begin her new role in August 2016.

Brennan is the Lillian L. Moehlman Bascom Professor at the University of Wisconsin at Madison's School of Nursing and College of Engineering. She also leads the Living Environments Laboratory at the Wisconsin Institutes for Discovery (Madison, Wisconsin), which develops new ways for effective visualization of high-dimensional data.

She has been a pioneer in the development of information systems for patients. She developed ComputerLink, an electronic network designed to reduce isolation and improve self-care among home-care patients. She directed HeartCare, a web-based information and communication service that helps home-dwelling cardiac patients recover faster and with fewer symptoms. She also directed Project HealthDesign, an initiative designed to stimulate the next generation of personal health records. Brennan also conducts external evaluations of health-information technology architectures and works to repurpose engineering methods for health care.

A recipient of many awards, Brennan is a past-president of the American Medical Informatics Association and a member of the National Academy of Medicine (formerly the Institute of Medicine). "[Dr. Brennan is] ideally suited to lead the NLM in the era of precision medicine, as the library becomes the epicenter for biomedical data science, not just at NIH, but across the biomedical research enterprise," said NIH Director **Francis Collins** when announcing Brennan's appointment in May.

Holland Named NIAID Scientific Director

Steven M. Holland has been appointed scientific director of the National Institute of Allergy and Infectious Diseases (NIAID), succeeding **Kathryn Zoon**, who retired recently. NIAID Principal Deputy Director **Hugh Auchincloss** was acting scientific director after Zoon stepped down last year. Holland, who is an NIH Distinguished Investigator, has served as NIAID's chief of the Laboratory of Clinical Infectious Diseases (LCID) since 2004 and as NIH deputy director for intramural clinical research since 2011. His research areas have included Job's syndrome, a rare immunodeficiency disorder, and the genetic conditions predisposing people to mycobacterial infections.

More recently, Holland has been interested in genetic conditions associated with severe coccidioidomycosis—an infection caused by inhaled spores of a soil fungus found in the southwestern United States, parts of Mexico, and Central and South America—and acquired forms of anticytokine autoimmunity that predispose one to opportunistic infections.

Excerpted from the July 1, 2016 edition of the NIH Record (https://nihrecord.nih.gov/newsletters/2016/07_01_2016/milestones.htm).

New Associate Director for AIDS Research

Maureen M. Goodenow was recently appointed as NIH associate director for AIDS research and director of the NIH Office of AIDS Research (OAR). She brings nearly 30 years of experience in AIDS and human immunodeficiency virus (HIV) research and advocacy to the position. She is expected to join NIH in July 2016 to lead OAR's efforts. She will work closely with the NIH institutes and centers to pursue new tools for preventing HIV infection including a vaccine, improved treatments, and ultimately, a cure.

Before coming to NIH, Goodenow was a professor of pathology, immunology, and laboratory medicine and the Stephany W. Holloway University Endowed Chair for AIDS Research at the University of Florida at Gainesville. She was also the director of the Center for Research in Pediatric Immune Deficiency. She led a research program in molecular epidemiology, pathogenesis, and vaccines for HIV-1 and related viruses, including viruses that cause cancer.

Appointment of a New Chief of BTRIS

On July 10, Jose Galvez became the new chief of the Biomedical Translational Research Information System (BTRIS) in the NIH Clinical Center. He was the program director of Clinical and Translational Informatics with the NIH's Center for Biomedical Informatics and Information Technology. NIH-wide resource supporting clinical-research studies across the Intramural Research Program (IRP), and as the interface between the IRP and extramural investigators. ●

Read longer versions online at http://irp.nih.gov/catalyst/v24i4/news-briefs.

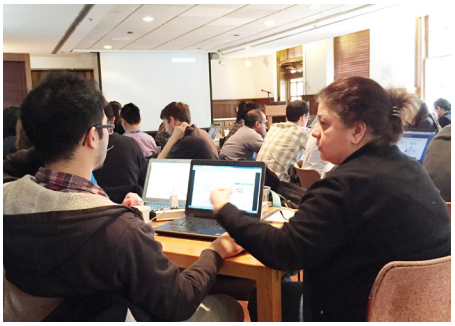
Crowdsourcing for Data Analysis

Web Platform Makes Public Gene-Expression Data More Accessible

BY HILLARY HOFFMAN, NIAID

The 29 immunologists who gathered in the Rathskeller Room, nestled in the basement of NIH's Cloisters (Building 60), were brandishing only laptops—not beer steins—as they took part in the Omics Compendia Commons (OMiCC) Jamboree in April. They were eager to gain hands-on experience exploring publicly available gene-expression data sets and delving into the crowdsourcing web platform that was developed by scientists at the National Institute of Allergy and Infectious Diseases (NIAID).

John Tsang, chief of the Systems Genomics and Bioinformatics Unit in NIAID's Laboratory of Systems Biology, began developing OMiCC three years ago after he noticed one of his postdoctoral fellows struggling with her project because she didn't have the computational expertise to make good use of public data. Data retrieval, processing, and analysis typically require computer programming skills that many experimental biologists lack, Tsang noted. As a result, the wealth of public data remains largely untapped, accessible only to researchers who have the appropriate computational skills and experience. The OMiCC web interface, however, enables biologists without that experience to explore data and perform simple analyses and "helps to democratize the mining of public data sets," said Tsang.



NIAID

Jamboree participants were eager to gain hands-on experience exploring publicly available gene-expression data sets and delving into the capabilities of OMiCC, a crowdsourcing web platform developed by NIAID.

Tsang and his team designed OMiCC as a community-based platform to capitalize on the biological expertise of its users. Public database entries typically contain raw study data that need to be structured for analysis. In OMiCC, researchers can create groups of data, use a standardized vocabulary to annotate them, and assign parameters such as sample-type and disease. OMiCC saves these user-created groups and associated metadata, making them available to other users for reuse.

"It's kind of like Wikipedia, but instead of user-generated articles, you end up with annotations and groups of data that can be reused to conduct new analyses, generate new hypotheses, and address novel scientific questions," said Tsang. "We hope to kick off a positive feedback loop: As more people group and annotate data, the OMiCC platform will become even more useful, and more people will join the OMiCC community."

To introduce OMiCC to the NIH community and help test its capabilities, Tsang and his team, including NIAID clinical fellow **Rachel Sparks**, organized the OMiCC Jamboree, the first such event they've led. Their goal was for the jamboree participants—25 from NIH, two from FDA, and two from nearby universities—to meta-analyze and compare autoimmune diseases in humans and mouse models.

At the beginning of the day, Tsang's team divided the participants into groups of three based on their individual expertise and assigned each a particular area to explore such as mouse studies of multiple sclerosis or human studies of lupus. The participants had to identify relevant data and form comparison-group pairs (CGPs). Each CGP comprises two collections of gene-expression profiles from a single study. For example, researchers could create a CGP to compare blood samples from people with lupus with those from healthy control subjects. Throughout the day, members of Tsang's team circulated through the room to answer questions and offer advice.

Within OMiCC, users can perform statistical analyses on CGPs from different studies to search for biological relationships. Taking such a meta-analysis approach to pool information from multiple studies has the potential for uncovering more robust biological signals, Tsang explained. OMiCC users also can generate basic visualizations and export the underlying data for further analysis with other programs. Currently, Tsang and his team are compiling preliminary results stemming from the work done during the April jamboree.

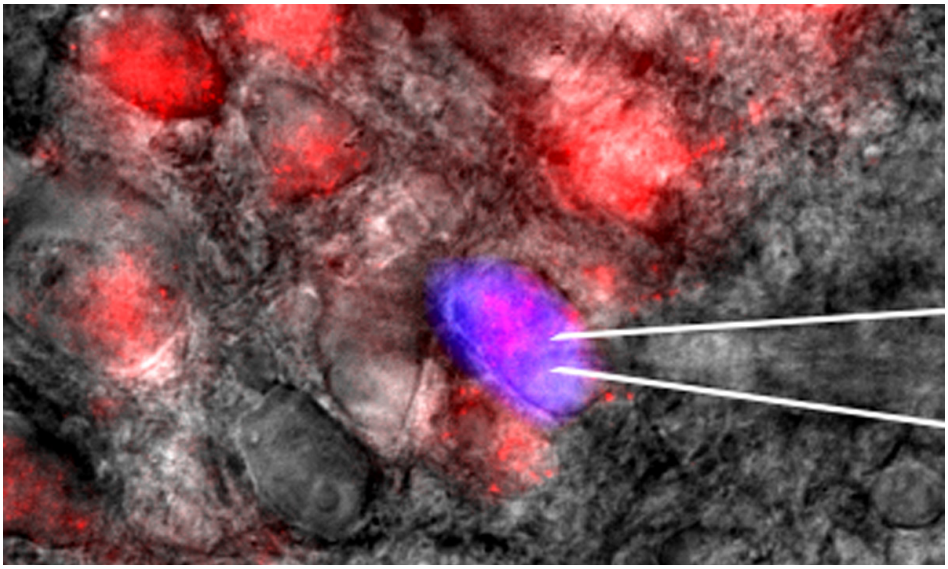
Tsang hopes that using OMiCC to analyze data from multiple studies will help biologists obtain fresh insights and inform the design of new experiments. But, he cautioned, OMiCC is not intended to replace collaborations with statistical and bioinformatics experts to perform advanced data analysis. His team hopes to host more jamborees in the future to further assess whether convening teams of volunteers to use public datasets is an effective way to generate and test research ideas. ●

The OMiCC platform (and perhaps future jamborees) is applicable to other biomedical researchers, too. Researchers can access OMiCC at http://omicc.niaid.nih.gov. The website also provides videos and a step-by-step tutorial to help users navigate the platform.

New Tool Enables Studies of Brain Structure and Function

NIEHS Researchers Developed Genetically Modified Mouse Lines to Help Identify Brain-Cell Types

BY ROBIN ARNETTE, NIEHS



PATRICIA JENSEN, NIEHS

Tool identifies individual brain cells. This micrograph displays brain cells, from one of Patricia Jensen's new mouse lines, that express hM3Dq when activated by the agent clozapine N-oxide. In the color version of this image, the cells appear red as a result of the fluorescent protein mCherry, which is co-expressed with hM3Dq. Electrodes (white lines) are used to measure the cellular activity of a cell expressing hM3Dq-mCherry (blue dye indicates the cell being measured).

Researchers at the National Institute of Environmental Health Sciences (NIEHS) recently designed genetically modified mice that will help neurobiologists address one of the most fundamental questions in brain research: What are the different cell types in the brain, and what are their functions?

The new mouse lines will let scientists identify specific populations of brain cells and determine how they control behavior. The findings will advance our understanding of neurological disorders such as Alzheimer disease, drug addiction, and depression.

It took about six years to develop and characterize the seven mouse lines, said NIEHS scientist **Patricia Jensen**, who is the corresponding author of the article that appeared recently in the journal *Cell Reports* (*Cell Rep* **15:**2563–2573, 2016) and of a companion paper published in 2015 in the journal *Development* (*Development* **142:**4385–4393, 2015).

Identifying distinct cell populations

The mouse lines allow researchers to identify distinct populations of brain cells defined by the expression of different genes during development, determine where these populations are located, and investigate their function.

The 2015 paper described mouse lines in which fluorescent proteins were used to label and visualize cells. The mouse lines described in the 2016 article allow researchers to noninvasively increase the activity of cells and observe the behavioral and physiological effects in freely moving animals. This control of cell activity is achieved by the expression of a laboratory-created mutated cell-surface receptor hM3Dq.

Developed by Bryan Roth at the University of North Carolina at Chapel Hill, hM3Dq is most often introduced into brain cells by injection with engineered viruses. But the viral-injection procedure has drawbacks, said NIEHS staff scientist **Nicholas Plummer**, who shared first authorship on the *Cell Reports* paper with postdoctoral fellow **Natale Sciolino.**

"Using viruses limits you to examining fairly compact populations of cells," Plummer said. "With our mouse lines, we can label and control the activity of widely dispersed cells, and we can activate them any time during development."

Current research

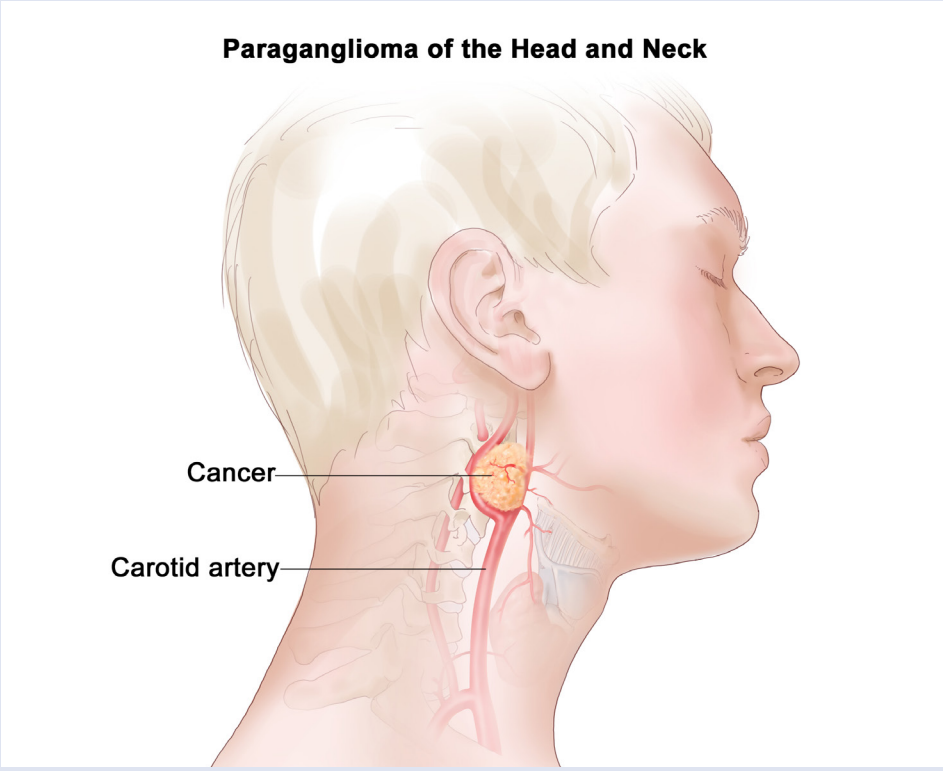
The mouse lines will help researchers answer key questions about developmental and functional diversity within the noradrenergic system—the neurons that use the neurotransmitter norepinephrine, also called noradrenaline. The noradrenergic system is disrupted in several conditions such as anxiety disorders, depression, Alzheimer disease, Parkinson disease, and drug addiction.

"For the first time, we'll be able to manipulate small subsets of these neurons and ask which ones are important for anxiety-type or impulsive behaviors," Sciolino explained.

Although Jensen's group is studying the nervous system, the mouse lines may also be used to investigate almost any type of cell, including pancreatic beta cells and hepatocytes.

"The system can be used in virtually any cell that has the Gq-coupled signaling pathway," Jensen said. ●

For more NIEHS research news, check out the online NIEHS *Environmental Factor* newsletter at http://www.niehs.nih.gov/news/newsletter/2016/7/.



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Paraganglioma, a rare tumor that often forms near the carotid artery, is one of two types of tumors that may cause the same symptoms as attention-deficit hyperactivity disorder (ADHD) in children. It may also form along nerve pathways in the head and neck and in other parts of the body.

NICHD, CC: RARE CANCERS MAY MASQUERADE AS ADHD IN CHILDREN

Rare tumors called pheochromocytomas and paragangliomas may cause the same symptoms as attention-deficit hyperactivity disorder (ADHD) in children, leading to inappropriate treatment that could worsen their symptoms and potentially endanger their health. The tumors secrete catecholamines—substances that stimulate the central nervous system. NICHD and CC researchers evaluated 43 children with these tumors from January 2006 to May 2014. Nine of the children (21 percent) had been diagnosed with ADHD before their tumors were discovered. Four of the nine had been treated with stimulant drugs typically prescribed for ADHD (amphetamine, dextroamphetamine, or methylphenidate), which caused some to develop headaches, excessive sweating, and hypertension. After their tumors were removed, three of the nine children no longer experienced ADHD symptoms. The study authors suggest that high blood pressure accompanying a diagnosis of ADHD could be a warning sign that the child may have something more than a hyperactivity disorder and that pheochromocytomas and paragangliomas should be on the list of potential causes. (NIH authors: M. Batsis, A. Stratakis, T. Prodanov, G.Z. Papadakis, K. Adams, M. Lodish, and K. Pacak, *Horm Metab Res* DOI:10.1055/s-0042-106725, http://dx.doi.org/10.1055/s-0042-106725).

NCI: INCREASED PHYSICAL ACTIVITY ASSOCIATED WITH LOWER RISK OF 13 TYPES OF CANCER

A new study by NCI researchers reports that more leisure-time physical activity (such as walking, running, swimming, and other moderate-intensity to vigorous activities) is associated with a lower incidence of 13 different types of cancer. Past research showed that physical activity reduces the risk of heart disease and death from any cause in addition to lowering the odds of developing colon, breast, and endometrial cancers. However, much less is known about its influence on other cancers.

To examine this issue, the investigators evaluated data on self-reported physical activity levels and the prevalence of 26 different types of cancer from 12 datasets that were part of the Physical Activity Collaboration of NCI's Cohort Consortium. Altogether, the data included information on 1.44 million American and European adults, ages 19 to 98. The analysis confirmed that leisure-time physical activity is associated with a lower risk of colon, breast, and endometrial cancers. It also determined that leisure-time physical activity was associated with a lower risk of 10 additional cancers, with the greatest risk reductions for esophageal adenocarcinoma, liver cancer, cancer of the gastric cardia, kidney cancer, and myeloid leukemia. Myeloma and cancers of the head and neck, rectum, and bladder also showed risk reductions that were significant, but not as strong. Risk was reduced for lung cancer, but only for current and former smokers; the reasons for this are still being studied.

The authors propose that physical activity may reduce cancer risk by altering concentrations of certain hormones such as estrogen and insulin; by reducing inflammation and oxidative stress; and by boosting immune function. Future studies by the group will examine how specific types and amounts of physical activity affect cancer risk. (NIH authors: S.C. Moore, J.N. Sampson, C.M. Kitahara, S.K. Keadle, H. Arem, A. Berrington de Gonzalez, P. Hartge, D.P. Check, N.D. Freedman, M.S. Linet, C. Schairer, and C.E. Matthews, *JAMA Intern Med* **176**:816–825, 2016, http://archinte.jamanetwork.com/article.aspx?articleid=2521826)

NCI BRIEF PREPARED BY BRANDON LEVY (NINDS)

NIAID, CC: INVESTIGATIONAL MALARIA VACCINE PROTECTS HEALTHY ADULTS

An experimental malaria vaccine protected a small number of healthy, malaria-naïve adults in the United States from infection for more than one year after immunization, according to results from a phase 1 trial. The vaccine, known as the PfSPZ vaccine, was developed and produced by Sanaria Inc. of Rockville, Maryland, with support from several Small Business Innovation Research (SBIR) awards from NIAID. NIAID researchers and collaborators at the University of Maryland School of Medicine in Baltimore conducted the clinical evaluation of the vaccine, which involved immunizing and exposing willing, healthy adults to the malaria-causing parasite *Plasmodium falciparum* in a controlled setting.

The phase 1 trial took place at the NIH Clinical Center and at the University of Maryland Medical Center (Baltimore) and enrolled 101 healthy adults aged 18 to 45 years who had never had malaria. Of these volunteers, 59 received the PfSPZ vaccine; 32 participants served as control subjects and were not vaccinated. Vaccine recipients were divided into several groups to assess the roles of the route of administration, dose, and number of immunizations in conferring short- and long-term protection against malaria.

Collectively, the data showed that the PfSPZ vaccine provided malaria protection for more than one year in 55 percent of people without prior malaria infection. In those individuals, the vaccine appeared to confer sterile protection, meaning the individuals would be protected against disease and could not transmit malaria to others. The vaccinations were also well-tolerated by participants, and there were no serious adverse events attributed to vaccination.

Additional results showed that antibodies may play a role in malaria protection early after the final immunization, but inducing T cells in the liver is likely necessary for durable protection. Long-term, reliable protection is important for people who are vaccinated but not exposed to malaria for months, such as travelers and military personnel. Durable protection is also important for mass vaccination campaigns aimed at interrupting transmission in malaria-endemic regions, according to the authors. (NIAID authors: A.S. Ishizuka, A. DeZure, F.H. Mendoza, M.E. Enama, I.J. Gordon, L.-J. Chang, U.N. Sarwar, K.L. Zephir, L.A. Holman, S.H. Plummer, C.S. Hendel, M.C. Nason, L. Novik, P.J.M. Costner, J.G. Saunders, B. Flynn, W.R. Whalen, J.P. Todd, J. Noor, S. Rao, K. Sierra-Davidson, G.M. Lynn, B.S. Graham, M. Roederer, J.E. Ledgerwood, R.A. Seder; CC authors: H. DeCederfelt, M.A. Kemp, and G.A. Fahle, *Nature Med* **22**:614–623, 2016, http://www.nature.com/nm/journal/vaop/ncurrent/full/nm.4110.html).

FOGARTY: ANALYSIS OF 1976 EBOLA OUTBREAK HOLDS LESSONS RELEVANT TODAY

With the recent Ebola epidemic in West Africa reviving interest in the first outbreak of the deadly hemorrhagic fever 40 years ago, scientists led by **Joel Breman** of NIH's Fogarty International Center have released a report highlighting lessons learned from the smaller, more quickly contained 1976 outbreak. (NIH author: J.G. Breman, J Infect Dis DOI:10.1093/infdis/jiw207, http://jid.oxfordjournals.org/content/early/2016/06/28/infdis.jiw207.abstract)

NIDDK: SOME "BIGGEST LOSERS" GAIN BACK THE WEIGHT

It's hard enough to lose weight, but when the body counters your efforts by slowing your resting metabolic rate (RMR) and burning fewer calories, it's hard to keep the weight off. An NIH follow-up study of 14 contestants in the TV show *The Biggest Loser* found that six years later they'd regained an average of 90 pounds after having lost an average of 130 pounds. In addition, their RMR was, on average, as low as it had been at the end of the competition. Despite the weight regain, the show's participants "overall were quite successful at long-term weight loss compared with other lifestyle interventions," the researchers reported. "Therefore, long-term weight loss requires vigilant combat against persistent metabolic adaptation that acts to proportionally counter ongoing efforts to reduce body weight." (NIH authors: E. Fothergill, J. Guo, L. Howard, R. Brychta1, K.Y. Chen, M.C. Skarulis, M. Walter, P.J. Walter, and K.D. Hall, *Obesity* DOI:10.1002/oby.21538, http://onlinelibrary.wiley.com/doi/10.1002/oby.21538/abstract)

Read more briefs online at http://irp.nih.gov/catalyst/v24i4/research-briefs.

NIAMS, NIAID: RAPID-RESPONSE IMMUNE CELLS ARE FULLY PREPARED BEFORE INVASION STRIKES

Through the use of powerful genomic techniques, NIAMS and NIAID researchers have found that during the development of immune cells called innate lymphoid cells (ILCs), these cells gradually become better prepared for rapid response to infection. ILCs appear to play a critical role in defending the body's barrier regions, such as the skin, lungs, and gut, through which microbes must pass to make their way into the body. Working in mice, the researchers analyzed regions of the genome that control the cytokine genes produced by both ILCs and T cells. The study reflected earlier findings that ILC and T-cell subclasses produce similar sets of cytokines, but those earlier studies also revealed differences in how the two cell types control the activities of these key immune response genes. While the regulatory landscapes of ILCs are primed for a quick defense upon infection, those of T cells are minimally prepared when the pathogen invades. Only after infection are modifications in the landscape made that enable T cells to launch their attack. (NIH authors: H.-Y. Shih, G. Sciumè, Y. Mikami, L. Guo, H.-W. Sun, S.R. Brooks, J.F. Urban Jr., F.P. Davis, Y. Kanno, and J.J. O'Shea, *Cell* **165**:1120–1133, 2016, http://dx.doi.org/10.1016/j.cell.2016.04.029) ●

Demystifying Medicine

CONTINUED FROM PAGE 1

Win Arias

course at Tufts University School of Medicine (Boston) for eight years. Arias was a professor and chair of cellular and molecular physiology at Tufts before coming to NIH in 2001 for what was to have been a nine-month position as a Fogarty Scholar. He has been at NIH ever since and is now a senior scientist emeritus in the National Institute of Child Health and Human Development, an assistant to the Deputy Director for Intramural Research, and director of the NIH's "Demystifying Medicine" course.

Arias, who has an M.D. degree and considers himself a physician-scientist, has done pioneering research in the pathobiology of acquired and inherited liver disease that has led to a better understanding of how the liver functions. He discovered the mechanisms of inheritable jaundice; that ATP-binding cassette transporters (ABC transporters) mediate bile transport; and that AMP kinase and liver kinase-B1 regulate hepatocyte polarization, mitochondrial fusion, ATP production, and bile transporters.

Physician-scientists combine investigator, clinician, and teacher skills and were a flourishing breed from World War II through the 1970s. But as basic-science research became more complex and research and training budgets began shrinking, medical schools could no longer incorporate basic-science training into the curriculum, and consequently M.D. students had little exposure to research. To make matters worse, Ph.D. programs in the biomedical sciences did not provide training in pathobiology, so graduates of those programs had little understanding of clinical disease, advances in diagnosis and therapy, and the major unsolved clinical problems that challenge basic research.

Arias created the course as one way to bridge the ever-increasing gap between advances in basic biology and their application to human disease.

"The whole idea of training Ph.D.'s about disease is so they can communicate with clinicians," said Arias. It's about "building bridges" between the basic scientists and the clinicians. And bringing in patients "puts a human face on the disease."

The 20-week course, made up of weekly two-hour classes and held from January through May each year, reaches national and international audiences. About 900 Ph.D. and M.D. students, fellows, and staff register annually; each week, an average of 85 people attend classes in person and about 250 attend via live videocast; and thousands more in the United States and around the world view the archived videocasts later either through the NIH videocast archive or on YouTube. The course has also been replicated at 21 institutions in North America and in 18 foreign countries.

The topics are wide ranging and have included sessions on all types of cancer; emerging and re-emerging infectious diseases; AIDS and human immunodeficiency virus; heart disease; diabetes; obesity; sleep; prions; autoimmune diseases; stem cells; transplantation; all types of dementia and other neurological disorders; aging; hearing loss; agents of potential bioterrorism including smallpox and anthrax; three-dimensional (3-D) and 4-D imaging to study organs and cells; genetic screening; inflammatory diseases; addiction; undiagnosed diseases; precision medicine; the microbiome, and much, much more.

Most of the presenters are NIHers—some are even institute directors such as **Anthony Fauci** (National Institute of Allergy and Infectious Diseases), who has given talks on Ebola, the Zika virus, and other infectious diseases.

The 2016 session was kicked off by Nobel laureate **Eric Kandel** (Columbia University, New York) who spoke about "The Age of Insight: The Quest to Understand the Unconscious in Art, Mind, and Brain from Vienna 1900 to the Present." Kandel, who trained in neurobiology at NIH in the 1950s and in psychiatry at Harvard Medical School (Boston), shared the 2000 Nobel Prize in Physiology or Medicine with Arvid Carlsson and Paul Greengard for discoveries about signal transduction in the nervous system.

Fauci talked about "Ebola, MERS and Likelihood of More Epidemics"; and **Eric Green**, the director of the National Human Genome Research Institute, talked about "The Future of Medicine: Personalized, Precision, and Other." The rest of the 2016 season was equally exciting with such topics as the microbiome, aging, trauma, cancer, and the effect of space flight on humans.

You can read this month in the *NIH Catalyst* about two of the sessions: "Global Warming: Effect on Vector Distribution, Disease, and Natural Product Research" and "Robotic Planetary Exploration and Thoughts about Human Spaceflight." ●

For more about the course—which is administered by the NIH Clinical Center—including speakers' CVs, selected references, and PowerPoint presentations, go to https://demystifyingmedicine.od.nih.gov. You can view past videocasts at https://videocast.nih.gov/PastEvents.asp?c=45.

Demystifying the Health Effects of Global Warming

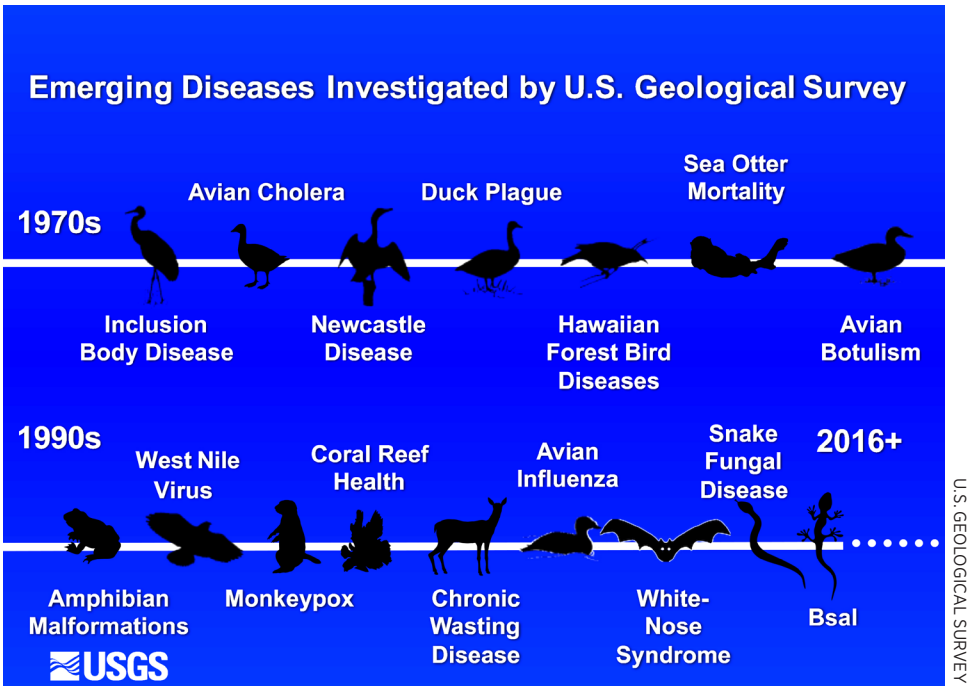
Nature's Bounty at Risk!

BY MANJU BHASKAR, NINDS

Scientists are shedding light on how global warming may be adversely affecting biodiversity, triggering the spread of diseases, and threatening the supply of medically useful natural products. Jonathan Sleeman, director of the National Wildlife Health Center at the United States Geological Survey (USGS), and **David Newman**, former chief of the National Cancer Institute's Natural Products Branch, talked about the threats at the April 12, 2016, "Demystifying Medicine" lecture.

Sleeman explained that climate change—with rising global temperatures, rising sea levels, and changes in precipitation patterns—is already having significant impacts on animal and human diseases and on the incidence and geographic distribution of pathogens. For example, the bluetongue virus—an insect-borne viral disease of cattle, sheep, goats, and yaks as well as of wild deer, elk, and other ruminants—is spreading northward in Europe and the United States. Warmer temperatures allow the insect—a midge—to survive at higher latitudes and altitudes and increase its ability to carry and transmit the virus. The economic costs of such a hard-to-treat disease include reproductive losses, damaged wool, and decreased milk production.

Sleeman also talked about efforts to understand how avian influenza virus strains evolve and how scientists are trying to develop methods to prevent outbreaks. Wild waterfowl serve as natural reservoirs for the low-pathogenic flu virus, which can jump to domestic poultry and then to people. In addition, he discussed the human-health and agricultural implications of white-nose syndrome, which has killed millions of insect-eating bats in North America since the winter of 2007–2008.



U.S. GEOLOGICAL SURVEY

To monitor and control public-health threats, Sleeman explained, a "One Health" approach is being promoted. The concept is ancient, but the name is recent. One Health recognizes how the health of humans is connected to the health of animals and the environment.

David Newman, an international expert in the development of therapeutics based on natural products, discussed how changes in the environment worldwide are affecting plants and other sources of medically useful natural products, the increasingly devastating effects and challenges for saving, creating repositories, and detecting unexpected mutations affecting natural product synthesis in biologic specimens.

He described how human activities and global environmental change have affected the rich biodiversity of the Antarctic and southern oceans. Coral bleaching, for example, was triggered by a temperature spike due to the El Niño weather pattern, which added to the already warmer waters caused by climate change. Warmer temperatures can kill the tiny marine algae required to maintain the health of coral and give it color.

Newman also talked about how genome mining—targeted discovery of new natural products from microbes obtained from extreme environments—has led to the identification of a gene cluster directing the biosynthesis of a lasso peptide that could be used as a therapeutic. ●

To view the videocast of the April 12 Demystifying Medicine lecture "Global Warming: Effect on Vector Distribution, Disease, and Natural Product Research" by Jonathan Sleeman (U.S. Geological Survey) and David Newman (NCI), go to http://videocast.nih.gov/launch.asp?19618.

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Demystifying Medicine
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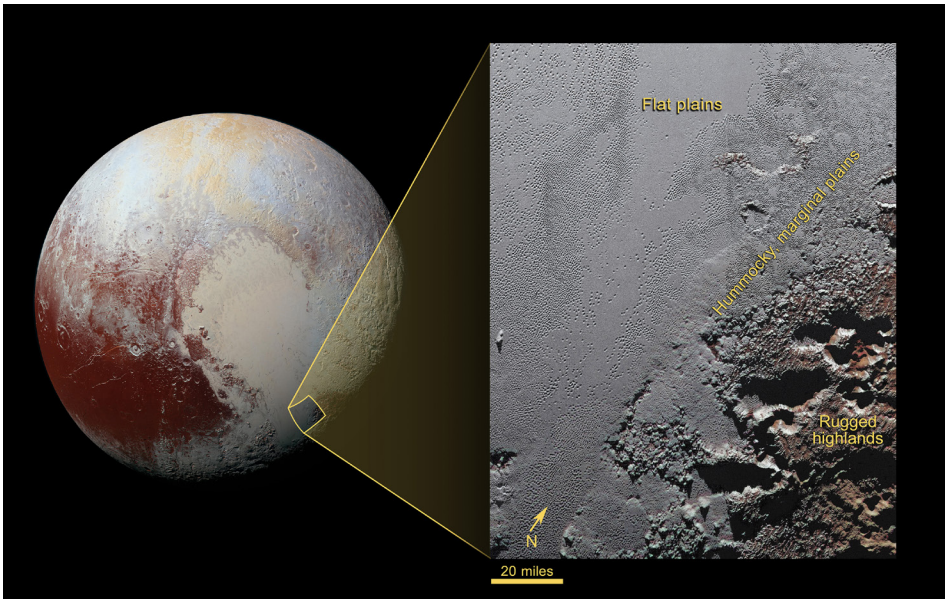
Demystifying Space Medicine

The Health Risks of Spending Time in Outer Space

BY EMILY MULLIN, NIAID



NASA/JOHNS HOPKINS UNIVERSITY APPLIED PHYSICS LABORATORY

The "Demystifying Medicine" class that focused on the effects of spaceflight on health, featured space scientist Stamatios "Tom" Krimigis, who helped design NASA's New Horizons spacecraft that orbited Pluto. This enhanced view from New Horizons zooms in on the southeastern portion of Pluto's great ice plains, where at lower right the plains border rugged, dark highlands informally named Krun Macula.

As NASA and private companies such as SpaceX and Blue Origin plot manned missions to Mars, human space flight beyond the moon may be inevitable in the next few decades. But space scientist and physicist Stamatios "Tom" Krimigis, a longtime champion of robotic technology to explore space, doesn't think humans are ready to go to Mars—yet.

One of the major hurdles of long-term manned space flights is that scientists don't yet know enough about how extended time in space affects the human body, Krimigis recently told an NIH audience at a "Demystifying Medicine" lecture on May 10.

Krimigis is the only scientist in the world to have built instruments that have flown to every planet in the solar system. He has pioneered the exploration of our solar system and beyond for more than 45 years while serving in various positions at the Johns Hopkins University Applied Physics Laboratory in Laurel, Maryland, where he is the emeritus head of the Space Department. The Space Department has designed, built, and operated more than 64 spacecraft and 200 instruments, and it conducts space science and engineering research for both civilian and national security applications. Krimigis was the principal investigator on several NASA spacecraft, including Voyagers 1 and 2, and a co-investigator on many others. He is still active on missions to Mercury, Saturn, Pluto, and the heliosphere.

He is widely credited with resurrecting the idea of a space-probe exploration to Pluto. NASA had planned but then canceled a mission to the dwarf planet in 2000. Krimigis formed the New Horizons team, which engineered the interplanetary space probe. The New Horizons probe was launched in 2006, and in July 2015, it made headlines around the world when it completed the first flyby of Pluto.

NASA has also been developing the capabilities needed to send humans to Mars by the 2030s. To do so, researchers will need to learn more about human physiology in space and the necessary adaptation for long-term manned spaceflights.

During his talk at NIH, Krimigis said astronauts traveling in space for long periods of time likely have a higher risk for a wide range of medical problems, including balance disorders, visual alterations, cardiovascular deconditioning, bone loss, and cancer. Isolation and confinement in space may also lead to behavioral issues and sleep disorders. The distance from Earth also means astronauts can't come home for medical treatments, driving the need for autonomous medical care.

Krimigis cited NASA data showing that, during space travel, astronauts' percentage of muscle decreased during 161-day and 194-day missions on the International Space Station (ISS). "Some of the astronauts have a hard time walking when they get back," he said.

Studies have also shown that bone-mineral density, a measurement of how much calcium and other types of minerals are in bone, dropped for astronauts who spent time in space. The most troubling aspect of long missions that last more than 90 days is the potential for radiation exposure, which may increase the risk for cancer, Krimigis said. He explained that astronauts aboard the Russian Space Station Mir, which operated from 1986 to 2001, were exposed to about 70 millisieverts (mSv) of radiation over 90 days while in orbit. The

average person living in the United States is exposed to 3.1 mSv per year, according to the United States Nuclear Regulatory Commission. A 100-day mission to Mars could expose humans to 1,000 mSv of radiation, dramatically increasing cancer risk, Krimigis said.

NASA scientists are working on mathematical models to gauge radiation and other risks, but Krimigis said there is a huge need for more research.

"Animal models will be needed to assess clinical significance," he said. That represents an area that NIH scientists could investigate.

Krimigis also said that biomarkers will be needed to assess individuals' sensitivity and risk to radiation before astronauts are selected for manned missions. During these missions, pharmaceutical and nutritional countermeasures against radiation could be used to mitigate risk to radiation exposure. After returning to Earth, astronauts may need special occupational health care, personalized cancer screening, and even individualized cancer treatment.

Although a manned mission to Mars—or to any planet for that matter—is likely still many years away, Krimigis said it will be important for biomedical scientists to determine the effects that space travel will have on humans, address the medical concerns, and ensure the health and safety of astronauts and others who may venture into outer space. ●

To see a videocast of the May 10, 2016, Demystifying Medicine lecture "Robotic Planetary Exploration and Thoughts about Human Spaceflight" by Stamatios Krimigis, go to http://videocast.nih.gov/launch.asp?19675.

THE SIG BEAT

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

NEW: FIBROSIS

The Fibrosis SIG provides a forum for individuals from NIH and the extramural community to discuss basic, translational, and clinical research related to fibrosis. The SIG will meet monthly to organize seminars and engage in interactive discussions. The inaugural meeting will be held on Wednesday, September 7, 4:00–5:00 p.m., in CRC conference room 5-2550, Building 10. For more information and/or to join the SIG's LISTSERV, contact **Resat Cinar** (NIAAA; resat.cinar@nih.gov) or **Bernadette Gochuico** (NHGRI; gochuicb@mail.nih.gov).

NEW: MYALGIC ENCEPHALOMYELITIS/ CHRONIC FATIGUE SYNDROME

The SIG is open to all interested intramural and extramural investigators and hopes to foster new research collaborations across the NIH campus. It is led by NINDS Clinical Director **Avi Nath**, who is the primary investigator of the Intramural ME/CFS initiative, and moderated by lead associate investigator **Brian Walitt** (NINR). The ME/CFS SIG will present a bimonthly seminar series and more. For information and notices of meetings and events, join the LISTSERV (https://list.nih.gov/cgi-bin/wa.exe?SUBED1=ME-CFS&A=1) or contact Brian Walitt at brian.walitt@nih.gov.

NEW: DATA SCIENCE IN BIOMEDICINE

The goal of the Data Science in Biomedicine SIG is to foster the growing community of biomedical data scientists at NIH through improving communications, providing a forum for scientific discussions, and catalyzing collaborations. The SIG will work with established SIGs and community groups that focus on components of data science to coordinate activities and increase awareness of opportunities in data science. This SIG will meet quarterly on campus, sometimes with other SIGs, and host a seminar series featuring NIH and outside speakers, organize an annual poster session, and collect user input on workshops and courses needed at NIH. To join, add your name to the NIH-DATASCIENCE-L LISTSERV at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=nih-datascience-l&A=1. Announcements will be posted at http://datascience.nih.gov/community/datascience-at-nih/sigs. For questions, contact **Ben Busby** at busbybr@ncbi.nlm.nih.gov.

NOTE: The recently established **Research Repositories and Patient Registries SIG** will be incorporated under the Data Science in Biomedicine SIG. Please register for the NIH-DATASCIENCE-L LISTSERV described above.

NEW: STATISTICS

This SIG, which will meet quarterly, will support the growing community of statisticians at NIH. The focus is on statistical methods used in the design and analysis of clinical trials and in explorations in epidemiology and population science, as well as on biomedical science. To join, add your name to the STATISTICS-NIH-L LISTSERV at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=STATISTICS-NIH-L&A=1. Announcements will be posted at http://datascience.nih.gov/community/datascience-at-nih/sigs. For questions, contact Tammy Massie (tammy.massie@nih.gov).

NEW: TEXT MINING

This SIG will provide a community for NIH researchers who use text mining in their work and would like to learn more about what is being done in this area at NIH. The SIG will hold meetings, provide networking opportunities, and host a clearinghouse of descriptions of text-mining tools that can be used on campus or can be promoted more widely. The SIG also intends to work closely with the Data Science in Biomedicine Interest Group to provide expertise about text mining as a specific discipline within data science. To join the SIG distribution list, e-mail **Lena Pons** at lena.pons@nih.gov. ●

Read more online at http://irp.nih.gov/catalyst/v24i4/the-sig-beat.

Digitizing Medical History

CONTINUED FROM PAGE 1

The Arabic manuscript entitled *The Comprehensive Book on Medicine*, dated 1094, is one of the NLM's oldest items.

Comprehensive Book on Medicine (*Kitab al-Hawi fi al-tibb*), by one of the era's great physicians, Abū Bakr Muhammad ibn Zakarīyā al-Rāzī (circa 850–circa 925), known in the Western world as Rhazes.

The NLM's newest collections, comprising websites and social media about the recent Ebola and Zika outbreaks, will be the historical records of the future. And perhaps one of the most remarkable 20th-century items and available for anyone to explore online and experience through a traditional visit to the NLM, is the first summary of the genetic code—on several sheets of standard, taped-together paper—by 1968 Nobel laureate **Marshall Nirenberg**, whose research career at NIH spanned 50 years.

Scholars from around the world use the NLM's historical collections to advance their research. Educators use them to teach and inspire. Students use them to learn about the human condition. By carefully digitizing these collections and making them more accessible than ever before, we're liberating a global and centuries-long record of medicine to help inform research, education, and learning in the 21st century. The NLM's Digital Collections repository currently offers more than 80,000 items, including books, films, and images, and is rapidly growing. This resource complements PubMed Central, NLM's free, full-text archive of biomedical and life-sciences journal literature, now including 3.9 million articles spanning the early 19th-century to the present day.

But digitization is only part of the story. Our responsibility extends to being a good steward, which means preserving the collection for future generations by taking good care of it both during and long after we make digital copies of it. It also means ensuring that a wide audience knows about and appreciates the collection for the vast knowledge and experience it can offer.

The NLM's award-winning exhibition program has been achieving this last goal for many years, revealing important stories about the human condition to hundreds of thousands of individuals via its traveling banner exhibitions that travel the world and to millions more via its companion exhibitions on the web. The library's blog, Circulating Now, which recently marked its third anniversary, shines a light every week onto the rich collections. (See sidebar.)

The NLM is also working with other organizations such as the National Endowment for the Humanities (NEH) to support new ways of studying its growing digitized collections and related data sets as well as the related digitized collections and associated data of historical medical libraries and archives around the world. Along these lines, during the past three years, NLM and NEH have collaborated on several initiatives in cooperation with several organizations and institutions. On April 11–13, the NLM hosted the NEH-funded interdisciplinary workshop "Images and Texts in Medical History: An Introduction to Methods, Tools, and Data from the Digital Humanities." ●

Jeffrey Reznick is the chief of the History of Medicine Division at NLM. To read about the workshop, go to http://irp.nih.gov/catalyst/v24i4/nlm-workshop-images-and-texts-in-medical-history.

Some of the many contributors to NLM's blog.

Three Times Around and Still Circulating

POSTED ON JULY 1, 2016

Three years ago, we launched the website Circulating Now to explore, share, and celebrate the value of NLM's world-renowned historical collections and programs for research, education, enrichment, and learning about the human condition.

By several measures, we've achieved our goal. In three years Circulating Now has given voice to over 100 individuals—from guest writers to event speakers to our own talented staff—who have shared their own perspectives.

With over 500 posts, Circulating Now has offered readers worldwide insights on a wide and wonderful range of subjects in the history of medicine—military history, women's history, African-American history; public health, advocacy, legislation; botany, genetics, biotechnology; to name just a few.

Circulating Now has showcased the varied formats of the NLM's historical collections, enabling readers to experience and learn from our monographs, manuscripts, photographs and prints, films, audio files, and born-digital collections. And it has highlighted the range of NLM resources that support historical research and make the collections available—from the NLM's Digital Collections, to the IndexCat database of millions of bibliographic citations spanning centuries; from the NLM's award-winning Exhibition Program to historical content in PubMed Central; and from "Profiles in Science" to "Medical Movies on the Web." Read more online at https://circulatingnow.nlm.nih.gov/2016/07/01/three-times-around-and-still-circulating/.

AIDS at 35

The NIH Played a Major Role in Discovering the AIDS Virus

BY MICHAEL GOTTESMAN, DDIR

Sometime in the early 1970s, or perhaps even earlier, a virus capable of severely compromising the human immune system made its way from central Africa to the United States via Haiti. With a long incubation period before symptoms appeared, and with limited incidence of infections, the virus was on no one's radar screen. But that situation changed dramatically on June 5, 1981, when the Centers for Disease Control and Prevention (CDC) published a report in its *Morbidity and Mortality Report* newsletter about a mysterious cluster of Pneumocystis pneumonia (PCP) in five homosexual men in Los Angeles (http://www.cdc.gov/mmwr/preview/mmwrhtml/june_5.htm).

Although the public wouldn't be aware of the burgeoning epidemic for a few more years, public-health experts—including those at the NIH—were both intrigued and concerned by the report. "The patients did not know each other and had no known common contacts or knowledge of sexual partners who had had similar illnesses," the report stated. "Three patients had profoundly depressed in vitro proliferative responses to mitogens and antigens."

And so the mystery began. Over the next 18 months, health experts discovered more PCP clustering and cases of Kaposi's sarcoma among gay men in California cities, giving rise to the term gay-related immune deficiency, or GRID. Yet this GRID syndrome was also seen in heroin users, people with hemophilia, and people from Haiti, leading some researchers to use the term "4H disease." It wasn't until July 1982 that the CDC coined the name that would stick, acquired immune deficiency syndrome (AIDS).

The NIH played a major role in identifying the virus in the early 1980s. The first "AIDS" patient came to the NIH Clinical Center in 1981, before anyone knew what the disease was. In 1986, **Bob Gallo** (National Institute of Allergy and Infectious Diseases, NIAID) would earn his second Lasker award for determining that human immunodeficiency virus type 1 (HIV-1) causes most cases of AIDS.

The NIH developed the first blood tests to detect HIV, too. A wonderful telling of these early events is captured in a virtual exhibit and collection of oral histories titled "In Their Own Words: NIH Researchers Recall the Early Years of AIDS," created by the Office of NIH History in the 1990s (https://history.nih.gov/NIHInOwnWords/).

What's hinted at in these oral histories, collected between 1988 and 1993, is the cocktail of treatments developed in the 1990s that would transform AIDS from a death sentence into a manageable chronic disease, at least in wealthier countries. The NIH intramural program has been instrumental in developing these therapies.

On June 15, 2016, as part of the Clinical Center Grand Rounds series, NIAID Director **Anthony Fauci** delivered a talk titled "AIDS at 35: Is the End in Sight?" (http://videocast.nih.gov/launch.asp?19752). Fauci is perhaps the most knowledgeable person on Earth when it comes to AIDS, both its history and its pathology. His talk was an enlightening overview of an epidemic for which much work still needs to be done.

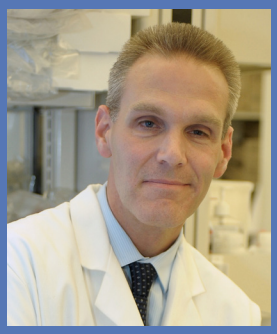
The NIH is making history today with its work on Ebola and Zika, and its past successes and experiences, both good and bad, can guide us here. This is one of the reasons why capturing and remembering our history is so important. ●

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CDC: Centers for Disease Control and Prevention
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

Recently Tenured

ROBERT L. HANSON, NIDDK



JAMES W. HODGE, NCI

CHARLES MATTHEWS, NCI

STEFAN A. MULJO, NIAID

MIHAELA SERPE, NICHD

ROBERT L. HANSON, M.D., M.P.H., NIDDK

Senior Investigator, Head, Genetic Epidemiology and Statistics Unit, Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Education: University of Kansas, Lawrence, Kan. (B.A. in chemistry); University of Kansas School of Medicine, Kansas City, Kan. (M.D.); Columbia University School of Public Health, New York (M.P.H.)

Training: Residency in internal medicine, University Hospital, State University of New York (SUNY) at Stony Brook (Stony Brook, N.Y.); residency in Preventive Medicine and Public Health, SUNY–Stony Brook; U.S. Public Health Service Epidemiology Fellow, NIDDK (Phoenix, Ariz.)

Came to NIH: In 1991 for training; became staff scientist in 1998 and staff clinician in 2011

Selected professional activities: Member, American Diabetes Association Grant Review Committee

Website: http://irp.nih.gov/pi/robert-hanson

Research interests: The Phoenix Epidemiology and Clinical Research Branch conducts research on the causes and correlates of type 2 diabetes, obesity, and diabetic complications. My research has focused on the epidemiology of these disorders, particularly on the genetic and molecular aspects, in American Indian and other populations. We use classical techniques of epidemiology (descriptive, analytic, and experimental) as well as genetic epidemiology to study the genetic and nongenetic risk factors for diabetes, obesity, and complications of diabetes. We also study gene transcription, protein expression, and cellular metabolism. The branch is also investigating the effect of lifestyle interventions, such as promoting weight loss, in helping to prevent diabetes and its complications.

We have conducted several clinical trials to intervene in the natural history of diabetes and to prevent the development of the disease and its resulting severe complications. Although our genomic and molecular research does not have immediate clinical applications, it is helping us gain an understanding of the processes that lead to diabetes and related conditions. Ultimately, we hope that this knowledge will lead to better treatments and preventive strategies for these diseases.

The technology for studying the genetic and molecular aspects of diabetes is continuing to improve. The greatest challenge is to develop analytical methods that will allow scientists to interpret the results from these technical advances and to ensure that diverse populations are included in genomic and molecular research.

JAMES W. HODGE, PH.D., MBA, NCI-CCR

Senior Investigator; Head of the Recombinant Vaccine Group, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute

Education: University of Tennessee, Martin, Tenn. (B.S. in biology and chemistry); University of Tennessee, Knoxville, Tenn. (M.S. in microbiology; Ph.D. in comparative and experimental medicine); George Washington University, Washington, D.C. (M.B.A. in medicine and health care)

Training: Intramural Research Training Award postdoctoral fellow, NCI

Came to NIH: In 1993 for training; held positions of senior staff fellow, staff scientist, and senior scientist (1996–2011); became investigator in 2011

Selected professional activities: Chairman, Immunomodulation Committee, NRG Oncology; senior visiting professor (adjunct), Department of Radiation Oncology and Surgery, Albert Einstein College of Medicine (New York)

Outside interests: Running marathons and triathlons

Website: http://irp.nih.gov/pi/james-hodge

Research interests: My group is developing novel recombinant vaccines and vaccine-combinatorial therapies. We study both mechanistically and operationally how certain radiation modalities, chemotherapy agents, small-molecule targeted therapies,

and immune modulators alter tumors or their microenvironments to make them more sensitive to immunostimulatory vaccines.

Immune consequences of cancer therapy include both direct effects on tumor cells and modulation of the immune system. My laboratory has focused on immunogenic modulation and immune subset conditioning.

Immunogenic modulation describes how anticancer therapies alter the biology of the surviving tumor cells to render them more sensitive to immune-mediated killing. The modulation encompasses a spectrum of molecular alterations in the cancer cell biology that independently or collectively make the tumor more amenable to cytotoxic T-lymphocyte–mediated destruction.

Immune subset conditioning describes how anticancer therapies mediate the peripheral and/or intratumoral reduction of negative regulatory elements into a more immune-permissive environment for vaccine immunotherapy. Understanding the underlying mechanisms of these areas provides a rationale for the use of immunotherapy in combination with radiation, chemotherapy, small-molecule inhibitors, and immune modulators.

Our team has worked independently and collaboratively with the Laboratory of Tumor Immunology and Biology on the design, engineering, and development of recombinant poxvirus and yeast-based cancer vaccine platforms. The poxviral vector–based vaccines contain transgenes for tumor antigens and for multiple synergistic costimulatory molecules. These vaccines based on three costimulatory molecules (TRICOM) have led to several clinical trials showing improved patient survival for a range of human carcinomas. The prostate-specific antigen (PSA)–TRICOM vaccine, designed to generate a robust immune response against PSA-expressing tumor cells, is in a phase 3 clinical trial for metastatic prostate cancer.

CHARLES MATTHEWS, PH.D., NCI-DCEG

Senior Investigator, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: University of Massachusetts Amherst, Amherst, Mass. (B.S. in exercise science; Ph.D. in epidemiology); University of South Carolina, Columbia, S.C. (M.S. in exercise science)

Training: Postdoctoral fellow, Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School (Worcester, Mass.)

Before coming to NIH: Assistant professor of medicine, Vanderbilt University School of Medicine (Nashville, Tenn.)

Came to NIH: In 2009

Selected professional activities: Associate editor, *Medicine and Science in Sports and Exercise*, American College of Sports Medicine's flagship journal; epidemiology and biostatistics representative on Program Committee for the 2016 American College of Sports Medicine Annual Meeting

Outside interests: Enjoying family meals; riding bikes; playing with dogs; watching baseball; listening to music; digging for vinyl LPs

Website: http://irp.nih.gov/pi/charles-matthews

Research interests: I study the relationship between physical-activity behaviors and the development of cancer. These behaviors range from the purely sedentary to high-intensity physical activity such as running; they reflect the continuum of human movement that we engage in each day. An individual's overall profile of physical behavior has an important influence on the amount of energy he or she expends each day and the underlying metabolism. In my etiologic studies, I seek to understand how the full spectrum of physical behavior influences cancer risks, the dose-response relationships between active and sedentary behaviors and cancer, and the biological mechanisms underlying these relationships.

Research has shown that moderate- to vigorous-intensity exercise is associated with reduced risk of many cancers with the most evidence available for colon cancer, postmenopausal breast cancer, and endometrial cancers. But we don't know precisely how much exercise is required to reduce the risk for these malignancies or what the metabolic mediators are. I am currently conducting studies to better understand the minimal amount of exercise needed to provide benefit, the effect of aerobic exercise on circulating hormones, and other metabolic factors that could explain the observed associations. I am also exploring whether excessive sedentary behavior ("too much sitting") may be linked to an increased risk for certain cancers independent of the effect of exercise. My long-term goal is to understand the optimal ratio of sedentary time (which is a necessity for many in modern life) to physically active time for lower cancer risk and better health.

To help achieve this goal I engage in methodological research to develop better tools to measure the full spectrum of physical-activity behaviors in large population-based studies. We have learned a great deal about the important role that exercise can play in cancer prevention using simplistic questionnaires, but it may be that our traditional questionnaire-based approach limits our ability to rigorously test new hypotheses about sedentary behavior and the potential benefits from routine activities of everyday living. We are now testing and refining next-generation measurement methods that rely on mobile technologies and accelerometers to capture a more complete, accurate, and precise measure of human behavior. I hope that by implementing these tools in future studies, we will accelerate discoveries that could lead to fundamentally new strategies for cancer prevention through increased physical activity.

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Recently Tenured

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STEFAN A. MULJO, PH.D., NIAID

Senior Investigator, Chief, Integrative Immunobiology Section, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases

Education: Johns Hopkins University, Baltimore (B.A. in biology honors program; M.H.S. in molecular microbiology and immunology; Ph.D. in molecular biology and genetics)

Training: Visiting postdoctoral researcher, Department of Molecular and Cell Biology, University of California, Berkeley (Berkeley, Calif.); postdoctoral research fellow, Department of Pathology, Harvard Medical School (Boston)

Came to NIH: In 2008

Selected professional activities: Advisory board member (Immunology section) of *Oncotarget*; faculty member of NIH-Penn Immunology Graduate Partnership Program

Outside interests: Cooking; eating; traveling; talking about science with his wife (also a scientist); keeping their kids entertained and out of trouble

Website: http://irp.nih.gov/pi/stefan-muljo

Research interests: The Integrative Immunobiology Section is interested in understanding how gene-expression programs are orchestrated as cells differentiate from stem cells into various lineages in the immune system. In particular, my lab studies how these systems are controlled by microRNAs, long noncoding RNAs, and RNA-binding proteins. Our major goal is to discover novel molecular circuits that control cell fates in the hematopoietic and immune systems because perturbations in their genetic programming underlie many diseases and disorders including cancer, immunodeficiency, autoimmunity, inflammation, allergy, and infectious diseases.

To address these fundamental issues, we use an integrative systems-biology approach to reverse engineer the molecular logic of cellular differentiation. We combine genome- and transcriptome-wide measurements with experimental perturbations in order to test and refine our models. As one example of our success, we identified the RNA-binding protein LIN-28 homolog B (LIN-28B), which causes hematopoietic stem cells (HSCs) from bone marrow of adults to acquire some of the attributes of fetal HSCs.

We helped show that human Lin-28B can activate a program that includes fetal hemoglobin expression during erythroid differentiation, providing a novel avenue toward the treatment of beta-thalassemia and sickle-cell disease, inherited conditions that affect hemoglobin and arise from mutations in adult beta-globin. Furthermore, using LIN-28B–reprogrammed adult HSCs in a transplant, particularly in pediatric patients or someday in utero, offers the potential for the blood and immune systems to develop anew, similar to how the immune system develops in a fetus or a newborn. Converting adult human HSCs into more fetal-like cells with LIN-28B also offers an easy and ethical way to further study fetal HSCs in the laboratory.

Recently Tenured?

If you have been tenured within the past year, the *NIH Catalyst* will be contacting you for your help in preparing an article about you. We will ask for your CV and a photo, consult your website, and then draft an article for your review. You'll be able to revise and make additions. We look forward to working with you.

The Editors, *NIH Catalyst*

MIHAELA SERPE, PH.D., NICHD

Senior Investigator; Head of the Section on Cellular Communication, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Education: University of Bucharest, Bucharest, Romania (M.S. in biochemistry); State University of New York at Buffalo, Buffalo, N.Y. (Ph.D. in biochemistry)

Training: Postdoctoral training in developmental biology and neurobiology, University of Minnesota and Howard Hughes Medical Institute (Minneapolis)

Came to NIH: In 2008

Selected professional activities: Organizer of the Genetics Society of America Drosophila meeting (2014)

Outside interests: Listening to all kinds of music (from jazz to classical); hiking; baking

Website: http://irp.nih.gov/pi/mihaela-serpe

Research interests: The purpose of my lab's research is to understand the mechanisms of synapse development and homeostasis. We focus on three key processes in synaptogenesis: 1) trafficking of components to the proper site, 2) organizing those components to build synaptic structures, and 3) the maturation and homeostasis of the synapse to optimize its activity. My laboratory addresses the underlying mechanisms using a powerful genetic system, *Drosophila melanogaster*, and a comprehensive set of approaches including genetics, biochemistry, molecular biology, super-resolution imaging, and electrophysiology recordings in live animals and reconstituted systems.

We use the neuromuscular junction (NMJ) as a model for glutamatergic synapse development and function. Individual NMJs are uniquely suited for in vivo studies on synapse assembly, growth, and plasticity, because they can be reproducibly identified from animal

to animal and are easily accessible for electrophysiological and optical analysis.

Although many neurological disorders are linked to defects in synaptogenesis, the initial clustering functions are poorly understood. We discovered an obligatory auxiliary protein, neuropilin and tolloid-like (Neto), which is absolutely required for the ionotropic glutamate receptors (iGluRs) clustering and NMJ functionality.

Neto belongs to a family of highly conserved auxiliary proteins that regulate glutamatergic synapses, the major excitatory synapses in the human brain. Our investigations uncovered essential roles for Neto during synapse development and support the notion that Neto tightly regulates the trafficking of iGluRs on the muscle membrane, their synaptic recruitment and stabilization, and their function. Furthermore, Neto appears to be at the center of trans-synaptic complexes that monitor synapse activity and relays this information to the presynaptic bone morphogenetic protein (BMP) signaling pathway.

We have recently discovered a completely novel BMP-signaling modality that is genetically distinguishable from any other known BMP pathways. At the NMJ, this novel BMP pathway is triggered by selective postsynaptic iGluRs and acts locally to promote the stabilization of these receptors at synaptic sites. Thus, BMPs may monitor synapse activity and coordinate it with synapse growth and maturation. We are currently trying to elucidate the molecular components, regulation, and function of this novel BMP-signaling modality, which appears to have a broad, ancestral role in regulating cellular junctions. ●

New Members of NAS

Ronald Germain and **Eugene Koonin** have been elected to the National Academy of Sciences (NAS) for 2016. They join the more than 40 active NIH scientists in this prestigious academy. On June 8, they presented their research at a minisymposium honoring their election. (To view the videocast, go to http://videocast.nih.gov/launch.asp?19738.)

Germain is an NIH Distinguished Investigator in the NIAID Lymphocyte Biology Section, where he studies basic aspects of innate and adaptive immune function, with an emphasis on the biochemical mechanisms involved in discrimination between self and foreign peptide-associated major histocompatibility complex (MHC) molecules by T cells as well as on T-cell antigen-presenting cell interactions and the subsequent delivery-of-effector function. Germain was elected to the National Academy of Medicine, formerly the Institute of Medicine, in 2013. For more on Germain's work, go to http://irp.nih.gov/pi/ronald-germain.

Koonin is a senior investigator in the NLM NCBI Evolutionary Genomics Research Group. His research is in many areas of evolutionary genomics and takes advantage of the advances of comparative genomics and systems biology to address fundamental problems in evolutionary biology. He hypothesized in 2005 that "spacer DNA" in the clustered regularly interspaced short palindromic repeats (CRISPR) loci of bacteria and archaea, which matched sequences of bacteriophages, could be a key part of a sort of adaptive immune system. For more on Koonin's research, go to http://irp.nih.gov/pi/eugene-koonin.

Leonard and Lichten Elected to "Older" AAAS

Warren Leonard and **Michael Lichten** have been elected to the American Academy of Arts and Sciences, which was founded in 1780.

Leonard, an NIH Distinguished Investigator in the NHLBI Laboratory of Molecular Immunology, applies a broad range of methodologies to both human cells and mouse models and relies on the continual interplay between basic research, which teases apart the signaling mechanisms that underlie normal immune-cell development, and the study of primary human cells and mouse models. His laboratory has discovered multiple specific forms of immunodeficiency including those caused by mutations in the genes encoding the intracellular signaling molecule Janus kinase 3. For more about Leonard's work, go to http://irp.nih.gov/pi/warren-leonard.

Lichten is a senior investigator in the NCI Laboratory of Biochemistry and Molecular Biology. He uses budding yeast as a model system to study homologous recombination and chromosome structural changes that occur during meiosis. Recombination and its crossover products are essential for proper chromosome segregation during meiosis. Chromosome mis-segregation, caused by defects in meiotic recombination, leads to chromosome imbalance in gametes. These chromosome imbalances are a leading cause of infertility and birth defects in humans. For more about his work, go to http://irp.nih.gov/pi/michael-lichten.

Service to America Medal Finalist

BY ROBIN ARNETTE, NIEHS

NIEHS epidemiologist **Allen Wilcox** is one of 32 federal employees named as finalists for the 2016 Samuel J. Heyman Service to America Medals (also known as Sammies), in recognition of his "pioneering the epidemiologic study of human reproduction, fundamentally changing both scientific and public understanding of fertility and pregnancy." The winners will be announced at a black-tie gala in September.

Wilcox is a senior investigator and head of the NIEHS Reproductive Epidemiology Group. For more about his work, go to http://irp.nih.gov/pi/allen-wilcox. ●

Read longer versions online at http://irp.nih.gov/catalyst/v24i4/announcements-kudos.

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CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

READ ANNOUNCEMENTS AS WELL AS LONGER VERSIONS OF THESE ARTICLES ONLINE (IN COLOR) AT http://irp.nih.gov/catalyst/v24i4

FROM THE ANNALS OF NIH HISTORY

The IBM 370: Computers a GoGo

BY MICHELE LYONS, OFFICE OF NIH HISTORY

NIH STETTEN MUSEUM, OFFICE OF NIH HISTORY

This computer technician appeared in the IBM 370 Systems Manual in 1975. NIH used IBM 370s, which were mainframe computers, from 1971 until the mid-1990s, along with DEC System 10 mainframes, to store and process scientific and personnel data. In 1976, the National Library of Medicine (NLM) got its own IBM 370, which it used for updating master records, controlling inventory, and quickly processing overdue notices. By 1984, NIH had five IBM 370 Model 3081 computers, 115 magnetic-tape drives, 344 disk drives, two mass-storage systems, 11 high-speed printers, dozens of card readers and card punches, and countless microfiche output units. The system also had over 1,200 telephone lines serving hundreds of remote terminals at NIH and other federal agencies.

Today, the NIH Center for Information Technology (CIT) handles the many kinds of computer interactions required by a biomedical research campus. The NIH High-Performance Computing Core Facility replaces much of what the IBM 370 systems did by providing computing systems specifically for the intramural NIH community. (Read more at http://irp.nih.gov/catalyst/v24i3/from-the-annals-of-nih-history-computers.) ●

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