THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 20 ISSUE 6 • NOVEMBER-DECEMBER 2012

Intramural Detectives

Investigate Klebsiella Mystery

BY BEN PORTER (NINDS) AND L.S. CARTER

"Microorganisms can live in all sorts of extreme environments," Chief of Clinical Care Medicine **Henry Masur** told an audience at a Clinical Center (CC) Grand Rounds in September. "They can live without oxygen . . . in boiling water . . . on ice, and they can live with all sorts of antibiotic pressure."

That ability to resist antibiotics can transform even harmless bacteria into dangerous pathogens that can sicken hospitalized patients, especially those with already weakened immune systems. In the summer of 2011, a strain of *Klebsiella pneumoniae* that was resistant to the powerful antibiotic carbapenem began working its way through some of the CC's most gravely ill patients. Even infection-control procedures failed to stop the spread before seven patients died.

"We were deeply saddened by their deaths," said Clinical Center Director **John Gallin**. "We were determined to stop this infection in its tracks and do everything possible to protect our patients."

So the Clinical Center did what no ordinary hospital could. It marshaled the forces of NIH's intramural program: Intramural Sequencing Center scientists and technicians, CC microbiologists and epidemiologists, and National Human Genome Research Institute researchers pitched in to help.

The story was first told in the August 2012 issue of *Science and Translational Medicine*, then retold—sometimes incorrectly—by dozens of national media outlets.

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Today's Discoveries, Tomorrow's Cures

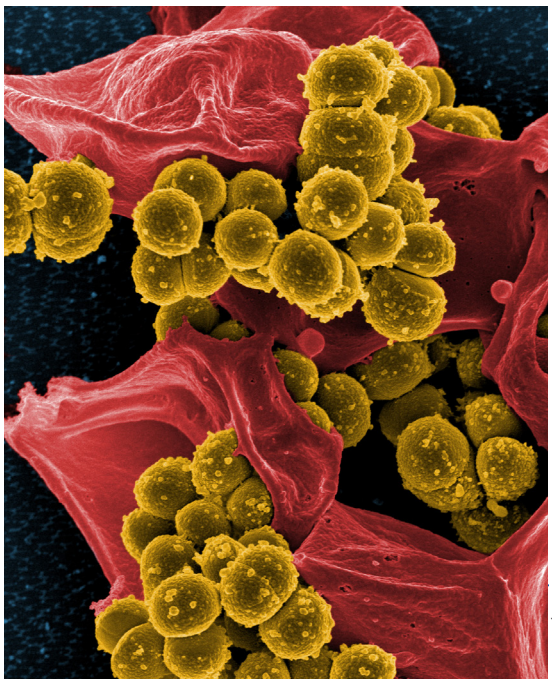
Report From the 2012 Research Festival

BY MEGHAN MOTT, NIAAA

Only one event brings together the intramural community year after year, and that's the NIH Research Festival. What began as "NIH Research Day" on September 25, 1986, has evolved into a four-day festival featuring scientific talks, posters, exhibits, and more.

"It's gotten bigger and better every year," said NIH Director **Francis Collins**. "This year is the biggest ever."

This year's festival featured a unique plenary program, concurrent symposia with 26 topics and 148 talks, more than 500 posters, special exhibits, and a scientific equipment tent show. There was also a special session with U.S. Congressman Andy Harris (Maryland), a trained physician and recipient of NIH grants, who talked about the importance of NIH's biomedical research.



FRANK DELEO, NIAID

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria (ball-like structures) are bursting out of a dead neutrophil. This scary image serves as a reminder of our past battles with epidemic diseases such as cholera, plague, and smallpox, as well as our current challenges with emerging threats such as MRSA.

The festival took place October 9 through 12 and merged with the NIH National Graduate Student Research Conference, giving 120 graduate students studying at U.S. universities the chance to present their work to intramural scientists and learn about research going on at the NIH.

The 2012 Research Festival was particularly momentous because it marked NIH's quasquicentennial, or 125th anniversary. Four institutes also achieved milestones this

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Response to a Public Health Dilemma

BY MICHAEL GOTTESMAN, DDIR

The problem of hospital-acquired (nosocomial) infections has been with us for many years. These organisms tend to be resistant to most antibiotics in common use, since hospital patients are exposed routinely to potent, broad-spectrum antibiotics. These organisms cause significant, and sometimes fatal, infections in patients whose immune systems are compromised.

The recent cluster of carbapenem-resistant *Klebsiella pneumoniae* (KPC) at the NIH Clinical Center, fatal to seven of 19 infected or colonized patients with compromised immune systems, represents the tip of an iceberg illustrating the increasing intransigence of microbes to treatment with antibiotics. It also demonstrates how the NIH intramural research program is able to apply cutting-edge technology to identify an important public health problem and develop a strategy to deal with it.

The story began in 2011 when a cluster of KPC cases in the Clinical Center resulted from the transfer of a patient from a hospital in New York City. In a paper that appeared in *Science Translational Medicine*, **Evan Snitkin** and numerous colleagues at the NIH including **David Henderson** and **Tara Palmore**, our hospital infection officers, and **Julie Segre**, a senior investigator in NHGRI who studies the human microbiome, described the cluster of patients and how whole KPC genome sequencing was used to identify the course of transmission to 17 patients who were infected after the index case. (The transmission to the 18th patient was discovered after the paper was published; *Sci Transl Med* **4:**148ra116, 2012.)

This sophisticated approach showed unequivocally that most of the patients had not been in direct contact with each other, and that transmission from silently colonized patients was largely responsible for the cluster.

Rigorous infection-containment approaches targeting the typical modes of transmission of nosocomial infections—such as grouping the clinicians treating KPC-colonized or KPC-infected patients into cohorts, isolating infected individuals and carriers, using direct observation to ensure scrupulous attention to hand washing, and paying attention to the details of disinfection of the environment and sterilization of equipment—enabled containment of the outbreak.

KPC is not the only organism that can become intractable to antibiotic therapy. Acinetobacter species, methicillin-resistant *Staphylococcal aureus* (MRSA), *Clostridium difficile*, *Mycobacterium tuberculosis*, and other organisms can be responsible for infections that prove fatal because they no longer respond to antibiotics. This, of course, is not a new problem. When I was a medical intern from 1970 to 1971, *Klebsiella pneumoniae* infections were often fatal because of the limited armamentarium of antibiotics then available. For awhile, the pharmaceutical industry kept pace with the development of antibiotic resistance, but we are now seeing, at an accelerating pace, antibiotic resistance spreading faster than the production of new antibiotics.

Many internal and public discussions of the implications of the KPC cluster have occurred. The intramural program has contributed in a meaningful way to this discussion by providing important data that define the extent and nature of the problem and by offering several ways forward.

The Snitkin et al. paper sets a new standard for hospital epidemiologic investigations. In addition, clinical and scientific leadership at the NIH has recognized the importance of launching a trans-NIH research program focusing on the development of treatments for multidrug-resistant bacteria. NIAID has taken the lead in this effort, with its scientific director, **Kathryn Zoon**, developing a program to enhance our research expertise in nosocomial infections and antibiotic-resistant organisms, joining our considerable investment in studying MRSA and *M. tuberculosis*.

The Clinical Center, NHGRI, NCATS, and other NIH microbial physiology experts will participate in a trans-NIH effort to turn the challenges posed by the KPC cluster into learning experiences to improve public health. They plan to identify new targets for antimicrobials and develop antimicrobial compounds. This activity is in the best tradition of NIH efforts to deal with public health risks whenever they arise. If the past is any indication of the future, we are likely to make considerable contributions to international research on this ubiquitous problem. ●

Klebsiella Mystery

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Finally, at the September grand rounds, CC epidemiologist **Tara Palmore** and NHGRI senior investigator **Julie Segre** joined Masur (who was not one of the authors on the paper) to describe how skillful sleuthing, advanced genomic technologies, epidemiological practices, and surveillance enabled the NIH team to hunt down and contain an elusive bacteria.

It all began on June 13, 2011, when a woman (Patient 1) with a rare lung disease was transferred from a New York City hospital to the 243-bed CC hospital. She was known to be colonized with (a carrier of) a strain of carbapenem-resistant *Klebsiella pneumoniae* (KPC). The clinicians took every precaution to keep it from spreading. She was kept separate from the rest of the patients and placed in a private room; staff and visitors had to wear gloves and gowns when entering; and strict hand-washing protocols and other infection-control procedures were in place. She also spent two 24-hour periods, in isolation, in the intensive care unit (ICU).

Klebsiella is a normally harmless bacteria found in the intestines. It can, however, cause difficult-to treat-infections—such as pneumonia and bloodstream infections—in immunocompromised patients. Hospital-acquired infections—such as methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, KPC, and others—complicate about five percent of hospital admissions across the country and kill nearly 100,000 people a year, according to the Centers for Disease Control.

When Patient 1 was released from the CC on July 15, it appeared as if the KPC had not spread. But three weeks later, another patient, who had never been exposed to Patient 1, tested positive for the organism. Eventually the CC's first-ever cluster of KPC infections, which was largely ICU-based, involved 19 patients, seven of whom died from the infection. (The latest death was in September 2012; Patient 1 is still alive.)

It's not uncommon for bacteria to lurk silently and pop up again weeks after their source is gone. Still, the doctors wondered whether the cases were linked to Patient 1 or whether there were other sources of KPC.

The usual methods of investigation would not be enough to solve the mystery. Standard molecular typing methods—such as pulsed-gel electrophoresis—could identify similar strains of Klebsiella but were unable to detect the small genetic differences that could provide clues about how the infection was spreading. Fortunately, NIH intramural researchers have access to powerful rapid-genetic-sequencing tools that can map entire genomes in a day (the process used to take years and be prohibitively expensive) and to sophisticated methods for analyzing the information.

Bioinformatics specialist **Evan Snitkin**, a postdoctoral fellow in Segre's lab, developed an algorithm to reconstruct the outbreak transmission based on whole-genome sequencing and epidemiological data that traced the location of patients throughout their hospital stay.

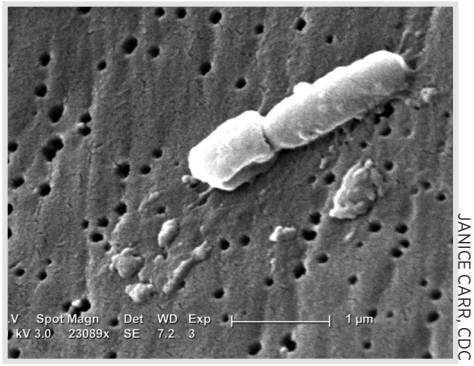
By observing changes in the nucleotides as the bacteria reproduced, we "were able to track the evolution of this organism," to other patients, said Segre. The KPC strains in all 19 patients could be genomically traced back to Patient 1.

The researchers also used extreme measures in their investigation. "We threw the kitchen sink at these hospital-acquired organisms," quite literally removing and decontaminating six sink drains colonized with the bacteria, said Palmore. Although a ventilator remained contaminated after thorough cleaning, it was not used on patients afterwards and therefore not linked to spreading the infection.

NIH is the first organization to use real-time, whole-genome sequencing to track an infection of this sort. Eventually, as the technology advances and its costs decline, hospitals will be able to "apply these novel technologies to track hospital transmission routes and find specific opportunities for intervention," said Segre.

MAGGIE BARTLETT, NHGRI

Left to right, Evan Snitkin, Tara Palmore, and Julie Segre (above) were part of the intramural team that investigated the cluster of *Klebsiella pneumoniae* cases among gravely ill, immune-compromised patients at the NIH Clinical Center. This scanning electron micrograph (below) reveals some of the ultrastructural morphologic features of a *Klebsiella pneumoniae* bacterium.



JANICE CARR, CDC

In the case of the CC, the findings reinforced the need to adhere to stringent infection-control precautions. The CC even hired monitors to make sure everyone was following all the protocols.

"The cooperation of the entire Clinical Center staff, and our patients and their families to stop transmission has been extraordinary," said Gallin. "It's a model for other hospitals." ●

To read the journal article go to http://www.sciencemedicine.org/content/4/148/148ra116.full. (*Sci Transl Med* 4:148ra116, 2012).

To view the September 5, 2012, CC Grand Rounds, visit http://videocast.nih.gov/launch.asp?17542.

SPECIAL ESSAYS

Keep the Thread: Balancing Family with Your Science Career

BY SARAH RHODES, NIMH

For many of us, responsibilities for child rearing and other family requirements fall exactly at the time when our scientific careers are taking off. This puts many postdocs in a quandary: Should we postpone having children until after we obtain a secure position, take a break from our careers to attend to family responsibilities, or attempt to balance these equally urgent requirements?

In an effort to alleviate some of the challenges for postdocs with family responsibilities and to help retain fellows who might otherwise drop out of science, the Committee on the Intramural Research Program of the NIH Working Group on Women in Biomedical Careers has been exploring re-entry and accommodation options. As a result, the "Keep the Thread" pilot program has just been launched. This program will offer postdocs several options for increasing flexibility, temporarily reducing hours, and staying connected to their research and the NIH community.

Individual circumstances may vary, and specific arrangements must be mutually agreed upon by the fellow, the principal investigator (PI), and their scientific director (SD). Accommodations may include telework, flexible scheduling, and temporary reduction in hours to part-time status. The agreement also includes a re-entry plan that specifies when the fellow plans to return to full-time research and how the PI will fill the position in the meantime.

"Keep the Thread" will be open to female and male NIH postdoctoral fellows (but not visiting fellows because of visa restrictions) who have been at the NIH for at least six months and have an established research project. These policies may be implemented upon returning from parental leave (Intramural Research Training Award fellows are entitled to eight weeks of paid leave after the birth or adoption of a child) or when faced with family situations not covered by the NIH parental-leave policy. At the end of the three-year trial period, "Keep the Thread" will be evaluated to determine whether the program meets the needs of NIH fellows, PIs, and SDs.

In a nutshell, "Keep the Thread" is intended to clarify intramural family-friendly policies, publicize their availability, encourage PIs to work with their fellows to establish a plan, and reduce the stigma often associated with accepting accommodations. Although the pilot program is largely composed of family-friendly policies already in existence at NIH, some policies have been enhanced to facilitate re-entry into full-time research.

Balancing research with family will always be difficult, but "Keep the Thread" will help postdocs navigate this challenging yet rewarding time of their lives. ●

To find out more about this initiative go to http://sourcebook.od.nih.gov/prof-desig/Keep_the_Thread_2012.docx.

Speed Networking for Scientists

BY SARAH NAYLOR, NIMH

Your heart pounds. Your palms sweat and become clammy. Your mind goes blank. All because someone asked, "So, what about you?"

It's time to describe your work, in two minutes or less, without visual aids, to a fellow scientist in a different discipline.

Welcome to speed networking for scientists. It's like speed dating only you're not looking for a romantic companion. In the last several years, speed networking has become a popular way to meet informally and even find potential collaborators. Recently, a group in Germany offered to fund collaborations that originated from speed-networking interactions.

My speed-networking experience took place in August 2012 at a meeting of the Potomac Chapter of the Society for Neuroscience (SFN). The encounters generated discussions about research, interests outside the lab, and hints for improving these two-minute pitches. As a new postdoctoral fellow at NIMH, I worked out the kinks in my brand new pitch about my research on neural circuits that govern innate behaviors.

One of the people I met via speed networking was NINDS postdoctoral fellow **Ben Porter**, who recently reactivated the Potomac Chapter (renamed the Washington D.C. Metro Area Chapter), which had closed a few years ago. He thought a speed-networking event would make for a good first meeting and be a great way for the chapter members—scientists from NIH and nearby universities and companies as well as others with an interest in neuroscience—to get acquainted. And who knows, maybe some of us will decide to collaborate, too. ●

To learn more about the local SFN chapter, contact Ben Porter (porterba@mail.nih.gov or 301-594-0365). Events are held monthly in the D.C. metro area, including on the NIH campus., and range from professional networking and development, to volunteering, to discussions of neuroscience, to giving practice presentations about your job, research, or skills.

Update

Material Transfer Agreements Made Even Easier

BY TAD SUPPORT TEAM

Material Transfer Agreements (MTAs) just became even easier to manage and maintain thanks to the new and improved Transfer Agreement Dashboard (TAD). New features include an online catalog of frequently requested NIH materials and the ability to create MTAs for transfers of materials into the NIH.

MTAs are agreements that govern the transfer of tangible research materials between two organizations when the recipient intends to use the material for his or her own research purposes. The kinds of materials that can be transferred under MTAs include unique reagents, cell lines, plasmids, chemical compounds, vectors, and other types of research materials and resources such as animal models and software.

The Transfer Agreement Dashboard

The TAD Web site was developed to make the MTA process simpler and more efficient. TAD takes the guesswork out of managing MTAs by providing easy-to-use Web forms and automatically sending agreements to the appropriate people for negotiation and signature. TAD also saves valuable time by providing preloaded MTA templates and offering electronic signature capability, thereby eliminating the need to print or scan documents.

The new TAD Material Catalog enables external researchers to browse and request NIH materials available for transfer. TAD facilitates the entire request process, including lab approval and the creation of a new MTA. For example, when the recipient researcher receives approval for the transfer, TAD will automatically begin the MTA process using the material information available in the catalog. This step reduces errors in the agreement by ensuring that the document contains the appropriate information. Lab staff members can manage their lab's list of available materials by using their TAD account.

MTAs for transfers into the NIH increase access to critical materials available from the external research community. TAD encourages external technology transfer offices to use the built-in NIH templates whenever possible to mitigate the need for extensive negotiation. For organizations that prefer using unique terms and conditions, TAD offers the option to reuse the language of a previously executed MTA to help streamline the negotiation process.

Registering for TAD is quick, easy, and free. Simply fill out the form on the TAD user registration page at http://techtransferagreements.nih.gov/Pages/User-Registration.aspx. ●

Want to learn more about TAD? Feel free to contact the TAD support team at NIHTADSupport@mail.nih.gov or visit the TAD Web site at http://techtransferagreements.nih.gov. You can also read an article in the November-December 2011 *NIH Catalyst* at http://irp.nih.gov/catalyst/v19i6/news-you-can-use.

CORRECTION

In the article entitled "An NIH Research Dynasty in Building 3: A Who's Who of Biomedical Researchers" (*NIH Catalyst*, September-October 2012 issue), Sue Goo Rhee was incorrectly referred to as a former Stadtman postdoc. In fact he was Boon Chock's former postdoc in NHLBI's Laboratory of Biochemistry (the lab's chief was Earl Stadtman). In 1994, Rhee was named chief of the Laboratory of Cell Signaling and was still chief when it was moved to Building 50 in 2001.

NEWS FROM AND ABOUT THE NIH SCIENTIFIC INTEREST GROUPS

New SIG: Bioinformatics

The Bioinformatics Interest Group brings members of the intramural bioinformatics community together to interact and collaborate. With an emphasis on fundamental and specific bioinformatics concepts and methodologies, this group also provides novices with an opportunity to learn from and discuss career advice with experts in the field. Whether you are new to the field or a master, you're welcome to join. Meetings occur four times a year, and each consists of two 30-minute talks in one of the bioinformatics areas—functional genomics, systems biology, bioimaging, or proteomics and structural modeling—and a social event. The talks focus on research methodology, including software development and usage, parameters, interoperability of datasets, and applicability to specific biological questions. The social event provides a venue for networking and discussion. The first meeting, which will be held on Wednesday, December 5, 4:30 to 6:00 p.m., will feature Hari Shroff (NIBIB), who will discuss high-speed and high-resolution imaging techniques, and Richa Agarwala (NCBI), who will talk about genomic data at NCBI. A social event in Bethesda follows. Locations TBA. For more information, join the LISTSERV at https://list.nih.gov/cgi-bin/wa.exe?A0=bioinformatics-sig-l or contact Ben Busby at busbybr@ncbi.nlm.nih.gov.

TRANSLATIONAL RESEARCH

Lecture Series, Thursdays, 1:00-2:00 p.m. Lipsett Amphitheater (Building 10) unless otherwise noted

December 13: "Developing Drugs to Treat Substance Use Disorders"; Phil Skolnick (NIDA)

January 10: TBA; Building 10 Rm. 2-C116; Gustavo Pacheco-Rodriguez (NHLBI)

For more information on other TRIG lectures, visit http://sigs.nih.gov/trig/.

Taming Dreaded Diseases in the 1800s

Joseph Kinyoun, the Hygienic Laboratory, and the Origins of the NIH

BY EVA ÅHRÉN, OFFICE OF NIH HISTORY

NATIONAL INSTITUTES OF HEALTH

Portrait of Joseph J. Kinyoun (1860–1919) by Walmsley Lenhard (1891–1966). The oil painting is based on a photograph from 1918, making Kinyoun look much older than he was during his years as director of the Hygienic Laboratory, the predecessor of the National Institutes of Health.

In Building One on the NIH campus, next to the main floor elevators, hangs a portrait of a middle-aged man with rolled-up sleeves, one hand on his hip, the other on a shiny brass microscope. A plaque identifies the subject as "Joseph J. Kinyoun, Director of the Hygienic Laboratory, 1887-1899."

The National Institutes of Health traces its origins back to the Hygienic Laboratory (HL), the first federal laboratory of medical bacteriology. At first a modest facility of applied science, it later expanded its scope of research, budget, staff, and facilities. It was renamed the National Institute of Health in 1930, 11 years after Kinyoun's death, and the National *Institutes* of Health in 1948.

Bacteriology was a hot topic in the 1880s. German physician Robert Koch's description of the life cycle of the anthrax bacillus in 1876 (and his subsequent discovery of the tuberculosis bacillus in 1882 and the cholera vibrio in 1883) excited physicians and biologists and spurred many of them to search for disease-causing germs. The first generation of microbiologists in the United States was not one of basic scientists, but of physicians, veterinarians, and chemists working for the federal government or state and municipal health departments.

Joseph Kinyoun was one of those physicians. The son of a surgeon in the Confederate Army, he received his M.D. degree from Bellevue Hospital Medical College in New York in 1882 and trained at the Carnegie Laboratory (also in New York) in 1885. In 1886 he entered the Marine Hospital Service (MHS), a seemingly inauspicious career move that would catapult him into becoming an important figure in the history of microbiology and public health.

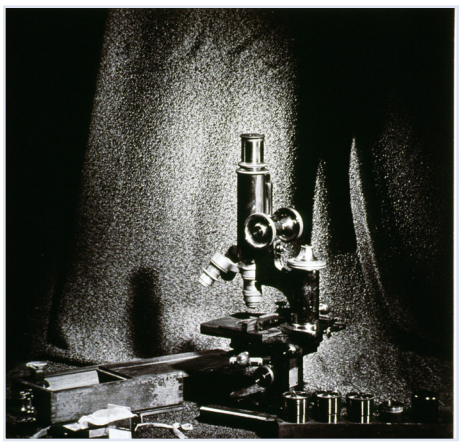
Surgeon General John B. Hamilton selected Kinyoun to set up the HL because he was one of just a handful of Americans trained in bacteriological techniques at the time and the only one in the MHS (predecessor of the Public Health Service). The laboratory was first located at the Stapleton Hospital (Staten Island, N.Y.), one of several facilities in the Port of New York that catered to newly arrived immigrants and seamen, treating the sick among them and placing carriers of infectious diseases in isolation.

But, already in 1888, the laboratory's mission was much broader than serving quarantine activities with bacteriological analysis: It also dealt with matters "pertaining to the successful administration of national quarantine and the dealing with public sanitation and hygiene."

Kinyoun modeled the HL on Koch's laboratory in Berlin (but on a smaller scale), including "Zeiss's latest improved microscope objectives and microphotographic apparatus." Kinyoun soon used this microscope to study cholera, one of the most dreaded diseases in the 19th century. The opportunity to conduct this research presented itself in September 1887, when an Italian steamship arrived in New York. Eight immigrants on board were sick with cholera; eight others had died during the voyage. The ship went straight to quarantine and the sick passengers were hospitalized. More cases developed and more deaths occurred during the following weeks.

William H. Smith, the quarantine health officer, described the disease as "very virulent and rapid in its fatality in a majority of the cases; in several instances patients that were well at inspection in the afternoon were nearly or quite pulseless within twelve hours." The whole ship, every passenger, all the cargo and luggage, and every piece of clothing were disinfected twice. The ship was held for two weeks and repainted before being released.

Together with his colleague Samuel Treat Armstrong, Kinyoun collected samples of "excreta" from isolated cholera patients and cultivated them on agar plates. Three days later, they found "characteristic colonies of the comma bacilli…conforming in every particular to the description given by Koch."



NATIONAL LIBRARY OF MEDICINE

Kinyoun's Zeiss microscope, which he used to study cholera, was very advanced and expensive in the 1880s.

NATIONAL INSTITUTES OF HEALTH

From the first location of the Hygienic Laboratory in the Marine Hospital Service facility at Stapleton Hospital (Staten Island, N.Y.). Kinyoun's microscope can be seen in the center on the bench by the window.

This was the first time cholera was identified by means of a microbial investigation in the Americas. "As the symptoms, in the cases examined, were by no means always well defined, the examinations were confirmatory evidence of the value of bacteria cultivation as a means of positive diagnosis," they wrote in the *New York Medical Journal* in 1887.

Kinyoun then went on to test the waters in New York Harbor to determine whether cholera could survive and spread through the water. The answer was yes. Therefore, the "dejecta" of cholera patients needed to be handled safely (presumably by sanitizing latrines and burying their contents instead of simply emptying them into the water). Although this study was of minor scientific importance, the medical community and the general public received it as chilling, sensational news. Medical journals and newspapers kept referring to the study throughout the spring of 1888. Even in faraway Iowa, the *Cedar Rapids Evening Gazette* commented, "It is extremely unpleasant to know that Dr. J. J. Kinyoun, of the Marine Hospital Service, has proved that the Asiatic cholera spirilla thrives and reproduces ad libitum in the water of New York Bay."

With these studies Kinyoun made his name and laboratory known. He began appearing frequently in the national arenas of medicine and science: He often represented the MHS at meetings of the American Medical Association and the American Public Health Association and published articles in their journals. Newspapers reported on his work and his travels to European laboratories and international congresses. Health departments around the country called on him to assist with investigations and to teach their physicians how to conduct bacteriological tests or "biological examinations," as they were called at the time.

When Walter Wyman became surgeon general in 1891, he moved the HL to MHS headquarters in Washington, D.C., across the street from the United States Capitol.

LIBRARY OF CONGRESS

Marine Hospital Service headquarters in Washington, D.C., at 222 New Jersey Avenue SE. The whole top floor belonged to the Hygienic Laboratory.

The HL was now a few blocks from the Army Medical Museum and Library and close to other government agencies such as the Department of the Treasury and the Department of Agriculture with its Bureau of Chemistry.

The move—from a peripheral hospital to a place next door to the federal government—made the HL more visible to policymakers. Kinyoun began to take on broader issues and assumed a higher profile. His work became less clinical and more scientific, administrative, and political. When a second cholera outbreak afflicted the Port of New York in 1892, Wyman and Kinyoun were successful in getting new legislation passed that increased the power of the MHS over local and state authorities.

Kinyoun was one of a growing group of physicians and scientists in the United States and abroad who enthusiastically adopted the new science of microbiology and harnessed it to serve the interests of public health. During his 12 years at the HL, he published papers on bacteriology and public health; inspected disease-ridden ships and disinfected them; studied the efficiency of various disinfecting agents and methods; analyzed the microbial environment of railway cars, the water of the Potomac, and the air of the House of Representatives; compiled an exhibit on the Marine Hospital Service for the 1893 World's Columbian Exposition in Chicago; produced and advocated the use of diphtheria antitoxin; and drafted public health legislation. This was what public health was all about at the end of the 19th century: a combination of microbiology, epidemiology, and sanitary science and engineering. ●

To read more about Kinyoun's life, visit http://www.niaid.nih.gov/about/whoweare/history/josephjkinyoun/indispensableman/Pages/default.aspx.

KINYOUN FAMILY ARCHIVES

Assistant Surgeon Joseph James Kinyoun of the Marine Hospital Service. Studio portrait from 1887, the year he opened the Hygienic Laboratory, predecessor of the NIH.

Research Festival

CONTINUED FROM PAGE 1

year: It is the 10th anniversary of the National Institute of Biomedical Imaging and Engineering (NIBIB), the 50th for the National Institute of Child Health and Human Development (NICHD) and the National Institute of General Medical Sciences (NIGMS), and the 75th for the National Cancer Institute (NCI).

The theme of the 2012 festival, "The NIH at 125: Today's Discoveries, Tomorrow's Cures," was reflected in the festival artwork used on posters, program booklets, and the Web site. Created by **Frank DeLeo**'s group at the National Institute of Allergy and Infectious Diseases (NIAID), it depicts methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria bursting out of a neutrophil. This scary image serves as a reminder of our past battles with epidemic diseases such as cholera, plague, smallpox, and yellow fever, as well as our current challenges with emerging threats such as MRSA.

During his opening remarks at the plenary session, Collins encouraged intramural scientists to use the Research Festival as an opportunity to interact and trigger collaborations with researchers at other institutes. "We all have our own circles that we mix and mingle with in terms of our research interests," said Collins, "but here's a chance to enlarge your circle in a much bigger and broader way…to really expand your horizons."

The plenary session included three dynamic big-vision talks that featured eminent cutting-edge research within the intramural program and proposed future applications for research at the NIH. "The plenary session was fantastic because it captured the very essence of NIH intramural programs," said **Antonello Bonci** (scientific director in the National Institute on Drug Abuse), who co-chaired the event with **Constantine Stratakis** (scientific director at NICHD). "It was diverse in scientific interests and disciplines," Bonci continued. "Cutting-edge and highly innovative yet very much in synergy with each other."

ERNIE BRANSON

Joseph James Kinyoun, the founder of the precursor to NIH in 1887, made an appearance at the 2012 Research Festival to address the things that continue to haunt him 93 years after his death. Kinyoun was played by intramural scientist David Robinson (NIAID) who enjoys being an actor in his spare time.

"It was our very own voyage of the Intrepid, led by four fearless NIH explorers, past and present," said Stratakis.

Gary Gibbons described his research on the etiologies of racial health disparities in cardiovascular disease (CVD) using a multilevel biosocial approach. His group conducted a study that found that obesity prevalence was a key driver in CVD. Certain lifestyle determinants, including lower physical activity and lower fruit and vegetable intake, serve as drivers for obesity. "We recognized that where you live, work, and play [has] an impact on your health," said Gibbons, who's the director of NHLBI. While studying health maladies from a social context is provocative, it is now supported by research that demonstrates how behavior permeates through a social network. Ultimately, biosocial systems may predict who is at risk for a particular disease and to design preemptive treatments long before clinical symptoms develop.

Jennifer Lippincott-Schwartz (NICHD) studies cellular organization and function using photoactivatable fluorescent proteins and a technique she helped develop at NIH, known as photo-activated localization microscopy (PALM). Unlike conventional microscopes that have a best resolution of 250 nanometers, a PALM setup has an X-Y resolution of 20 nanometers, which creates sharp super-high-resolution images. Lippincott-Schwartz pointed out "how important technology is in order for us to continually move forward in our discoveries about basic scientific processes as well as diseases." She explained how navigating the cellular landscape with new optical probes and imaging strategies, allows her group to quantify and monitor protein and organelle turnover in cells and determine how molecules are organized and clustered for signaling within the plasma membrane.

Ron Germain (NIAID) uses multiphoton intravital imaging to study the role of anatomy in the operation of the immune system. When tissue is damaged, neutrophils rapidly congregate in the region of damage. "But how do these cells know that there is damage there and to [go] into this region?" Germain the audience. He explained how his research shows that integrin-mediated adhesion is essential for neutrophil migration to the central lesion.

Germain is also interested in what keeps pathogens from spreading in the lymph before the adaptive immune system kicks in. His group found that macrophages in

lymph nodes are critical in preventing bacterial movement into the lymphatic system. His work also indicates that the lymph node is a site of adaptive immunity, where lymphocytes are localized to the periphery near pathogen entry portals. These fantastic voyages into the heart of the immune system will drive future multiscale approaches in predictive immunology.

To celebrate the history of NIH, a very special guest addressed the audience next. **Joseph James Kinyoun** was the founder and first director of the Marine Hospital Service Laboratory of Hygiene in 1887. Although Kinyoun died in 1919, he made an appearance at the 2012 Research Festival to address three things that continue to haunt him 93 years after his death. "I have been resting uneasy with unfinished business," announced Kinyoun (played by **David Robinson**, assistant scientific director at NIDCD), who referenced several diseases that were rampant during his lifetime, the need for the transfer of organs to extend human life, and the need for federal investment in a national research enterprise. Deputy Director of Intramural Research **Michael Gottesman** assured Kinyoun that he could rest easy knowing that many of those diseases have since been eradicated, that the technique of organ transplantation is in use today, and that in 1930 Congress renamed Kinyoun's Laboratory of Hygiene the National Institute of Health. A 64-page booklet of Kinyoun's legacy, *The Indispensable Forgotten Man*, written by **David Morens** and **Anthony Fauci**, can be downloaded from the festival Web site (http://researchfestival.nih.gov/2012/kinyoun.pdf). An article about Kinyoun also appears in this issue of the *Catalyst* (page 6).

The plenary session ended with a panel of three distinguished intramural investigators—William Paul, Judy Rapoport, and Stephen Katz—who discussed their experiences at NIH and why they choose to do their research here. **William Paul** (NIAID), who first came to NIH as a medical student in 1959, pointed out that there is a sense of noncompetitiveness in the intramural community that doesn't exist in other research institutions. "I can count on my colleagues to want my work to succeed and to do everything they can do to help it," said Paul. "And I feel the same way [about their work]."

Judy Rapoport (NIMH) was one of the first investigators to start child psychiatry research at NIH. One of the strengths of working at NIH, according to Rapoport, is the ability to study rare disorders such as childhood schizophrenia. "It's been the sense of an imaginative, flexible, and very empathic administration, together with other things easing the road for clinical research, that has made it very hard to consider moving anywhere else."

Stephen Katz (NIAMS), who came to NIH in 1974 as a principal investigator in dermatology, said that part of what makes NIH such a great place to work is the ability to join clinical practice with basic science. "We have time here," said Katz. "We have time for patients, we have time for research, and we have time for collaborations."

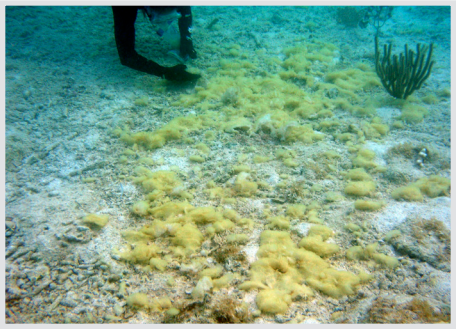
SELECTED SYMPOSIA

USING CHEMISTRY TO UNRAVEL BIOLOGY

BY LAURA STEPHENSON CARTER

Chemists make the world go round … in the way that their work helps scientists understand biology in action.

To understand the biology of addiction, **Amy Newman** (NIDA) uses chemistry to develop fluorescent tropane-based tools to visualize monoamine transporters in action in the central nervous system. Cocaine, a highly addictive drug that binds to all three



MICHAEL BEWLEY

Carole Bewley (NIDDK) shown collecting rare *Chrysophaeum taylori* algae when she was scuba diving in the Virgin Islands. In the lab, she extracted chrysophaentin A, a natural compound that killed every gram-positive drug-resistant organism it came into contact with.

monoamine transporters, is a tropane-based molecule and provides the template for these tools. Newman confessed that 20 years ago, when she was doing her postdoctoral training in NIDDK, she published research on another fluorescent compound she had developed, but her paper was never cited.

"I'd like to think we were ahead of our time," she told the chemistry fans who had gathered to hear her talk. But today, her papers are cited aplenty. Her work demonstrates that the combination of state-of-the-art synthetic organic chemistry techniques with molecular modeling and interpretation of pharmacological data has resulted in the discovery of important molecular probes for studying neurochemical targets. She hopes this multidisciplinary approach will provide new leads toward the development of pharmacotherapeutic agents that can be used to treat addiction.

To understand the biology of antibiotics, **Carole Bewley** (NIDDK) uses chemistry to trap anti-infective targets of marine natural products. She told a story of how in 2007, she was snorkeling with her family in the Virgin Islands when she found a fluffy yellow organism. She gathered some samples, took them back to her NIH lab, and extracted what she thought was a cyanobacterium. But the isolate turned out to be a rare alga that produced chrysophaentin A,

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a natural compound that killed every gram-positive drug-resistant organism—such as methicillin-resistant *Staphylococcus aureus*—it came into contact with. With the help of the postdocs and a graduate student in her lab, Bewley determined that the compound inhibits the bacterial cytoskeletal protein FtsZ, an enzyme necessary for the replication of bacteria. Bewley's discovery has been patented by NIH; NIDDK is looking for collaborators to further develop, evaluate, or commercialize the chrysophaentin antibiotics.

Many other NIH chemists are developing and using molecular tools to help their colleagues—chemists and nonchemists alike—gain a better understanding of biology.

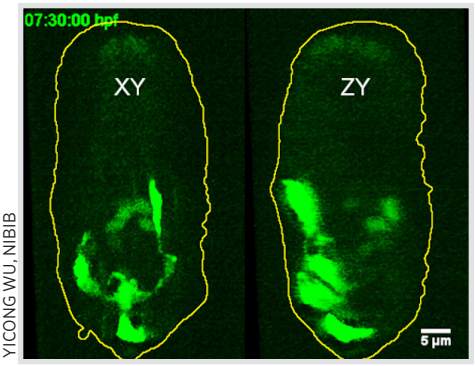
From the 2012 Research Festival's session "Molecular Tools; Using Chemistry To See, Wrestle, Unravel, and Trap Biology," chaired by Amy Newman (NIDA) and Dan Appella (NIDDK); held on October 10, 2012.

QUANTITATIVE BIOLOGY AT THE SINGLE-CELL LEVEL

BY LESLEY EARL, NCI

Whether individual cells make up the developing brain, the salivary gland, or a cancer mass, each has a unique story of growth, migration, and signaling. NIH researchers use a variety of live-cell imaging techniques to study real-time changes in individual cells.

What's important, said **Hari Shroff** (NIBIB), is figuring out how to capture images of cells without killing them. "Usually, if you try to increase the resolution or try and go faster, you end up destroying the cell, also faster." His solution is inverted microscope selective-plane-illumination spectroscopy (iSPIM), a technique in which a thin sheet of light illuminates a single plane within a three-dimensional specimen. Using iSPIM, Shroff captures images of



YICONG WU, NIBIB

Hari Shroff used iSPIM, an advanced imaging technique, to view neurons migrating in the developing roundworm embryo. Lateral (left) and axial (right) fluorescent images are depicted seven and a half hours into embryogenesis.

neurons as they grow and migrate within live, developing *Caenorhabditis elegans* (roundworm) embryos.

Myong-Hee Sung (NCI) takes a different approach. She uses mathematical modeling and an optical imaging technique called fluorescence recovery after photobleaching (FRAP) to study the dynamics of the transcription factor nuclear factor–kappa light-chain-enhancer of activated B cells (NF-kappaB) as its activity oscillates on and off. By using single-cell imaging, Sung reveals continuing asynchronous oscillations of NF-kappaB activity in individual cells, oscillations that dictate unique transcription events. And with new technologies, such as temporal image-correlation spectroscopy, which improves upon conventional FRAP, Sung is beginning to study the spatial heterogeneity of NF-kappaB within the nucleus itself.

From the 2012 Research Festival's session "Quantitative Biology at the Single Cell Level," co-chaired by Eric Batchelor (NCI) and Myong-Hee Sung (NCI) and held on October 9, 2012.

To see a videocast of the 2012 Research Festival plenary session presented on October 9, 2012, go to http://videocast.nih.gov/launch.asp?17606

BEYOND THE FIG LEAF

BY ERIKA GINSBURG, NCI

Biomedical scientists are beginning to realize that they must take sex and gender into consideration when studying diseases or developing treatments and therapeutic devices. Sex (male or female) and gender (behavioral, cultural, or psychological traits associated with one sex) are terms used to categorize similarities and differences in perception, experience, treatment, and outcome of disease.

Cardiologist **Nakela Cook** (NHLBI) presented staggering data on the prevalence of heart disease in women. Cardiovascular disease (CVD) kills about 400,000 women each year—more than cancer. Each year, about one in 31 female deaths is from breast cancer, but one in four is from heart disease. Yet there is an underperception of risk and an under-recognition of symptoms in women. Smoking, obesity, and high blood pressure put both sexes at risk for heart disease, but in women other risk factors include pre-eclampsia (hypertension in pregnancy), gestational diabetes, and a total cholesterol concentration of over 200 milligrams per deciliter of blood.

Men and women have different symptoms, too. Both may experience chest pain during a heart attack, but a man may feel a vise-like pressure whereas a woman may feel a stabbing, pulsating, or sharp pain. Women are also more likely to report nausea, shortness of breath, or abdominal pain—unexpected symptoms that can lead to misdiagnosis and delays in treatment.

Compounding the problem is that clinical trials for CVD therapies and devices have tended to enroll fewer women than men and have failed to report sex-specific results. Cook emphasized the need for an increased enrollment of women in trials for heart disease.

The battle of the sexes is not over when it comes to pain, according to Women and

Sex/Gender Differences Research Coordinator **Cora Lee Wetherington** (NIDA). Pain disorders are more prevalent in women than in men, including pain disorders of the head (migraines are more common in women and cluster headaches in men), neck, shoulder, hips, mid-abdominal, finger joint, and mandibular areas. In addition, more women than men suffer from fibromyalgia, rheumatoid arthritis, osteoarthritis, and multiple sclerosis.

Women's increased sensitivity to pain may be attributable to differences in the nervous system's processing of pain, sex hormones, genetics, gender roles, mood, emotions, and stress and coping mechanisms. Women even respond differently to treatments for pain. Research on sex-differences data analysis in animal-models and better studies that include women could provide clues to effectively managing chronic pain in both men and women, said Wetherington. And that's good news for everyone.

From "Beyond the Fig Leaf: The Science of Sex and Gender Differences," chaired by Janine Clayton (Director, ORWH) and held on October 9, 2012. To see a videocast, go to http://videocast.nih.gov/launch.asp?17607

ONE GENE, ONE DISEASE, TWO RACES: A TRANSATLANTIC JOURNEY

BY TANIA LOMBO, NCI

Given the way humans migrate throughout the world, few ethnic groups are completely free of genetic mixing. NIH researchers are trying to understand how ethnic differences—and the underlying genetics—may play a role in noncommunicable diseases.

Cheryl Winkler (NCI's Frederick National Laboratory for Cancer Research) and **Jeffrey Kopp** (NIDDK) are using admixture mapping to trace genetic traits in people of mixed ancestry such as African Americans. Compared with European Americans, African Americans have a higher risk of developing chronic kidney disease (CKD).

Winkler and Kopp and collaborators at Harvard Medical School (Boston) found that two sequence variants (G1 and G2) of the apolipoprotein-1 gene (APOL1), on chromosome 22, increased the risk of the kidney diseases focal segmental glomerulosclerosis, human-immunodeficiency-virus-associated nephropathy, and hypertension-attributed kidney disease. Recently Winkler reported on a strong association between CKD and APOL1 variants in African Americans with hypertension: Those with two risky variants of the gene are much more likely to develop progressive kidney disease (*Kidney Int* DOI:10.1038/ki.2012.263).

The APOL1 variants are not all bad, however. They are also key to the host defense against *Trypanosoma brucei*, the parasite responsible for African sleeping sickness. A single copy of the renal risk allele protects against sleeping sickness whereas two copies increase the risk for kidney disease. In the United States, 46 percent of African Americans carry one of the two APOL1 risk variants and 11 to 15 percent carry both.

On the other side of the Atlantic, these variants—especially G1—occur more often in West Africans. APOL1 risk variants also occur frequently in populations with recent African ancestry and are absent in other populations. Winkler and colleagues hypothesize that the risk variants, while critical for survival in Africa, may contribute to the high rates of renal disease in African Americans.

Winkler will continue to investigate the relationship of APOL1 risk alleles as well as the molecular mechanisms of the ApoL1 protein in CKD. She hopes her work will lead to improved diagnostic and therapeutic options for people with kidney disease. She and her colleagues will explore whether there is a role for APOL1 genetic testing in personalized medicine to identify individuals at particular risk for kidney disease and if so, to initiate periodic health screening and early therapy.

From the 2012 Research Festival's session "Health Disparities: Advances in Translational, Clinical, and Population Sciences," co-chaired by Anil Wali (NCI) and Jeffrey Kopp (NIDDK); sponsored by the NIH Translational Research Interest Group and held on October 10, 2012.

UNDERSTANDING PARKINSON DISEASE

BY KRISTINA MCLINDEN, NINDS

Parkinson disease (PD) is an insidious neurodegenerative disease that affects more than one million older adults in the United States and destroys dopaminergic neurons within a region of the midbrain known as the substantia nigra. PD causes tremors, slowed movement, rigid muscles, difficulty walking, and changes in speech. At the first noticeable sensation of motor impairment, up to 80 percent of these neurons have already succumbed to the disease. Researchers such as **Honglei Chen** (NIEHS) understand the importance of developing a means to detect PD early. He is using data from several large population studies to track patients with clusters of premotor symptoms such as loss of smell, constipation, and sleep disturbances. None of these symptoms guarantee that an individual will develop PD, but Chen hopes to identify and predict who is at risk for the disease and to understand the early disease etiology.

Postdoctoral fellow and Fellows Award for Research Excellence (FARE) winner **Sarah Rothman** (NIA) is also unraveling the mysteries of PD. She is focusing on a mutation in the gene that codes for

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the protein alpha-synuclein, which makes up Lewy bodies (abnormal aggregates of protein) that develop in dopaminergic neurons in PD patients. She noticed that mice with the mutation did not gain weight even when fed a high-calorie diet. Rothman then reviewed published clinical literature on human PD patients and learned that certain patients experienced weight loss and a lower rate of diabetes. Rothman went back to her mouse studies and confirmed that PD mice fed a high-calorie diet expended more energy, showed better insulin regulation, and had less body fat than normal mice fed the same high-calorie diet. She explained that a possible mediator of this effect might be decreased concentrations of leptin—a hormone responsible for suppressing appetite—in the mouse model and in people with PD.

From the 2012 Research Festival's "Translational Research of Aging" session, co-chaired by Francesca Macchiarini (NIAID) and Ron Johnson (NCI); sponsored by the Geroscience Interest Group, and held on October 10, 2012.

THE PERILS OF "NO" DYSREGULATION

BY MARIE SIWICKI, NIAID

The role of nitric oxide (NO) in malaria and sickle cell disease stole the show as one of the hot new research topics featured at the 2012 Research Festival. In healthy individuals, NO is a vasodilator that promotes vascular homeostasis and proper blood flow. But different conditions disrupt normal NO function, impeding its production or siphoning it away from its everyday targets.

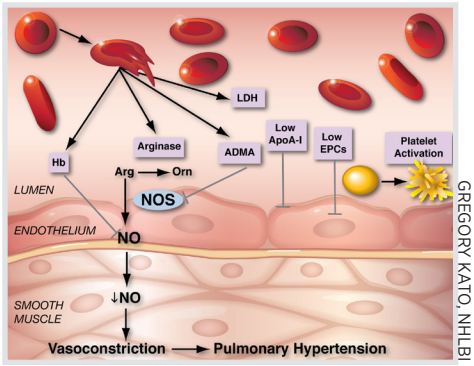
The malaria and sickle cell research teams are working together to understand how an acute infection (malaria) and a chronic genetic disorder (sickle cell) cause disruption in blood flow to vital organs. They hope to test new therapeutics to restore red blood cell and vessel-wall function.

Matthew Alkaitis, a graduate student in **Hans Ackerman**'s lab (NIAID), does research on NO depletion during malaria. Malaria is caused by Plasmodium parasites, which are transmitted by certain mosquitoes. Symptoms of severe malaria are linked to vascular dysfunction—blood vessels become stressed and constricted, the parasites cling to vessel walls, and red blood cells have a harder time squeezing through small capillaries. These problems appear to have their roots in disrupted NO signaling.

Normally, NO formation depends on both the amino acid arginine and the cofactor tetrahydrobiopterin (BH4). While it is known that arginine concentrations drop in people with malaria, Alkaitis is examining an apparent reduction in BH4 as well. He is exploring whether BH4 could be a tool for restoring healthy NO signaling and stabilize the vascular system of infected patients while they undergo antiparasite treatments.

Gregory Kato (NHLBI) studies NO in the context of sickle cell disease, a genetic disorder causing crescent-shaped red blood cells that are rigid and fragile. When these cells rupture, free-floating hemoglobin spills into the bloodstream and binds up NO, stealing it away from its normal targets. The shortage of NO appears to contribute to the development of pulmonary hypertension and possibly leg ulcers. Kato has been pioneering ways to study and prevent these types of blood-system disruptions in sickle cell disease in order to shed light on associated life-threatening complications.

From the 2012 Research Festival's session "Common Molecular Mechanisms Underlying Pathogenesis and Treatment of Human Diseases," co-chaired by Minkyung (Min) Song (NCI) and Joel Moss (NHLBI); sponsored by the Translational Research Interest Group, and held on October 11, 2012.



GREGORY KATO, NHLBI

In sickle cell disease, when red blood cells burst, one result is the release of free hemoglobin (Hb), that aggressively binds up nitric oxide (NO), stealing it away from its normal targets. Life-threatening problems such as pulmonary hypertension can result.

CANCER STEM CELLS (ALMOST) IN A DISH

BY CHRISTOPHER WANJEK

Cancer stem cells (CSCs) are enigmatic players in the cancer field, and some scientists even question their existence. But **Tom Misteli**'s lab (NCI) has created something that behaves a lot like a CSC, and this feat has many in the field excited.

Paola Scaffidi, a staff scientist in NCI's Cell Biology of Genomes Group, which Misteli heads, has generated human cells with CSC properties in a culture dish by reprogramming somatic cells. Her work has demonstrated, for the first time, that somatic cells still possess enough plasticity to acquire CSC properties through oncogenic manipulation and may be the origin of some cancers.

This work also may provide a controlled system to study the biology of CSCs, which has been hampered by scientists' inability to isolate pure CSC populations and manipulate them ex vivo.

According to the CSC hypothesis, cancers are hierarchically organized; a subset of cells, the CSCs, drives cancer growth. These CSCs are defined by their ability to

initiate tumors and maintain their growth, to self-renew, and to differentiate into heterogeneous, nontumorigenic cancer cells.

Scaffidi and Misteli pulled off this trifecta with human skin fibroblasts. They built upon the work of the Bob Weinberg lab at the Massachusetts Institute of Technology (Cambridge, Mass.) by stably expressing human telomerase reverse transcriptase (hTERT), the oncogenic HRASV12 mutant protein, and the simian vacuolating virus 40 large T- and small T-antigens.

Their process transformed a subpopulation of fibroblasts into a more primitive, multipotent cell type that possessed all the hallmarks of CSCs and subsequently generated hierarchically organized tumors when injected into immunocompromised mice.

Much of this work was performed last year and described in a *Nature Cell Biology* paper (*Nat Cell Biol* **13:**1051–1061, 2011). Scaffidi said she has since begun to characterize genetic and epigenetic events associated with CSCs' tumorigenicity with the goal of uncovering new mechanisms of tumorigenesis and therapeutic targets.

These cells might be the first step toward understanding CSCs, along the lines of the aphorism scrawled on famed physicist Richard Feynman's chalkboard, "What I cannot create, I do not understand." Look for Scaffidi's grand rounds talk on November 16, 2012, at which she will further explain her most recent work.

From the 2012 Research Festival's session "Stem Cells in Development and Disease," chaired by Steven Hou (NCI) and held on October 10, 2012.

MATRIX BIOLOGY AND REMODELING

BY SILVIYA ZUSTIAK, NICHD

Extracellular matrices (ECMs)—various interlocking meshes in which cells are embedded and that are composed of fibrous proteins, proteoglycans, and other molecules—make up the scaffolding that supports our cells, segregates tissues, and regulates intercellular communication. A well-functioning ECM is essential for development, morphogenesis, wound healing, and other physiological processes. But a misregulated matrix can cause damage ranging from macular degeneration, to arthritis, to tumor metastasis.

To fully understand how the ECM works, scientists need to study it in as natural an environment as possible. The trouble is that, until recently, most research was based on studies in conventional two-dimensional (2-D) cell culture. **Kenneth Yamada** (NIDCR), however, has been promoting the use of cell- and tissue-culture systems that mimic the natural ECM. His research team explored how matrix dimensionality (a fiber, a flat surface, or a gel, referred to as 1-D, 2-D, and 3-D, respectively) and matrix type (collagen, fibrin, or cell-derived matrices) regulate cell behavior.

Each different dimension and type of ECM tested had distinct effects on cell signaling and migration. For example, in 2-D environments, the signaling activity of Rac and other proteins at the front of the cell direct it to migrate forward. But Yamada's team recently discovered that, in a 3-D cell-derived ECM, the same signaling is not required for efficient cell migration. Consequently, scientists need to rethink how cell migration is regulated in 3-D environments.

Yamada then expanded on the recent concept that ECM molecules can have major signaling roles beyond their structural functions, by describing two examples. The ECM proteins fibronectin and anosmin turn out to have distinct, dramatic effects on cell signaling, expression of specific genes, and even on the activities of individual growth factors during embryonic morphogenesis of salivary glands and the face.

Yamada's work on cell-matrix interactions sheds light on how cells interact naturally with the ECM and lays the groundwork for developing ideal microenvironments for tissue engineering.

From the 2012 Research Festival's session "Matrix Biology and Matrix Remodeling," chaired by Keir Neuman (NHLBI) and held on October 10, 2012.

MYSTERIES OF THE MICROBIOME

BY STEPHANIE COOPERSTEIN

There are trillions of microbes on or in the human body—10 times as many organisms as the number of human cells—and most of them are beneficial to us. As part of the Human Microbiome Project (HMP), which NIH launched in 2007, researchers at universities, scientific institutions, and NIH are characterizing the microbes found in different regions of the body, including the nose, mouth, skin, digestive tract, and vagina.

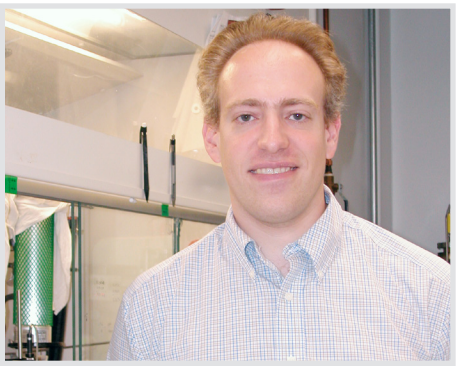
Christian Abnet (NCI) is characterizing the upper gastrointestinal tract's microbiome and investigating the roles of poor oral health and bacteria in the development of cancers of the esophagus and stomach. **Laurel Lagenaur** (NCI) is doing research on biotherapeutic approaches to preventing human immunodeficiency virus infection. To read more about their work in an expanded version of this article, go to: http://irp.nih.gov/catalyst/v20i6/nih-research-festival-bigger-and-better.

From the 2012 Research Festival's session "Microbiome Research at the NIH: From Disease to Therapeutics," chaired by Rashmi Sinha (NCI) and Leigh Greathouse (NCI); sponsored by the Microbiome Working Group and held on October 10, 2012

Lin Asks Why

A Small-Molecule Drug to Kill HIV: An Interview with Dan Appella

BY LIN WANJEK, SPECIAL TO THE *NIH CATALYST*



BELLE WARING, OD

NIH CHEMIST DAN APPELLA (NIDDK)

Dan Appella leads the Synthetic Bioactive Molecules Section in the Laboratory of Bioorganic Chemistry in the National Institute of Diabetes and Digestive and Kidney Diseases. He works collaboratively with NIH researchers on a variety of projects including the design of a small molecule that kills human immunodeficiency virus (HIV). Dan sat down recently with inquisitive five-year-old *NIH Catalyst* intern Lin Wanjek-Yasutake, who cut to the chase with a set of hard-hitting questions.

Lin: What are you doing?
Dan: I'm making molecules.

Lin: Why?
Dan: Well, if we know how some of these molecules affect biology, we can use them to help people who are sick.

Lin: Why?
Dan: Because people who are sick want to feel better. For example, one of the projects I'm working on is to make a new medicine for HIV that we think won't create new resistant viruses. It's a very simple molecule, which I think is nice.

Lin: Why?
Dan: With a simple molecule—very easy to make, two steps done in one pot—we can more easily study the biology to make sure it works well and that it's safe in a variety of animal models. What's most interesting is that the molecule attacks the virus through a different mechanism than what most people think about. There's great potential here.

Lin: Why?
Dan: Well, most of the drugs stop the virus from working by attacking protease or integrase or reverse transcriptase. But we are trying to target a nucleocapsid protein, which has been attacked before but by molecules that are not as good. We have molecules now that are a lot better than what were studied in the mid- to late-1990s. And so far, our molecule seems to be nontoxic. The key difference is that our drug modifies the protein permanently so it can never work again.

Lin: Why?
Dan: Because a transfer of an acyl group from our molecule to this nucleocapsid protein makes it fall apart. This is quite different from how a lot of drug development works today. Most people want noncovalent binders.

Lin: Why?
Dan: Binders are very sticky. They gum up a virus. For a long time, drug companies have been trying to get away from covalent-modifying drugs because many are toxic. But now there's interest in re-examining some of these things. Look at aspirin—it covalently modifies lots of things. We are still trying to figure out our molecule, but we believe it has features that give it good specificity to the HIV target.

Lin: Why?
Dan: The guiding principle is the HIV target itself; it's a unique structure that is very different from what you would see in a healthy human being. The proof, of course, is in the final experiments so we continue to study this.

Lin: Why?
Dan: The payoff would be huge. This is a collaborative project with several NIH investigators. In fact, I'm working on this, in part, with my dad, who...

Lin: My dad?
Dan: No, my dad [Ettore Appella]. I think your dad [Christopher Wanjek] is a writer. My dad is a researcher at the National Cancer Institute and has been studying the approach for years. I've come in as the chemist to help move the project forward. We published a paper about the mechanism of this molecule in *Nature Chemical Biology* in 2010 [*Nat Chem Biol* 6:887–889, 2010]. The mechanism is interesting—instead of one molecule taking out one target, ours does one covalent transfer, and then the cells reactivate it to its active form again. So you have this catalytic turnover that attacks the HIV target. We are hoping we can pick up on that aspect of this molecule.

CHRISTOPHER WANJEK

IF YOU HAVE A HIGH-RISK, HIGH-REWARD PROJECT TO RELAY, CONTACT US AND WE'LL SEND LIN WANJEK-YASUTAKE (ABOVE) TO GRILL YOU ON THE DETAILS.

Lin: Why?

Dan: This recycling aspect is very intriguing. The molecule keeps on going to kill all the viruses. Also, it's my gut instinct that, to clear the virus, you will have to have something very small that circulates extensively through the body. It's clear that the HIV virus hides very, very well. A small molecule could permeate every hiding place where this virus could be.

Lin: Why?

Dan: Well, precisely because it is small. The molecule itself would find the nucleocapsid protein in an infected cell, knock it out, and prevent the virus from maturing. Now, if I can anticipate your next question, let me repeat that there's a transfer of an acyl group from our molecule to the protein target. That transfer results in an unfolding of this protein. Its actual place on the protein is a zinc finger. There's a zinc atom in the middle, and it's coordinated by amino acids, like a loop. Upon our molecule's transfer to the finger, the zinc falls out, the protein falls apart, and it can no longer bind HIV RNA and further maturation.

Lin: Why?

Dan: Well, the interesting thing is that the virus still buds off the infected cell, but it no longer works. We are messing up the maturation of the virus in a way that's similar to protease inhibitors.

Lin: Why?

Dan: Protease inhibitors prevent the protease enzyme from making maturation-essential cleavages in the proteins made by virus. There's a similarity between the actions of our molecule and protease inhibitors, but some strains of HIV have become resistant to protease inhibitors. Our molecule may be able to avoid the resistance problem. But with any drug development, you want to know, what's the likelihood this molecule will become a drug? The odds are against us. This is a high-risk, high-reward project.

Lin: Why?

Dan: It will take a long time to prove whether our molecule is beneficial, and there's a chance that it won't be. But, from my standpoint, this is an overlooked area of drug development. What I like the best is that our molecule can knock out more than one target. Our serendipitous discovery is interesting for future drug-design studies even if it turns out that our molecule isn't great for HIV. Perhaps the recycling and reactivation mechanisms can be translated to other therapies. I don't know of anything else like this in drug development.

Lin: Why?

Dan: Good question. That's what I'm wondering. Note, of course, there could be something we overlooked. The field of medicine is huge. There is this idea of pro-drugs—something that gets activated by the body and attacks the target. But our molecule, once it gets going, keeps reactivating itself. So, in light of all of this, I hope you can understand the potential of our drug.

Lin: OK. Bye.

Dan: Wait! Don't forget your stuffed kitty.

Lin: Oh, thanks!

NEW NAME

NCI-Frederick was renamed the Frederick National Laboratory for Cancer Research (FNL) recently. Find out more at its new Web site (http://frederick.cancer.gov/) and in an upcoming issue of the *NIH Catalyst*.

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
DOE: Department of Energy
FAES: Foundation for Advanced Education in the Sciences
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
NCCAM: National Center for Complementary and Alternative Medicine
NCBI: National Center for Biotechnology Information
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


MANFRED BOEHM,NHLBI


JASON BRENCHLEY, NIAID


SERGI FERRÉ, NIDA


MICHAEL SACK, NHLBI


KELLY TEN HAGEN, NIDCR

MANFRED BOEHM, M.D., NHLBI

Senior Investigator, Center for Molecular Medicine

Education: University of Heidleberg, Germany (M.D.)

Training: Residency in internal medicine at the Franz Volhard Clinic (Berlin); research fellow at Max Delbrueck Center for Molecular Medicine (Berlin)

Came to NIH: In 1999 as a research fellow in NHLBI; became investigator in 2003

Outside interests: Spending time with his family

Research interests: My primary research interests are in vascular biology and the genetics of vascular remodeling in human diseases. My group developed complex animal models and patient-specific disease models, including induced-pluripotent-stem-cell–based systems, to understand the cellular and molecular mechanisms of vascular remodeling in rare or unknown inherited and acquired vascular diseases. We revealed new signaling pathways pivotal for balanced vascular wound repair, described a new concept of cellular contributions during vascular remodeling, and identified a new inherited vascular disease that causes arterial calcifications in adults. By gaining a more comprehensive knowledge of the cellular contributions and pathways involved in vascular remodeling, we hope to contribute to the development of potential therapeutic applications in regenerative medicine.

JASON BRENCHLEY, PH.D., NIAID

Senior Investigator, Laboratory of Molecular Biology

Education: Idaho State University, Pocatello, Idaho (B.S. in microbiology and chemistry; M.S. in chemistry); University of Texas Southwestern Medical Center at Dallas (Ph.D., Immunology)

Training: Postdoctoral fellowship in NIAID's Vaccine Research Center

Came to NIH: For training in 2004; in 2008 joined the Laboratory of Molecular Microbiology

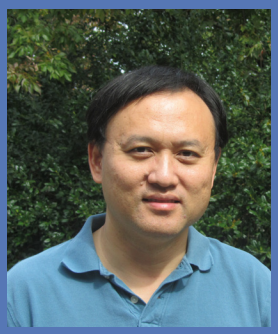
Selected professional activities: Deputy director, Wellcome Trust NIH Ph.D. Program: Scientific Advisory Committee member of amfAR, the Foundation for AIDS Research

Outside interests: Snowboarding; hiking; fishing

Research interests: We aim with our work to better understand the mechanisms that underlie the progression of human immunodeficiency virus (HIV) disease. The immune system, particularly its T-cell arm, plays a central role in HIV pathogenesis. Our long-term goal is to use the knowledge gained through these studies to develop novel therapeutic approaches. We use multiple nonhuman primate models with differing disease progression courses. We also study T-cell immunology in people infected with HIV and nonhuman primates infected with simian immunodeficiency virus (SIV) to elucidate mechanisms of disease progression. In one of our main areas of research, we are investigating the mechanisms underlying lack of disease progression in natural hosts of SIV. Several species of African nonhuman primates are naturally infected with SIV but do not develop simian AIDS. SIV-infected African green monkeys, for example, are capable of downregulating the CD4 receptor for SIV. We are studying the molecular mechanisms responsible for this downregulation and trying to determine whether other natural hosts for SIV are also able to downregulate CD4.

In a study with Asian macaques, we have shown that one cause of immune activation during the chronic phase of SIV infection is the translocation of microbial products from the lumen of the gastrointestinal tract into peripheral circulation. Moreover, our data suggest that the epithelial barrier of the gastrointestinal tract is damaged during chronic infection and allows

If you have been recently tenured, the *NIH Catalyst* will be contacting you soon about including you on these pages.



KAI YU, PH.D., NCI-DCEG

microbial products to translocate directly into the lining. In our studies with pigtail macaques, we aim to link the rapid disease progression with increased microbial translocation. We will then study therapeutic interventions aimed at decreasing microbial translocation and disease progression in these animals.

SERGI FERRÉ, M.D., PH.D., NIDA

Senior Investigator; Chief, Integrative Neurobiology Unit

Education: Faculty of Medicine, Central University of Barcelona, Spain (M.D.); Faculty of Medicine, Autonomous University of Barcelona, Spain (Ph.D.)

Training: Residency in neurology, Hospital de Sant Pau, Faculty of Medicine, Autonomous University of Barcelona; postdoctoral training at the Karolinska Institute (Stockholm)

Before coming to NIH: Tenured investigator, Spanish Research Council, Barcelona; guest scientist at the Karolinska Institute

Came to NIH: In October 2000

Selected professional activities: Guest professor in biochemistry and molecular biology at the University of Barcelona; adjunct associate professor in pharmacology and experimental therapeutics at the University of Maryland School of Medicine (Baltimore)

Outside interests: Opera singing; swimming; running; spending time with family

Research interests: We are interested in the role of receptor heteromers as targets for drug development in neuropsychiatric disorders and drug addiction. Receptor heteromers are higher-order molecular entities that have unique biochemical and functional properties that may be harnessed for therapeutic purposes. Our research deals with the discovery of heteromers of receptors that are localized in brain circuits involved in addictive behaviors and include metabotropic receptors (G-protein-coupled receptors) such as those for dopamine, glutamate, cannabinoid, and adenosine. We analyze the biochemical and pharmacological properties of these receptors at the cellular level as well as in vivo.

At the cellular level, we use mammalian cell lines transfected with the receptors to demonstrate receptor heteromerization. We then look for the unique receptor heteromer's biochemical properties, which can be used as a "biochemical fingerprint" to identify it in the brain. We use in vivo models—including intracranial electrical stimulation, in vivo microdialysis, and functional magnetic resonance imaging—to evaluate the functional significance of receptor heteromers. The cellular and in vivo models complement each other and are the basis for finding receptor heteromer–selective drugs.

MICHAEL SACK, M.D., PH.D., NHLBI

Senior Investigator, Laboratory of Mitochondrial Biology and Metabolism

Education: Medical School: University of the Witwatersrand, South Africa (MBBCh, MSC in medicine); University of Cape Town, Medical School, South Africa (Ph.D. in molecular biology)

Training: Residency in internal medicine at Georgetown University Medical Center (Washington, D.C.); cardiology fellowship at Washington University Medical Center, Barnes Hospital (St Louis, Mo.)

Before coming to NIH: Senior lecturer at University College London Medical School; assistant professor at the University of Cape Town Medical School, South Africa

Came to NIH: In January 2003

Selected professional activities: Organized Keystone Mitochondrial Meeting and International Mitochondrial Meetings at NIH; established a cardiovascular disease–discovery clinical protocol enabling research into uncommon diseases with cardiovascular risk or manifestations

Outside interests: Spending time with family and friends; hiking; cooking; reading nonfiction literature; following European soccer

Research interests: My laboratory focuses on the biology of mitochondrial regulation in diabetes and cardiovascular disease. We are investigating the role of the mitochondrial acetylome (the complete set of acetylated mitochondrial proteins) as a nutrient and caloric-load sensing program in modulating mitochondrial homeostasis. In one of our studies, we are identifying and characterizing the counter-regulatory mitochondrial acetyltransferase molecular machinery of the protein sirtuin 3 (SIRT3). We recently showed that SIRT3-dependent deacetylation of mitochondrial proteins increases acetaminophen liver toxicity. We have also identified a principal component of the mitochondrial acetyltransferase program and are exploring its role in mitochondrial function and in caloric-excess-associated diseases.

We are also studying the protein Parkin, which plays a pivotal role in mitochondrial quality control and when mutated is linked to some cases of premature-onset Parkinson disease. We were surprised to find that Parkin stabilizes the fatty acid translocase CD36 and that Parkin deficiency protects against fatty liver and insulin resistance in mice. We are now exploring this interaction

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

between lipid metabolism and the pathophysiology of Parkinson disease in patients with Parkin mutations who are participating in a study at the Clinical Center.

KELLY TEN HAGEN, PH.D., NIDCR

Senior Investigator; Chief, Developmental Glycobiology Section

Education: Cornell University, Ithaca, N.Y. (B.S. in biology); Stanford University, Stanford, Calif. (Ph.D. in genetics)

Before coming to NIH: Research assistant professor at the University of Rochester (Rochester, N.Y.)

Came to NIH: In 2001 as senior research fellow in NIDDK; in 2005, was appointed chief of NIDCR's Developmental Glycobiology Unit

Selected professional activities: Federal liaison for the Society for Glycobiology; editorial board member for *Glycobiology* and the *Journal of Biological Chemistry*

Outside interests: Skiing; ice skating; traveling; seeing movies; enjoying relaxing rides home on I-270

Research interests: Cells of the body are decorated with a variety of sugars or more complex carbohydrates that serve many diverse functions. These molecules not only act as a protective barrier on the outside of the cell, but also play a role in communication and signaling events in many systems. Our group studies one type of sugar addition to proteins—mucin-type O-linked glycosylation, which is initiated by the polypeptide GalNAc transferase enzyme family. It is known that O-glycosylation of proteins is associated with several human diseases, but the mechanism is not fully understood. My lab is trying to determine how O-glycosylation influences basic biological processes in development and disease.

O-glycosyltransferases are components of the secretory apparatus and responsible for the modification of secreted and membrane-bound proteins. We hypothesize that the modifications play crucial roles in the secretion, localization, stability, and function of proteins and may influence cell adhesion, communication, morphology, and proliferation. Using *Drosophila melanogaster*, we have determined that at least five members of the multigene family are essential for fruit fly viability.

We have also discovered a role for one O-glycosyltransferase in the secretion of an extracellular matrix integrin ligand that influences matrix composition and cell adhesion during Drosophila development. We have also demonstrated that another O-glycosyltransferase can influence extracellular matrix composition during mammalian development, with resultant effects on cell proliferation and organ growth. Our studies highlight novel roles for O-glycosylation in conserved cell biological processes and may elucidate how changes in this modification contribute to disease susceptibility and progression.

KAI YU, PH.D., NCI-DCEG

Senior Investigator, Biostatistics Branch

Education: Fudan University in Shanghai, China (B.S. in mathematics); Beijing University of Posts and Telecommunications in Beijing, China (M.S. in applied mathematics); University of Pittsburgh (Ph.D. in biostatistics)

Training: Postdoctoral training in statistical genetics at Stanford University (Calif.)

Before coming to NIH: Statistical geneticist at Millennium Pharmaceuticals, Inc. (Cambridge, Mass.); research assistant professor of biostatistics at Washington University (St. Louis, Mo.)

Came to NIH: In November 2005

Outside interests: Swimming; playing basketball with his son

Research interests: My research specializes primarily in statistical genetics and addresses challenges in the design and analysis of modern genomic studies. Since beginning my biostatistics research at NCI, I have been the lead statistician for the design and analysis of a variety of genetic epidemiology studies, with a major emphasis on genome-wide association studies (GWAS) of cancer. GWAS—and other studies that exploit high-throughput technologies for measuring genes, metabolites, and other biological markers—are proving to be powerful research approaches. The complex information collected by those studies poses a wide range of statistical questions that have motivated my methodologic work. I also developed an adaptive design framework, a multistage design that relies on accumulating data to modify aspects of a study without undermining its validity and integrity. The framework can be used to design a follow-up study for validating previous genetic association findings while accounting for the potential of "winner's curse" (a genetic marker chosen for replication because of an extreme observed effect size that tends to be less extreme in the second study).

Recently, I proposed an efficient P-value evaluation method for resampling-based procedures that can reduce computing time by a factor ranging from 1/100 to 1/500,000. The method can be applied to a test statistic with an unusually large value that only occurs—or can be observed—less than one in a million times by chance (a common occurrence in genomic studies in which over a million markers are evaluated). ●

DEMYSTIFYING MEDICINE 2013

Tuesdays, starting January 8, 2013
4:00-5:30 p.m.; Bldg. 50 Conference Room

The "DeMystifying Medicine" course, in its 11th year, bridges the gap between advances in biology and their application to human disease. Each class features presentations by a clinician, researcher, and often a patient. For more information, visit http://demystifying-medicine.od.nih.gov or contact Win Arias at ariasi@mail.nih.gov.

January 8: "Telomerase and Telomeropathies"; Neal Young (NHLBI)
January 15: "Genomic Paradigm for Cancer Diagnosis and Therapy: Melanoma"; Yardena Samuels (NHGRI) and Paul Robbins (NCI)
January 22: "Hepatitis C and HIV: the Borgia Effect"; John Coffin (NCI) and Shyamasundaran Kottilli (NIAID)
January 29: "Hepatitis B and the T cell"; Jay Hoofnagle (NIDDK) and Ron Germain (NIAID)
February 5: "Sexually Transmitted Diseases"; Thomas Quinn and colleagues (NIAID)
February 12: "Pain: How It Happens and What Can Be Done"; Catherine Bushnell (NCCAM) and Raymond Dionne (NINR)
February 19: "Preventing Aging"; Raphael de Cabo (NIA) and Jay Chung (NHLBI)
February 26: "Ethics and Translational Medicine"; Christine O'Grady (CC)
March 5: "Biomedical Technology: New Frontiers"; David Bluemke (NIBIB) and Ronald Summers (NIMH)
March 12: "Autoimmunity: Diseases and Mechanisms"; Michael Lenardo (NIAID) and Abner Notkins (NIDCR)
March 19: "Ticks: Lyme and Other Diseases"; Tom Schwan and Andrea Marquez (both NIAID)
March 26: No session
April 2: "Turner's Syndrome: The X Chromosome"; Caroline Bondy, Vladimir Bakalov (both NICHD)
April 9: "New Hepatitis Viruses and an Old Persistent One"; Harvey Alter (CC) and Jake Liang (NIDDK)
April 16: "Vision and Blindness in the Genomic Era"; Emily Chew (NEI) and Paul Sieving (NEI)
April 23: TBA
April 30: "The Mitochondrion and Its Diseases"; Jennifer Lippincott-Schwartz (NICHD) and Lynne Wolfe (NHGRI)
May 7: Finale (TBA)

DIRECTOR'S SEMINAR SERIES

Fridays, 12:00–1:00 p.m.; Wilson Hall (Bldg. 1)
December 7: "Sickle Cell Trait Interferes with the Diagnosis of Diabetes by A1C"; Anne Sumner (NIDDK)
January 11: Amy Berrington (NCI)
February 8: Dorian McGavern (NINDS)
More information at http://www.nih.gov/about/director/dirsem.htm.

STEPHEN E. STRAUS DISTINGUISHED LECTURE

"Natural Products: Drugs and Medicines for All Reasons and All Seasons"
Wednesday, December 5, 2012
9:00-10:00 a.m.; posters 10:00-11:00 a.m.
Lipsett Amphitheater (Building 10)
Free and open to the public

David G.I. Kingston (Virginia Polytechnic Institute and State University) will review successes of the natural products approach, emphasizing anticancer activity and the reasons for the success of natural products as drugs and herbal medicines. His talk is part of NCCAM's annual Stephen E. Straus Distinguished Lecture in the Science of Complementary Health Therapies, named for its founding director. More information: http://nccam.nih.gov/news/events/lectures or http://nccam.nih.gov.

NICHD SCIENTIFIC COLLOQUIUM

Wednesday, December 5, 2012
8:30 a.m.–5:00 p.m.; reception follows
Masur Auditorium (Building 10)

Celebrate NICHD's 50th anniversary. Outstanding speakers will reflect on accomplishments and anticipate future opportunities in research and health care. For more information, visit http://www.nichd.nih.gov/about/meetings/2012/120512-50th.cfm or contact Katie Rush at katie.rush@nih.gov or 301-402-2205.

NIH SCIENCE EDUCATION CONVERSATIONS

Thursdays, 3:00–4:15 p.m.
Building 50, Room 1328/1334

November 29: "Bringing Underrepresented Populations into the Sciences: What Difference Does Difference Make?"; Shirley Malcom (AAAS)
December 20: "Attending to Student Thinking in Science: Becoming a Responsive Teacher"; Daniel M. Levin (University of Maryland)
More information at http://science.education.nih.gov/sciedconversations or contact Jennifer Gorman Wright at gormanj@od.nih.gov or 301-402-2469.

AWARDS

DAN KASTNER ELECTED TO IOM

Dan Kastner, NHGRI's scientific director, has been elected to the Institute of Medicine (IOM). Election to this prestigious advisory body is among the highest honors in the area of health and medicine and indicates recognition of individuals who have made major contributions to the advancement of medical science, health care, and public health. Last year Kastner was inducted into the National Academy of Sciences, an elite body of distinguished U.S. scientists and engineers who advise the federal government on science and technology.

NIH ALUM WINS NOBEL PRIZE IN CHEMISTRY

NIH alumnus **Robert J. Lefkowitz** was named co-winner, with Brian K. Kobilka, of the 2012 Nobel Prize in Chemistry for studies of protein receptors that let body cells sense and respond to outside signals. Now a HHMI investigator and professor of medicine and biochemistry at Duke University Medical Center (Durham, N.C.), Lefkowitz was a clinical and research associate at NIH from 1968 to 1970 and worked with Ira Pastan and Jesse Roth at NIDDK, where they developed the original concept of cell surface receptors. This was at a time when there was still much skepticism as to whether receptors really existed.

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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.

Online only: Carolyn Graybeal's article on NSF Director Sabra Suresh's recent visit to NIH. Go to: http://irp.nih.gov/catalyst/v20i5/features/subra-suresh-at-the-interface-of-engineering-and-biology.

LABORATORY CONFESSIONS

Ode to DeMystifying Medicine

BY MYRA SKLAREW

Stem cell, versatile progenitor,
creature of many faces—Come, wake up!
Show us the types of cells you can engender.

Smell, with you we travel
across time in an instant.
But if we lose you and cannot sense
the burning toast or spring lilacs
that bear no emblem of their perfume,
forget steroids, antibiotics.
Send us a growth factor to awaken
our sleeping stem cells.

Though the doctor reassures his patient,
"Your brain, my dear, has shrunk a bit
but for an aged one it's nothing
out of the ordinary," don't fret.
He means no harm. If all is lost upstairs
I tell you, Song will stay.

And may we thank Aretaeus belatedly
for his detective work on celiac disease.
May the villi rise, the lymphocytes
find other homes.

Just when it seems the world's gone sour,
tanks and missiles, war never to end,
take heart. The wondrous minds
of curious folks at work in labs
are puzzling out intricate designs,
the keys to how molecules assemble.
In the ventricle of memory new
constellations arise.

Biologist, poet, and writer Myra Sklarew is a professor emerita of literature at American University (Washington, D.C.). She attends the "Demystifying Medicine" lectures and confesses that she wrote this poem for its director, Win Arias. For information about the 2013 season, see page 19.

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

Address correspondence to:
Building 1, Room 333, NIH
Bethesda, MD 20892
Ph: 301-402-1449
Fax: 301-402-4303
e-mail: catalyst@nih.gov

The NIH Catalyst online:
http://irp.nih.gov/catalyst

PUBLISHER
MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS
JOHN I. GALLIN
Director, NIH Clinical Center
HENRY METZGER
Scientist Emeritus

MANAGING EDITOR
LAURA STEPHENSON CARTER

WRITER-EDITOR
CHRISTOPHER WANJEK
Director of Communications, OIR

COPY EDITOR
SHAUNA ROBERTS

EDITORIAL INTERN
TANIA LOMBO

CONTRIBUTING WRITERS
EVA ÅHRÉN, BEN BUSBY, STEPHANIE COOPERSTEIN, LESLEY EARL, ERIKA GINSBURG, KRISTINA MCLINDEN, MEGHAN MOTT, SARAH NAYLOR, BEN PORTER, AMY REITER, SARAH RHODES, MARIE SIWICKI, MYRA SKLAREW, SILVIYA ZUSTIAK

PHOTOGRAPHERS/ILLUSTRATORS
MAGGIE BARTLETT, MICHAEL BEWLEY, ERNIE BRANSON, JANICE CARR, FRANK DELEO, GREGORY KATO, BELLE WARING, YICONG WU

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