THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 23 ISSUE 2 • MARCH-APRIL 2015

No Footprints?

NIH Scientists Find Possible Flaw in ENCODE Technique

BY REBECCA BURGESS, OD

NIH researchers have found a flaw in an important tool that is supposed to identify certain functional elements of the human genome. The finding, that some proteins bind too briefly with DNA to leave "footprints," may prompt a rethinking of how best to map regulatory regions in DNA.

Although the human genome was fully sequenced in 2003, the function of most of its three billion base pairs is unknown. Only about one percent of the pairs is in protein-coding regions; the rest of the genome contains other functional, but non-protein-coding, elements that turn genes on or off, delineate chromatin structure, or sequences that produce regulatory RNA molecules.

The daunting task of identifying all the protein-coding and noncoding areas is akin to assigning street- and household-level information to satellite images of towns and cities around the globe. To meet the challenge, the National Human Genome Research Institute organized a consortium of 32 international genomics laboratories to collaboratively build an ENCyclopedia of DNA Elements, or ENCODE, which would systematically map the precise location of all protein-coding and non-protein-coding functional elements within the genome. Ultimately, ENCODE is to help scientists understand how genomic information

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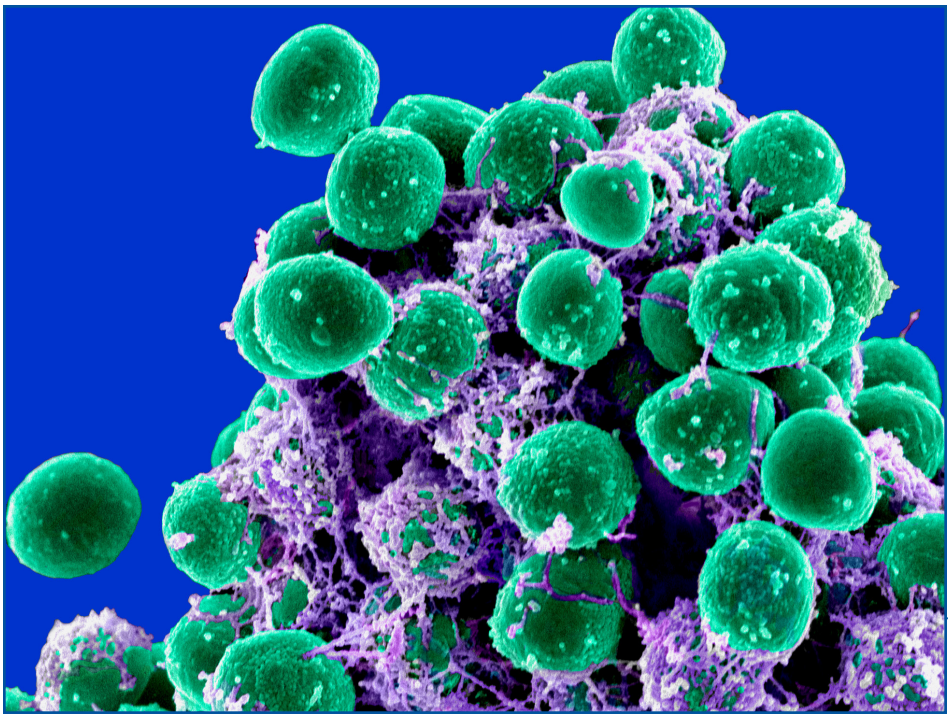
Wonder Drugs and Super Bugs

The Rise of Antibiotics...and Antibiotic Resistance

BY SARAH RHODES, OD



ELECTRON MICROSCOPY UNIT, ROCKY MOUNTAIN LABS, NIAID

Michael Otto (NIAID) studies the mechanisms of pathogenicity in Staphylococci, including the formation of multicellular bacterial agglomerations called biofilms. Antibiotics often cannot penetrate these dense, sticky matrices, and even if they do, the metabolism of these cells is such that they are not susceptible to the drugs. Shown: Scanning electron microscopy of a Staphylococci biofilm (balls) embedded in an exopolysaccharide matrix.

Ever since 1928 when penicillin mold was discovered to secrete an antibacterial substance, doctors have been developing antibiotics to fight bacterial infections. Now the bacteria are fighting back. But NIH scientists are seeking ways to thwart antibiotic-resistant bacteria, developing new antibiotics that work differently than the older ones, and even trying to understand antibiotic resistance from a historical perspective.

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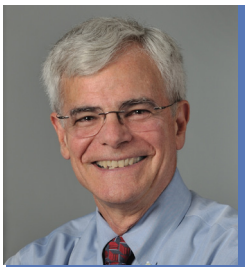

There Is No Substitute for Credibility in Science

BY MICHAEL GOTTESMAN, DDIR

"When you lose your credibility, you lose everything."
—the late Robert Chanock, former chief of NIAID's Laboratory of Infectious Diseases

AT THE FOUNDATION OF EVERYTHING that scientists do is the absolute need for the highest integrity in conducting, reporting, and evaluating research activities. At a practical level, this means that every scientist should be his or her own severest critic and not be satisfied with anything less than an honest and complete appraisal of the quality and value of his/her own work.

Every scientist should also be committed to the fair and truthful analysis of the work of others and the appropriate stewardship of critical scientific resources such as animals, human subjects, funds, and research equipment and facilities. The term "responsible conduct of research" has been used to describe this foundation of research integrity, and the NIH leadership is committed to training all of our scientific and support staff in the principles underlying this concept.

To this end, the NIH scientific directors have recently endorsed a new program of training and discourse on research integrity that is aimed at our trainees but also engages established scientists at all levels at the NIH. The program will add new training activities to our existing computer-based orientation training and the annually held sessions on case studies in research ethics. The goal is to create a "buzz" about the interesting and complex ethical quandaries that every scientist deals with almost daily, to encourage ongoing discussions so that each scientist will be comfortable making difficult decisions during their career, and to provide information about resources to help guide appropriate action. Most of the training will consist of interactive experiences and will be initiated soon after trainees arrive at the NIH. (Incidentally, all NIH-supported trainees are already required to receive instruction in the responsible conduct of research.)

The intent is to provide approximately eight hours of introductory material for all trainees at the NIH during their years here: a six-hour core research-integrity program and at least two hours of additional activities.

The six-hour core program will consist of the already mentioned orientation computer-based training course (one hour) and the annual case discussions (one hour) and will be augmented with 1) a two-hour institute- or center-based discussion led by our training directors, 2) a series of four short videos on reproducibility in science accompanied by discussion at the lab or branch level, and 3) orientation sessions with the lab or branch chiefs to discuss expectations for record-keeping, authorship, collaboration, and replication of results.

For the additional two hours of activities, trainees will be able to choose from coursework in "ethical writing"; information about how to avoid and/or recognize research misconduct; criteria for authorship; either in-person attendance or viewing of archived videos of the workshop series on "Reproducibility of Data Collection and Analysis" (http://wals.od.nih.gov/reproducibility); and one or more of the specialized courses in clinical research. As they become available, the choices will be posted on the Office of Intramural Training and Education Web site (https://www.training.nih.gov) or listed in the Office of Intramural Research Sourcebook (http://oir.nih.gov).

I am especially enthusiastic about the "Reproducibility of Data Collection and Analysis" workshops that **Paul Liu** and I have organized; we have had one already on specialized techniques in cell biology ("Modern Technologies in Cell Biology: Potentials and Pitfalls," which you can view at http://videocast.nih.gov/launch.asp?18749), and a second one on structural biology took place on March 13, 2015.

We are beginning to plan a third session on genomics and biostatistics that will take place in late spring and a fourth on medical imaging scheduled for the fall. These workshops include presentations at the NIH by world experts on the power of and problems with techniques that are widely used, but sometimes poorly understood by some practitioners and many readers of the scientific literature as well as discussions by top journal editors of how to recognize and avoid the pitfalls of these technologies.

You will be hearing much more about these research-integrity activities at the NIH. I hope you will "catch the wave" and feel the exhilaration of joining a "culture of integrity." My goal is to make research integrity a subject of water cooler, cafeteria, break room, and hallway discussions that is integrated into every aspect of our work at NIH. ●

VARMUS STEPPING DOWN AS NCI DIRECTOR

Harold Varmus, who has led the National Cancer Institute (NCI) for nearly five years, announced that he will step down from his post effective March 31, 2015.

NCI Deputy Director **Douglas Lowy** will become acting director beginning April 1, 2015. Lowy, a long-time NCI intramural researcher, received the National Medal of Technology and Innovation from President Barack Obama in 2014 for his research that led to the development of the human papillomavirus vaccine.

In 1989, Varmus was co-recipient of the Nobel Prize in Physiology or Medicine for the "discovery of the cellular origin of retroviral oncogenes." From 1993 to 1999, he served as the director of NIH under President Bill Clinton. After leaving NIH and before returning to run NCI in 2010, Varmus served as president of Memorial Sloan-Kettering Cancer Center in New York.

Varmus has had a long-standing association with NIH, dating back to 1968–1970 when, as a young Public Health Service officer, he studied bacterial gene expression with **Ira Pastan**, who is currently chief of NCI's Laboratory of Molecular Biology.

MATTHEW SEPTIMUS, MEMORIAL SLOAN-KETTERING

Harold Varmus is stepping down as the director of the National Cancer Institute at the end of March.

Varmus will be returning to New York to establish a modestly sized research laboratory in the Meyer Cancer Center at the Weill-Cornell Medical College and serve as a senior advisor to the dean. In addition, he plans to assist the recently founded New York Genome Center as it develops its research and service functions and helps regional institutions introduce genomics into cancer care. ●

For more information, including Varmus's letter to NCI staff, go to http://www.cancer.gov/aboutnci/director/messages/harold-varmus-resignation.

PRECISION MEDICINE INITIATIVE

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time," said President Obama in his State of the Union Address on January 20, 2015. "Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases [such as] cancer and diabetes—and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

"Precision medicine" means much the same thing as personalized medicine: treatments chosen for each person based on their unique genetic makeup and possibly also on the traits of their disease. It is the opposite of the "one size fits all" treatment approach used for many conditions today.

Advances in basic research, including molecular biology, genomics, and bioinformatics, have made such an approach possible. The immediate focus of the Precision Medicine Initiative is on cancers, and the long-term goal is to put the initiative into practice on a larger scale.

The President's 2016 budget will dedicate $215 million to the NIH, together with the Food and Drug Administration (FDA) and the Office of the National Coordinator for Health Information Technology (ONC), to support this effort including:

- $130 million to NIH for the development of a voluntary national research cohort of a million or more volunteers to set the foundation for a new way of doing research through engaged participants and open, responsible data sharing;
- $70 million to the NCI to scale up efforts to identify genomic drivers in cancer and apply that knowledge in the development of more-effective approaches to cancer treatment;
- $10 million to the FDA to acquire additional expertise and advance the development of high-quality, curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health;
- $5 million to ONC to support the development of interoperability standards and requirements that address privacy issues and enable secure exchange of data across systems.

"The promise of precision medicine [means] delivering the right treatments at the right time, every time, to the right person," said Obama on January 30 in announcing details of the initiative. "The time is right to unleash a new wave of advancements just [as] we did with genetics 25 years ago." ●

For more information, go to http://www.nih.gov/precisionmedicine.

SPECIAL FROM THE NATIONAL CANCER INSTITUTE

LEA(R)N: Lead, Encourage, Apply, (Retain), Network

BY ERIKA GINSBURG, NCI

Sheryl Sandberg, chief operating officer of Facebook and author of *Lean In: Women, Work, and the Will to Lead*, is famous for highlighting the barriers that keep women from getting ahead. Sallie Rosen Kaplan, however, is not so famous. She may have been as ambitious as Sandberg, but her circumstances were different. Kaplan was accepted at the University of Michigan (Ann Arbor, Michigan), in the 1930s, but unable to attend because of family responsibilities. Still, she was committed to the education of women and helped support biomedical research at NIH.

After she died in 1998, her estate established a fellowship to recruit postdoctoral women to biomedical research at the National Cancer Institute (NCI). Since the inception of the Sallie Rosen Kaplan (SRK) Postdoctoral Fellowship for Women Scientists in Cancer Research in 2000, all awardees have gone on to have successful scientific careers. In 2013, the SRK fellowship began to address a specific issue—how to retain women in the scientific pipeline.

Women outnumber men at the undergraduate and graduate levels, receiving over half of the doctorates awarded in the life sciences. At the NIH this trend continues: Half of postdoctoral fellows are female. However, recent observational, longitudinal, and intervention studies show that women in science are significantly more likely to leave research careers earlier than men, especially as they try to transition from mentored scientists to independent investigators.

According to a 2007 report by the NIH and appearing in *EMBO Reports*, "women are more likely to quit at the post[doctoral]-to–principal investigator transition" and, according to the National Research Council, women are underrepresented in academic leadership roles and may feel isolated. In the NIH intramural program, only 20 percent of senior investigators are female.

What happens during the transition from trainee to independent investigator? According to these reports, one contributing factor is self-confidence. "Fear is the root of so many of the barriers women face," Sandberg writes. "Fear of being judged and fear of failure." Could having successful female scientists as role models—women who combine career and family, lead, and make decisions—encourage female postdoctoral fellows who might question their ability to succeed as principal investigators?

The SRK fellowship embraced the challenge of how to better retain and advance the careers of women in science. The yearlong program pairs fellows with successful female scientists who serve as role models and mentors. It provides networking, seminars, and workshops to help NCI's female postdocs strengthen their leadership skills, become better equipped to face the competitive job market, and remain in a research career as independent investigators.

Although the SRK fellowship is limited to NCI postdoctoral women, the lessons learned through the program are useful for everyone. Here are a few tips:

- Find a role model; a mentor can come from the unlikeliest of places.
- Dream big; you will never get ahead if you don't try.
- Team spirit is great, but don't undervalue your contributions. It's all right to give yourself credit and speak in the "I."
- Don't be afraid to interrupt. Politely. You may have the next great idea or comment.
- Sit at the table so you appear as a potential contributor and not only as a participant.
- Build your confidence (and credibility) by taking on a more active leadership role in professional associations, committees, and other activities.
- Be honest with yourself. Daily work-life "balance" doesn't really exist. Some days, one need outweighs the other. It's what works now, and it's always changing.

The SRK mentors all echoed their enthusiasm for the program. The SRK fellows have more confidence and a stronger sense of what they want and how to get there. "I am much more willing to jump in, take risks, [and] make connections," said NCI postdoc and SRK alumna **Kristin Litzelman**. "That has helped me be more productive, happier, and more excited about my career." ●

For more information about the SRK fellowship, go to http://www.cancer.gov/researchandfunding/cancertraining/atnci/srk.

Additional Reading

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- National Research Council, *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering* (Washington, D.C.: The National Academies Press, 2007).
- E. Reuben, P. Sapienza, and L. Zingales, "How stereotypes impair women's careers in science," *PNAS USA* 111:4403–4408, 2014.
- S. Sandberg, *Lean In: Women, Work, and the Will to Lead* (New York: Knopf, 2013).

NIH Imaging and Probe Development Center

Synthesizing Noncommercial Probes

BY SOMA CHOWDHURY, OD

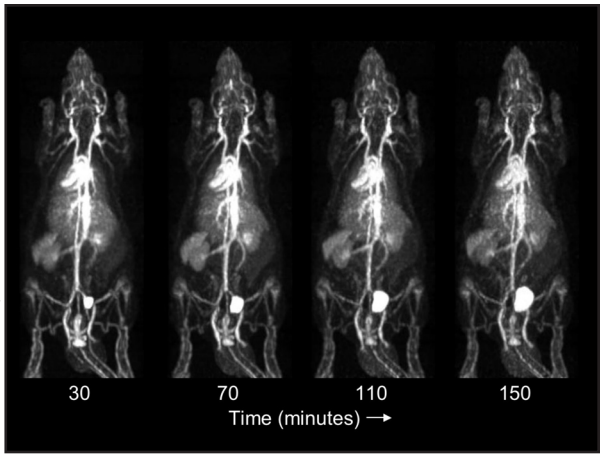
With its emeralds, nanodiamonds, and gold particles sparkling upon countertops and bench tops, NIH's Imaging and Probe Development Center (IPDC) might be mistaken for a jewelry factory. But what's being produced here is arguably more valuable than jewels, at least to the scientists that the IPDC serves.

A trans-NIH resource housed in the National Heart, Lung, and Blood Institute (NHLBI), the IPDC produces materials that are not commercially available. It synthesizes small molecules, peptides, and diverse nanomaterials for a range of imaging applications including fluorescence microscopy, magnetic resonance imaging, positron-emission tomography (PET), and single-photo emission computerized tomography.

"We make strictly noncommercial probes," said IPDC Director **Rolf Swenson**, who came to NIH from industry in 2014. And very importantly, "20 percent of the probe development is done by nontenured or new [principal investigators] who might lack their own synthetic chemistry support."

Swenson oversees IPDC's two labs that have state-of-the-art equipment for making novel probes: a 5,000-square-foot facility in Rockville, Maryland, and a 2,700-square-foot PET lab in the NIH Clinical Center on the Bethesda campus. The center has a combined staff of 15 chemists—including organic, medicinal, analytical, and inorganic chemists as well as radiochemists and biochemists—who have expertise in different fields of molecular imaging.

Swenson has a Ph.D. in organic chemistry from Cornell University (Ithaca, New York) and trained as a synthetic organic chemist at the University of Geneva and the University of Wisconsin in Madison. In the biotech arena, he managed international discovery and chemistry efforts for novel imaging agents that resulted in clinical trials for a radiotherapeutic and a contrast-enhanced ultrasound product. Today, he is helping NIH scientists solve problems that are similar to ones he dealt with in industry.



MICHAEL V. GREEN, NCI

In one project, IPDC chemists created a F-18 labeled albumin that NCI's Molecular Imaging Program used in PET blood-pool imaging studies that showed how injected albumin distributes throughout the body. Shown: consecutive whole-body maximum-intensity projection images of a rat following the administration of F-18 albumin. As desired, albumin labeled with this method does not accumulate in any organ except for the bladder, from where it is excreted (lower right in each image).

Projects: In fiscal year 2014, the center had 35 projects, supported researchers in eight institutes, and synthesized 42 different compounds. In one project, the chemists created a labeled serum albumin for PET studies to see whether injected conjugates were evenly distributed throughout the bloodstream without accumulating in any organs. Another project involved labeling a candidate drug that's used to treat the neurodegenerative disorder Niemann-Pick disease, so that the drug could be evaluated for brain uptake. Currently, the facility is doing discovery research in which the probes are mainly used in cells and animals for proof-of-principle experiments that form the basis for translational clinical imaging, research, and diagnostics.

The center also has the ability to work with extramural researchers who have collaborations with intramural PIs.

Initiating a Project: Any PI interested in having the IPDC develop a probe should first meet with Swenson or his deputy, **Olga Vasalatiy**, to define the scope of the project. The PIs usually have an idea about "what imaging modality they want to pursue," said Swenson. They have a lead or an idea about what the compound could be, he added.

The IPDC and the PI jointly compose a two-page proposal, which must then be approved by the PI's scientific director (SD) for funding, and the IPDC Steering Committee. The steering committee, made up of chemists and imaging specialists from several NIH institutes, oversees the chemical feasibility of the projects. The IPDC is supported through the SDs' Shared Resources Subcommittee, with 25 percent of each project already paid for from a pooled fund from all the institutes and 75 percent paid for by the requesting institute, based on hours worked. Probes are typically delivered between two and six months after initiation.

The "unit cost of production is going down as more and more people are using the facility," said Deputy Director for Intramural Research **Michael Gottesman**, who sees the facility as a source of expertise. "Research is altered in a positive way." ●

For more information on the IPDC, go to http://1.usa.gov/1GTWtr4.

The Science of Mentoring Women Scientists

Judith Walters: Mentor Extraordinaire

BY RACHEL SCHEINERT, NIMH

According to a U.S. Census Bureau report, men outnumbered women three-to-one in the science, technology, engineering, and math (STEM) work force in 2011. In the following article, NIH scientist Judith Walters speaks candidly about the struggles of being a woman in science, the mentors who helped her along the way, and how her experiences have shaped her mentoring style.

Judith "Judie" Walters is a self-described "product of a women's college"—Mount Holyoke College in South Hadley, Massachusetts. She was confident she could tackle academic challenges and assume leadership roles in whatever she chose to do. At college she had fallen in love with the emerging field of neuropharmacology—the study of how drugs affect the brain. There was no question in her mind that she would go on to pursue a career in science. But when she applied to graduate school in the late 1960s, one male interviewer asked, "Why do you want to get a Ph.D.? You're a woman!"

Unfazed, Walters applied and was admitted to the University of California, San Francisco, and later transferred to Yale University School of Medicine (New Haven, Connecticut) to study the pharmacology and neurophysiology of the dopamine system in the basal ganglia. When she arrived at Yale, only one other woman had graduated with a Ph.D. from the Department of Pharmacology. Today Walters is chief of the Neurophysiological Pharmacology Section in the National Institute of Neurological Disorders and Stroke (NINDS).

She attributes much of her early success not only to the confidence instilled in her by going to an all-women's college, but also to having good mentors during critical times in her career. At Yale, she did graduate work under the guidance of neuropharmacology pioneer Robert Roth, who, she said, proved to be a mentor with an unbiased and supportive style.

Walters also did a project with neurophysiology pioneer George Aghajanian, who became her co-mentor. Aghajanian—in the 1960s—was the first to record the single-cell activity of the newly discovered serotonergic, noradrenergic, and dopaminergic neurons in the brain. "It was an absolutely exciting time," said Walters who did the first in-vivo recordings of dopamine neurons in the rat and developed evidence for the existence of autoreceptors on the terminals of dopamine neurons in the basal ganglia.

In Aghajanian's lab, Walters met, trained with, and later collaborated with Benjamin "Steve" Bunney, a young resident from New York University who went on to became the chair of Yale's Psychiatry Department and a leading expert on dopamine. "It was fun," Walters said, "we were mentoring each other in a way."

After completing her postdoctoral training, Walters became an assistant professor in Yale's Department of Psychiatry. In 1975, she came to the NIH as a staff fellow in the lab of **Thomas Chase** (also a Yale School of Medicine grad), who was the chief of NINDS's Experimental Therapeutics Branch. Chase was known for his research in Parkinson disease and other movement disorders. "He was a good mentor," Walters said. "He was very well connected; he helped me to go to meetings and get to know people."

These are the same words that Walters's lab members now use to describe her. "Judie is so excited about science, she makes you love science, too, and [want to] do your best here," said **Kristin Dupre**, a postdoc in Walters's lab.

Walters is always available and accessible, said **Katrina Furth**, who's a graduate student at Boston University (Boston) and is doing her doctoral research with **Andres Buonanno** in the Laboratory of Developmental Neurobiology in the National Institute of Child Health and Human Development. Furth is collaborating with the Walters lab to study the role of the dopamine system in schizophrenia.

Walters has an open-door policy and welcomes interruptions. Furth feels less intimidated taking early drafts of her manuscripts to Walters than to other mentors. "With Judie it can be a little messy," Furth said, adding that Walters's input along the way helps her to learn faster.

While collaborations are great for science and having two PIs means two recommendation letters, it's not always an easy balance, and Furth wouldn't recommend it for everyone. "The hardest thing is keeping my mentors all on the same page," Furth admitted. But the benefit is having double the number of people to approach about ideas and techniques, each with different strengths. "Andres is very supportive of the things I want to do," said Furth. Not only did he set up the initial meeting where they both met with Walters, but he also "encouraged me by granting me a lot of intellectual freedom."

Walters and her lab of young mothers have shown that it is possible to balance having a family and doing good science, said Furth, who gave birth to a daughter not long after she was interviewed for this article. She is taking a year off, but is a special volunteer so she can continue some of her work at NIH.

Surprisingly, Walters thinks it was easier when she was younger, even though there was no maternity leave or lactation rooms where new moms who returned to work could express breast milk in private. And, as a young PI, she faced strong social disapproval for going back to work when her children were young. But, she said, she had a live-in nanny five days a week because childcare was far less expensive than it is today.

"I think society is more approving of men making a more equal contribution to parenting tasks than in the past, and they are contributing more," she said. "However, a lot still ends up on the new mother's plate."

"Men certainly have challenges balancing a family and a career, but these challenges are different and less demanding, simply based on biology," said Dupre, who has a one-year old son. Women go through the physical and emotional changes of pregnancy, followed by labor and delivery, which requires healing time. Adjusting to life with a newborn is difficult for both women and men, but if women choose to breastfeed, they face the additional challenge of finding the time and place to pump breast milk at work. Although NIH has a supportive Nursing Mother's Program, Dupre finds "it is utterly exhausting trying to care for your baby and work full time."

Walters believes that parenting has had a big influence on her own mentoring style. "To me it's more of a natural extension of loving research and sharing it and wanting to see people developing their own interests and skill sets, finding their own strengths, and following their instincts," she said. Mentoring is "really just to encourage, support, and provide." This strategy has worked well for both the men and women in her lab. Because you can't expect everyone to be good at everything, you find what they are good at and recognize and encourage that as a mentor, said Walters.

Dupre describes herself as quiet, shy, and reserved, but says Walters has encouraged her to speak up. In fact, Walters had her entire lab read the book *Lean In* by Facebook Chief Operating Officer Sheryl Sandberg. Sandberg argues that young women would be more willing to "lean in" (stand their ground) if they had more role models who balance work and family life. However, Sandberg says, "Searching for a mentor has become the professional equivalent of waiting for Prince Charming."

According to an article in the 2010 *Harvard Business Review*, women are less likely than males to have a sponsor (someone to advocate for them) despite the fact that both women and men with a sponsor are more likely to ask for higher pay and to be satisfied with their rate of advancement.

Perhaps the solution is to create more mentors (or sponsors) for women in science. As a postdoc, Dupre is learning how to be an effective mentor herself. She has mentored three summer interns and two postbacs. "I like to think that I mentored them not just in terms of scientific research—how to perform experiments and analyses—but also in terms of their next steps," said Dupre. She has offered guidance on choosing a college major and applying to graduate school and has provided tips for a healthy work-life balance. "I do not believe that I mentor women versus men differently but rather adapt my mentoring style based on the individual."

Walters shared some advice on mentoring: When picking students, look for enthusiasm, motivation, and interest in what the lab is doing. For new mentors like Dupre, Walters advises, "Go with what students are interested in and curious about and build on their background."

ERNIE BRANSON

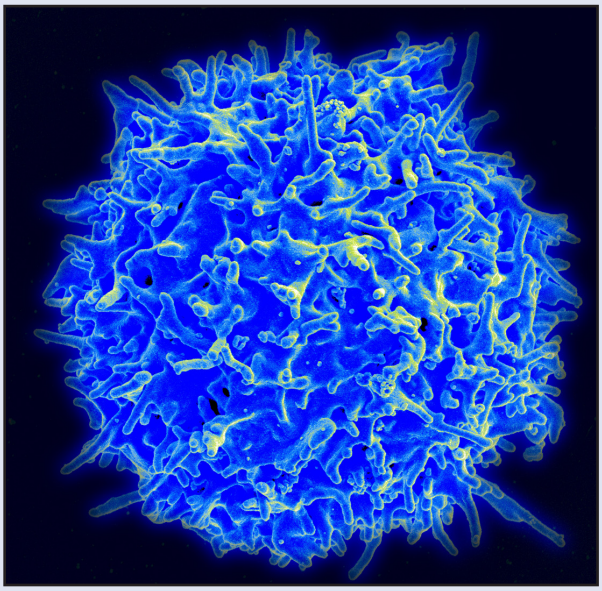
Judie Walters enjoys mentoring young scientists.

For anyone looking for a mentor, Walters advises talking to others in the lab to get an idea of the mentoring environment. Look for someone with a reputation for being available and supportive, but who also loves his or her research and is working on a question that intrigues you.

And, to women in science, she advised, "Keep your foot in the door of something that gives you intellectual capital"—wealth in the form of knowledge. "It's great to be an expert." With her own sons grown (two are musicians and the third a tenure-track scientist at a university), Walters is grateful to have her science and her students to keep her busy and rewarded. "I just feel lucky," she said. "I love what I do!" ●

For additional information on mentoring: The Office of Intramural Training and Education (https://www.training.nih.gov) offers seminars to help fellows become better mentees and mentors; the Fellows Committee Mentoring Subcommittee (https://www.training.nih.gov/felcom/mentoring).

Intramural Research Briefs



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

NIAMS and other NIH investigators have discovered the genomic switches of a blood cell key to regulating the human immune system. Shown: Scanning electron micrograph of a human T lymphocyte from the immune system of a healthy donor.

NIAMS, NHGRI, NCI: GENE REGULATORY ELEMENTS AND AUTOIMMUNE DISEASES

NIH investigators have discovered the genomic switches of a blood cell key to regulating the human immune system. The findings open the door to new research and development in drugs and personalized medicine to help those with autoimmune disorders such as inflammatory bowel disease and rheumatoid arthritis. People with autoimmune diseases possess unique genetic variants, but most of the alterations are found in regions of the DNA that do not carry genes. Scientists have suspected that the variants are in DNA elements called enhancers, which act like switches to control gene activities.

The NIH researchers wondered whether the alterations might lie in a newly discovered type of enhancer called a super-enhancer (SE). Earlier work at NIH had shown that SEs are especially powerful switches and that they control genes important for the function and identity of individual cell types. In addition, many disease-associated genetic alterations were found to fall within SEs. The team used genomic techniques to comb the T-cell genome for regions that are particularly accessible to proteins, a hallmark of DNA segments that carry SEs. Several hundred such regions were identified. Further analysis showed that they largely control the activities of genes that encode cytokine and cytokine receptors, which enable T cells to mount an immune response. But the researchers' most striking observation was that a large fraction of previously identified alterations associated with rheumatoid arthritis and other autoimmune diseases localized to these T-cell SEs. When the scientists exposed human T cells to tofacitinib, a drug used to treat rheumatoid arthritis, the activities of genes controlled by SEs were profoundly affected compared with other genes without SEs. This result suggests that tofacitinib may bring about its therapeutic effects in part by acting on SEs to alter the activities of important T-cell genes. (NIAMS: G. Vahedi, Y. Kanno, K. Jiang, J.J. O'Shea, Y. Furumoto, M. Gadina, and V. Sartorelli; NHGRI: S.C.J. Parker, M.R. Erdos, and F.S. Collins; NCI: S.R. Davis, R. Roychoudhuri, and N.P. Restifo, *Nature* DOI:10.1038/nature14154)

NIA: INSULIN RESISTANCE AS BIOMARKER IN ALZHEIMER DISEASE

Researchers from the National Institute on Aging, working with scientists from four other organizations, have developed a blood test that shows that the brains of patients with Alzheimer disease (AD) do not respond normally to the action of insulin. Numerous epidemiological studies have shown that both type 2 diabetes (DM2) and insulin resistance are risk factors for AD. Many patients with AD exhibit reduced cerebral glucose metabolism similar to patients with DM2, making insulin resistance a contributing factor to the pathophysiology of AD. The researchers measured the blood levels of a phosphorylated form of a signaling protein called type 1 insulin receptor substrate (IRS-1) in neurally derived plasma exosomes. The samples came from 26 people with AD, 20 elderly cognitively normal individuals with DM2, 16 people with frontotemporal dementia (FTD), and matched case-control subjects.

In addition, the researchers tested blood samples obtained at two points from 22 individuals—at the time of diagnosis of AD and one to 10 years before when they were cognitively normal. The study showed that the concentrations of two factors—P-serine 312-IRS-1 and P-pan-tyrosine-IRS-1—as well as the ratio of these two factors, termed the insulin resistance index, were significantly different in patients with AD, DM2, and FTD than in the control subjects; were higher for patients with AD than for patients with DM2 or FTD; and accurately predicted the development of AD up to 10 years before clinical onset. If the findings are replicated in large, longitudinal controlled prospective studies, this test may be used for early diagnosis of AD and to measure responses to new treatments. (NIA authors: D. Kapogiannis, A. Biragyn, E.J. Goetzl; *FASEB J* **29**:589–596, 2015)

NIDCD, NHLBI: PROTEIN LINKED TO FORM OF HEREDITARY HEARING LOSS

For the first time, NIH researchers have purified a key part of myosin 15, a molecular motor protein that helps build healthy hearing structures in the inner ear. Mutations in the *myosin 15* gene (*MYO15A*) have been linked to a form of hereditary deafness in humans. Using a novel approach to express the protein, the researchers revealed the first detailed insight into the molecule's structure and function,

CONTRIBUTORS: SWAGATA BASU, NICHD; KRYSTEN CARRERA, NIDDK

laying the foundation for new treatments for some forms of hearing loss. The new approach to expressing *myosin 15* may also help the study of other types of myosin motors, such as skeletal and cardiac muscle myosins, which could accelerate the development of targeted drug therapies for heart disease and other health conditions. (NIH authors: J.E. Bird, Y. Takagi, N. Billington, M.-P. Strub, J.R. Sellers, and T.B. Friedman, *Proc Natl Acad Sci USA* **111**:12390–12395, 2014)

NIAAA: MANY AMERICANS AT RISK FOR ALCOHOL-MEDICATION INTERACTIONS

In the United States, nearly 42 percent of adults who drink also report using medications known to interact with alcohol, based on a recently released NIH study. Among those over 65 years of age who drink alcohol, nearly 78 percent report using alcohol-interactive medications. Such medications are widely used, prescribed for common conditions such as depression, diabetes, and high blood pressure.

The research is among the first to estimate the proportion of adult drinkers in the United States who may be mixing alcohol-interactive medications with alcohol. The resulting health effects can range from mild (nausea, headaches, loss of coordination) to severe (internal bleeding, heart problems, difficulty breathing). Older adults are particularly at risk for experiencing alcohol-medication interactions. Not only are they more likely to be taking medications in general, but also certain alcohol-interactive medications, such as diazepam (Valium), are metabolized more slowly as one ages, creating a larger window for potential interactions.

The data was from more than 26,000 adults ages 20 and older who participated in the National Health and Nutrition Examination Survey (1999–2010). The survey asks participants about alcohol use in the past year and prescription drug use in the past month. The main types of alcohol-interactive medications reported in the survey were blood-pressure medications, sleeping pills, pain medications, muscle relaxers, diabetes and cholesterol medications, antidepressants, and antipsychotics. (NIAAA authors: R.A. Breslow, C. Dong, A. White, *Alcohol Clin Exp Res* **39**:371–379, 2015)

NHGRI, NCATS, OD: TACKLING THE THORNY SIDE OF GENE THERAPY

NIH investigators have uncovered a key factor in understanding the elevated cancer risk associated with the use of adeno-associated virus (AAV) as a gene-therapy vector. AAVs, small viruses that infect humans but do not cause disease, are uniquely suited for gene-therapy applications. Usually there are no toxic side effects. But a prior study found an association between AAV and the occurrence of liver cancer.

The present research addresses this problem in gene therapy for an inherited disease in children called methylmalonic acidemia (MMA), which affects as many as one in 67,000 children born in the United States. Affected children are unable to properly metabolize certain amino acids, an inability that can damage several organs and lead to kidney failure. MMA patients also suffer from severe metabolic instability, failure to thrive, intellectual and physical disabilities, pancreatitis, anemia, seizures, vision loss, and stroke. The most common therapy is a restrictive diet, but doctors must resort to dialysis or kidney or liver transplants when the disease progresses.

In prior MMA gene-therapy studies, researchers showed that mice bred to develop the condition could be restored to health by AAV gene-therapy injection shortly after birth. These mice survived into adulthood and were free from the effects of MMA, but in a long-term follow-up after they reached about two years of age, the researchers documented a 50–70 percent higher occurrence of liver cancer in the AAV-treated mice compared with a 10 percent liver cancer rate in untreated mice. The scientists determined that the AAV vector triggered the cancer.

In other experiments, the research team determined that in many mice that developed liver cancer, the AAV vector targeted a region of the mouse genome called Rian, near a gene called *Mir341*, which codes for a microRNA molecule. When the AAV was inserted near *Mir341*, the vector caused elevated expression of the gene, which the researchers believe contributed to the occurrence of liver cancer in the mice. *Mir341* is found in the mouse genome; however, it is not present in humans.

When the researchers used an alternate AAV vector to deliver the corrected gene in a study of just 10 mice, that vector did not insert itself where it would elevate the expression of nearby genes, and it did not cause liver cancer. The researchers found that this modification made for a safer gene therapy and that lower doses of AAV resulted in reduced rates of liver cancer. The hope is that the methodologies described in their research will be used by others to study the toxicity of AAV vectors in preclinical trials. (NIH authors: R.J. Chandler, M.C. LaFave, G.K. Varshney, N.S. Trivedi, N. Carrillo-Carrasco, J.S. Senac, W. Wu, V. Hoffman, A.G. Elkahloun, S.M. Burgess, C.P. Venditti, *J Clin Invest* **125**:870–880, 2015) ●

Read more online at http://irp.nih.gov/catalyst/v23i2/research-briefs.

NIDDK: DISCOVERY PROVIDES INSIGHT INTO IMMUNITY

NCATS, NICHD, CC: TEAMING WITH INDUSTRY TO DEVELOP TREATMENTS FOR NIEMANN-PICK DISEASE

NCCIH: SHIFTS IN AMERICANS' USE OF NATURAL PRODUCTS

B Cells, T Cells, and Natural Killers, Oh My!

Elaine Jaffe Puts Lymphomas in Their Place

BY BRANDON LEVY, NIMH

Elaine Jaffe has conducted pioneering studies on the classification, diagnosis, and treatment of lymphomas.

CANCERS ARE NOT CREATED EQUALLY. NIH hematopathologist **Elaine Jaffe**, whose work focuses on cancers of the blood-forming system, knows all too well how subtle variations can have an impact on diagnoses and treatment. Indeed, she has exploited those variations in her search for treatments. In scrutinizing minute differences among malignant lymphomas, Jaffe has conducted pioneering studies related to their classification and has led an international effort for consensus among clinicians and pathologists.

As head of the Hematopathology Section in the National Cancer Institute's (NCI's) Laboratory of Pathology, she is continuing to explore the pathophysiology and prognosis of all sorts of lymphomas, especially the interrelationship between Hodgkin lymphoma (a cancer of the lymph nodes) and diffuse large B-cell lymphomas and the genetic or epigenetic mechanisms that cause a B cell to become a Hodgkin cell.

Jaffe, now a member of the Institute of Medicine (IOM), discovered her passion for pathology as a second-year medical student at Cornell Medical College (New York) before transferring to the University of Pennsylvania Medical School (Philadelphia) and graduating in 1969.

"I saw pathology as laying the groundwork for the understanding of all disease states," she told the *American Society for Hematology News Daily* upon the occasion of winning the organization's prestigious Henry M. Stratton Medal in 2013. "An astute pathologist can discern many facets of the patient history and course from a single slide—[such as] the age, sex, clinical symptoms, sites of disease, and patterns of spread. To me, the power of the visual microscopic image is as great as a gene-expression microarray reporting on the activity of thousands of genes."

After graduating from medical school, Jaffe completed a one-year internship in pathology at Georgetown University Hospital (Washington, D.C.) before moving to the residency program in the NCI's Laboratory of Pathology in 1970. She arrived there just as a paradigm shift was occurring in the field of cancer therapy.

"For the first time it was shown that chemotherapy could cure patients with lymphomas and Hodgkin disease," she said. In fact, two NCI scientists—**Paul Carbone** and **Vincent DeVita**—received Lasker Awards in 1972 for their contributions to the concept of combination chemotherapy to successfully treat Hodgkin disease.

At the same time, the understanding of the immune system was exploding. And immunologists around the world were developing techniques to identify the specific types of immune cells, or lymphocytes, that certain lymphomas were derived from. Lymphomas can emerge from one of three types of lymphocytes: T cells, B cells, or natural killer (NK) cells, each of which has numerous subtypes. "Under the microscope, a T cell and a B cell look the same," Jaffe explained. "But immunologists were discovering surface markers on cells that could allow you to identify [them] in terms of their cell of origin."

These developments—the discovery that chemotherapy could cure certain cancers and the development of techniques to identify the immune cells that cancer cells were derived from—made hematopathology an exciting field. It's not surprising, then, that Jaffe decided to remain at the NCI as a fellow in hematopathology and pursue her interests in blood diseases. Along with her mentor, **Cos Berard**, and National Institute of Allergy and Infectious Disease (NIAID) immunologists **Ira Green**, **Michael Frank**, and **Ethan Shevach**, Jaffe applied those new techniques to lymphoma for the first time.

"If lymphomas were malignancies of lymphocytes, then we should be able to characterize them as to their T-cell or B-cell origin," she said. They ultimately showed that a type of lymphoma then called nodular lymphoma came from a specific type of lymphocyte called a follicular B cell (*N Engl J Med* **290:**813–819, 1974).

"It was one of the very first studies to show that you could identify the cell of origin of a lymphoma," Jaffe explained. This was the first time the technique had been applied to tissue sections in their normal environment. That paper was so heavily cited by other scientists that it became a "citation classic."

The ability to precisely classify lymphomas carried large implications for cancer

treatment: Certain therapies may be more or less effective against specific types of cancer. But it also created conflicts among different systems of classification. In the 1970s, "it led to a lot of confusion because different groups in different parts of the world were coming up with their own independent classification systems," Jaffe explained. For example, the Kiel classification system was widely used in Europe, while the Rappaport classification system was popular in the United States. Some classification systems lumped several types of lymphoma together under the same name, whereas others treated them as distinct entities.

"Most of [the classifications] were based on morphologic observations that were made under the microscope with not a lot of scientific validation," Jaffe said. "So there were differences in the number of different diseases that were described, how they were diagnosed, and how they might be treated."

To settle the issue once and for all, Jaffe joined a group of hematopathologists from around the world to establish the International Lymphoma Study Group in 1991. Working face to face, the 19 international participants found it easy to develop consensus, and, in 1994, the group published the Revised European-American Lymphoma (REAL) classification, which quickly became the gold standard for classifying lymphomas (*Blood* **84:**1361–1392, 1994).

The REAL classification system paper, which described more than 50 different types of lymphoma, became one of the five most highly cited papers in clinical medicine over the next 10 years.

Jaffe has also contributed to her field through her work outside the lab: She has served on the editorial boards of 18 different journals; was president of the Society for Hematopathology as well as of the United States and Canadian Academy of Pathology; and has won numerous awards in recognition of her work. In 2008, she was elected to the IOM. She takes special pride, however, in her work as director of the NCI's two residency programs.

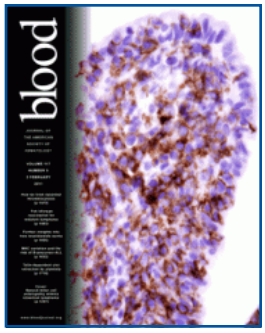
"I enjoy teaching at the microscope and helping people understand pathology and, in particular, hematopathology," she said. "I have a very close relationship with most of my former fellows [and] residents. They keep in touch with me on a regular basis. [It's] very rewarding to see them succeed on their own and make their mark in the field."

One former clinical fellow who has made his mark is **Joo Song**, who worked with Jaffe from 2009 to 2011. He is now an assistant clinical professor in the Department of Pathology at the City of Hope (Duarte, California), an NCI-designated comprehensive cancer center. Song credits Jaffe with helping him develop a love of research. "She was paramount in teaching me to conduct meaningful research and [to] also have a critical eye when reviewing the literature."

Jaffe attributes her success to the support of her husband and two sons and to a strong dedication to her work. She offers this advice to others: "Finish what you start." She cautioned that, "if you're new and you're very excited about everything that's happening, there's always a risk of becoming diffuse and starting a project and not finishing it."

There have been times, however, when she hasn't followed her own advice. "It's always easier to tackle the easy problems," she admitted. "Some of the difficult ones get put aside, and it's sometimes hard to get back to them. I have a mental file of things that didn't get finished, unfortunately."

Indeed, Jaffe's work is far from done. Nowadays, her research takes advantage of new techniques for analyzing the DNA of tumor cells. "I think the field of oncology is really undergoing revolutionary change with the ability to sequence essentially all human tumors," she said. "We're beginning to understand the genomic complexity of human tumors, and I think this will lead to a better understanding of the pathways of oncogenesis, but also probably influence the classification of disease and hopefully the treatment of disease as well."



Along the way Jaffe has identified new disease entities. She is particularly proud of a 2011 study describing NK-cell enteropathy, which was featured on the cover of the journal *Blood* (*Blood* **117:**1447–1452, 2011). It is a benign disorder that simulates lymphoma under the microscope. "With NK-cell enteropathy, probably a lot of those cases were called T-cell lymphoma, and patients were treated aggressively and received therapy that they really didn't need or didn't benefit from," Jaffe said. "So identifying [NK-cell enteropathy] as a disease and alerting people to its existence so future patients are not misdiagnosed is a significant achievement."

Although English physician Thomas Hodgkin first described lymphoma in 1832, it took more than 180 years before the REAL classification producbed a reliable and broadly supported system for distinguishing among its many forms. But as Jaffe's recent research shows, there remain categories of the disease yet to be rigorously defined. ●

Wonder Drugs

CONTINUED FROM PAGE 1

"I don't think we can fully appreciate our present options with respect to global antibiotic development, usage, and resistance without a deeper understanding of the historical forces that have brought us to this point," Harvard medical historian Scott Podolsky said in an interview with the National Library of Medicine's (NLM's) *Circulating Now* blog. In November, Podolsky, who is the director of Harvard's Center for the History of Medicine (Boston), delivered an NLM History-of-Medicine lecture—"Antibiotic Pasts and Futures: Seven Decades of Reform and Resistance"—based on his research at NLM for a new book that has just been published.

In his talk, Podolsky provided a whirlwind tour of the history of antibiotics from the 1940s on, exploring the evolving relationships among industry, academia, medicine, regulators, and the public. One of the key themes was concern over antibiotic resistance (AR). AR isn't a new problem—we have known about the ability of bacteria to evolve in response to selective pressure from antibiotics since the beginning. However, an inherent lack of stewardship—namely, the overuse and misuse of antibiotics both in the human population and in animals used for food—has put the AR process in overdrive.

In the United States alone, antibiotic-resistant bacteria are estimated to cause at least two million infections a year and 23,000 deaths; many more people die from other conditions complicated by an antibiotic-resistant infection (http://1.usa.gov/1n5K4VF). AR has become a national security and public health issue, which is all the more worrying because at the same time the antibiotic-development pipeline needed to replenish our arsenal has effectively dried up, according to **Amy Patterson**, former NIH associate director for Biosecurity and Biosafety Policy.

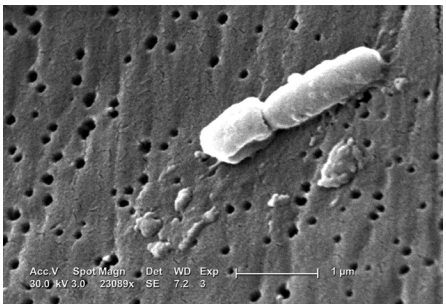
In 2013, the team of NIHers that worked on an antibiotic-resistant form of the Klebsiella bacteria received the Samuel J. Heyman Service to America Medals (Sammies) for "stop[ping] the spread of a deadly hospital-acquired infection through the first-ever use of genome sequencing." From left: Julie Segre, Evan Snitkin, Tara Palmore, ABC News political correspondent Cokie Roberts, and David Henderson.

"Addressing the issue will require efforts in a variety of areas such as antibiotic stewardship, disease surveillance, [and] basic and applied research as well as ultimately new diagnostics and therapeutics," said Patterson at a July 2014 NIH workshop on the development of new antibacterial products (http://videocast.nih.gov/launch.asp?18549).

At the same meeting, NIH Director **Francis Collin**s emphasized that "AR is a high priority for this administration." In fact, on September 18, 2014, President Obama issued an Executive Order releasing the *National Strategy for Combating Antibiotic-Resistant Bacteria (CARB)* and directing the government to take action to combat the rise in AR (http://1.usa.gov/ZrXYwP).

The NIH is taking a multifaceted approach to address this challenge. The NIH and the Food and Drug Administration have jointly sponsored workshops exploring issues related to antibacterial product development, including public-private partnerships and the streamlining of clinical trials and regulatory pathways. NIH will also offer a $20 million prize to facilitate the development of a rapid point-of-care diagnostic test to identify highly resistant bacterial infections (http://1.usa.gov/1wMF0yM). This initiative will aid both the surveillance and more judicious use of antibiotics.

Several intramural PIs in different institutes work on AR, some with grants from the Director's Challenge Innovation Award Program, which in 2013–2014 supported 10 intramural projects on AR. **Julie Segre**, chief of the Translational and Functional Genomics Branch at the National Human Genome Research Institute (NHGRI), received one of these awards for her work studying the microbiome of Clinical Center (CC) patients who are at risk of infection with multidrug-resistant bacteria.



JANICE CARR, CDC

This scanning electron micrograph reveals some of the ultrastructural morphologic features of a *Klebsiella pneumoniae* bacterium that Julie Segre and others are studying.

"Hospital infections are one of the looming crises facing the delivery of health care," she said. With the paucity of new antibiotics in the pipeline, hospital infection control is crucial in the fight against multidrug-resistant organisms such as carbapenem-resistant *Klebsiella pneumoniae* (KPC).

Segre uses genomic sequencing to study modes of transmission in microorganisms such as bacteria and has leveraged these techniques to tackle AR. In 2011, she collaborated with CC epidemiologists **Tara Palmore** and **David Henderson** and NHGRI bioinformatics specialist **Evan Snitkin** to lead the NIH's response to the spread of KPC, which resulted in the deaths of several patients at the CC. The team used whole-genome sequencing of the bacterium with epidemiological analysis to track the spread of KPC and to determine why it progressed in spite of the early implementation of infection-control procedures.

Their findings provided evidence for unexpected transmission routes (for example, some patients who showed no symptoms were carriers) and were used to drive a change in infection-control procedures (*Sci Transl Med* **4:**148ra116, 2012).

"Samples used in surveillance for AR bacteria are now collected on admission to the hospital, twice weekly in the intensive-care unit, and monthly from all inpatients," said Segre. Ongoing surveillance by her lab shows that there have not been any transmissions of KPC for two years in the CC.

In recognition of their efforts, Segre and the CC response team received Samuel J. Heyman Service to America Medals for "stop[ping] the spread of a deadly hospital-acquired infection through the first-ever use of genome sequencing to identify the source and trace the transmission of antibiotic-resistant bacteria, creating a groundbreaking model for the health-care industry."

National Institute of Diabetes and Kidney Diseases (NIDDK) Senior Investigator **Carole Bewley** also refocused her research after the KPC outbreak. Bewley can be thought of a drug hunter of sorts, extracting novel molecules from natural sources and testing their potential as antibiotics.

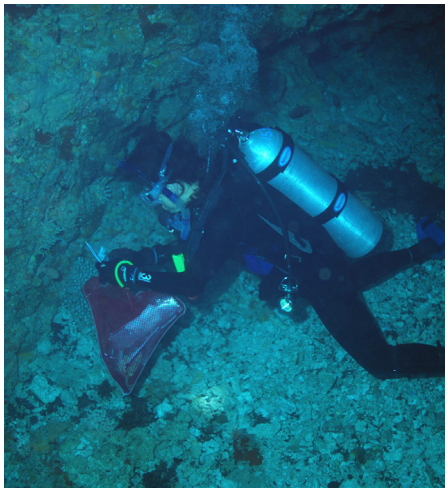
"We are trying to discover new antibiotics that have either different mechanisms of action or different chemical scaffolds so that they will hit a target on a bacterium that is resistant to known antibiotics," she said. For example, Bewley's lab discovered a rare species of marine algae that produces a substance that kills all drug-resistant forms of gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.

Bewley has been collaborating with CC Microbiology Chief **Karen Frank** (who also has a Director's Challenge Innovation Award) to test the effectiveness of novel antibiotic isolates against antibiotic-resistant bacteria such as KPC. Bewley's lab has identified several compounds that are effective because they have a novel target on the bacterium; her lab is now doing whole-genome sequencing to try to work out what the target actually is.

Although research into AR is a trans-NIH venture, the National Institute of Allergy and Infectious Diseases (NIAID) is responsible for the lion's share of NIH's basic, translational, and clinical research. NIAID considers its program a "race to outsmart bacteria by working around the mechanisms that cause resistance" according to the AR Strategic Plan. Several NIAID PIs conduct AR research, including molecular microbiologist **Michael Otto**, chief of the Pathogen Molecular Genetics Section in NIAID's Laboratory of Human Bacterial Pathogenesis.

Otto studies the mechanisms of pathogenicity in Staphylococci, including the formation of multicellular bacterial agglomerations called biofilms. Antibiotics often cannot penetrate these dense, sticky matrices, and even if they do, the metabolism of these cells is such that they are not susceptible to the drugs. "AR in biofilms is categorically different [from] other mechanisms of resistance [such as] a bacterial enzyme that degrades an antibiotic or a pump that pumps antibiotics out of the cell," Otto explained. "Biofilms confer resistance in a nonspecific way, therefore resisting all antibiotics." Understanding how biofilms work may help scientists develop drugs or vaccines that interfere with their immune-evasion mechanisms, providing alternatives to antibiotics.

In a related line of research, Otto has been collaborating with another NIAID PI, **Yasmine Belkaid**, chief of the Mucosal Immunology Section in the Laboratory of Parasitic Diseases. They are investigating the interactions between the "bad bacteria" such as *Staphylococcus aureus* and the "good bacteria" that inhabit our bodies to see whether their benefits might extend to combatting Staphylococci. Belkaid is also collaborating with Frank and Segre to develop a mouse model of KPC infection.



PAT COLIN, CORAL REEF RESEARCH FOUNDATION, PALAU

Carole Bewley collecting samples at Blue Hole Cave in Palau. On this trip, her lab collected the sponges that have yielded the novel antibiotics that Bewley's group is studying.

AR is clearly an urgent global issue, perhaps as big as the AIDS problem was in the 1980s, said Otto.

These sentiments were echoed by Podolsky. AR is a "ticking time bomb," he said. "There has been attention [paid] to AR for the past 30 years—what we need now is more than just attention…we need to galvanize action!"

The good news is that we are making progress.

As Collins eloquently stated in the antibacterial products workshop, "I envision a future where we stay one, two, or even three steps ahead of AR by working together to develop innovative solutions that we haven't even dreamed of yet." ●

To read an interview with Scott Podolsky on NLM's *Circulating Now* blog, go to http://1.usa.gov/1BjZiRI. His new book is *The Antibiotic Era: Reform, Resistance, and the Pursuit of a Rational Therapeutics* (Baltimore: The Johns Hopkins University Press, 2014).

ENCODE

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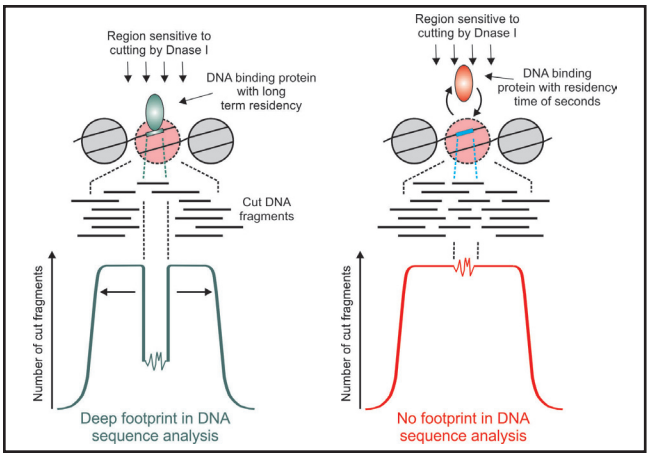

M. SUNG AND G. HAGER, NCI

Among the many ENCODE methods used to identify DNA elements—both protein-coding and non-protein-coding—is genomic footprinting. This method involves cutting chromatin with the enzyme DNase I and mapping accessible regions by sequencing. A bound protein will protect a short sequence from DNase I and leave a "footprint" in the computational analysis. NIH scientists led by Gordon Hager, however, have discovered that only proteins that bind DNA for longer periods of time leave detectable footprints (left). Some proteins, such as the many transcription factors that bind to DNA for shorter amounts of time, do not leave footprints (right). Consequently, genomic footprinting cannot be used to predict DNA-binding patterns for numerous transcription factors.

is choreographed to create a complex organism and how that choreography can go awry in disease.

Among the many methods used to identify the DNA elements is genomic footprinting, also called digital genomic footprinting. This method is an extension of DNase-seq, which involves cutting chromatin with the enzyme DNase I and mapping accessible regions by sequencing. Within these "open chromatin" regions a bound protein will protect a short sequence from the DNase I and leave a "footprint" in the computational analysis. One set of ENCODE elements, published in 2012, relied on the footprinting tool to create an extensive map of locations where transcription factors bind to DNA to control the reading of the genomic information at protein-coding or RNA-coding sites.

Gordon Hager in the National Cancer Institute and his colleagues were surprised to discover that footprinting analysis failed to detect binding sites for proteins that only briefly bind to DNA. Hager studies the action of steroid receptors, including the glucocorticoid receptor (GR) and the estrogen receptor (ER), which act as transcription factors when bound by specific hormones. His work, using diverse experimental methods including biochemistry and single-molecule imaging studies, shows that these receptors interact surprisingly transiently with their DNA targets, for roughly 10 seconds. And they don't leave footprints!

To understand why, staff scientists **Myong-Hee Sung** and **Songjoon Baek** in Hager's group developed a sensitive footprint-detection algorithm called DNase2TF. Using the ENCODE data as well as other published DNase footprinting data, they blind tested the software for footprint detection and evaluated their predictions against independently confirmed transcription-factor binding sites. Their software was able to predict transcription-factor sites more effectively than all the available footprint-detection algorithms, but it still could not detect footprints at a large number of confirmed transcription-factor binding sites, including the GR-binding elements.

With postdoctoral fellow **Michael Guertin**, they confirmed that many dynamic transcription factors such as GR, ER, and serum response factor, a transcription factor involved in cell growth and differentiation, also bind DNA without an associated footprint. Only transcription factors with longer DNA residency times generate footprints. The well-studied transcription-factor CTCF (with a DNA residency time of about five minutes) leaves deep footprints, whereas other factors that bind DNA longer than GR, but more briefly than CTCF, leave shallower ones.

Hager's group is currently strengthening this correlation between DNA association time and footprint depth by analyzing the footprints and binding dynamics of a range of transcription factors.

This work demonstrates that footprinting is "not yet a mature methodology," said Sung.

The current next-generation sequencing produces unprecedented amounts of genomic data from ENCODE (and elsewhere). Mining meaningful information and patterns in the data requires not only sophisticated software and computational tools, but also an integration with knowledge gleaned from other disciplines. Hager's collaboration with imaging laboratories and their integration of data from a wide range of experimental systems have been vital in capturing the in vivo behavior of transcription factors.

To fully understand the complexities of the human genome and protein dynamics, more collaborative efforts among scientists in different disciplines are needed. "We can't work alone in silos," said Hager. "The genomics people need to work with the biochemists and with the single-molecule imaging experts." ●

Hager's study can be read in *Molecular Cell* (*Mol Cell* **56**:275–285, 2014).

The ENCODE footprinting study can be found in *Nature* (*Nature* **489**:83–90, 2012).

DNase2TF is available at http://sourceforge.net/projects/dnase2tfr/.

seqToSign is available at https://github.com/mjg54/seq_to_sign.

HHS Secretary Sylvia Burwell

Greets NIHers at Town Hall Meeting

BY SWAGATA BASU, NICHD

On January 28, 2015, Health and Human Services Secretary **Sylvia Burwell** spent a few hours at NIH for whirlwind tours of labs and clinics, for meetings with several NIH scientific leaders to get research updates, and as the guest of honor at a town hall meeting in Masur Auditorium (Building 10).

At the town hall meeting, NIH Director **Francis Collins** praised Secretary Burwell for her "consistent and effective" support of the "scientific innovation at the NIH" which is essential for the health and economy of the United States.

Burwell, who spent 10 years in the field of philanthropy—first at the Bill and Melinda Gates Foundation and then at the Walmart Foundation—is a former director of the Office of Management and Budget (2013–2014). She described the mission of HHS as making sure that "people have the building blocks of healthy and productive lives." She acknowledged NIH's importance as an "anchor" in accomplishing this mission. NIH has played a pivotal role in the BRAIN initiative, and the development of the Ebola and universal flu vaccines.

After Burwell's brief remarks, Collins moderated a question-and-answer session. The questions had been submitted electronically beforehand.

ERNIE BRANSON

HHS Secretary Sylvia Burwell answered questions at NIH's January 28 town hall meeting.

What are some of your greatest challenges as HHS Secretary?

• Negotiating the "unpredictable incoming" of unforeseen crises such as the 57,000 unaccompanied children who crossed the U.S. borders and whose wellbeing became HHS's responsibility; and the Ebola outbreak in West Africa that emerged as a major public health concern.

• "Shortness of time" [because] there is always a great sense of urgency, which is why setting priorities and staying focused are so important.

What role do you see for global health in the HHS agenda as we go forward?

The role of HHS in global health with issues [such as] Ebola is going to be at the front and center. Partnerships with agencies like USAID, FDA, CDC, and NIH are very important in understanding the problems and coming up with possible solutions by recognizing what we are good at. On Ebola, we have an incredibly important role to play.

What do you think are the prospects for NIH to grow and thrive in the current political and economic climate?

NIH's prospects are better than most. At the bipartisan breakfasts I hold, there is always general agreement about the important role that NIH plays in scientific and medical research. ●

To watch a video of the town hall meeting, go to http://1.usa.gov/1GkXvM4 (NIH and HHS only).

Read more onine at http://irp.nih.gov/catalyst/v23i2/nih-town-hall-meeting-with-hhs-secretary-sylvia-burwell.

NIH ABBREVIATIONS

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

Recently Tenured

DAPHNE BELL, NHGRI

MICHELE EVANS, NIA

MARK GILBERT, NCI, NINDS

IVAN OVCHARENKO, NLM-NCBI

ROSE YANG, NCI-DCEG

DAPHNE W. BELL, PH.D., NHGRI

Senior Investigator, Cancer Genetics and Comparative Genomics Branch, National Human Genome Research Institute

Education: Queen's University, Belfast, Northern Ireland (B.S. in zoology and genetics; Ph.D. in biology and biochemistry)

Training: Postdoctoral training at Fox Chase Cancer Center (Philadelphia)

Before coming to NIH: Assistant professor of medicine, Harvard Medical School and Massachusetts General Hospital (Boston)

Came to NIH: In 2006

Selected professional activities: Member, Uterine Task Force of the NCI Gynecologic Cancer Steering Committee; associate editor-in-chief, *Journal of Genomics*

Outside interests: Enjoying the outdoors, swimming, photography, and art

Web site: http://irp.nih.gov/pi/daphne-bell

Research interests: My team studies uterine cancer, the seventh leading cause of cancer death among women in the United States. Most uterine cancers arise from the inner lining of the uterus, or endometrium, and are called endometrial cancers.

Most human cancers, including endometrial cancers, are caused by the lifetime acquisition of genetic mutations known as driver mutations. During the past 20 years, it has become clear that the proteins made by some driver mutations can be turned off by cancer drugs that target the mutated protein. Tumor cells die while normal cells remain unharmed. Therefore, detecting mutations that are present in human tumors, but absent in normal cells, is the first step toward identifying genetic targets that may be exploited clinically.

Although most endometrial cancers are associated with high cure rates, certain endometrial cancers—including the less-common serous endometrial cancers that typically arise in postmenopausal women—are clinically aggressive and associated with poor outcomes. My laboratory seeks to identify driver mutations that cause these aggressive cancers and, where appropriate, to determine their clinical relevance. We have found novel, high-frequency somatic mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3-kinase) in endometrial tumors; previously unrecognized cohorts of patients may benefit from therapies that target the PI3-kinase pathway.

Recently, we reported one of the first whole-exome sequencing studies of serous endometrial carcinomas: We discovered frequent mutations in genes that regulate chromatin remodeling and ubiquitin-mediated protein degradation, thus implicating these genes as likely drivers of serous endometrial cancer. In ongoing research we are assessing how mutations in these genes affect protein function, and we are expanding our search for additional genomic alterations that drive clinically aggressive endometrial tumors.

MICHELE K. EVANS, M.D., NIA

Senior Investigator, Laboratory of Epidemiology and Population Science; Deputy Scientific Director, NIA

Education: Barnard College of Columbia University, New York (A.B. in biology); Rutgers University, The Robert Wood Johnson Medical School, Piscataway, N.J. (M.D.)

Training: Residency in internal medicine at Emory University School of Medicine (Atlanta); fellowship training in medical oncology at NCI

Selected professional activities: Editorial Board, *New England of Journal of Medicine*; chair, External Advisory Board for the Lazarex-MGH Cancer Care Equity Program, Massachusetts General Hospital (Boston)

Outside interests: Girl Scout leader; Montgomery County Swim League referee and Stroke and Turn official; gardening

Web site: http://irp.nih.gov/pi/michele-evans

Research interests: I conduct interdisciplinary clinical and basic-science research that examines the underlying cause of health disparities—specifically the

disproportionate incidence, morbidity, and mortality of age-related disease—among minority and low socioeconomic status (SES) Americans. My work dissects the interaction of race, SES, culture, behavior, environmental exposure, biologic vulnerabilities, genetics, social environment, health-care access, and quality of health care.

By pursuing related hypotheses at the bench and in the field, my work provides a two-way bridge between basic science and clinical epidemiological research. The ultimate goal of this approach is to transform scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce the incidence, morbidity, and mortality of age-associated diseases with particular interest in cancer and health disparities.

A major element of my work has been the development of the "Healthy Aging in Neighborhoods of Diversity across the Life Span Study" (HANDLS). HANDLS is a longitudinal, epidemiologic study of health disparities among socioeconomically diverse African-Americans and whites who reside in Baltimore. We designed HANDLS to disentangle the effects of race and SES on risk factors for morbidity and mortality; examine the incidence and progression of preclinical disease; and follow, over time, the development and persistence of health disparities, health status, and health risks. Data from this research are also used to investigate the mechanisms or biologic and molecular pathways that influence health and longevity trajectories of individuals.

The study, currently in its fourth longitudinal wave, examines the following domains: cognitive function, nutrition, neighborhood environment, anthropometry (human body measurements), renal function, cardiovascular health, physical performance, health services, molecular markers, genomic markers, and psychology. For more information about HANDLS, go to http://handls.nih.gov; to watch a video, go to https://www.youtube.com/user/NIAsHANDLS.

MARK GILBERT, M.D., NCI-CCR AND NINDS

Senior Investigator and Chief, Neuro-Oncology Branch, National Cancer Institute-Center for Cancer Research and National Institute of Neurological Disorders and Stroke

Education: Johns Hopkins University, Baltimore (B.A. in human biology; M.D.)

Training: Residencies in internal medicine and neurology and fellowship training in neurology and neuro-oncology at Johns Hopkins

Before coming to NIH: Professor and deputy department chair, Department of Neuro-Oncology, Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center (Houston)

Came to NIH: In November 2014

Selected professional activities: Co-chair, Brain Tumor Committee, Radiation Therapy Oncology Group (Philadelphia); founder and leader of the Collaborative Ependymoma Research Network (CERN); founder and leader of the Brain Tumor Trials Collaborative (BTTC)

Outside interests: Hiking; rock climbing; mountaineering

Research interests: At M.D. Anderson, I developed and led large-scale, comprehensive, hypothesis-based clinical trials focused on finding treatments for malignant brain tumors. I led a clinical trial on the efficacy of the angiogenesis-inhibitor bevacizumab as a therapeutic for patients with newly diagnosed glioblastoma, the most common and lethal form of brain cancer. Although other studies had shown bevacizumab to have positive results in treating the disease, ours—the first randomized, double-blind study with the drug—demonstrated that it failed to increase overall survival or statistically significant progression-free survival. We established a new benchmark by successfully incorporating both real-time tumor analysis and patient-outcomes measures, including symptom burden, neurocognitive testing, and health-related quality of life.

At NIH, I am leading the Neuro-Oncology Branch, a collaboration between the National Cancer Institute (NCI) and National Institute of Neurological Disorders and Stroke (NINDS). We are working to develop new therapies for patients with primary brain and spinal-cord tumors. My vision is to build a highly collaborative, robust translational research program centered on finding treatments for central-nervous-system tumors; basic research observations will be rapidly translated into preclinical testing and then hypothesis-based clinical research trials, including important correlative studies.

Our areas of clinical research include exploring genetic changes in brain tumors to better understand how these cancers develop and become resistant to treatment; determining the impact of these tumors on the immune system by carrying out clinical trials designed to stimulate patients' immune systems to help destroy the cancer; investigating the metabolism of cancer cells; and examining the impact of disease and treatment on cognitive function, symptoms, and quality of life.

In addition, we are using NCI's and NINDS's advanced-imaging technologies to develop new ways to image brain tumors so we can determine tumor activity, better define tumor location, and see whether therapeutic drugs are getting to—and working against—the cancers.

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

IVAN OVCHARENKO, PH.D., NLM-NCBI

Senior Investigator, Computational Biology Branch, National Center for Biotechnology Information, National Library of Medicine

Education: Novosibirsk State University, Novosibirsk, Russia (M.S. in physics; Ph.D. in physics and mathematics)

Training: Postdoctoral research at University of California at Berkeley and Lawrence Berkeley National Laboratory

Before coming to NIH: Principal investigator, Lawrence Livermore National Laboratory (Livermore, Calif.)

Came to NIH: In 2007

Selected professional activities: Associate editor, *Bioinformatics and BMC Bioinformatics*

Outside interests: Hiking; skiing

Web site: http://irp.nih.gov/pi/ivan-ovcharenko

Research interests: My group is deciphering the semantics and studying the evolution of the gene regulatory code in eukaryotes.

With less than two percent of the human genome having been sequenced, the search for noncoding functional DNA is an unsophisticated treasure hunt. We currently lack a fundamental understanding of the genomic language that governs the temporal and spatial dynamics of gene-expression regulation. To bridge the gap between genome sequencing and sequencing-data interpretation, we are developing pattern-recognition methods to functionally characterize noncoding DNA.

Understanding the gene regulatory landscape of the human genome will pave the way for studies of population variation in noncoding functional elements and promote the identification of disease-causing mutations residing outside of genes. Because mutations in gene-regulatory regions might be linked to an increased susceptibility to disease—not necessarily resulting in the disease itself—our research has a potential for mapping key regulatory elements in the vicinity of disease-associated genes. Computationally defined datasets of human regulatory elements tailored to common diseases (including heart disease, obesity, diabetes, and cancer) will facilitate the discovery of novel disease-susceptibility measurement methods.

To infer the function of noncoding genes, we use a variety of techniques—comparative genomics, Bayesian statistics, multiple sequence alignments, libraries of transcription-factor binding sites, microarray gene-expression data, sequence-pattern recognition techniques, dynamic programming, population genetics, and transgenic-animal experimentation (the latter through collaborations)—and the analysis of sequence data and evolutionary trends. Our research relies on collaborative studies with several research and clinical groups within the NIH and other research universities and institutions.

XIAOHONG (ROSE) YANG, PH.D., M.P.H., NCI-DCEG

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

Education: Beijing Normal University, Beijing (B.S. in biology; M.S. in cell biology); Lombardi Cancer Center, Georgetown University, Washington, D.C. (Ph.D. in physiology); Johns Hopkins Bloomberg School of Public Health, Baltimore (M.P.H. in epidemiology)

Training: NCI-DCEG

Came to NIH: In 2000 for training; became tenure-track investigator in 2006

Selected professional activities: Editorial board for *Cancer Epidemiology, Biomarkers and Prevention*; adjunct associate professor at the Chinese University of Hong Kong

Outside interests: Walking; playing tennis

Web site: http://irp.nih.gov/pi/rose-yang

Research interests: I combine statistical genetic analyses and cutting-edge genomic technologies to identify susceptibility genes for familial cancers including chordoma and cutaneous malignant melanoma/dysplastic nevi syndrome. I am also assessing the etiologic heterogeneity of breast cancer by integrating breast-cancer risk factors with genomic alterations in tumors.

My group spent more than 10 years searching for the genes implicated in familial chordoma, a rare type of bone tumor. In 2009, we identified the duplication of a specific gene as a major susceptibility factor. We used new technology—high-resolution array-based comparative genomic hybridization—that complemented traditional gene-mapping strategy.

Recently, we used exome-sequencing to identify a rare inherited mutation in a gene involved in maintaining telomere stability in melanoma-prone families. Finding genes in high-risk families may reveal important pathways involved in carcinogenesis in the general population.

In my investigation of the etiologic heterogeneity of breast cancer, I used tissue microarray to characterize the molecular signature of tumors and integrated tumor-profiling analyses to identify risk factors for specific cancer subtypes. I am leading breast-cancer studies in mainland China, Hong Kong, and Malaysia to identify distinct molecular alterations in tumors and adjacent normal tissues among Asian women and to examine the associations of these molecular changes with genetic and environmental risk factors, breast-tissue composition and density, and breast-cancer subtypes. Identifying unique exposure-subtype relationships in understudied populations will fill a critical knowledge gap concerning the observed racial heterogeneity of breast cancer and improve the risk stratification. ●

TRIBUTE TO MARSHALL NIRENBERG

A "triplet" of events will be held to celebrate the 1965 completion of the genetic code, an effort led by **Marshall Nirenberg** and NIH.

Tuesday, March 17, 2015, 1:00–3:30 p.m.
National Library of Medicine (NLM)
Lister Hill Auditorium (Building 38A)

This special public program will formally mark the NLM's acquisition of Marshall Nirenberg's Nobel prize and certificate through a generous donation by Myrna Weissman (Columbia University Mailman School of Public Health); recognize the publication of Frank Portugal's new book about Nirenberg; and include remarks by David Serlin (University of California, San Diego), curator of NLM's new "Turning the Pages" project that involves the Nirenberg genetic code charts.

Wednesday, May 20, 3:00–4:00 p.m.
Nirenberg Lecture
Masur Auditorium (Building 10)

The second event will be held in conjunction with the Annual Marshall Nirenberg Lecture. NIH Director Francis Collins will provide a historical and scientific perspective on the genetic code. David Page, director of the Whitehead Institute (Cambridge, Mass.), will deliver the Nirenberg lecture, a scientific talk titled "Lost in Translation: Do Males and Females Read Their Genomes Differently?"

Fall 2015

This event will further explore Nirenberg's legacy from historical, social, and scientific perspectives. Details not yet confirmed.

WSA SCHOLARS SYMPOSIUM

March 20, 2015, 2:30 p.m.
Wilson Hall (Building One)

Each year the NIH Women Scientist Advisory (WSA) Committee selects two or three female FARE award winners as WSA Scholars for their outstanding scientific research. The 2014 WSA Scholars are Bari Ballew, Barbara Nicol, and Christine Jao, who will each give a presentation on her work. Reception follows.

POSTDOCTORAL RESEARCH ASSOCIATE (PRAT) PROGRAM

Accepting Applications until March 17, 2015

PRAT fellows conduct research in an NIH intramural research program (IRP) lab. For more information, see http://www.nigms.nih.gov/Training/Pages/PRAT.aspx or contact Jessica Faupel-Badger at badgerje@mail.nih.gov.

MEDICINE AND THE MEDIA: A MORNING WITH SANJAY GUPTA, M.D.

March 25, 2015, 10:00–11:15 a.m.
Masur Auditorium; overflow in Lipsett Amphitheater (Building 10)

Neurosurgeon Sanjay Gupta, an Emmy Award–winning journalist and chief medical correspondent for CNN, will deliver the annual J. Edward Rall Cultural Lecture. Seating is on a first-come, first-served basis. For more information or to request reasonable accommodation, contact Jacqueline Roberts at 301-594-6747 or robertsjm@mail.nih.gov or the Federal Relay, 800-877-8339. To watch the lecture online, visit http://videocast.nih.gov.

OMICS IN THE CHARACTERIZATION, CLASSIFICATION, AND TREATMENT OF AUTOIMMUNE DISEASES AND CANCER

Monday, April 13, 2014, 8:25 a.m.–4:15 p.m.
Lipsett Amphitheater (Building 10)
Registration deadline: April 3
Web site: http://1.usa.gov/1EmQqvB

See Web site for agenda, featuring experts from the NIH and beyond. More information will be posted soon. For questions, contact Howard Young at younghow@mail.nih.gov. The event is sponsored by the NCI, NIAID, NIAMS, NIH Cytokine Interest Group, and the NIH Office of Research in Women's Health.

NIH-KOREA SYMPOSIUM

Thursday, April 16–Friday, April 17, 2015
Lipsett Amphitheater (Building 10)

The symposium, which will feature lectures and a poster session, will review the relationships and collaborations between NIH and three Korean institutes (the Korean National Institute of Health, the Korean Health Industry Development Institute, and the Korean National Cancer Center). For information, contact Jacqueline Roberts at 301-594-6747 or robertsjm@od.nih.gov.

PRECISION MEDICINE IN ACTION

Anita B. Roberts Lecture Series
Tuesday, April 21, 1:00–2:00 p.m.
Lipsett Amphitheater (Building 10)

Hannah Valantine, NIH's chief officer for Scientific Workforce Diversity, will present "Precision Medicine in Action: Applying Genomic Tools to Improve Patient Outcomes after Organ Transplantation." Sign-language interpreters will be provided upon request. Those who need reasonable accommodation should contact Margaret McBurney at 301-496-1921 and/or the Federal Relay, 1-800-877-8339, five days before the lecture.

LECTURES ON COMPLEMENTARY/ INTEGRATIVE HEALTH

Mondays (once a month), 10:00–11:00 a.m.
Web site: https://nccih.nih.gov/news/events/IMlectures

April 13: Pieter Dorrestein, Ph.D. (University of California, San Diego). Location: Masur Auditorium (Building 10).

POSTBAC POSTER DAY

Thursday, April 30, 10:00 a.m.–3:30 p.m.
Natcher Conference Center (Building 45)
Web site: https://www.training.nih.gov/postbac_poster_day

Audrey J. Murrell (University of Pittsburgh) will present the keynote address at 12:00 noon. There will be poster sessions and an awards ceremony, too. The day provides an opportunity for postbacs to share their research and develop their scientific communication and networking skills. Investigators, staff scientists, and scientific administrators can make an important contribution to Postbac Poster Day by visiting posters and engaging their authors in discussion. ●

Read more online at http://irp.nih.gov/catalyst/v23i2/announcements.

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CATALYTIC REACTIONS?

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

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

READ MORE ARTICLES, AND EXPANDED VERSIONS OF THE ONES IN THIS ISSUE, ONLINE AT http://irp.nih.gov/catalyst/v23i2

FROM THE ANNALS OF NIH HISTORY

Women's History: 1930s Meningitis Research

BY MICHELE LYONS, OFFICE OF NIH HISTORY

OFFICE OF NIH HISTORY, 1937

"Know your enemy" describes the work of **Sara Branham** (1888–1962), who is credited with the discovery and isolation of the virus that causes spinal meningitis. She dedicated her career to understanding meningitis and developing the effective tests and treatments for the disease with antiserum and sulfa drugs. In this 1937 photo, Branham and technician **Robert Forkish** inoculate a mouse with meningococcal antiserum to determine whether it would protect against meningitis. Branham left a faculty appointment at the University of Rochester to come to the Division of Biologics Standards at the NIH's precursor agency, the Hygienic Laboratory, where she ultimately rose to the level of chief of the Division's Section on Bacterial Toxins. In the 1930s, Branham represented the United States at the first two international microbiology conferences. She retired in 1958. To learn more about her life and career, go to http://1.usa.gov/1HjgpUA. ●

EXCERPTED FROM A MARCH 4, 2015, POST ON THE INTRAMURAL RESEARCH PROGRAM BLOG: HTTP://IRP.NIH.GOV/BLOG.

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

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