THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 23 ISSUE 3 • MAY-JUNE 2015

WHIM Syndrome

Whimsically Cured by Chromosome Shattering

BY RACHEL SCHEINERT, NIMH

It was a medical mystery that only the NIH could solve: How a woman was spontaneously cured of a rare disease more than 20 years ago after first being diagnosed. Researchers at the NIH recently unraveled this mystery cure in the journal *Cell*.

In 1964, a nine-year-old girl was featured in two case studies in the *New England Journal of Medicine* as the first person ever diagnosed with myelokathexis, the inability of certain white blood cells to leave the bone marrow, enter the bloodstream, and fight infection (*N Engl J Med* **270:**699–704, 973–979, 1964). This extremely rare inherited immunodeficiency disease later came to be known as WHIM syndrome [warts, hypogammaglobulinemia (low concentrations of immunoglobulins), infections, and myelokathexis (white blood cells trapped in the bone marrow)]. In 2003, researchers found that the syndrome is caused by mutations in the chemokine receptor gene *CXCR4*, which is expressed on most white blood cells (*Nat Genet* **34:**70–74, 2003).

Two years ago, a 58-year-old woman contacted the National Institute of Allergy and Infectious Diseases (NIAID), where a team of scientists was studying WHIM syndrome and *CXCR4*. She said that she and two of her three daughters, ages 21 and 23, wanted to be evaluated for WHIM syndrome. It turned out that the woman

CONTINUED ON PAGE 14

NIH Rare Disease Day 2015

Teamwork of Scientists and Community Brings Treatments to Fruition

BY LESLEY EARL (NCI) AND EMILY PETRUS (NINDS)

EURORDIS

Trip after trip to the doctor. Misdiagnosis followed by confusion. More visits to specialists. Few, if any, answers. For those with a rare disease, this cycle of uncertainty rarely ends even with a diagnosis. Of the more than 6,000 known rare diseases, only 300 have any treatment at all. Nevertheless, with a diagnosis of a rare disorder comes a community of patients and their families, as well as scientists, clinicians, and others, all traveling the same path together.

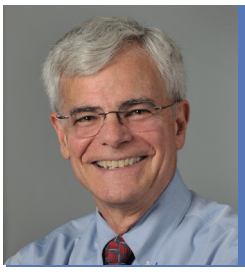
More than 500 members of that rare-disease community gathered at NIH—and an additional 329 watched online—on February 27, 2015, for the international Rare Disease Day symposium, which highlighted recent progress in bringing new therapies to the clinic.

CONTINUED ON PAGE 12

CONTENTS

FEATURES • |1| WHIM Syndrome |1| Rare Disease Day |4| Telomeres, Sex, and Hospital Infections |6| Environmental Exposures and Obesity |7| NEI Gene-Therapy Trials |10| Journalist Sanjay Gupta Visits NIH |15| Expansion of Medical Research Scholars Program

DEPARTMENTS • |2| DDIR: Making Cancer History |3| News Briefs: U.S. Senators; Nirenberg |5| News You Can Use: New OIR Web site |8| Research Briefs |15| Abbreviations |16| Colleagues: Recently Tenured |19| Announcements |20| Laboratory Confessions



Making Cancer History

BY MICHAEL GOTTESMAN, DDIR

Those of you who tuned into the six-hour PBS documentary *Cancer: The Emperor of All Maladies*—a Ken Burns production based on a Pulitzer prize–winning book by Siddhartha Mukherjee—may have noticed how closely the history of cancer advances parallels the history of the NIH intramural research program. From combination chemotherapy for lymphoma and leukemia, through the discovery of virus vectors and the development of vaccines, to immunotherapy and the promise of personalized medicine, that was us making cancer history.

I was in college and medical school at Harvard in the 1960s when I started hearing about all the amazing work being done at the National Cancer Institute (NCI) and the Clinical Center. Imagine the stark reality back then: Nearly every child with leukemia died of that disease.

The pioneering work of NCI's **Emil Frei** and **Emil Freireich** and their four-drug approach placed us on the road to a 90 percent survival rate. The "two Emils"—with the same first name and neighboring labs on the 12th floor of Building 10, but utterly different personalities—were both featured in the Ken Burns documentary, as was NCI Clinical Director **C. Gordon Zubrod**, who was NCI scientific director during this time. All three ultimately won Lasker awards for their chemotherapy work.

Other NIH heroes—and Lasker winners—of this era include **Paul Carbone** and **Vincent DeVita** (combination therapy to treat Hodgkin disease); **Roy Hertz** and **Min Chiu Li** (treatment of gestational choriocarcinoma); **James F. Holland** (use of combination therapy to treat acute leukemia in children); and **John L. Ziegler** (increasing the cure rate for Burkitt's tumor by chemotherapy).

If I could insert another episode into Ken Burns' three-part series, it would include the NIH's profound contributions to the basic science of cancer. During those heady clinical advances of the 1960s, NCI's **Michael Potter** was studying plasmacytomas, antibodies, and the genetic factors leading to the susceptibility and resistance to tumor growth. He would win the Lasker Award in 1984. During the 1970s, NCI's **Robert Gallo** was exploring retroviruses and their role in cancer; he'd win the Lasker for that work in 1982 (he also won in 1986 for determining that HIV caused AIDS).

> The history of cancer advances parallels the history of the NIH intramural research program.

Meanwhile, NCI's **Ira Pastan** (who mentored **Harold Varmus** and **Robert Lefkowitz**) and **Jesse Roth** were pioneering the field of receptor biology. In the National Institute of Allergy and Infectious Diseases (NIAID), **Anthony Fauci** helped spearhead the concerted efforts to understand and control human immunodeficiency virus and its associated immunodeficiencies and cancers.

Decades of research by NCI's **Douglas Lowy** and **John Schiller** paid off with the staggeringly successful vaccine against the human papillomavirus, the leading cause of cervical cancer (and a significant cause of many other cancers, too.) Among their high-profile awards for this achievement was the National Medal of Technology and Innovation in 2014 (http://1.usa.gov/1bvnZRY).

Similarly, **Harvey Alter** of the Clinical Center co-discovered the hepatitis B virus and laid the groundwork for the detection of the hepatitis C virus, both major causes of liver cancer. Alter won the Lasker in 2000 and the Gairdner award in 2013. In NIAID, **Robert Purcell's** work on various strains of hepatitis also led to vaccine development and has reduced the incidence of liver cancer, particularly in China. Although vaccines were mentioned in the cancer documentary only in passing, the work of these NIH scientists will save countless lives. With all these Lasker awardees, it's no wonder that the Clinical Center itself earned a Lasker, in 2011, for transforming scientific advances into innovative therapies and providing high-quality care to patients.

Palliative care has come a long way, too. Work by NCI's **Lori Wiener** and the National Institute of Mental Health's **Maryland Pao** on helping teenagers better face an early death was featured in the *New York Times* on Sunday, March 29, 2015 (http://nyti.ms/1H1Kzxn).

There's much more to highlight, as you can imagine. I'd like to think my own research on cancer drug resistance has deepened our understanding of cancer…at least in terms of why it is so difficult to cure.

Cancer: The Emperor of All Maladies ended, as expected, on a message of hope, focusing on cancer immunotherapy, named the 2013 scientific breakthrough of the year by the journal *Science* (http://bit.ly/1QjLc9x). NCI's **Steve Rosenberg**, featured heavily in the documentary, is one of the fathers of this field. His, too, has been a decades-long research journey quite possibly on the threshold of profound success.

It was fun to marvel at all of the NIH alumni featured in the Ken Burns documentary: **David Nathan**, **Michael Bishop**, **Harold Varmus**, **Rick Klausner**, and probably a few more luminaries who trained here in the 1960s and 1970s. But Senator Ben Cardin, in his address to the NIH staff on April 2, aptly noted that the true star of the documentary was NIH itself—that is, you, as members of the vast research enterprise (http://videocast.nih.gov/launch.asp?18925).

As Eric Lander of the Massachusetts Institute of Technology so skillfully summarized in the documentary, advances may seem slow at one level—cancer continues to be a major killer—but considering the complexity of cancer, it is mind-boggling how far the science and treatments have progressed in the last 50 years. I'm not so cynical to think, as some do, that the war on cancer has been lost. The battle rages on, and I dare say we are winning. ●

To view the PBS documentary *Cancer: The Emperor of All Maladies,* go to http://video.pbs.org/program/story-cancer-emperor-all-maladies/. To see the list of NIH's Lasker winners, go to http://irp.nih.gov/about-us/honors/lasker-award.

SENATORS PLEDGE SUPPORT FOR BIOMEDICAL RESEARCH

When United States Senators Barbara Mikulski (D-Maryland) and Ben Cardin (D-Maryland) visited NIH a few weeks ago, they pledged their support for getting more federal funding for biomedical research. Mikulski toured the National Center for Advancing Translational Science facility in Rockville on March 31. The facility has a high-speed robotic screening system that analyzes chemical compounds that are candidates for drug treatments.

Cardin held a town hall (his third) for NIHers in Masur Auditorium (Building 10), on April 2, and fielded questions and comments from the audience. To see a video of the town hall event, for NIH viewers only, go to http://videocast.nih.gov/launch.asp?18925. You can also read the full account of the senators' visits in the April 24 issue of the *NIH Record* at http://nihrecord.nih.gov/newsletters/2015/04_24_2015/story1.htm. ●

ERNIE BRANSON

U.S. Senator Ben Cardin (D-Maryland) shown with NIH Director Francis Collins (left), fielded audience questions and comments after his town hall meeting at NIH, on April 2.

CELEBRATING MARSHALL NIRENBERG

Marshall Nirenberg, the first NIH intramural scientist to win a Nobel prize, was a "scientist's scientist," and a "mentor's mentor," according to NIH Director **Francis Collins**. To celebrate the 50th anniversary of Nirenberg's cracking of the genetic code, the National Library of Medicine (NLM) held "A Tribute to Marshall Nirenberg," on March 17, 2015. The tribute was the first of a triplet of events. The second is scheduled for May 20 with David Page from the Whitehead Institute (Cambridge, Massachusetts), 3:00–4:00 p.m., Masur Auditorium (Building 10). The third event is planned for the fall.

The tribute included remarks by friends, family, and colleagues, including Nirenberg's widow Myrna Weissman and former colleague Frank Portugal, who wrote the book *The Least Likely Man: Marshall Nirenberg and the Discovery of the Genetic Code* (MIT Press, 2015). In addition, two experts in preserving the Nirenberg materials spoke: **George Thoma**, chief of NLM's Communications Engineering Branch, who launched the new Turning-the-Pages interactive presentation of Nirenberg's work; and David Serlin (University of California, San Diego), who curated NLM's Profiles in Science Web site on Nirenberg's papers. Nirenberg's Nobel medal and certificate were also presented to NLM for permanent display in the NLM Visitor Center. Read more online at http:/irp.nih.gov/catalyst/v23i3/celebrating-marshall-nirenberg. ●

Telomeres, Sex, and Hospital Infections

WSA Scholars Discuss Their Research

BY BRANDON LEVY, NIMH

WSA Scholars, clockwise from left: **Bari Ballew** (NCI) wants to understand the link between telomere biology and cancer risk; **Barbara Nicol** (NIEHS) is investigating how environmental chemicals interfere with the genetics of sex differentiation; and **Christine Jao** (NIDDK) is looking for ways to stop the growth of dangerous bacteria.

Bari Ballew's investigations on shortened telomeres may lead to a cure for a rare genetic disorder. **Barbara Nicol's** efforts to understand the genetics of sex differentiation may shed light on how environmental chemicals do their damage. And **Christine Jao's** use of structural biology to learn the secrets of a nasty bacterium may contribute to the prevention of hospital-acquired infections. So it's not surprising that all three women are winners of the Women Scientist Advisors (WSA) Scholar Award and were invited to present their work at the annual NIH WSA Scholar Seminar held on March 20, 2015.

"Telomere biology and cancer etiology are closely linked," explained Ballew, who wants to understand the relationship between the two. Telomeres are repetitive DNA sequences that protect the ends of chromosomes. She described her research on dyskeratosis congenita (DC), a rare genetic disorder characterized by drastically shortened telomeres. People with the disorder are at increased risk of developing severe life-threatening conditions including bone marrow failure and cancer.

She and colleagues at the University of Michigan (Ann Arbor, Michigan) discovered two previously unrecognized genetic mutations—in a person with DC and several family members—that impair the function of a protein encoded by the gene *ACD*. The protein is part of a larger complex called shelterin, which protects telomeres against damage and in some cases recruits the enzyme telomerase to repair them (*Genes Dev* **28:**2090–2102, 2014). She hopes the discovery will influence the treatment of DC.

Ballew earned her Ph.D. in biology from the University of California, San Diego, and works in **Sharon Savage's** lab in the National Cancer Institute, Division of Cancer Epidemiology and Genetics.

Barbara Nicol is exploring the genetic factors that cause mice to develop male or female sexual organs during embryogenesis. She hopes to better understand the basic process of organ formation as well as the potential implications of exposure to environmental chemicals.

Mammalian fetuses have undifferentiated precursor cells called the gonadal ridge that can develop into either testes or ovaries depending on the balance between pro-testis pathways activated by the *SOX9* gene and pro-ovary pathways triggered by the *CTNNB1* gene, which codes for beta-catenin.

Nicol described how knocking out the two genes *SOX9* and *CTNNB1* caused both genetically female and genetically male cells to develop testis-like traits, suggesting the existence of pro-testis genes that can function without *SOX9*. Indeed, she identified several pro-testis genes that were active even when *SOX9* and *CTNNB1* were nonfunctional. In addition, she observed that male cells became more masculinized than female cells when both genes were disabled.

Nicol, who received her Ph.D. in the biology of reproduction from the French National Institute for Agricultural Research and the University of Rennes (both in Rennes, France), is part of **Humphrey Yao's** lab in the Reproductive and Developmental Biology Laboratory of the National Institute of Environmental Health Sciences (Research Triangle Park, North Carolina).

Christine Jao investigates methods for combating hospital-acquired infections. She has done postdoctoral work in two NIH labs since earning her Ph.D. in biochemistry and molecular biology from the University of Southern California (Los Angeles)—first in **James Hurley's** lab at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and now in **Susan Buchanan's** lab at NIDDK's Laboratory of Molecular Biology.

Jao is particularly interested in how to interfere with bacterial growth by tweaking its zinc-uptake system. Bacteria need trace amounts of metals to survive; previous research focused on how infectious bacteria take in iron.

She helped figure out the crystal structure of a zinc transporter in *Acinetobacter baumannii*, a multi-drug-resistant bacterium that often infects patients during hospital stays. The transporter, called zinc uptake receptor D1 (or ZnuD1), resides on the bacterium's outer membrane, making it a potential drug target.

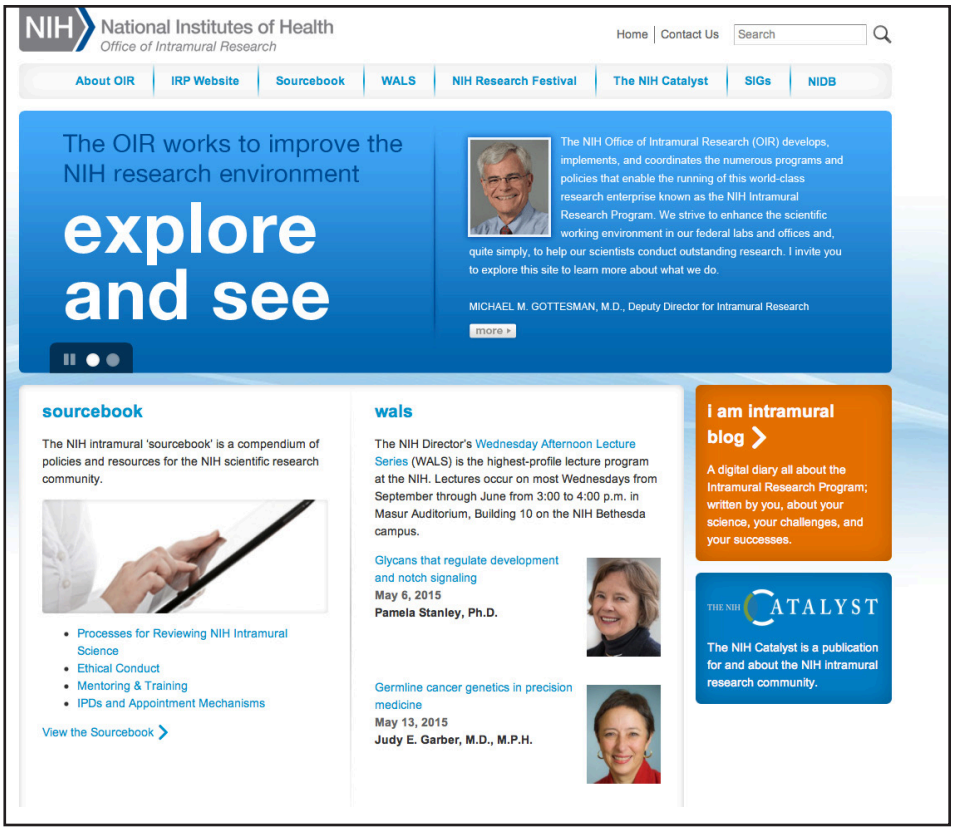
Zinc receptors in other bacteria are likely to be similar. "So the hope is," said Jao, "if we find a chemical that stops growth in Acinetobacter, we can also use it for other types of pathogens." ●

To learn more about the WSA, visit http://sigs.nih.gov/wsa/Pages/default.aspx.

Meet the Office of Intramural Research

Announcing the New OIR Web Site and Sourcebook

BY MICHAEL GOTTESMAN, DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH



I'M EXCITED TO TELL YOU ABOUT AN expanded resource from the Office of Intramural Research (OIR), which I direct. We have created a new Web site at http://oir.nih.gov that consolidates information on the numerous programs and activities that OIR oversees.

A prominent feature of this site is what has been known for many years as the NIH "Intramural Sourcebook," a compendium of policies and resources for the NIH scientific research and administrative community. The revamped Sourcebook captures several thousand distinct and important bits of information—hiring and work–life balance benefits, through mentoring and publication procedures, ethical conduct, sabbaticals and retirement options, and more. We revamped the Sourcebook not only to remain transparent about NIH intramural policies but also to promote what I consider to be the best work environment for biomedical research in the world.

The new Web site also features information on trans-NIH offerings that my office coordinates: the Wednesday Afternoon Lecture Series (WALS), the NIH Research Festival, *The NIH Catalyst*, the NIH Intramural Database, and the NIH Scientific Interest Groups. The OIR site is also integrated with the popular site about intramural research at http://irp.nih.gov (which you really should explore, if you haven't already), which includes information on all IRP principal investigators, our research accomplishments, and career and training opportunities.

The OIR has not had a Web site before now. I hope this new site will provide a full picture of the various components of the OIR that keep this vast research enterprise running as efficiently and pleasantly as possible: Office of Intramural Training and Education; Office of Animal Care and Use; Office of Human Subjects Research Protections; Office of Technology Transfer; and Office of NIH History and Stetten Museum.

You can learn more about the creation and features of the site by visiting the "I am Intramural" blog, at http://irp.nih.gov/blog/oir-website. We hope you find this new online resource to be helpful. Make sure to bookmark it! ●

Visit the new OIR Web site at http://oir.nih.gov

IRP WEB SITE: BLOGS, RESPONSIVE DESIGN, AND MORE

NIH's Intramural Research Program (IRP) Web site, launched in September 2011, brings together information about NIH's research advances, tells scientific stories (often in the investigators' own words), and highlights the numerous employment and training opportunities available within the IRP. There's a Google-search functionality that allows users to find content more easily; a responsive design that allows the site to automatically adjust how it's displayed based on the device it's being viewed on; and an "I am Intramural" blog (http://irp.nih.gov/blog). Check out the new and improved IRP site at http://irp.nih.gov.

The Role of Environmental Exposures in Obesity

Are Environmental Chemicals Making It Harder to Control Our Weight?

BY KELLY LENOX, NIEHS

Although exercising and healthy eating play crucial roles in the fight against obesity, current research is reshaping our understanding of the complex roots of the global obesity epidemic. At the National Institute of Environmental Health Sciences (NIEHS) and elsewhere, scientists are examining the interactions between genetic factors and environmental exposures that may be contributing to the obesity problem.

"We want to try to tease apart that interaction [and] reinforce the concept that obesity—with its attendant comorbidities, such as diabetes and metabolic syndrome—is a multifactorial outcome," said NIEHS Director **Linda Birnbaum** to an international audience that gathered in March at the NIEHS campus (Research Triangle Park, North Carolina) for an Institute of Medicine (IOM) two-day workshop on "The Interplay Between Environmental Exposures and Obesity." Birnbaum, who is also the director of the National Toxicology Program (NTP), posed the question that presenters would shed light on: "We have to ask whether environmental chemicals are making it harder for us all to control our weight."

"Only when we understand the complex origins of the likelihood of becoming obese will we be able to deal with this huge health and economic problem," said Frank Loy, chair of the group that convened the workshop—the IOM Roundtable on Environmental Health Sciences, Research, and Medicine. Nearly 600 people registered for the Webcast, and more than 100 attended in person to hear researchers from academia, government, public health, and industry discuss the issue.

Scientists shared results of their investigations ranging from multigenerational studies of the effects of specific chemicals, to large-scale epidemiologic research, to economic analyses.

Kristina Rother (National Institute of Diabetes and Digestive and Kidney Diseases) discussed in vitro and in vivo studies showing that noncaloric sweeteners appear to increase insulin secretion and adipogenesis and decrease the sense of reward. "There is no convincing evidence that artificial sweeteners prevent or alleviate obesity," she said. (*J Clin Endocrinol Metab* **97:**2597–2605, 2012)

Molecular toxicologist **Scott Auerbach** (NTP) shared data-mining approaches for identifying chemicals to test for possible obesity and diabetes outcomes. The National Center for Advancing Translational Science (NCATS) PubChem database provides public access to data collected through the ToxCast and Tox21 projects, which are collaborative efforts between NIEHS and the NCATS Chemical Genomics Center. The researchers selected biological processes associated with obesity and then obtained expert recommendations on which ToxCast assays were most relevant. Another approach, called sentinel chemical correlation, is a data-driven method used to identify groups of chemicals with similar biological action. These and other approaches can be useful in screening chemicals for further study.

Obesity Society President Nikhil Dhurandhar (Texas Tech University in Lubbock, Texas) shared research that linked adenovirus 36 infection with a greater potential for preadipose tissue to differentiate into adipose tissue. He showed a series of maps in which the pattern of obesity increase in the United States resembled the spread of an infectious agent (influenza) more than it did the spread of a noninfectious disease (asthma).

STEVE MCCAW, NIEHS

"This [obesity] problem is not restricted to the U.S. or technologically advanced countries, but is increasing in less-developed countries as well," said NIEHS Director Linda Birnbaum at the recent IOM workshop held at NIEHS.

Other presenters included Barbara Corkey (Boston University School of Medicine), whose research suggests that food additives and environmental factors may trigger metabolic changes such as pancreatic beta cells secreting too much insulin; Beverly Rubin (Tufts), who has found evidence linking perinatal bisphenol-A exposure in mice to increases in inflammation and systemic insulin resistance; and John Rogers, a microbiologist with the U.S. Environmental Protection Agency, who said that low concentrations of BPA and other agents could stimulate obesity, but increasing doses can lead to other toxic mechanisms that can ultimately drive weight down.

Sessions also covered neurological factors that affect appetite and activity, changes in the composition of meat and produce over the past 50 years, and decreases in the duration of sleep. Many speakers echoed a familiar refrain: The traditional focus on energy balance explains only part of the obesity epidemic. ●

For presenters' slides, videos, and more, go to http://www.iom.edu/chemicalsandobesity.

News From the National Eye Institute

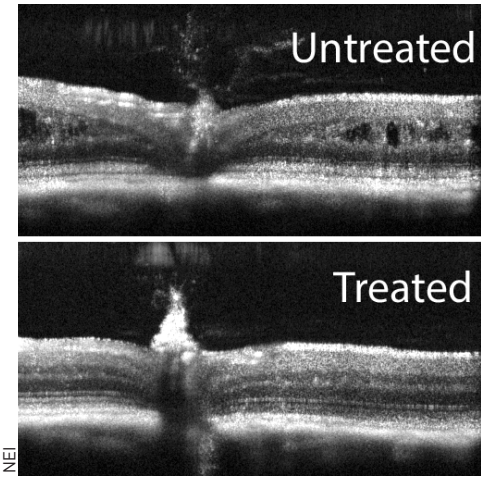
Human Gene Therapy Trial for Retinoschisis Underway

BY DUSTIN HAYS, NEI

The National Eye Institute (NEI) recently launched the first-ever human gene-therapy trial for the vision disorder X-linked retinoschisis (XLRS). The researchers are conducting the trial at the NIH Clinical Research Center.

XLRS is a genetic disorder that causes splitting through the layers of the retina, the light-sensitive neural tissue in the back of the eye. XLRS gene mutations are inherited from the mother; however, typically only males develop symptoms. Vision loss usually is evident by early grade-school age and slowly worsens over the next several decades as cells in the retina lose function and die.

The causative gene was identified in 1997 and named *Retinoschisin 1* (*RS1*). The gene codes for the retinoschisin protein, which normally works like double-sided tape, providing lateral adhesion that holds retinal cells together. *RS1* gene mutations alter the protein and thereby interfere with the ability of cells to maintain proper structure of the retina.



NEI

Cross-sectional images of the retina from retinoschisin-deficient mice, untreated (top) and treated with XLRS gene therapy.

The XLRS gene therapy technique uses an adeno-associated virus (AAV) as a vector to shuttle normal *RS1* DNA into cells of the retina. This virus does not cause human disease. In preclinical studies, the NEI team successfully demonstrated use of the vector to deliver the *RS1* gene into an XLRS mouse model. When treated, the mouse eyes showed improvements in retinal structure and visual function.

A similar treatment strategy with an AAV vector, loaded with a different gene, was used in the groundbreaking gene-therapy trials for Leber congenital amaurosis (https://www.nei.nih.gov/lca/blindness), another degenerative retinal disease. The XLRS gene-therapy trial is one of the first ever at NIH to use the AAV vector.

Although the XLRS study seeks to optimize the gene-therapy dose, as a phase 1/2a clinical trial it is primarily designed to address safety.

"This is the first clinical trial of gene therapy for XLRS, and our first priority is to ensure it is safe," said **Paul A. Sieving**, who is leading the trial. "An important secondary goal is also to look for benefit to vision." Sieving is the director of NEI and a senior investigator in the National Institute on Deafness and Other Communications Disorders.

The first participant has been treated and is being monitored closely. Results from the trial are expected in 2016. ●

For more information about this trial, go to https://clinicaltrials.gov. For more on Paul Sieving, go to https://www.nei.nih.gov/about/director_bio and http://irp.nih.gov/pi/paul-sieving.

NEI

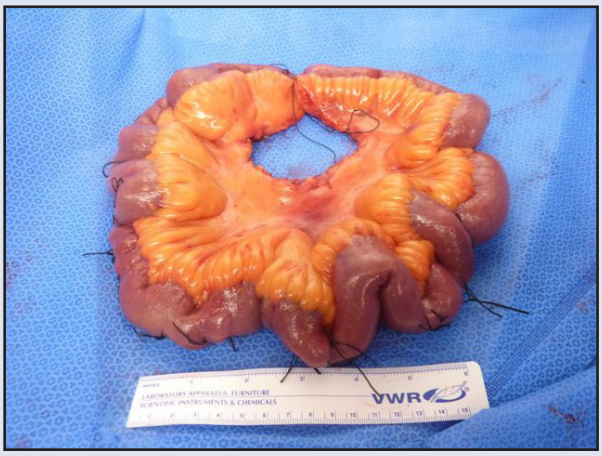
Paul A. Sieving, M.D., Ph.D.

NEI Director Paul Sieving is known internationally for studies of human progressively blinding genetic retinal neurodegenerations, including retinitis pigmentosa, and rodent models of these conditions. His laboratory study of pharmacological approaches to slowing degeneration in transgenic animal models led to the first human clinical trial of ciliary neurotrophic factor for treating retinitis pigmentosa, published in the *Proceedings of the National Academy of Sciences* in 2006. He developed a mouse model of X-linked retinoschisis and has embarked on human gene therapy for this condition. He maintains a small clinical practice at NEI for patients with these and other genetic retinal diseases.

Before becoming the director of NEI in 2001, Sieving was the Paul R. Lichter Professor of Ophthalmic Genetics and the founding director of the Center for Retinal and Macular Degeneration in the Department of Ophthalmology and Visual Sciences at the University of Michigan Medical School (Ann Arbor).

Sieving did undergraduate work in history and physics at Valparaiso University in Indiana; studied nuclear physics at Yale Graduate School; attended Yale Law School; and received his M.D. from the University of Illinois College of Medicine and a Ph.D. in bioengineering from the University of Illinois Graduate College. He completed an ophthalmology residency at the University of Illinois Eye and Ear Infirmary in Chicago. After postdoctoral study of retinal physiology at the University of California, San Francisco, he did a clinical fellowship in genetic retinal degenerations at Harvard Medical School, Massachusetts Eye and Ear Infirmary. ●

Intramural Research Briefs



GASTROENTEROLOGY 2015

NIH researchers found a genetic link for small intestinal carcinoid, a rare digestive cancer. Shown is a section of the small intestine with the wide distribution of multiple carcinoid tumors identified by sutures.

NIDDK, NHGRI, NCI, CC, NCBI: GENETIC LINK FOR RARE INTESTINAL CANCER

NIH researchers found that heredity accounts for up to 35 percent of small intestinal carcinoid, a rare digestive cancer, that had long been considered to occur randomly rather than to be inherited. Conducted at the NIH Clinical Center, the study screened 181 people from 33 families, each with at least two cases of small intestinal carcinoid. The researchers discovered the disease in 23 people who had not yet developed symptoms and successfully removed all tumors in 21 of them. Genetic linkage analysis revealed a target DNA region shared by all affected members of a large family. Genome sequencing narrowed that finding to a gene defect passed from one generation to the next, suggesting that the gene is an inherited risk factor for the disease. (NIH authors: Y. Sei, S. Wank, S. Szymczak, Q. Li, J. Bailey-Wilson, et al., *Gastroenterology* DOI:10.1053/j.gastro.2015.04.008)

NIAID: NO EVIDENCE OF ACCELERATED EBOLA VIRUS EVOLUTION IN WEST AFRICA

The Ebola virus circulating in humans in West Africa is undergoing relatively few genetic mutations, none of which appear to make the virus more severe or transmissible, according to a study by scientists at NIAID's Rocky Mountain Laboratories (Hamilton, Montana). The study compared virus sequencing data from samples taken in 2014 from patients in Guinea, Sierra Leone, and Mali. Despite extensive human-to-human transmission, the virus is not mutating at a rate beyond what is expected. Further, it is unlikely that the types of genetic changes observed would impair diagnostic measures or affect the efficacy of candidate vaccines or potential treatments. (NIAID authors: T. Hoenen, T. Schwan, R. Sakai, M. Niang, and M. Pineda, *Science* **348**:117–119, 2015)

NIEHS: RESPONDING TO ENVIRONMENTAL CUES REQUIRES CROSS-TALK BETWEEN SIGNAL TRANSDUCTION AND TRANSCRIPTION

NIEHS researchers determined that control of developmental signaling in mouse embryonic stem cells (ESCs) can be accomplished through RNA polymerase II (Pol II) pausing, a phenomenon in which Pol II pauses during early transcription of messenger RNA. The finding is important because it sheds light on a mechanism that can be used to calibrate ESC responsiveness to environmental and developmental cues. Pausing of Pol II was known previously to be widespread in ESCs, but its function was unclear. A popular model predicted that disruption of pausing would cause genes involved in cell differentiation to be activated, resulting in spontaneous cell differentiation and development. The NIEHS team found, however, that the loss of pausing had the opposite effect: ESCs would be unable to respond to differentiation cues from their environment because developmental signaling machineries were repressed. Thus, mice lacking the key pause-inducing factor, negative elongation factor, died early in embryonic development because they were unable to detect and respond to information from their environment. (NIEHS authors: L.H. Williams, G. Fromm, N.G. Gokey, T. Henriques, G.M. Muse, A. Burkholder, D.C. Fargo, G. Hu, and K. Adelman, *Mol Cell* **58**:311–322, 2015)

CONTRIBUTOR: ROBIN ARNETTE, NIEHS

NCI: CIRCULATING TUMOR DNA IN BLOOD CAN PREDICT RECURRENCE OF LYMPHOMA

Measurement of circulating tumor DNA (ctDNA) in blood can be used to detect the recurrence of a curable form of cancer known as diffuse large B-cell lymphoma (DLBCL), the most common type of lymphoma. The disease recurs in up to 40 percent of patients and the recurrence is often incurable. NCI investigators used advanced sequencing techniques to analyze serum from 126 patients with DLBCL and found that measurement of ctDNA enabled the detection of microscopic disease before it could be seen on computerized tomography (CT) scans (the current standard for disease assessment). Monitoring for recurrence by testing blood samples may reduce the need for multiple CT scans that increase a patient's exposure to radiation and add to health-care costs. And earlier monitoring may improve the ability of physicians to successfully treat the disease at the time recurrence is diagnosed. (NCI authors: M. Roschewski, K. Dunleavy, S. Pittaluga, M. Shovlin, E.S. Jaffe, L.M. Staudt, et al., *Lancet Oncol* DOI:10.1016/S1470-2045(15)70106-3)

NICHD: ANTI-HERPES DRUG MAY CONTROL HIV

Valacyclovir, a drug commonly used to control the virus that causes genital herpes, appears to reduce the concentration of human immunodeficiency virus (HIV) in patients who do not have genital herpes, according to a study by researchers from NICHD, Case Western Reserve University, Emory University, and Asociación Civil Impacta Salud y Educación. The study enrolled 18 HIV-infected patients, none of whom were infected with herpes

simplex virus–2 (the type that causes genital herpes), and treated them with valacyclovir. When the patients took the drug, their blood HIV concentrations declined significantly. If valacyclovir's effectiveness can be confirmed in a larger cohort, it could be added to the mix of drugs used to suppress HIV and might prove helpful in cases in which HIV has developed resistance to other drugs. (NICHD authors: C. Vanpouille, A. Lisco, J. Grivel, and L. Margolis, *Clin Infect Dis* DOI:10.1093/cid/civ172)

NCATS, NIDDK: ALLERGY DRUG INHIBITS HEPATITIS C IN MICE

NCATS and NIDDK researchers have found that an over-the-counter drug used to treat allergy symptoms limited hepatitis C virus (HCV) activity in infected mice. Using a high-throughput screening process, the researchers identified chlorcyclizine HCl (CCZ) as a potent inhibitor of hepatitis C. HCV causes liver inflammation and often leads to serious complications such as cirrhosis. Early diagnosis and treatment of HCV can prevent liver damage. Drugs are available to treat HCV, but costs can reach tens of thousands of dollars. The study found that CCZ blocked the early stage of HCV infection, likely by impairing the ability of the virus to enter human liver cells grafted in the mice. The outcome was similar to that of commonly used antiviral drugs but without those drugs' toxic side effects. The researchers will next study how the drug affects people. CCZ is currently used for the treatment of allergies, not for HCV. The scientists caution that people should not take CCZ to treat their hepatitis C until it has been demonstrated that CCZ can be used safely and effectively for that purpose. (NIDDK authors: S. He, B. Lin, T.J. Liang, et al.; NCATS authors: X. Hu, J. Xiao, et al., *Sci Transl Med* DOI:10.1126/scitranslmed.3010286) ●

Read longer briefs online at http://irp.nih.gov/catalyst/v23i3/research-briefs.

Signals From Epithelial Progenitor Cells Promote Organ Innervation During Development

BY WENDY KNOSP, NIDCR

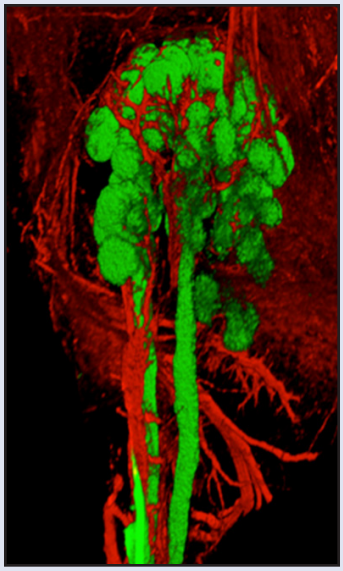
A key process in embryonic development is the integration of different cell types to form organs. In some developing organs such as the salivary glands and pancreas, innervation occurs during organ formation, with neurons clustering together and sending out axonal projections along the epithelium in three dimensions. Using ex vivo tissue cultures and molecular techniques, scientists in the National Institute of Dental and Craniofacial Research (NIDCR) identified cells and signals that drive innervation within the embryonic salivary gland. They are the first to describe how the gland regulates its own innervation.

In a mouse embryo, the salivary glands bud, branch, and form hollow ducts within two weeks of conception. The resulting architecture, which resembles a cluster of grapes, depends on a precise coordination of molecular signals from epithelial cells, mesenchymal cells, nerve cells, and other cell types. NIDCR's developmental cell biologists in the Matrix and Morphogenesis Section have identified the signals that initiate the development of the innervation of the salivary gland. Senior investigator **Matthew P. Hoffman** and colleagues recently reported in *Developmental Cell* that Wnt signals from keratin-5-positive (K5+) progenitor cells in each developing salivary gland's epithelial compartment are driving the process of innervation.

Using double-knockout mouse embryos that had been genetically modified to lose the ability to properly regulate fibroblast growth factor (FGF) signaling, they discovered a striking loss of innervation in the developing salivary glands. They also found a dramatic reduction in epithelial Wnt expression in the knockout salivary glands and demonstrated that FGF signaling suppresses Wnt expression. In addition, they found that Wnt signaling is essential for nerve-cell survival and proliferation and thus for innervation of the gland.

To rescue innervation in the knockout salivary glands, the scientists administered an oral formulation of a Wnt activator called CT99021 while reducing FGF signaling. In addition, the NIDCR researchers were able to extend the findings to the embryonic pancreas.

Their work builds on their previous finding published in *Science* in 2010 that the nervous system maintains the K5+ cells in the epithelial compartment; without the appropriate signals from nerves, the K5+ cells differentiate, and gland development is impaired (*Science* **329:**1645–1647, 2010). These studies are part of the groundwork for future clinical application of tissue repair and regeneration by re-establishing communication between nerves and transplanted progenitor cells. (NIDCR authors: W.M. Knosp, S.M. Knox, I.M.A. Lombaert, C.L. Haddox, V.N. Patel, and M.P. Hoffman, *Dev Cell* **32:**667–677, 2015) ●



WENDY KNOSP, NIDCR

Scientists in NIDCR have identified cells and signals that drive innervation within the embryonic salivary gland. Shown: image of an immunostained salivary gland (grapelike clusters) and the surrounding nerves.

Crossroads of Medicine and the Media

Insights from Neurosurgeon/Science Journalist Sanjay Gupta

BY SOMA CHOWDHURY (OD) AND LAURA STEPHENSON CARTER

"I don't think there's enough science journalism out there, certainly not in the broadcast area," Emmy Award–winning CNN Chief Medical Correspondent Sanjay Gupta told the crowd that gathered in Masur Auditorium on March 25 to hear him deliver the J. Edward Rall Cultural Lecture. "If it's done well, it can make a difference in people's lives."

In addition to being a successful journalist, Gupta is a practicing neurosurgeon at Emory University School of Medicine and Grady Memorial Hospital (both in Atlanta). He received his M.D. in 1993 from the University of Michigan Medical School in Ann Arbor, Michigan, where NIH Director **Francis Collins** was his genetics professor.

Gupta got his start at translating medical science when he did a stint as a White House fellow (1997–1998) and served as a special advisor to First Lady Hillary Clinton. He joined CNN (Atlanta) in 2001 and was soon covering such stories as the September 11, 2001, terrorist attacks and the anthrax attacks that occurred soon afterward.

He reported from Iraq and Kuwait when he was embedded with the U.S. Navy "Devil Docs" in 2003; covered the 2004 tsunami in Sri Lanka; and contributed to CNN's Peabody Award–winning coverage of the 2005 Hurricane Katrina and the 2010 oil disaster in the Gulf of Mexico. He was awarded two Emmys for his coverage of the 2010 earthquake in Haiti. He reported on the earthquake and tsunami that devastated parts of Japan in 2011. And he continues to cover a range of medical topics today.

"I think of myself as someone who can nurture and foster conversations" about medical issues, he said. "You want to inform people, make sure they have all the facts. After that we want to be sure they are discussing these issues themselves."

But first, to make sure *he* understands the issues, Gupta relies on experts such as **Anthony Fauci**, director of the National Institute of Allergy and Infectious Diseases. In 2001, for example, after letters laced with anthrax spores were mailed to news media outlets and two United States senators, Gupta interviewed Fauci to get the facts about anthrax.

"If you present the science as we did with anthrax, it can help calm the fears of a very worried nation," Gupta said.

Nowadays, however, "doing in-depth science reporting is becoming more challenging," he said. Not only are the concepts more complicated, but "the time that television networks allow us to devote to them is shrinking—most of the segments are two minutes long," Gupta continued. In addition, people are bombarded with news that comes in simple, short bursts via Twitter feeds and other social media messages.

Still, Gupta tries to address scientific and medical issues in depth. "We have a responsibility to do good science journalism," he said. He hopes the knowledge people gain will change their lives.

After Gupta's remarks, he and Collins sat onstage and engaged in a conversational talk-show-style question-and-answer session, with some of the questions having been submitted electronically beforehand. The following selection of questions has been edited for clarity and length. Read more online at http://irp.nih.gov/catalyst/v23i3/crossroads-of-medicine-and-the-media.

How do you choose a story?

We look for stories that will impact a large population of people; or that may affect a small number of people in a significant way; or that have a gee-whiz quality that can't be ignored.

What tips do you have for scientists who have to talk to reporters?

Think of the reporter like a patient, your mom, or a good friend. You want to make sure that they understand what you are trying to say. You may have to explain terms. Be able to share the broad applications of the concept. Think of it as a conversation.

How do you explain basic research in an engaging way?

I ask the scientists to tell me why they are interested and why the work is fundamentally important. You can also use something in the news as an opportunity to educate people. For example, when President Clinton had heart problems, we did a lot of reporting about cardiac disease, obesity, and why too much sugar can contribute to higher cholesterol concentrations.

ERNIE BRANSON

Emmy Award-winning CNN Chief Medical Correspondent Sanjay Gupta visited NIH in March to chat about his work as a science journalist and a neurosurgeon.

ERNIE BRANSON

To make sure he understands the issues when he is doing story, Gupta interviews experts such as NIAID Director Anthony Fauci.

How do you tackle the vaccine story?

I don't feel a need to pay homage to the fear that vaccines can cause autism. I state the facts. People count on me to be accurate. Although I try not to use my own family stories too much, I have explained that after looking at the studies, I made sure my children were vaccinated on schedule. When I said that, people listened.

Is it true that science journalists take a complicated subject, wildly oversimplify it, and then exaggerate significantly?

You might have to emphasize the excitement to get the ball rolling with the editors. But then you tell the story that's honest, genuine, and accurate. If you overstate or exaggerate things, you risk losing credibility. Diving in, eyes wide open, and not being sure what to expect, can lead to the best stories.

How do you deal with the short attention span of news media?

Just because you're not seeing a story on the front page or it's not the lead story of the hour, doesn't mean we aren't covering it. Other stories may take priority. For example, we had been reporting on antibiotic-resistant bacteria for some time, but it was overshadowed by other stories. Still, we were gaining more knowledge and building relationships with people. People started paying attention when, on a slow news day, we were able to do a story on how endoscopes contaminated with antibiotic-resistant bacteria contributed to the deaths of several patients who had had routine endoscopic procedures. Ebola is another example. I was in West Africa last year. We thought Ebola was important, but people in this country only started paying attention when patients were flown here.

How do you juggle everything?

There is never enough time for all the things you want to do. I split my work time 50-50 between being a doctor—operating and taking care of patients—and being a journalist. The split is similar to what other academic doctors do, only my split is between patient care and the media and theirs is between patient care and doing research or giving lectures. For me, the medical work informs my reporting, and being a journalist has helped me be more curious about my patients' stories. I wish I spent more time with my family. I am on the road a lot and travel to dangerous places. But I don't do these things because I'm an adventurer. I do them because I want to make a difference.

Most people know who NASA and CDC are, but only 20 percent know who we are. How can we do a better job of telling the NIH story?

People associate NASA with the moon landing, exploration, and adventure. And they associate CDC with infectious disease. Defining mission is hard for any organization, especially for NIH because it is so vast and does so many things. NIH's role in contributing to medical advances needs to be constantly trumpeted. If everyone could define the NIH mission in a sentence or two, it would an important starting point…and it would help journalists. ●

The videocast can be watched online and is available to all Department of Health and Human Services employees at http://videocast.nih.gov/launch.asp?18910.

ERNIE BRANSON

Sanjay Gupta met with some of NIH's aspiring neurosurgeons who are fellows in NIH's Medical Research Scholars Program. He is a "role model" for young neurosurgeons, said John Heiss, director of NIH's Neurosurgery Residency Program and chair of NINDS's Surgical Neurology Branch. Shown (from left): Jason Hsieh, Jeyan Kumar, Gupta, Martin Piazza, and Michael Feldman.

Rare Disease Day

CONTINUED FROM PAGE 1

For rare diseases, such progress depends on tight collaboration among researchers, clinicians, regulatory agencies, advocacy organizations, and most of all, patients, their families, and other caregivers.

"Translation is a team sport," said **Christopher Austin**, director of the National Center for Advancing Translational Sciences (NCATS). But "that is easier said than done."

A rare disease is defined as one that affects fewer than 200,000 people in the United States–about one in every 1,500. But with 5,000 to 7,000 rare diseases known so far, "having a rare disease is not so rare," said NIH Clinical Center Director **John Gallin**. "It's about 10 percent of our population."

The NIH Clinical Center plays an important role in the study of these diseases. "We have an unusual ability to assemble cohorts of patients with rare diseases," Gallin continued. In fact, the day of the symposium, the Clinical Center's tally included studies of 584 different rare diseases, with 948 clinical protocols and more than 30,000 patients with rare diseases.

Rare-diseases research, although critical for patients and families desperately awaiting treatments, has a long history of coming up with new therapies for common diseases. For example, **William H. Theodore** (National Institute of Neurological Disorders and Stroke) described how his work on the rare metabolic disorder succinic semi-aldehyde dehydrogenase deficiency has led to a possible new drug—now in clinical trials—that targets the pathway of neurons that produce gamma–aminobutyric acid and may also benefit patients with Down syndrome.

NIH CLINICAL CENTER

The NIH Clinical Center plays an important role in the study of rare diseases. Its tally includes studies of 584 different rare diseases, 948 clinical protocols, and more than 30,000 patients with rare diseases.

DANIEL SONE, NCI

Matt Might, the parent of the first child diagnosed with N-glycanase deficiency, found that a critical bottleneck was locating a cohort of patients–both for the science and for moral support. His blog post received millions of views and he was able to find about a dozen children from around the world with the same disease. He brought them to the NIH for a natural-history clinical trial.

Likewise, Gallin's lab recently made a discovery about an abnormality in a rare inherited immunodeficiency disorder that may lead to a therapy to prevent atherosclerosis. The disorder is chronic granulomatous disease (CGD) in which certain immune system cells are unable to kill some types of bacteria and fungi. In CGD, an abnormality of the enzyme nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) results in reduced phagocyte production of reactive oxygen species and related products such as hydrogen peroxide and hypochlorous acid (bleach). Studies at the NIH and elsewhere have helped to define supportive therapy for CGD with use of interferon-gamma and prophylactic antibiotics such as Bactrim and intraconazole. Some patients have been cured with bone-marrow transplantation. In addition, gene therapy is an area of intense investigation.

Gallin's lab found that the loss of NADPH oxidase function in CGD is protective against developing carotid artery atherosclerosis (*Circulation* **130:**2031-2039, 2014). It's possible, therefore, that NADPH oxidase might be a therapeutic target for atherosclerosis in normal subjects. Thus, CGD is an example, said Gallin, of "a rare disease providing insights into a common disease."

As with many common diseases, there are significant scientific, financial, and organizational gaps between discovery and effective treatments. For some rare diseases, advocacy organizations, parents, and caregivers have helped cross this gap, recruiting and galvanizing patient cohorts or forming nonprofits and even virtual biotech organizations to catalyze the transition from the lab to the clinic. Matt Might, the parent of the first child diagnosed with N-glycanase deficiency, found that a critical bottleneck was locating a cohort of patients–both for the science and for moral support.

Might talked about his and his wife's efforts to build a community; he even wrote a blog post about his son's rare disease that received millions of views in a few weeks. He was able to find about a dozen children from around the world with the same disease. He brought them to the NIH for a natural-history clinical trial. "We are pushing every living patient with this disorder through the NIH."

For other rare diseases, the science is there, but the critical path to clinical trial has proven elusive. Jill Wood is the mother of a child diagnosed with Sanfilippo syndrome, a disease that causes behavioral and motor problems. Frustrated by the lack of treatment options, she formed a nonprofit organization to fund and stimulate research. But then she found herself at an impasse.

"Okay, the science is here now," she said. "We're gonna have a treatment, [but] we're still ultra rare. Nobody's come knocking on my door, saying, 'Oh, can I sponsor your clinical trial? Can I take your treatment to market?'" Rather than wait for outside assistance, she formed a virtual biotech company to shepherd her treatment through its first clinical trial.

Beginning in 2011, NCATS began taking on the challenge of bridging the gap between bench research and clinical trials. Austin shared a recent success story of bringing a therapeutic medication to the clinic for Niemann-Pick disease type C, a lipid-storage disease characterized by progressive neurodegeneration.

"It started when several separate groups of parents walked into my office and asked if there was something we could do to help to develop a treatment for Niemann-Pick C disease during the lifetimes of their children," Austin said. Working from there, the Therapeutics for Rare and Neglected Diseases (TRND) program at NCATS recruited a diverse team that included intramural and extramural scientists, advocacy and patient organizations, and industry partners. Human clinical trials for a new therapeutic for Niemann-Pick type C, 2-hydroxypropyl-beta-cyclodextrin, are currently ongoing, supported by the pharmaceutical company Vtesse (Gaithersburg, Maryland).

"We are still working on what the secret sauce is that goes into this," said Austin. "But I can tell you one of the things that's absolutely clear is that this is due to teamwork; this is due to mutually dependent, mutually trusting relationships."

Stephen Seiler, from AesRX, LLC (now part of Baxter Pharmaceuticals in Reston, Virginia), is working with the TRND program to develop the only treatment made specifically for sickle-cell anemia. He emphasized the complex orchestration required to get a drug from the lab to the patient as "a multistage, multi-institute, public-private translational-research collaboration [that] was catalyzed by TRND funding."

The tricky bit was traversing the "biotech valley of death," the gap between discovery and the first clinical trial. Many translational projects flounder due to lack of funding. "Then we'd find a big pharma partner who would now take this de-risked program the rest of the way," Seiler continued. "You've got to imagine the endgame here if you really want to get a drug to patients." With the support of TRND and the rest of the research-collaboration partners, Aes-103 (5-hydroxymethylfurfural) has crossed that chasm and has been taken up by Baxter Pharmaceuticals for further development.

DANIEL SONE, NCI

The Rare Disease Day poster session presented opportunities for attendees to learn more about rare-disease research being conducted at NIH.

Robert Kotin, formerly a senior investigator in the National Heart, Lung, and Blood Institute (NHLBI) and now an inventor and vice president of production at Voyager Therapeutics, Inc. (Cambridge, Massachusetts), described a similar success story in his quest to deliver effective gene therapies to patients. Adeno-associated virus vectors (AAVs) have long been available for research, but producing the quantities required for human-scale gene therapy was a problem Kotin decided to tackle. While studying virus replication, he made a discovery that allowed him to produce recombinant AAV in the large quantities needed for human trials. Through the NIH and NHLBI technology-transfer offices, the NIH was able to secure patents and move clinical trials forward.

This technology has been licensed by uniQure (Amsterdam, Netherlands) that has recently gotten approval for their lipoprotein lipase deficiency treatment, Glybera. Généthon (Évry, France) also licensed it in hopes of using Kotin's AAV technology to combat Duchenne muscular dystrophy, a severe and rapidly progressing form of muscular dystrophy.

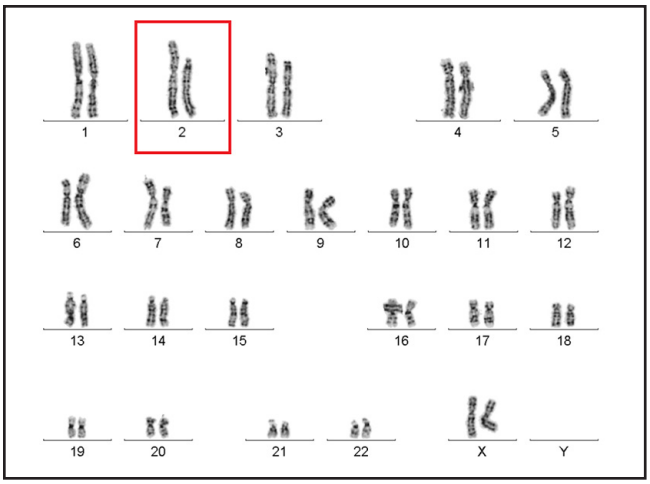
"It takes enormous talent [and] investment of time and money, and some serendipity helps along the way; and we need to depend on our whole ecosystem of private and public investment," said NIH Director **Francis Collins**. When it comes to developing new treatments for any disease, the road is difficult, but helping patients with rare diseases represents a larger challenge.

Rare Disease Day "puts faces to names and [lets us] hear firsthand how better we can collaborate to deliver the types of 21st-century cures the community anxiously awaits," said United States Congressman Leonard Lance (R-N.J.), co-chair of the Rare Disease Congressional Caucus. "There's a lot of work to do, but we shall do it together." ●

To watch an archived videocast of Rare Disease Day, go to http://videocast.nih.gov/launch.asp?18871.

WHIM Syndrome

CONTINUED FROM PAGE 1



NIAID

NIAID researchers discovered why a woman with WHIM syndrome was spontaneously cured of the disease. Her white blood cells were missing a large portion of chromosome 2, where the mutated WHIM allele resides. In essence, the patient had deleted the bad copy of the gene and was now cured. Shown: The above chromosome pairings, which are from her white blood cells, show that one copy of chromosome 2 (in box) is significantly shorter than the other.

had been that nine-year-old girl and that the disease had disappeared when she was in her 30s.

Of the 60 known individuals with WHIM syndrome, 29 of whom are patients at the NIH, there had been no record of a patient recovering. The researchers, led by **Philip M. Murphy**, chief of NIAID's Laboratory of Molecular Immunology, were intrigued and began a quest to unravel this medical mystery.

First, the team took blood samples to test for the genetic mutation in *CXCR4*. The daughters' blood tested positive for the mutation, but their mother tested negative. The researchers hypothesized that the mother was a genetic mosaic—a condition in which cells within the same person have a different genetic makeup—and only some of her cells carried the mutated gene. To validate this hypothesis, the scientists repeated the genetic screen for *CXCR4* in epithelial cells and fibroblasts, which tested positive for the mutation.

The team followed the trail to the source of blood cells—the bone marrow. They sent a bone-marrow sample for cytogenetic testing to examine the number and structure of her chromosomes. They discovered that the woman's white blood cells were missing a large portion of chromosome 2, where the mutated WHIM allele resides. In essence, the patient had deleted the bad copy of the gene and was now cured.

"At this point we were dealing with some kind of wild genetic instability we had never seen before," said Murphy.

Murphy's team then attended a Wednesday Afternoon Lecture Series presentation in 2013 by Frederick Alt (Harvard) on genetic instability in the immune system where they learned the name for what they were observing (http://videocast.nih.gov/launch.asp?17874). Alt mentioned that the phenomenon of chromothripsis, the shattering and rearrangement of a chromosome, is usually associated with cancer. This novel mechanism for genetic shuffling had only recently been described by other researchers (*Cell* **1441:**27–40, 2011).

Chromothripsis might be "something that happens all the time in everyone, maybe every day in some rare cells, but it is probably so catastrophic that the cell dies," Murphy speculated. "It's an invisible event; you never see it [and] you can only look for it when you have a bad cancer or a good cure."

In this case, chromothripsis resulted in a good cure. "Instead of causing cancer, it has [permitted a single] hematopoietic stem cell to take over the marrow," explained **David H. McDermott**, a staff clinician in Murphy's lab and first author on the 2015 *Cell* paper (*Cell* **160:**686–699, 2015). As the new cells with the deleted gene repopulated the patient's marrow, her symptoms vanished.

The team used whole-genome sequencing to try to understand how this one cell took over and cured the patient. They found that 17 large areas of chromosome 2 were missing and 164 genes had been deleted.

In order to focus on the deletion of the disease gene, staff scientist and co-first author **Ji-Liang Gao** used a mouse model in which only one copy of the *Cxcr4* gene was deleted. This single genetic mutation gave hematopoietic stem cells a strong growth advantage. When transplanted into another mouse with either wild-type or WHIM model mouse bone-marrow cells, the altered cells quickly took over as they had in the cured patient.

The lab plans to try to recreate this phenomenon in patients with WHIM syndrome by using genome editing to wipe out or correct the mutant allele in affected cells and then returning them to the patient. This technique was proposed in their recent U.S. patent application (http://1.usa.gov/1DUFuo9) and ultimately could be applied to treat countless other blood diseases as an adjunct to specific gene therapy.

The miraculously cured WHIM patient, now 60, is still doing well.

"She's got two *New England Journal of Medicine* papers and one *Cell* paper all about her," said Murphy. "I told her that if she was an academic that she could get tenure on that alone." ●

To read NIH Director Francis Collins's blog post on this mystery, go to http://directors-blog.nih.gov/2015/03/05/shattering-news-how-chromothripsis-cured-a-rare-disease.

NIH Expands the Medical Scholars Program

New Class Announced

BY OFFICE OF INTRAMURAL RESEARCH

The National Institutes of Health has selected 55 talented and diverse students, representing 37 universities accredited by the United States, for the fourth class of its Medical Research Scholars Program (MRSP), its largest class to date.

A yearlong residential program, the MRSP introduces medical, dental, and veterinary students to cutting-edge research, part of NIH's goal of training the next generation of clinician-scientists and biomedical researchers. The program places creative, research-oriented students in NIH laboratories and clinics, including within the NIH Clinical Center, to conduct basic, clinical, or translational research in areas that match their career interests and research goals.

A mentored research-training experience forms the core of this program and allows these future clinician-scientists and biomedical researchers to carry out research across the full spectrum of science in the interest of improving public health.

"The NIH has a proud history of training clinician-scientists, many of whom have gone on to win the Nobel prize or to lead major medical-research organizations," said **Michael Gottesman**, deputy director for intramural research at NIH. "These students will be introduced to incredibly innovative research, among the best in the world, and I know they will be up to the challenge."

The 55 selected participants include 54 medical students and one dental student; 25 are women, and 13 come from underrepresented minority groups.

"Competition for this program is intense, and we have had the good fortune of being able to pick from the very best of the best," said **Yvonne Maddox**, acting director of the National Institute on Minority Health and Health Disparities, a major financial supporter of this year's class. Maddox, a member of the MRSP recruitment team, also stated, "Our new class more closely resembles the diversity that has made the United States a world leader in technology and biomedical research and reflects a concerted recruitment effort to reach out to more segments of the research and academic communities."

In addition to following a rigorous research agenda, MRSP scholars participate in courses, journal club seminars, a structured lecture series, and clinical teaching rounds. They also present their research to the NIH community and at domestic professional conferences. Each scholar is assigned a tutor-advisor, who provides guidance in defining a well-articulated career-development plan and in selecting a dedicated NIH research mentor. Mentors are full-time NIH investigators with established basic, clinical, or translational research programs.

The MRSP is co-sponsored by the NIH and other partners, including the Doris Duke Charitable Foundation, American Association for Dental Research, Howard Hughes Medical Institute, Colgate-Palmolive Company, and other private donors, via contributions to the Foundation for the NIH. The 55 selected participants for the 2015–2016 NIH MRSP are listed at the second link below. ●

For more on the MSRP, go to http://cc.nih.gov/training/mrsp/index.html. For a list of the 2015–2016 participants, go to http://www.nih.gov/news/health/apr2015/cc-22.htm.

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

LISA CUNNINGHAM, NIDCD

ELISSA LEI, NIDDK

MARTIN MEIER-SCHELLERSHEIM, NIAID

RAJESHWARI SUNDARAM, NICHD

LUDMILA PROKUNINA-OLSSON, NCI-DCEG

LISA CUNNINGHAM, PH.D., NIDCD

Senior Investigator; Chief, Section on Sensory Cell Biology, National Institute on Deafness and Other Communications Disorders

Education: University of Tennessee, Knoxville, Tenn. (B.A. and M.A. in audiology); University of Virginia, Charlottesville, Va. (Ph.D. in neuroscience)

Training: Clinical fellowship in audiology at Indiana University Medical Center (Indianapolis); postdoctoral fellowship in auditory neuroscience at the University of Washington (Seattle)

Before coming to NIH: Assistant professor at the Medical University of South Carolina (Charleston, S.C.)

Came to NIH: In 2011

Selected professional activities: Organizer, Association for Research in Otolaryngology Symposium "Supporting Cells: Lessons from Studies of Glia"; class dean, NIH-Oxford-Cambridge Scholars Program; Graduate Partnership Program; NIH CSR Study Section service

Outside interests: Bicycling; hatching a plan to buy an RV

Web site: http://irp.nih.gov/pi/lisa-cunningham

Research interests: My research focuses on the mechanosensory hair cells in the inner ear that are responsible for normal hearing and balance functions. Specifically, my lab and I are interested in the molecular signals that regulate the survival, health, and death of these cells. Mammalian hair cells are not regenerated after they die, so in humans these cells must survive and function for up to a century in order to transduce sound and head movement into the neural signals of hearing and balance. During this lengthy period of time, hair cells may encounter many potentially toxic stresses, including exposure to excessive sound and/or to therapeutic drugs with ototoxic side effects. Hair cells must be able to respond rapidly and effectively to such cytotoxic stimuli if they are to survive and continue to function over the course of a lifetime.

Two major research areas are being investigated in my lab. From a basic science perspective, we are interested in the cellular and molecular mechanisms that determine whether a hair cell under stress ultimately lives or dies. From a clinical and translational perspective, we are examining how we can use the basic science of hair-cell death and survival to guide the rational development of clinical therapies aimed at preventing hearing loss in humans.

We have shown that stress-induced production of heat-shock proteins protects the inner ear against otherwise-lethal stresses. More recently we have shown that a neighboring cell type, the glia-like supporting cells, can protect sensory hair cells from dying. Our work indicates that supporting cells are important determinants of the fate (life or death) of hair cells under stress.

Currently the major translational goal in the lab is to develop clinical therapies that prevent hearing loss in patients who are receiving ototoxic drugs, such as aminoglycoside antibiotics or cisplatin. These are important drugs that save many lives, but they also result in permanent hearing loss in a significant portion of the patients who receive them. We are examining methods of protecting the hearing of these patients without interfering with the therapeutic benefit of the drugs themselves.

ELISSA LEI, PH.D., NIDDK

Senior Investigator, Laboratory of Cellular and Developmental Biology, National Institute of Diabetes and Digestive and Kidney Diseases

Education: The University of Texas at Austin, Austin, Texas (B.S. in molecular biology); Harvard Medical School, Boston (Ph.D. in cell and developmental biology)

Training: Postdoctoral fellow, Johns Hopkins

Came to NIH: In 2006

Outside interests: Attending opera; playing volleyball and tennis

Web site: http://irp.nih.gov/pi/elissa-lei

Research interests: The work we perform in my laboratory will help determine how the three-dimensional organization of DNA

within each cell affects cellular function and identity throughout an organism's development. We focus on chromatin insulators—complexes of DNA and protein that influence gene expression by establishing chromatin domains subject to transcriptional controls.

Loss of insulator activity can result in substantial changes in gene expression, culminating in disease, defects in development, and/or death. For example, the deletion of insulator binding sites has been implicated in the congenital growth disorder Beckwith-Wiedemann syndrome and a rare type of kidney cancer called Wilms' tumor.

Because chromatin insulators exist and function similarly in most multicellular animal organisms, we use the simple fruit fly, *Drosophila melanogaster,* as a model. The Drosophila system is extremely powerful for genetics as well as for biochemistry and cell biology techniques. Furthermore, the Drosophila genome has the largest diversity of known chromatin-insulator proteins.

We strive to understand the mechanisms by which chromatin insulators are regulated by RNAs and RNA-binding proteins. We made the striking finding that certain messenger RNAs (mRNAs) associate stably with insulator complexes within the nucleus. We speculate that these mRNAs also harbor a noncoding function such as acting as a scaffold for insulator complexes at specific subnuclear locations.

We also uncovered an RNA interference-independent role for the Argonaute 2 protein in promoting chromatin-insulator activity. Moreover, we identified two RNA-binding proteins as the first known tissue-specific regulators of insulator activity. We hope to move the field forward by achieving a better understanding of the mechanisms of chromatin-insulator function, including the identification of novel interactors and regulatory steps.

MARTIN MEIER-SCHELLERSHEIM, PH.D., NIAID

Senior Investigator; Chief, Computational Biology Section, Laboratory of Systems Biology, National Institute of Allergy and Infectious Diseases

Education: University of Konstanz, Konstanz, Germany (Bachelors degree in physics); University of Hamburg, Hamburg, Germany (M.S. in physics; Ph.D. in physics)

Training: Postdoctoral training in the Laboratory of Immunology, NIAID

Before coming to NIH: Research assistant at the University of Hamburg

Came to NIH: In 2001

Outside interests: Spending time with his kids; playing guitar; playing a variety of sports

Web site: http://irp.nih.gov/pi/martin-meier-schellersheim

Research interests: When discussing models of cellular behavior, many people refer to computational or mathematical modeling approaches. And indeed, when applied carefully (with a good sense of what is physiologically reasonable), such quantitative techniques can give us insights that go beyond what we could understand based on intuition and experimentation alone.

Before a computational model of a cell-biological process can be built, however, there has to be a set of hypotheses or a qualitative model about the workings underlying the observed behavior. Every biologist continuously creates and tinkers with such qualitative models because they are the frameworks that guide experimental work.

My colleagues and I found that, frequently, much information is lost when these qualitative models (based on experience, literature research, and intuition) are translated into quantitative, computational ones. Sometimes the computational models turn into overly simplified (some would say grotesque) caricatures of what the original set of hypotheses incorporated. This loss of information is mainly due to the technical challenges associated with developing good computational models.

To address this problem, my group has developed software, called Simmune, that even researchers with no prior experience in modeling can use. Simmune enables researchers to translate their hypotheses about molecular mechanisms underlying cellular signaling processes into quantitative simulations that can even take into account specific cellular morphological features. The software uses iconographic symbols—for cells, molecules, and their binding sites and interactions—and translates them into computational models whose behavior can be explored in various ways through accessible graphical interfaces.

RAJESHWARI SUNDARAM, PH.D., NICHD

Senior Investigator, Biostatistics and Bioinformatics Branch, Division of Epidemiology, Statistics and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Education: University of Calcutta, Kolkata, India (B.Sc. in mathematics); Indian Statistical Institute, Kolkata (M.Stat. in applied statistics and data analysis); Michigan State University, East Lansing, Mich. (Ph.D. in statistics)

Before coming to NIH: Assistant professor, Department of Mathematics, University of North Carolina (Charlotte, N.C.)

Came to NIH: In 2006

Selected professional activities: Associate editor, *Biometrics*

Outside interests: Cooking; hiking

Web site: http://www.nichd.nih.gov/about/staff/Pages/bio.aspx?nih_id=0012729610

Research interests: I am developing improved statistical methods for analyzing biomedical data. I am interested in survival analysis, a method in which we examine and model the time it takes for events to occur.

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

I have been the lead statistician in several reproductive epidemiology studies, including the Longitudinal Investigation of Fertility and the Environment. These studies have focused on time-to-pregnancy and other reproductive outcomes associated with pregnancy. I am developing survival-analysis methods to better model time-to-pregnancy while accounting for underlying biological factors and processes. I have developed joint models for various biomarkers (menstrual cycle patterns, intercourse, and fecundity) with a view toward creating risk calculators for subfertility and infertility.

I am also developing methods to incorporate high-dimensional exposures in the survival model that would assess the effects of environmental toxicants and pollutants on fecundity and other time-to-event outcomes. In addition, I am using multivariate survival-analysis methods to address various issues around the progression of labor in pregnant women and the progression of disease in general.

Read this section in upcoming issues of the *NIH Catalyst* to learn about other recently tenured colleagues, including:

Swee Lay Thein (NHLBI)
Jon Lorsch (NIGMS)
Francesco DeMayo (NIEHS)
Hannah Valantine (NHLBI)
Charles Venditti (NHGRI)
George Koob (NIDA)
Philip Bourne (NLM-NCBI)
Keir Neuman (NHLBI)
Hormuzd Katki (NCI-DCEG)
Histaka Kobayashi (NCI-CCR)
Deborah Citrin (NCI-CCR)
Xiaoling Li (NIEHS)
Edward Ginger (NINDS)

LUDMILA PROKUNINA-OLSSON, PH.D., NCI-DCEG
Senior Investigator, Laboratory of Translational Genomics, National Cancer Institute–Division of Cancer Epidemiology and Genetics

Education: Moscow State University, Moscow (M.Sc. in molecular genetics); Uppsala University, Sweden (Ph.D. in medical genetics)
Training: Visiting fellow with Francis Collins in NHGRI; research fellow in NCI-DCEG
Came to NIH: In 2005 for training; became a tenure-track investigator in 2010
Selected professional activities: Editorial board for *Cancer Research* and the *Journal of Interferon and Cytokine Research*; preceptor for the Introduction to Cancer Research Careers Program for and the Community College Enrichment Program of NIH
Outside interests: Knitting and sewing
Web site: http://irp.nih.gov/pi/ludmila-prokunina-olsson

Research interests: Recent genome-wide association studies (GWAS) have identified common inherited genetic susceptibility factors that may play a role in human diseases including cancers. The primary goal of my research is to identify the functional links between these genetic associations and molecular phenotypes, interpret genetic susceptibility, and develop precision-medicine tools based on genetic information.

Some genetic variants can affect coding sequences and lead to disease-causing changes in proteins, whereas other variants identified by GWAS are noncoding variants that regulate the function of important genes.

My laboratory is conducting follow-up studies on findings from several GWAS including bladder, breast, and prostate cancers as well as cancer-related outcomes of viral infections. We use a wide range of genetic and functional methods to identify molecular interactions within the genome, including DNA sequencing and genotyping, RNA sequencing, protein-expression studies, DNA-protein interaction analysis, cell culture, and epigenetic studies.

The post-GWAS work on bladder cancer has identified several novel molecular mechanisms of bladder cancer susceptibility and a genetic variant upstream of a cyclin E gene as the first germline genetic marker associated with the risk of development of clinically aggressive disease.

Persistent infection with hepatitis C virus (HCV) is a primary etiological factor for the development of chronic liver disease, including cirrhosis of the liver and cancer. After a recent GWAS on HCV clearance, we discovered a novel human interferon (IFN-lambda-4) that is created by a novel genetic variant. This discovery has explained the initial GWAS association, provided a novel genetic test for selection of treatment options for HCV, and suggested IFN-lambda-4 as an important player in clearance of HCV and other infections and cancer progression. I am interested in further translational development of these findings. ●

KUDOS

National Academy of Sciences:
Alan Hinnebusch (NICHD) and Warren Leonard (NHLBI)

2015 Albert B. Sabin Gold Medal Award:
Roger Glass, director of the NIH Fogarty International Center and associate director for international research at NIH

American Academy of Arts and Sciences:
Michael Lenardo (NIAID) and Wei Yang (NIDDK)

Read more online: http://irp.nih.gov/catalyst/v23i3/announcements-kudos.

ANNUAL KUAN-TEH JEANG LECTURE

Thursday, May 14, 2015; 2:00–3:00 p.m.

Masur Auditorium (Building 10)

T. Jake Liang, M.D., chief of the Liver Diseases Branch and Deputy Director of Translational Research, NIDDK, will present "Dissecting the Molecular Anatomy of HCV Infection at the Crossroads of Functional Genomics and Chemical Biology." For information about the lecture, contact Roland Owens at owensrol@mail.nih.gov or 301-594-7471. The event will be videocast live at http://videocast.nih.gov.

NIH CAREER SYMPOSIUM

Friday, May 15, 2015; 8:30 a.m.–5:00 p.m.

Natcher Conference Center (Building 35)

Registration: http://1.usa.gov/1Hu8cyy

Fellows and graduate students can learn about scientific career options and explore factors that lead to career success. For more information, visit the registration Web site.

LECTURES ON COMPLEMENTARY AND INTEGRATIVE HEALTH

Mondays (once a month), 10:00–11:00 a.m.

Lipsett Amphitheater (Building 10)

- **May 18:** Gervasio Lamas, M.D. (Columbia University; Mount Sinai Medical Center) does research on the treatment and prevention of cardiovascular disease.
- **June 8:** Steven Cole, Ph.D. (University of California, Los Angeles School of Medicine) analyzes the molecular pathways by which social and environmental factors influence the activity of human, viral, and tumor genomes.

JOHN DALY MEMORIAL LECTURE

"TRP Channels and Pain"

Wednesday, May 27; 1:00–2:00 p.m.

Masur Auditorium (Building 10)

Proteins such as pungent irritants from pepper, mint, and mustard plants elicit pain, detect noxious stimuli, and may be potential targets for analgesic drugs. Presenter: David Julius (UCSF). For information, call 301-496-9024 or e-mail kajacobs@helix.nih.gov. Videocast live: http://videocast.nih.gov.

NIH PAIN CONSORTIUM SYMPOSIUM

"Advances in Pain Research"

Tuesday, May 26: 12:30–5:30 p.m.

Wednesday, May 27: 8:30–4:40 p.m.

Natcher Conference Center (Building 45)

Web site: http://painconsortium.nih.gov/2015PCSymposium

Pre-registration deadline: May 20

The 10th Annual NIH Pain Consortium Symposium will highlight advances in pain research on neuro-glial mechanisms, genetics and epigenetics, brain-imaging discoveries, novel therapy development, and cognitive and emotional influences. This symposium features NIH-supported pain research that is of high interest and presents opportunities to advance the field. More than 20 NIH Institutes, Centers and Offices participate in the NIH Pain Consortium. The symposium will be videocast live on the Web: http://videocast.nih.gov.

TOWN HALL MEETING: THE OFFICES OF SCIENTIFIC WORKFORCE DIVERSITY AND EQUITY, DIVERSITY, AND INCLUSION WITH EMPLOYEE RESOURCE GROUPS

Tuesday, June 9, 2015; 1:00–2:30 p.m.

Building 49, Room 1A51/1A59

Hannah Valantine, chief officer for Scientific Workforce Diversity and Debra Chew, director, Office of Equity, Diversity, and Inclusion, will host a rich discussion on the important topic of workforce diversity and inclusion at the NIH. The discussion will focus on efforts to adopt best practices and to identify and remove barriers to an inclusive environment. For more information or to submit questions and comments for the discussion, e-mail COSWDevent@mail.nih.gov. Those who need reasonable accommodations should contact Trish Flock or Julia Casselle at 301-451-4296.

THE CHILDREN'S INN AT NIH: 25TH ANNIVERSARY SYMPOSIUM

"At the Intersection of Hope and Science: 25 Years of Advancing Medical Discoveries"

Thursday, June 18, 2015; 2:00–5:30 p.m.

Masur Auditorium (Building 10)

NIH physicians and families will share their stories and the fascinating scientific advances that have been made in treatment of their diseases. Check the Web site for details: http://www.childrensinn.org. For more information, contact Dorie Hightower at Dorie.Hightower@nih.gov or 301-451-3075.

NIH GRADUATE & PROFESSIONAL SCHOOL FAIR

Wed., July 15, 2015; 9:00 a.m.–3:30 p.m.

Natcher Conference Center (Building 45)

Register: https://www.training.nih.gov/gp_fair

NIH summer interns, postbacs, and other college students in the D.C. area, can explore educational programs leading to the Ph.D., M.D., D.D.S., M.D./Ph.D., and other graduate and professional degrees. More than 150 colleges and universities will be represented. More information can be found at the registration Web site. ●

CLINICAL CENTER GRAND ROUNDS

Wednesdays; 12:00–1:00 p.m.

Lipsett Amphitheater (Building 10)

Videocast: http://videocast.nih.gov

May 20: "Obesity and Brown Fat": Of Mice and Men: Marc Reitman (NIDDK); "Obesity Management in Adults": Susan Z. Yanovski (NIDDK)

May 27: "Ebola: From the Monrovia Medical Unit (MMU) to the ICU": Richard Childs (NHLBI); Anthony Suffredini (CC)

WEDNESDAY AFTERNOON LECTURE SERIES

Wednesdays, 3:00–4:00 p.m.

Masur Auditorium (Building 10)

Web site: https://oir.nih.gov/wals

May 20: Nirenberg Lecture: "Lost in Translation: Do Males and Females Read Their Genomes Differently?": David Page (MIT; Whitehead Institute)

May 27: "Origin and Evolution of the Vertebrate Neural Crest": Marianne Bronner (California Institute of Technology)

See Web site for June lectures. ●

Read more announcements online at http://irp.nih.gov/catalyst/v23i3/announcements.

U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
National Institutes of Health
Building 1, Room 333
MSC 0183
Bethesda, Maryland 20892

FIRST-CLASS MAIL
POSTAGE & FEES PAID
DHHS/NIH
Permit No. G-802
Publication No. 15-6250

Official Business
Penalty for Private Use $300

Printed on at least 20% recycled content paper and can be recycled as office white paper.

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.

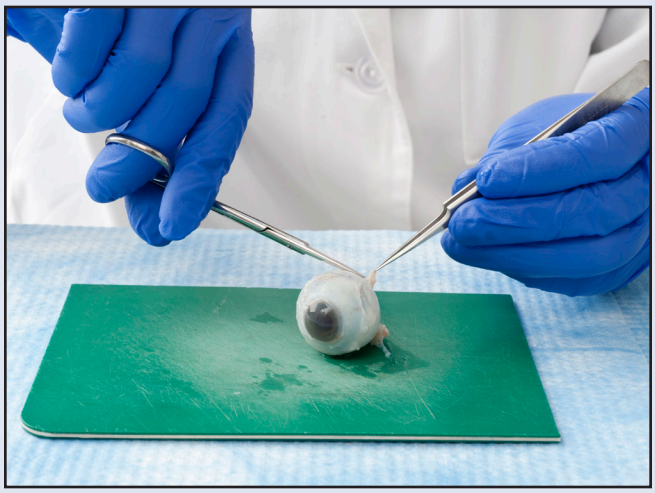
READ MORE ARTICLES, AND EXPANDED VERSIONS OF THE ONES IN THIS ISSUE, ONLINE AT
http://irp.nih.gov/catalyst/v23i3

LABORATORY CONFESSIONS

What I Learned on "Take Your Child to Work" Day

BY LIN WANJEK-YASUTAKE

April 23 was a day of discovery for me, because I followed my daddy to work at the National Institutes of Health. Here are the top seven things I learned:



RHODA BAER, NEI

- Magnified or not, the eyeball is just plain creepy.
- Apparently I wasn't supposed to say, "Oh, you must be *that* Rachel."
- The healthy human body contains 10 times as many microbial cells as human cells, and that's now my argument for not having to take a bath every night.
- The genetic code for the feline is more complicated than C-A-T. Who knew?
- Good bug, bad bug? Why wasn't this session simply called icky bug?
- My daddy doesn't have a lab, but there's something fuzzy growing in his coffee cup.
- All those paintings and cards I gave my daddy, which he said he'd take to work? Well, apparently they were in his "other office, off-campus." Hmmmm. ●

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

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

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

PUBLISHER
MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS
JOHN I. GALLIN
Director, NIH Clinical Center
PAUL H. PLOTZ
Scientist Emeritus, NIAMS

MANAGING EDITOR
LAURA STEPHENSON CARTER

WRITER-EDITOR
CHRISTOPHER WANJEK
Director of Communications, OIR

COPY EDITOR
SHAUNA ROBERTS

EDITORIAL INTERN
SOMA CHOWDHURY

CONTRIBUTING WRITERS
ROBIN ARNETTE
LESLEY EARL, EMILY PETRUS
DUSTIN HAYS
WENDY KNOSP
KELLY LENOX
BRANDON LEVY
RACHEL SCHEINERT
LIN WANJEK-YASUTAKE

PHOTOGRAPHERS/ILLUSTRATORS
RHODA BAER, ERNIE BRANSON,
WENDY KNOSP, STEVE MCCAW,
DANIEL SONE

EDITORIAL ADVISORY BOARD
CHRISTINA ANNUNZIATA, NCI
DAN APPELLA, NIDDK
LESLEY EARL, NCI (FELLOW)
MICHAEL ESPEY, NCI
SUSAN LEITMAN, CC
GERMAINE BUCK LOUIS, NICHD
DAVID MILLER, NIEHS
BERNARD MOSS, NIAID
HYUN PARK, NCI
JULIE SEGRE, NHGRI
ANDY SINGLETON, NIA
GISELA STORZ, NICHD
RONALD SUMMERS, CC
RICHARD WYATT, OIR
WEI YANG, NIDDK