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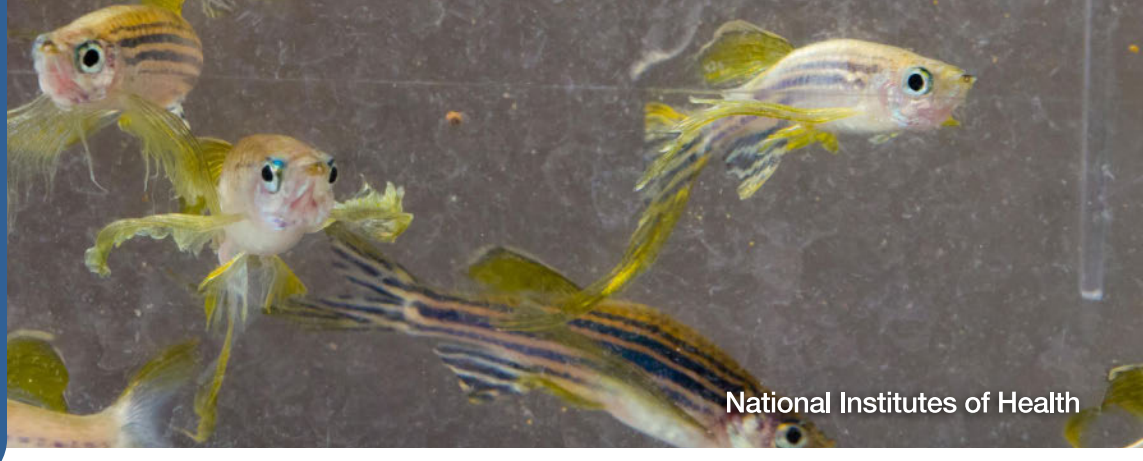
National Institutes of Health

ACD Supports Early Investigators, Applauds Collins' Reappointment

BY RICH MCMANUS

Two days before the 114th meeting of the advisory committee to the NIH director on June 8, the President invited NIH director Dr. Francis Collins to remain in that post permanently.

"I am grateful and honored to have received that invitation," said Collins, who had been serving as a holdover appointment since Jan. 18, "and I am happy, along with my wife Diane, to accept it."

The news was met with a round of applause before the ACD got down to a 2-day agenda that included announcement of the Next Generation of Researchers Initiative (NGRI) to support early and mid-career investigators; presentation of NIH's efforts to reduce the nation's opioid epidemic; and an argument for an accelerated pathway toward a universal influenza vaccine.

NIH director Dr. Francis Collins (l), flanked by ACD member Dr. Jose Florez of the Broad Institute of MIT and Harvard, told the group that he thought last December's ACD meeting might have been his last.

Not Ready for Prime Time

Collins traced the half-year history of the effort to reallocate NIH funding for early and mid-career scientists in a more optimum way, starting with what was known last fall as the Research Commitment Index. That effort, known temporarily as RCI, later morphed into the Grant Support Index, or GSI.

"[GSI] created quite a lot of interest—not all of it positive—about as much as I've seen in a grants funding policy in 8 years," said Collins. "We did hear significant concerns about the validity of the index, and how it might discourage collaboration." It became

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Bill Gates (l) talks global health at NIH, p. 12.

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JUNGLE TRAVEL NOT REQUIRED

Daly Lecturer Describes 21st Century Drug Discovery

BY CARLA GARNETT

Just recently back from a trip to South Africa, where she had a "pretty scary" face-to-face with a deadly black mamba snake, Dr. Fiona Marshall had the perfect introduction to NIH's 2017 Daly lecture.


Dr. Fiona Marshall

Renowned jungle explorer Dr. John W. Daly, the late NIDDK biochemist and pharmacologist for whom Marshall's talk was named, pioneered in natural product research.

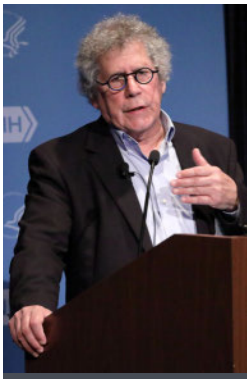
In much of the last half of last century, he

SEE **MARSHALL**, PAGE 6

Genetics, Evolutionary Biology Help Identify Rare Mendelian Disorders

BY DANA TALESNIK

If Charles Darwin had read the findings of Gregor Mendel, he might have saved himself a lot of grief. While Mendel was holed up in a monastery discovering hereditary traits by experimenting on pea plants, Darwin was struggling to prove his theories of natural selection and descent-with-modification.


Dr. David Valle

"Darwin's big problem was that, with descent-with-modification, there was no theory of genetics, no knowledge of

SEE **VALLE**, PAGE 8

Workshops on Work/Life and Well-Being

OHR and ORS are offering a free supervisory workshop titled "Work/Life @ NIH: A Supervisor's Guide to Enhancing Workforce Well-Being."

It provides an overview of workforce well-being and how it can benefit your organization; highlights the policies and programs NIH offers to promote workforce well-being; and provides supervisors with strategies to manage the use of various workplace flexibilities.

The workshop is led by NIH's own subject matter experts and has been approved for 2 Continuous Learning Points for supervisory refresher purposes.

Registration is available in the Learning Management System. You may register by searching for course ID #NIHWRD1003.

There are two remaining sessions for 2017: July 13 and Nov. 8. The July offering is currently full, but seats may become available via the waitlist. Can't attend these sessions? Stay tuned for announcements about 2018 offerings.

Questions? Email Courtney Bell, ORS (bellcd@mail.nih.gov) or Kelly Peralta, OHR (peraltakl@nih.gov) for more information.

10th Graduate & Professional School Fair Set, July 18

The 2017 NIH Graduate & Professional School Fair will be held on Tuesday, July 18 from 8:45 a.m. to 3:30 p.m. at the Natcher Conference Center.

The event provides an opportunity for NIH summer interns (especially those in college) and postbacs, as well as other college students in the D.C. area, to prepare for the next step in their careers by exploring educational programs leading to the Ph.D., M.D., D.D.S., M.D./Ph.D., and other graduate and professional degrees.

More than 195 outstanding colleges and universities from across the U.S. will be sending representatives of their graduate schools, medical and dental schools, schools of public health and other biomedically relevant programs to the fair to recruit NIH trainees.

The day will also include workshops on getting to graduate and professional school, M.D./Ph.D. programs, interviewing, careers in public health, computational biology/bioinformatics, psychology and dentistry. Exhibits will be open from 9:45 a.m. to 2:15 p.m.

Find a list of institutions planning to attend and registration information at https://www.training.nih.gov/gp_fair.

All Along the Water Towers

The two new water towers on campus are moving toward completion and will soon be familiar features of the local skyline. In the photo above, the top of the Industrial Water Storage System can be seen at left, already dressed in its masonry façade. Awaiting similar treatment in the foreground of that photo is the Thermal Energy Storage System (also shown at right), which has a bright yellow metal skin at the moment but will resemble its smaller cousin once complete.

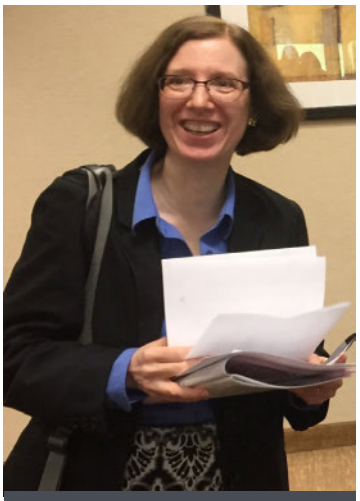
PHOTOS: RICH MCMANUS

Glass Mouse Cage Sought

Do you have a glass mouse cage like the ones in the photo above? If so, the DeWitt Stetten Jr. Museum of Medical Research would like to borrow it for an exhibit going into the Clinical Center on Michael Potter, NCI. The photo shows the mouse room of Dr. Lloyd Law's NCI laboratory in the 1950s. If you have a glass mouse jar like these, contact Michele Lyons, curator, at (301) 496-7695 or lyonsm@od.nih.gov.

Myositis Conference Joins Researchers, Patients

The second Global Conference on Myositis (GCOM 2017) brought together myositis researchers, patients and support group representatives from around the world. Dr. Fred Miller chaired the steering and scientific committees for the recent event, which took place at the Bolger Center in Potomac. Miller is head of the environmental autoimmunity group (EAG) at the National Institute of Environmental Health Sciences.



"The field has expanded greatly in terms of its research scope," said NIEHS's Dr. Lisa Rider. "This conference took it to a new level."

PHOTO: RITA VOLOCHAYEV

Myositis is a rare, multi-symptom disease that can affect people of all ages and involves dermatology, rheumatology, neurology and pulmonary disease, among others. Also known as idiopathic inflammatory myopathies, myositis consists of a diverse group of complex diseases that result from chronic muscle inflammation.

"Our main goal was to share state-of-the-art research covering all forms of myositis and to include basic researchers and all specialties caring for myositis patients," said Miller. "It was a great success and laid the groundwork for important future collaborations."

"The conference focused on trainees and young investigators," said Dr. Lisa Rider, deputy chief of the EAG and a leading researcher of juvenile myositis. Six trainees received abstract awards and made oral presentations, she noted. The event also offered a special mentoring session on how to become successful myositis researchers.

Dr. Hanna Kim, an NIAMS clinical fellow, received an outstanding abstract award for her research on juvenile dermatomyositis.

"This gave me the chance to give a plenary presentation," she said. "I got a lot of thoughtful feedback from international experts."

GCOM 2017 highlighted the involvement of patients and their advocates. Two major support groups, the Myositis Association and the CureJM Foundation, participated.

"As a rare, neglected disease, myositis doesn't get much official attention or funding," Miller said. "Patient support groups serve an important function in raising awareness and funding for research."

Dr. Adam Schiffenbauer, an EAG staff clinician, heard satisfaction expressed by many of the patients at the conference.

"A lot of the program was directed at addressing what patients want and what we are doing to support them," he said.

NIAMS director Dr. Stephen Katz and Dr. Andrew Mammen, a researcher in the NIAMS muscle disease unit, were also involved.

With 310 participants, the meeting was twice the size of the 2015 inaugural conference in Stockholm. Building on the success of this year's conference, the next of the biennial series, GCOM 2019, will take place in Berlin.

Ongoing clinical studies led by NIEHS, NIAMS and others are recruiting volunteers. In addition to support from NIEHS, the conference received funding from NIAMS and NINDS, as well as 20 patient support group and corporate sponsors.—**John Yewell**

Grantee Deisseroth Awarded Fresenius Prize

Germany's Else Kroner-Fresenius Foundation awarded the 2017 Fresenius Research Prize to Stanford University professor and Howard Hughes Medical Institute investigator Dr. Karl Deisseroth (l). He accepted the award at a ceremony on May 31 in Berlin. It recognized his achievements in optogenetics, hydrogel-tissue chemistry and research in depression. The Fresenius Research Prize is awarded every 4 years and is the world's largest monetary award—4 million euros—to a single researcher for scientific achievement. Deisseroth has been an NIH grantee since 2005, when he was selected for an NIH Director's Pioneer Award. He is shown here with NIBIB director Dr. Roderic Pettigrew following the 2016 Hector Lopez Memorial Lecture.

PHOTO: KATE EGAN

ON THE COVER: *Zebrafish group used in studies of behavioral genetics. One such program aims to identify brain cells that control the startle reflex, which may help us understand post-traumatic stress and other anxiety disorders in people.*

IMAGE: J. SWAN, NICHD

The NIH Record

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NIH National Institutes of Health
Turning Discovery Into Health

NIH principal deputy director Dr. Lawrence Tabak (l) explains the GSI brouhaha.

ACD

CONTINUED FROM PAGE 1

apparent, he said, that "the GSI approach is not ready for prime time."

Of the brouhaha that accompanied proposal of the GSI and its subsequent removal from the table, NIH principal deputy director Dr. Lawrence Tabak, who had outlined the plan before some 19 advisory councils in recent months, said, "This is the way this is supposed to work. Maybe there was some tension involved, but as the saying goes, without tension, there is no music."

Both the NIH-Wide Strategic Plan, which Tabak was involved in drafting, and the 21st Century Cures Act, call for creation of NGRI, which will extend the payline for early-stage investigators.

NGRI will also "prioritize support for those about to lose all NIH support and who are maybe likely to leave the workforce," said Tabak. It will also give a boost to those going for their second RPG, but who just missed the payline, the so-called "rising stars," he added.

NGRI is estimated to require about $210 million per year for 4-5 years, or a total of about $1.1 billion, Tabak continued. Inasmuch as NIH is not in the business of printing money, he quipped, the funds will come from reprioritization of budgets by the institute and center directors.

Dr. M. Roy Wilson (l) said the language of some critiques of GSI received at NIH was "really inappropriate."

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"We tried to create a simple framework [GSI], but it would not capture the incredible complexity of modern team science."

-DR. LAWRENCE TABAK

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"We tried to create a simple framework [GSI]," Tabak explained, "but it would not capture the incredible complexity of modern team science."

Ironically, the $1.1 billion in reallocated funds matches almost exactly the recommendations of an independent analysis of the same subject published in the *Proceedings of the National Academy of Sciences* just days before the ACD meeting, noted Dr. Michael Lauer, NIH deputy director for extramural research.

Dr. Richard Lifton said GSI might not help early-stage investigators at all.

Among concerns about limitations of the GSI approach—including that "a formula-driven approach to evaluating individuals flew in the face of...long-standing principles of making decisions based on individual merit," said Collins—is that GSI "offered no assurance that redistributed funds would go to early-stage investigators," said ACD member Dr. Richard Lifton, president of Rockefeller University. "The money could go from a 60-year-old with 6 grants to another 60-year-old with 2 grants."

Opioid Public Health Crisis

"I have never seen anything like this drug crisis in my career," said NIDA director Dr. Nora Volkow, who described a burgeoning U.S. opioid epidemic notable for three things: an "enormous number of people dying daily"; an origin in the health care setting itself, with a "massive over-prescription of medications" that, ironically, "hasn't improved outcomes for those in pain"; and the sheer width of the problem—"This crisis affects everybody, including those never exposed to drugs before."

Dr. Nora Volkow explains science of addressing opioid addiction.

Volkow said that, even though opioid prescriptions have been decreasing since 2010, fatalities are still increasing. Opioid overdose is the leading cause of death in those age 50 and younger, she said.

NIH's approach, outlined in three summer workshops held on campus, will focus on "acceleration points" in the science of addressing opioid use disorders, said Volkow. Three areas are targeted: pain management, through safer, more effective strategies; opioid addiction treatment using new medications and technology; and overdose reversal, including Narcan nasal spray, which Volkow dubbed "naloxone for dummies," since it doesn't require injection.

Dr. W. Ian Lipkin (c) thinks a flu vaccine that reduces mortality is valuable, even if it can't prevent the illness.

Volkow also decried the dramatic underutilization of a tool called MAT—medications assisted therapies for opioid use disorder—which includes methadone, buprenorphine and naltrexone.

"I know of no medical or dental schools that require opioid training," noted Dr. M. Roy Wilson, president of Wayne State University. "I intend to start it at Wayne."

Dr. Michael Lauer (r), NIH deputy director for extramural research, said a paper in *PNAS* concurred with NIH's own estimate of the cost of redistributing resources to help early and mid-career scientists. Shown at left is Dr. Michael Gottesman, NIH deputy director for intramural research.

PHOTOS: ERNIE BRANSON, RICH MCMANUS

Chasing After Pandemics Is Costly

NIAID director Dr. Anthony Fauci made a vigorous case for aggressive pursuit of a universal flu vaccine, given that seasonal flu vaccines are not consistently effective (in a good year, they offer 60 percent protection; in a bad year, none) and that chasing after a potential pandemic is both costly and ineffective.

"We shouldn't be chasing each year and then waiting for the big surprise," he said, noting that a late June meeting sponsored by NIAID would convene the best and brightest in the field.

Of the universal vaccine effort, he said, "We're going to do it with the resources we have, which is not a lot. We may have to reallocate some resources."

Some private funding may become available from a group of philanthropists that met recently in Palo Alto to discuss promising technologies such as a universal flu vaccine; Fauci addressed that group via video.

ACD member Dr. W. Ian Lipkin, a professor of epidemiology at Columbia University, attended the meeting and expressed optimism. "A reduction in [flu] mortality might be a goal," he noted, "not necessarily prevention."

Concluded Fauci, "Chasing after potential pandemic outbreaks costs a stunning amount of money—billions of dollars. It doesn't make any sense not to invest a fraction of that on universal flu vaccine research." R

'KIDNEY SUNDAYS'

NIAMS, NIDDK Partner to Increase Lupus Awareness

People often turn to their places of worship for guidance on how to live better. These faith-based settings offer "teachable moments" for providing relevant and reliable health information. Recently, NIAMS joined forces with NIDDK and Chi Eta Phi Sorority, Inc., to help community faith leaders raise awareness about lupus in their congregations as part of NIDDK's Kidney Sundays annual outreach program.

The initiative, promoted during National Kidney Month, brings attention to kidney disease as a prevalent health issue in the African-American community. This year, NIAMS helped hone the focus on lupus, an autoimmune disease that disproportionately affects African Americans. "Although some people may have heard of lupus, many don't know that it is a kidney-related disease," said Priscilla Murphy, first vice president of Chi Eta Phi, a professional organization for nurses dedicated to leadership and community service.

"Lupus is a complex disease and it can affect many parts of the body," said Anita Linde, director of the NIAMS Office of Science Policy, Planning and Communications. "This collaboration between NIH and Chi Eta Phi is a wonderful example of the power of partnerships to improve public health."

Lupus is most common in women, especially those in their childbearing years who are in the prime of their lives—raising families, going to school and building careers. African-American and Hispanic women tend to have more severe organ damage from lupus, especially to the kidneys. Lupus is also common in women of Asian and Native American descent. With symptoms such as fatigue, achy joints and sun sensitivity, lupus may look different for each person, making it difficult to diagnose.

"Working with NIAMS to highlight a condition that involves both our ICs' research areas makes perfect sense and really serves the affected audience," said Kathy Kranzfelder, director of NIDDK's Office of Communications and Public Liaison. "I'd love to see more of this sort of cross-reliance on the subject matter experts and cross-promotion of the resulting messages."

The collaboration reached 146 churches across 24 states nationwide. Each Kidney Sundays event provided opportunities to engage community members about healthier living, while offering free blood pressure checks and informational handouts.

NIDDK's Natalie Shuster (standing, fourth from l) and Eileen Newman (standing, r) and NIAMS's Colleen Dundas (standing, second from r) pose with Chi Eta Phi volunteers and church members at a local Kidney Sundays event.



The late NIDDK biochemist and pharmacologist Dr. John W. Daly, renowned for his jungle explorations, traveled to such places as Colombia, Peru, Ecuador and Madagascar, tracking down would-be medicines from their herpetological sources—frogs, lizards and snakes.

DALY PHOTOS: NIDDK LABORATORY OF BIOORGANIC CHEMISTRY, OFFICE OF NIH HISTORY

Marshall

CONTINUED FROM PAGE 1

traveled to remote locations in such places as Colombia, Peru, Ecuador and Madagascar, tracking down would-be medicines from their herpetological sources—frogs, lizards and snakes.

As a fellow laborer in pharmacological chemistry—albeit several generations removed—Marshall, chief scientific officer at Heptares Therapeutics in Hertfordshire, United Kingdom, recently presented "From the Jungle to the Synchrotron—Seven Millennia of Discovering Medicines Targeting G Protein-Coupled Receptors."

Black mamba encounter aside, she mainly described drug discovery done a lot closer to home.

"Although most venoms and toxins [secreted by animals] tend to work through ion channels because that's the fastest way of killing prey or getting away from predators, a number do work on GPCRs," Marshall pointed out. "That black mamba that I met produces venom that acts on potassium channels."

Spiders and Lizards and Frogs, Oh My!

She showed several animals and their GPCR-acting toxins: The green mamba snake native to India emits MTX, which works on the muscarinic receptor, for example, while the king cobra's venom acts on the beta adrenergic receptor. Both of those receptors are located on the heart; blocking them leads to cardiac arrest.

Other critters with interesting venoms that act on GPCRs include the cone snail, Gila monster, black widow spider and the Australian green tree frog.

• • •

"There's an increasing realization that GPCRs are not simple. There are many complex binding sites that can be accessed all over and even around the receptor, and intracellular sites as well..."

-DR. FIONA MARSHALL

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At NIH for nearly 50 years, Daly published more than 700 articles and worked on the chemistry of ligands for several GPCRs, including adenosine, adrenergic, histamine, serotonin and acetylcholine receptors. He died in 2008, but his legacy of natural drug discovery survives him.

It was Daly who discovered the chemical structure of batrachotoxin, the poisonous substance found in some frog skin that Amazon Indians used on blow darts. He described its mechanism of action through sodium channels and went on to reveal how toxins react with different proteins in humans. Daly subsequently introduced several other tools still used today for natural products research, including forskolin and epibatidine.

Tracing the history of natural substances back to before anyone realized how they worked, Marshall said the first GPCR drugs were most likely opioids and they were probably first used in religious ceremonies, then as medicines—some of the earliest anesthetics—in ancient Samaria, or what is now Iraq.

Marshall, founder and chief scientific officer at Heptares Therapeutics in Hertfordshire, U.K., describes the history of natural substances used as medicines.

LECTURE PHOTOS: ANDREW PROPP

Opium, cannabis and atropine were among the first known GPCR drugs.

It wasn't until the 1890s that the concept of chemoreceptors, substances in the human body that interacted with these plant-based medicines, was introduced.

From Gut Baths to High-Throughput

"The start of pharmaceutical drug discovery of GPCRs as we know it today came about in the 1950s and 1960s," Marshall said. "Tissues, mainly from animals such as the guinea pig and rat, were strung up in gut baths and analogs were made of the ligands... By then we knew quite a lot of GPCR ligands, although that's not what they were called. We

Dr. Kenneth Jacobson, chief of NIDDK's Laboratory of Bioorganic Chemistry, presents the 2017 Daly Award to Marshall.

knew a number of different chemicals that had a physiological effect."

Medicinal chemists, she explained, sketched out the analogs and tested them on gut baths, the classical pharmacological screening tool used to gauge a compound's interaction with organ tissue.

The field moved toward the molecular age in the 1970s, Marshall said, with the dawn of radio-labeling techniques—using a radioactive tracer to mark a substance. The new methods meant researchers could track the binding sites of substances as they interacted in tissues.

Through radio-labeling, scientists first purified and then cloned the first receptor, realizing that "GPCRs were actually part of a large, superfamily of proteins. This then followed a great era in cloning all of the other GPCRs," said Marshall.

About a decade later, with human genome sequencing, researchers could list around 800 human GPCRs, "about half of which are olfactory receptors used for smell and taste. About 400 others are non-olfactory receptors that we consider to be potential drug targets."

High-throughput screening, in which large libraries of compounds are tested against GPCRs, became the next phase for drug discovery, Marshall said. Not nearly as many substances made it to market this way, however. Tissue bath techniques had produced far more viable drugs.

The first GPCR structure was rhodopsin, purified from bovine retina and crystallized in 2000, giving scientists their first look at a GPCR in 3-D.

Next Gen Tech Solutions Emerge

It took another 7 years until the next GPCR was cloned—the beta2 receptor—by the teams of Brian Kolbilka of Stanford and Ray Stevens of Scripps.

Enter Heptares Therapeutics, the company Marshall cofounded in 2007 to take advantage of a uniquely designed technology that makes GPCRs more stable. The technology was first developed at the Laboratory of Molecular Biology in Cambridge, U.K.

"This has enabled us to do structure-based design, to design drugs that really fit the receptor much better, are much more specific and hopefully have a lower attrition rate as they go through development," Marshall explained.

Hepatares's first X-ray structure success was to solve the adenosine A_{2A} receptor, which Daly played such a crucial role in defining. Over the next decade, the team at Heptares identified potential drugs for a wide range of ailments, including Alzheimer's disease, migraine, schizophrenia, cancer, attention deficit hyperactivity disorder and Parkinson's disease.

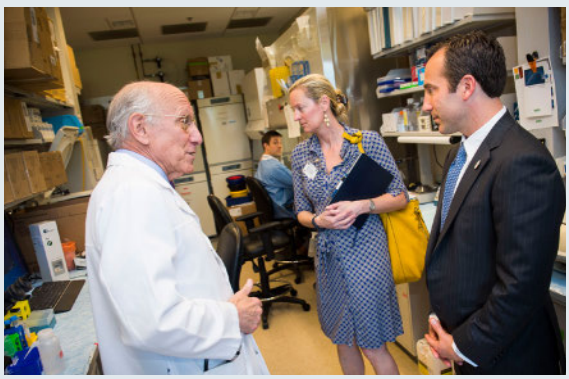
In 20 years of GPCR drug discovery from 1995 to 2015, 116 GPCR-targeted drugs have been approved by the FDA. That represents about 20 percent of all drugs approved in that time period. The newly discovered medicines modulate the activity of targets across all disease fields, from the central nervous system to the immune system.

Marshall touched briefly on her group's most recent work with the identification of structures of receptors involved in irritable bowel disease, Crohn's disease and inflammatory pain. She ended by summarizing what she described as a now wide-open field for GPCR-structure drug development.

"There's an increasing realization that GPCRs are not simple," she concluded. "There are many complex binding sites that can be accessed all over and even around the receptor, and intracellular sites as well... These all will have different allosteric actions and different therapeutic actions. Getting X-ray structures allows us to understand much more about the interaction of the drugs with the receptor and can enable further GPCR drug discovery."

Visit https://videocast.nih.gov/summary.asp?Live=23387&bhcp=1 to see the full presentation.

Administration, HHS Officials Take NIH Tour



Reed Cordish (top, second from r), assistant to the President for intragovernmental and technology initiatives, and Mary Sumpter Lapinski, counselor to HHS Secretary Tom Price, visited NIH on May 31 for a brief tour. They met with NIH director Dr. Francis Collins (top, second from l), Clinical Center CEO Dr. James Gilman (l) and NCI Surgery Branch chief Dr. Steven Rosenberg (below, l).

In tours of his office and lab, Rosenberg discussed research on immunotherapy, walking the group through computer scans and other tumor images before and after treatment.

He also introduced the officials to a 66-year-old patient with relapsed diffuse large B-cell lymphoma who'd had three lines of therapy prior to treatment at NCI. At NIH, he received low-dose chemotherapy followed by anti-CD19 CAR cells in September 2015 and was declared a complete responder 2 months after infusion. His scans remain clear now, 18 months after infusion, with no evidence of recurrent lymphoma.

PHOTOS: LISA HELFERT

Valle

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genetics, so he had no way of explaining how variations that were favorable were transmitted from one generation to the next," said geneticist Dr. David Valle at a recent Clinical Center Grand Rounds in Lipsett Amphitheater, Bldg. 10.

A century after Darwin, in the 1960s when Valle was a medical student, he never heard evolution mentioned. "Evolution was [thought to be] paleontology and fossils," said Valle, director of the Institute of Genetic Medicine and professor of pediatrics, ophthalmology, molecular biology and genetics at Johns Hopkins University. "But nothing could be more removed from medicine and the biology of human beings."

Biology and medicine are rooted in evolution, said Valle at this Great Teachers edition of rounds. "And genetics is emerging as the basic science of all medicine," he said. "Our genomes have to stand us in good stead throughout our lifetime."

We've come a long way from Mendel's cross-breeding of pea plants to advances in recent decades that led to sequencing whole genomes. With more than 60 million different SNPs (single nucleotide polymorphisms, or, genetic variations) in humans and more than 3 million between individuals, it's a wonder people get sick. But when genetic variations pull us from the median, combined with environmental stresses that bump us out of homeostasis, we're susceptible to illness.

"Getting sick is really a consequence of variation, natural selection and, [therefore], evolutionary biology," said Valle.

Human genome sequencing has given us a parts list, namely all 20,000 protein-coding genes. The challenge is figuring out how these proteins interact with each other in biological systems and how these systems function in tissues and organs. A genetic strategy to meet this challenge is to identify patients with mutations that result in malfunction of one of these systems and thereby tell us something about the role of the system in health and disease, said Valle.

Over the years, his lab has discovered the genetic causes of more than 20 diseases and continues to use genetic tools to find and understand rare Mendelian disorders. Most patients with these disorders have egregious

Valle presents at a Great Teachers edition of CC Grand Rounds.

PHOTOS: ERNIE BRANSON

defects, he said, and present early, often in childhood. They also are more likely to inherit a rare variant from both sides of the family and have multiple siblings or generations with the same disease.

In one curious case, a seemingly healthy 34-year-old male contracted an infection but was unresponsive to treatment. He developed confusion and arrived at JHU with cerebral edema. After interviewing

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"Getting sick is really a consequence of variation, natural selection and, [therefore], evolutionary biology."

-DR. DAVID VALLE

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the family, Valle learned that the patient's brother had drowned as a teenager. Upon further probing, Valle discovered that the teen showed signs of confusion the day he died and an autopsy revealed cerebral edema.

The patient survived what turned out to be ornithine transcarbamylase (OTC) deficiency. His parents kept his late brother's baby tooth and DNA testing confirmed the same variant; his mother and aunt also tested positive. The late brother had an episode of hyperammonemia secondary to OTC deficiency as a child; the surviving brother didn't show signs until adulthood.

"The only thing that got him was he had this severe environmental stress—which was infection and fever—perhaps augmented by a dose of steroids, which puts excessive demands on the urea cycle," said Valle. "It wasn't until his system was really stressed that this homeostatic vulnerability came to light."

Researchers increasingly are uncovering new gene variants for all kinds of Mendelian disorders thanks to rapid genome sequencing. While there are different advantages to single-gene and panel (20-30 genes) sequencing, whole exome sequencing has been especially useful in diagnosing patients with phenotypes caused by variants in genes not previously known to be responsible for disease. These efforts have not only identified hundreds of novel disease genes but also have explained many surprises. One example is patients who have two rare Mendelian disorders. These "multi-Mendels" have been difficult to diagnose because their blended phenotypes are hard to recognize, said Valle. A precise diagnosis from whole exome sequencing can be invaluable, he said, as it ends the diagnostic uncertainty, suggests specific management and informs the family of recurrence risk.

NHGRI established four Centers for Mendelian Genomics to recruit families from around the world to sequence whole exomes. The Baylor-Hopkins Center for Mendelian Genomics, where Valle is a principal investigator, so far has discovered 913 novel disease genes in its first 5 years.

Valle's group also developed two online databases to promote resource sharing. PhenoDB (www.phenodb.org) allows any provider to submit a case and features an analysis tool. GeneMatcher (https://genematcher.org) connects clinicians worldwide. As of March 2017, more than 6,000 genes were submitted by nearly 3,000 people. Although two-thirds of the genes remain unmatched, so far more than 15,000 matches have been found for some 2,000 genes.

The late biophysicist Max Delbrück once said, "Any living cell carries with it the experience of a billion years of experimentation by its ancestors." As we continue to evolve and learn more about our genes and disease-causing variants, investigators can identify new drug targets and develop better diagnostics and therapies.

"If we look carefully and across large populations," said Valle," I predict we will find Mendelian phenotypes for certain variants for nearly all genes in our genome."

Sandra Oh (front, c) leads the Korean Mae-Hwa Dancing Group, a high school alumnae dance troupe that reunites regularly to learn dance, share Korean culture and stay healthy.

Members of the Wong Family Lion Dance Group perform. Raymond Wong explained that the tradition brings good luck to all and can be found throughout Asia.

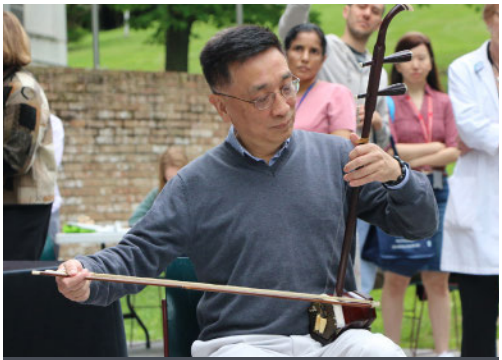
Asian American Heritage Month Celebrated at NIH

The NIH community enjoyed an outdoor program of Asian food and culture on May 24. Opening the event, Dr. Michael Gottesman, NIH deputy director for intramural research, explained that Congress designated every May to be Asian Pacific American Heritage Month. He highlighted contributions of Asian American scientists at NIH and in academia, industry, nonprofit organizations and other government agencies to the betterment of the global community.

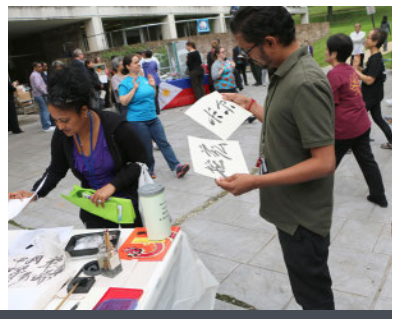
The event, which included music, dance, tai chi, art demonstrations and information tables, was organized by the NIH Asian and Pacific Islander American Organization (APAO), which also coordinated with Eurest Food Services to provide different Asian cuisines.

Attendees learned about services of the PHS Asian Pacific American officers committee, the NIH Employee Assistance Program, NIMHD, NIAMS, and the NIH Federal Credit Union. Area community groups provided information displays.

APAO, active at NIH since 1996, sponsors lectures and discussions and works closely with the Office of Equity, Diversity, and Inclusion to present training opportunities to the NIH community.



Dr. Xiaobin Guan of NHGRI plays the erhu, a two-string Chinese instrument.



Art in progress at NIH's 2017 Asian American Heritage Month Celebration: APAO members write out names in Chinese calligraphy (Hui Chen) and teach Japanese origami folding (Shioko Kimura).

ABOVE: At left are Huonggiang Le and Thomas Tran of the Association of Vietnamese Americans, which provides community services and promotes cultural understanding. In center photo, guest chef Robert Rivera is ready to serve Filipino chicken adobo platters. At right, Integral Tai Chi Group with instructor Hoang-Tam Hiltons (c) of NIH, demonstrated how regular practice of Tai Chi benefits balance, strength and a sense of well-being. BELOW: Attendees learn basic movements, which are closely tied to observations of nature and animals. **PHOTOS: KATIE CHAN**

Drinking Diet Beverages During Pregnancy Linked to Child Obesity

Children born to women who had gestational diabetes and drank at least one artificially sweetened beverage per day during pregnancy were more likely to be overweight or obese at age 7, compared to children born to women who had gestational diabetes and drank water instead of artificially sweetened beverages, according to a study led by researchers at NIH.

Childhood obesity is known to increase the risk for certain health problems later in life, such as diabetes, heart disease, stroke and some cancers. The study appears online in the *International Journal of Epidemiology.*

According to the study authors, as the volume of amniotic fluid increases, pregnant women tend to increase their consumption of fluids. To avoid extra calories, many pregnant women replace sugar-sweetened soft drinks and juices with beverages containing artificial sweeteners.

Citing prior research implicating artificially sweetened beverages in weight gain, the study authors sought to determine if diet beverage consumption during pregnancy could influence the weight of children.

"Our findings suggest that artificially sweetened beverages during pregnancy are not likely to be any better at reducing the risk for later childhood obesity than sugar-sweetened beverages," said study senior author Dr. Cuilin Zhang in the NICHD Epidemiology Branch. "Not surprisingly, we also observed that children born to women who drank water instead of sweetened beverages were less likely to be obese by age 7."

Scientists Discover Rare Genetic Susceptibility to Common Cold

Scientists have identified a rare genetic mutation that results in a markedly increased susceptibility to infection by human rhinoviruses (HRVs)—the main causes of the common cold. Colds contribute to more than 18 billion upper respiratory infections worldwide each year, according to the Global Burden of Disease Study.

Researchers at NIAID identified the mutation in a young child with a history of severe HRV infections. The case, published online June 12 in the *Journal of Experimental Medicine*, reveals an important mechanism by which the immune system responds to these viruses, say the study authors.

Several weeks after birth, the child began experiencing life-threatening respiratory infections, including colds, influenza and bacterial pneumonia. Because her physicians suspected she might have a primary immune deficiency—a genetic abnormality affecting her immune system—they performed a genetic analysis.

The analysis revealed that she had a mutation in the IFIH1 gene that caused her body to make dysfunctional MDA5 proteins in cells in her respiratory tract.

Previously, scientists had found that laboratory mice lacking functional MDA5 could not detect genetic material from several viruses, making them unable to launch appropriate immune responses against them.

Similarly, the NIH researchers found that mutant MDA5 in the girl's respiratory tissues could not recognize HRVs, preventing her immune system from producing protective signaling proteins called interferons. HRV thus replicated unchecked in the girl's respiratory tract, causing severe illness. These observations led the researchers to conclude that functional MDA5 is critical to protecting people against HRV.

With intensive care, the child survived numerous bouts of severe illness and her health improved as her immune system matured and formed protective antibodies against various infectious agents.

"The human immune response to common cold viruses is poorly understood," said NIAID director Dr. Anthony Fauci. "By investigating this unique case, our researchers not only helped this child but also helped answer some important scientific questions about these ubiquitous infections that affect nearly everyone."

Workshop Addresses Opioid Misuse During Pregnancy

Research is essential to determining how best to screen pregnant women for opioid use disorder, to treat pregnant women who have the disorder and to care for infants as they experience withdrawal symptoms, according to experts convened for a workshop co-sponsored by NICHD. A summary of the workshop appears online in *Obstetrics and Gynecology.*

Opioids are a class of drugs often used for pain relief. Approximately 91 people in the United States die every day from an opioid overdose, with more than 33,000 deaths in 2015—the highest on record—according to the Centers for Disease Control and Prevention.

Opioid prescriptions have quadrupled since 1999, putting large numbers of reproductive-age women at risk for developing opioid use disorder and their newborns at risk for drug withdrawal or neonatal abstinence syndrome.

"Opioid use disorder is an accelerating crisis in the United States, particularly among pregnant women," said NICHD director Dr. Diana Bianchi. "NICHD brought together experts to review the current evidence on how to best recognize, treat and manage this condition and to identify the research needed to improve outcomes for affected women, their newborn infants and their families."

Researchers Aim to Repurpose Cancer Therapy to Treat Muscular Dystrophy

Researchers at NCATS and the University of Nevada, Reno School of Medicine (UNR Med) have demonstrated that a drug originally targeted unsuccessfully to treat cancer may have new life as a potential treatment for Duchenne muscular dystrophy (DMD).

The candidate drug, SU9516, represents a different kind of approach for treating DMD, a degenerative muscle disease that usually begins in childhood and has no known cure. It is caused by a faulty gene that leads to progressive muscle weakness, with death often occurring around age 25.

Rather than trying to fix or replace the broken gene, SU9516 ramps up the muscle repair process, helping reinforce muscle structure.

NCATS Chemical Genomics Center acting branch chief Dr. Juan Marugan and UNR Med professor of pharmacology Dr. Dean Burkin led a team that screened more than 350,000 compounds to find SU9516, which had been previously developed as a treatment for leukemia. The research demonstrated that this compound improved muscle function in both laboratory and animal DMD models.

The results, published in *Molecular Therapy*, may provide a promising approach against the disorder and other muscle-wasting conditions.

Those with DMD lack dystrophin, a protein akin to a molecular shock-absorber that helps keep muscle cells intact. Without dystrophin, muscles are fragile and easily injured. Individuals lose muscle strength and the ability to repair damaged muscle tissue. Most die from heart or respiratory problems.

Linda Frances Anderson, NCI alumna

NCI Mourns Former Communications Staffer Anderson

Linda Frances Anderson, 67, formerly a member of the communications staff at the National Cancer Institute, died on June 11 at her home in Lake Charles, La., following a lengthy illness.

She was born in Houston and had relocated to Louisiana in October 2016. She had resided in the Washington, D.C., area since 1967, calling Kensington her home for the last 25 years.

Anderson graduated from the University of North Carolina at Chapel Hill with a bachelor's degree in journalism and earned her master's in public administration from Georgetown University. She worked for the federal government for more than 30 years, most recently in the NCI communications office and continuing after retirement as a private contractor.

She was a member of several informal beach and bridge clubs, played on USTA-ranked teams (later officiating) and was a long-time member of the Ski Club of Washington D.C. and Same Time Next Year Club. She was an avid supporter of the Shakespeare Theatre, the National Symphony Orchestra, the White House Christmas decorating group, Hillwood Estate & Museum and Brookside Botanical Gardens.

She is survived by siblings Sharon Anderson of Bryan, Tex.; Robin Conrad of Moss Bluff, La.; Janet Anderson of League City, Tex.; and James R. Anderson of Sugarland, Tex.; and by two nephews and five grandnieces. She is also survived by her husband Frank Wilson of St. Mary's, Ga.; stepdaughters Elizabeth Reichbart of New Jersey and Kate Wilson of North Carolina and six grandchildren.

Anderson was laid to rest in Lake Charles, alongside her parents. Memorial donations can be sent to Hillwood Estate & Museum, 4155 Linnean Avenue, NW, Washington, D.C. 20008.

CC Program Assistant Frazier Dies

Rhea Moore Frazier

Rhea Moore Frazier, program assistant in the Office of Clinical Research Training and Medical Education (OCRTME), passed away on May 30 at the age of 69.

Frazier joined OCRTME in 2009 and provided essential administrative and program support services to allow OCRTME to fulfill its mission within the Clinical Center. She was also responsible for communicating with medical students, physicians, researchers and administrators within NIH, and with extramural organizations, institutions of higher education and training partners on behalf of OCRTME.

Frazier will be greatly missed by her colleagues; she will be remembered for her contributions to the professional development of her team and the next generation of clinician-scientists.

FEEDBACK

Have a question about some aspect of working at NIH? You can post anonymous queries at https://nihrecord.nih.gov/ (click on the Feedback tab) and we'll try to provide answers.

Feedback: Hello, overall, I love working at NIH. However, I would like to know how do I report bullying on behalf of someone else? Is there an anonymous link, email address or central mailbox for such matters? Thank you for assistance.

Response from the NIH Civil Program: Bullying is managed by the NIH Civil Program, which works to address and prevent workplace violence. Civil defines violence broadly and helps the ICs manage a range of situations, from bullying and other types of intimidating behavior to more direct or physical types of violence such as threats, suicidal ideation and domestic violence. To keep the situation from escalating, bullying interactions should be immediately documented and reported to Civil. To contact a Civil Program coordinator, call 301-40C-IVIL (301-402-4845).

Civil is part of the Office of Human Resources and as such, is not confidential nor does it have an anonymous link or email address to report concerning behavior. However, for situations where employees wish to talk about concerns and action plans in a confidential setting, they can contact the Employee Assistance Program (301-496-3164) or the Office of the Ombudsman (301-594-7231). Civil is also not a substitute for calling 911 when police or emergency help is needed.

VOLUNTEERS

Vaccine Study Needs Healthy Volunteers

Researchers at NIAID's Vaccine Research Center need healthy volunteers 18-50 who are interested in participating in HIV vaccine development. Participants are not exposed to HIV and compensation is provided. To learn how to participate, call the Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010). Read more at https://go.usa.gov/xN9SQ. Refer to study 17-I-0030.



Above left, Vaccine Research Center deputy director Dr. Barney Graham (r) shows Bill Gates a molecule model produced using NIH's 3-D print technology. In the center photo, wearing virtual reality goggles, Gates explores key immunologic epitopes of an influenza H1 hemagglutinin molecule, used to target next generation influenza vaccines, color coded to show the binding footprints of a set of broadly neutralizing antibodies (yellow), as well as several glycosylation sites (red). On his left is Dr. Phil Cruz, a structural biologist in NIAID's Office of Cyberinfrastructure and Computational Biology, who collaborated with the translational sciences core in the Viral Pathogenesis Laboratory to adapt molecular structures for 3-D printing and VR visualization. At right, Gates talks with VR team member James Tyrwhitt-Drake (l), scientific visualization specialist in the NIAID Office of Cyberinfrastructure and Computational Biology, who put molecules into the VR software.

NIH Hosts 4th Workshop with Gates Foundation

For the fourth consecutive year, the Bill & Melinda Gates Foundation teamed with NIH for a consultative global health workshop. On June 2, researchers from the foundation, NIH and other federal agencies, academia and the public sector gathered for a full day of panel discussions on several topics including vaccine research and development on human papillomavirus prevention and therapy and structure-based immunogen design, point-of-care diagnostics for low-resource settings and the emergence of a coalition for African research and innovation.

Foundation cochair and trustee Bill Gates, NIH director Dr. Francis Collins, NIAID director Dr. Anthony Fauci, Fogarty International Center director Dr. Roger Glass and NIBIB director Dr. Roderic Pettigrew were among officials on hand for the session.

While here, the world renowned IT pioneer and philanthropist Gates got to sample a bit of tech wizardry used at the Vaccine Research Center. Gates donned virtual reality goggles for a demonstration of how scientists explore the molecular structures of influenza in 3-D. A handheld molecule—produced via 3-D printing technology—was also passed around.

From left, Gates, NIH director Dr. Francis Collins, NIAID director Dr. Anthony Fauci and FIC director Dr. Roger Glass listen in on presentations at the recent global health workshop.

The day ended with working group/breakout sessions on such subjects as HIV/AIDS; malaria and neglected tropical diseases; tuberculosis; maternal, neonatal and child health; pneumonia, enteric diseases and indoor air pollution; and contraceptive research.


ABOVE: Shown with Gates are (from l) Collins, Fauci and VRC scientists Dr. Mario Roederer, Dr. John Mascola, Dr. Rick Koup, Dr. Michelle Crank, Dr. Nancy Sullivan, Graham, and Dr. Marybeth Daucher. At right, NIBIB director Dr. Roderic Pettigrew, who moderated a panel session on point-of-care diagnostics for low-resource settings, chats with Gates.

PHOTOS: LISA HELFERT