THE NIH CATALYST

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NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 28 ISSUE 2 • MARCH-APRIL 2020

Five New Laskers

Part of the Next Generation of Clinical Researchers

BY LAURA STEPHENSON CARTER

Congratulations to the five investigators who recently joined the ranks of the Lasker Clinical Research Scholars Program, NIH's collaborative effort with the Albert and Mary Lasker Foundation to nurture the next generation of clinical researchers: **Sean Agbor-Enoh**, who's developing methods for early detection of and treatment for lung-transplant rejection; **Paule V. Joseph**, who's investigating how taste and smell are involved in metabolic disorders and substance-use disorders; **Joanna Klubo-Gwiezdzinska**, who is searching for optimal ways to diagnose and treat thyroid nodules and thyroid cancer; **Nirali N. Shah**, who is testing novel immunotherapeutic approaches to treat blood cancers in children, teens, and young adults; and **David Takeda**, whose research focuses on treatment-resistant prostate cancer.

The Lasker Clinical Research Scholars Program, which began in 2011, is an "intramural–extramural" endeavor that funds a small number of exceptional clinical researchers in the early stages of their careers to help them achieve independence. Lasker Scholars receive a unique combination of NIH funding for clinical research for up to 10 years.

In the first phase of the program, scholars receive appointments for five to seven years as tenure-track investigators, with independent budgets, within the NIH Intramural Research Program. In the second

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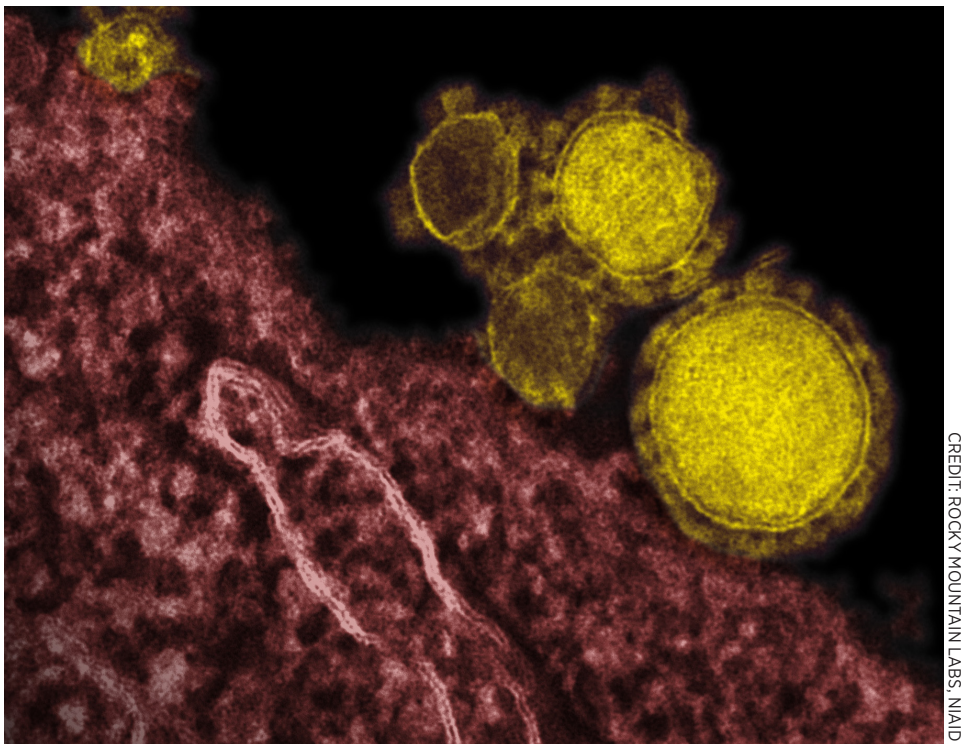
Remdesivir Is Active Against MERS Coronavirus

Drug Being Tested in Clinical Trials Against the New Coronavirus

BY BIJETA PRASAI, NHLBI



CREDIT: ROCKY MOUNTAIN LABS, NIAID

This electron micrograph shows Middle East respiratory syndrome coronavirus particles budding from a cell. The spikes around the surface of the particles give coronaviruses their name, crown-like.

The drug remdesivir has antiviral effects against a variety of viruses including Middle East Respiratory Syndrome coronavirus (MERS-CoV) in rhesus macaque monkeys, according to a study conducted by NIAID researchers at the Rocky Mountain Labs in Hamilton, Montana. "Because MERS-CoV and [the new coronavirus] are closely related viruses, we have reason to think remdesivir treatment will work against the new coronavirus as well," said **Emmie de Wit**, first author on the study which appeared in *Proceedings of the National Academy of Sciences*.

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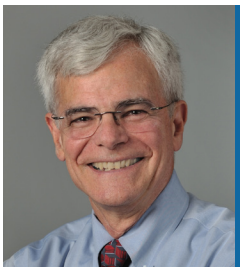


Bioengineering: A New Frontier for the NIH

BY MICHAEL GOTTESMAN, DDIR, AND BRUCE TROMBERG, DIRECTOR, NIBIB

Many of you have seen multiple messages encouraging your participation in NIH's Bioengineering Festival, which was originally scheduled to be held on March 20, 2020, but has been postponed to the fall (because of the novel coronavirus outbreak and NIH guidance to have large meetings held virtually or be postponed or cancelled). This festival recognizes the enormous potential of the NIH intramural research program (IRP) to make innovative bioengineering contributions to biomedical research. It features a welcome by NIH Director **Francis Collins**; a keynote address by **Jennifer Elisseeff**, who was a postdoctoral fellow at the National Institute of Dental and Craniofacial Research (1999–2001) and is now head of the Translational Tissue Engineering Center at Johns Hopkins University (Baltimore); and a series of talks, posters, and "lightning" presentations from our most inventive bioengineers.

The festival's host, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), was established in 2002 with the goal of advancing engineering and physical science in biology and medicine. Since that time NIBIB, and nearly every NIH institute and center (IC), has made major contributions to the enormous growth and impact of bioengineering throughout the world.

Because these gains have been primarily in the extramural research community, the goal of this festival is to focus our attention inward and ask, "How can NIH stimulate cutting-edge bioengineering across our intramural campuses?" One obvious way is to recruit more talented early-career scientists who are using bioengineering principles to attack important biomedical problems. This recruitment is already beginning to happen; if you attend the Bioengineering Festival, you will notice quite a few early-career investigators who were recruited to the NIH in recent years. We hope to recruit many more in the near future.

Many of our IRP scientists who use principles of bioengineering are trained in engineering, but most are quantitative biologists with backgrounds in physics, chemistry, computer science, bioengineering, and, yes, even biology. The physicists often gravitate to the design of new instrumentation to probe the biological universe: new tools for visualizing samples from the most microscopic (for example, cryoelectron microscopy), to the midrange (light microscopy and photonics), to human-sized clinical samples (magnetic-resonance imaging, positron emission tomography, and computed tomography).

Chemists choose to design new syntheses for drugs, molecular probes, and novel means of marking and selecting cells with desired properties. Biologists use engineering principles to design new pathways to alter growth, malignancy, and synthetic capacity of biological systems, as well as to explore the new world of single-cell biology. Physicians pursue engineering technologies to detect and diagnose disease, guide therapies, and construct artificial tissues. Everyone relies on data science, computational models, and artificial intelligence to analyze and interpret the vast amount of data generated in our expanding digital universe. There is no end to the variety of productive ways in which engineering principles can be applied to biomedical problems.

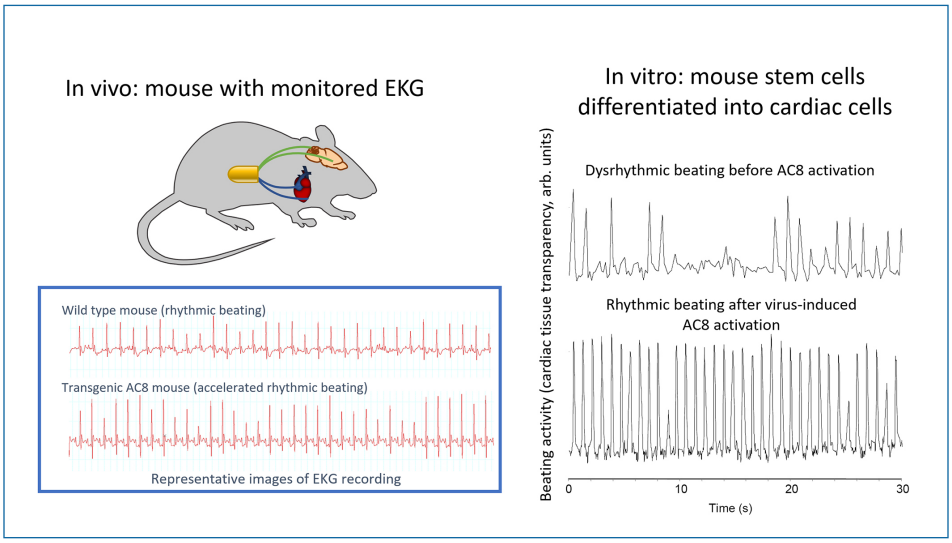
If we build it, will they come? NIH needs facilities that are user-friendly for bioengineers; buildings that can house increasingly complex equipment that we purchase and build here; and places where teams of engineers, biologists, and physicians can work together to design, fabricate, and test new technologies from "blackboard to benchtop to bedside." The long-term plan for the NIH campus includes creating such spaces. We would be remiss not to take advantage of the talent of our next generation of researchers by not providing the facilities that they need.

As we learn more and more about the biological world, we can and should be proactive in using engineering principles to design future instrumentation and novel organisms to help solve difficult biological problems. Interdisciplinary approaches are often the most innovative ways to solve problems, and bioengineering needs to be woven into the fabric of our work at the NIH. ●

The NIH Bioengineering Festival will take place this fall. Stay tuned for more information and check the website for details: https://ncifrederick.cancer.gov/events/conferences/nih-bioengineering-festival.

NIA Scientists Invent Biologically Engineered Pacemaker

BY DIPTADIP DATTAROY, NIDDK



V. MALTSEV AND E. LAKATTA, NIA; MOUSE: K.R. MCGRAW, NIA

NIA researchers developed a genetically engineered, cell-based biological pacemaker, which restores normal rhythmic heartbeat. Shown: (left) EKG recordings of heartbeats from a wild type mouse (top) and a transgenic AC8 mouse (bottom); (right) mouse cardiac cells showing dysrhythmic beating before AC8 activation (top) but rhythmic beating after virus-induced AC8 activation (bottom).

Staff scientist Victor Maltsev and senior investigator **Edward Lakatta** and colleagues at the National Institute on Aging (NIA) have invented and patented a genetically engineered biological pacemaker that may one day replace electronic pacemakers. Biological pacemakers restore normal heart rhythm in people with irregular heartbeats due to cardiovascular disease.

In the United States, about 200,000 electronic pacemakers are implanted annually; worldwide, it's about 1 million. Most have improved the lives of recipients, but about five percent fail and require surgery or other invasive procedures to repair or replace them. In addition, electronic pacemakers have limitations such as being prone to electrode fracture, having a limited battery life, posing a risk of infection, and being subject to electromagnetic interference from other devices. These problems could be circumvented with a genetically engineered, cell-based biological pacemaker, which would not only restore normal pacing but also integrate naturally into the heart.

The heart's natural pacemaker is a group of specialized cells residing in the sinoatrial node (SAN), which is in the upper right part of the heart's right atrium. The SAN generates electrical impulses, action potentials, at regular intervals that signal a healthy, resting heart to pump at a rate of 60 to 70 beats per minute. The NIA investigators found that certain unique intracellular components in the SAN cells are responsible for their pacemaker functions. By introducing these cellular components into heart cells, the investigators were able to convert them into pacemaker-like cells that regulate heart rhythm.

Through a series of discoveries that started in 2000, the NIA researchers found that pacemaker cells express the enzyme adenylate cyclase (AC types 1 and 8), which when activated by intracellular calcium, drives the pacemaker function and mediates heart rate (*Circ Res* **106:**659–673, 2010).

These enzymes, however, are absent in cardiac muscle cells. The NIA scientists and collaborators at University of Pittsburgh (Pittsburgh) used a genetically engineered lentivirus to deliver calcium-activated ACs (AC1 and AC8) to nonpacemaker heart cells and turned them into rhythmic and effective pacemakers.

In May 2009, the NIA inventors and their Pittsburgh collaborators filed an initial provisional patent application; a patent related to this initial application was granted in 2016 by the United States Patent and Trademark Office. This technology was tested further by scientists at Columbia University (New York) and colleagues who conducted an extensive study in dogs (*Circulation* **126:**528–536, 2013).

At present, this biological pacemaker technology is in the early development stage and is available for licensing and co-development. The inventors aim to further develop both a genetically engineered virus—with long-term action of AC1 and AC8—and a reliable surgical method to generate robust biopacemaking in the right location of the heart. This technology may be suitable for clinical and other trials. ●

NIH scientists are continually developing new drugs and medical technologies that show promise for relieving and curing human diseases. Such inventions often become available for licensing and collaboration agreements with biotech and pharmaceutical companies; many become commercially successful. To learn more, go to the Office of Technology Transfer's website at https://www.ott.nih.gov. In addition, you can read the *NIH Catalyst* story on Tech Transfer (May–June 2019 issue) at https://irp.nih.gov/catalyst/v27i3/news-you-can-use-technology-transfer.

From the Fellows Committee

Better Mentoring

BY CRAIG MYRUM, NIA

We can probably think of personal stories that demonstrate how the quality of mentor-mentee relationships have a profound impact on trainees' career trajectories. Several studies support this notion. One study, which surveyed 7,603 postdocs in 351 U.S. academic and nonacademic institutions (hospital, industry, and government labs) in 2016, found that the perceived quality of postdoctoral mentor support had a significant effect on the perception of both the preparedness of the postdoc for their desired career and their outlook on the job market (*eLife* **7:**e40189, 2018; DOI:10.7554/eLife.40189). The study also reported that postdocs who received training in mentorship were more satisfied with the mentoring they received than postdocs who did not. Nevertheless, only about 25% of postdocs actually received such training.

Postdocs are particularly well-suited for mentorship training because they are concurrently trainees (primarily mentored by their PIs) and mentors themselves (for postbaccalaureate fellows, graduate students, and high-school-age summer students). As such, postdocs can immediately adopt mutually beneficial mentoring practices, pass on those skills to their mentees, and learn how to improve relationships with their own mentors.

"Whatever career postdocs enter, they will have opportunities to mentor junior colleagues," said **Stephen Heishman**, who is the director of the National Institute on Drug Abuse's Office of Education and Career Development and leads an "Approaches to Mentoring" course each year. "Developing good communication skills as a postdoc and practicing those skills with postbacs and summer students is an invaluable experience for future success as a PI, team leader, or administrator."

> Mentoring is a two-way relationship, and there must be clear, continual communication between mentee and mentor.

Although trainees learn from their mentors—especially the good ones—not all mentors are great, he pointed out. "Good mentoring behavior is a learned skill and anyone can adopt these behaviors if they are willing to explore their own mentoring style and … to change what's not working. I also encourage postdocs to have multiple mentors." The advantage is that, compared with just one mentor per trainee, several mentors "can offer sound, experiential advice across the many aspects of research and career training."

In addition to the mentor-training workshops organized by individual institutes and centers, there are other opportunities for intramural fellows to learn and improve mentoring skills. For example, the Office of Intramural Training and Education (OITE) routinely holds "Improving Mentoring Relationships" workshops that offer strategies for enhancing communication and interpersonal interactions between mentors and mentees. For postdocs who are expecting to work with summer students, OITE also offers many sessions each spring that are tailored for preparing mentors for eight weeks of intensive mentoring. Be sure to check on future offerings in the "Upcoming Events" section on the OITE website at https://www.training.nih.gov/events/upcoming.

Heishman encourages all postdocs to attend some of the formal mentoring training at NIH. "The key to good mentoring is communication," he said. Mentoring is a two-way relationship, and there must be clear, continual communication between mentee and mentor. The expectations of both mentee and mentor should be fully discussed and agreed upon at the start of the relationship. As time goes on, those expectations should be revisited and tweaked if necessary. ●

For more information go https://www.training.nih.gov/events/upcoming.

"Becoming a Resilient Scientist"

Videocast of an OITE interactive workshop that explores strategies for building resilience and dealing with self-doubt and developing confidence. https://videocast.nih.gov/watch=34801.

A Giant Leap of Love, Faith, and Courage

A Husband-Wife's Quest to Cure a Genetic Prion Disease

BY SUNITA CHOPRA, NCI

CREDIT: CHIA-CHI "CHARLIE" CHANG

NIH Director Francis Collins (center) and WALS presenters Sonia Vallabh (left) and her husband Eric Minikel, who are in search of a cure for prion disease. Vallabh and Minikel are each holding a framed certificate commemorating their talk.

Sonia Vallabh and her husband Eric Minikel hadn't set out to build careers in science. Vallabh graduated with a law degree cum laude from the Harvard Law School (Cambridge, Massachusetts) in 2010 and joined a consulting firm in 2011. That same year, Minikel was working as a city planner after obtaining a master's degree from the Massachusetts Institute of Technology (Cambridge, Massachusetts) in transportation and city planning. A tragic event, however, would change their lives forever. The couple described their saga at the Wednesday Afternoon Lecture Series (WALS) talk held on December 4, 2019.

Vallabh's mother, Kamni Vallabh, underwent a catastrophic health decline that began late in 2009. What started out as failing eyesight, forgetfulness, and difficulty sleeping progressed rapidly to severe dementia. Within a year, Kamni was on life support, and in December 2010, she died. She was only 52 years old. An autopsy revealed that an incurable genetic prion disease called fatal familial insomnia had killed her.

Prion diseases occur in people and other mammals. Prions are misfolded proteins that induce the misfolding of the normal form of the same proteins in the brain; the accumulation triggers a rapidly progressing, always fatal, neurodegenerative disease. About 85% of cases are sporadic; 15% are genetic with mutations found in the prion protein gene, *PRNP*. Until recently, all attempts to find treatments had failed.

Another devastating realization for the couple came in December 2011 when Vallabh learned that she was carrying the fatal genetic mutation, too. It meant that she has a more than 90% chance of developing the disease, although it might not appear for 20 years. With the clock ticking, the couple decided that the only way to find a cure was to become patient-scientists themselves. They started learning all they could about prions. In early 2012, they enrolled in night classes at MIT and Harvard. They found entry-level jobs in science labs and applied to Ph.D. programs. They earned their Ph.D.'s in 2019 working on the prion question in the lab of Stuart Schreiber at the Broad Institute (Cambridge, Massachusetts). Their education also included brief predoctoral stints in the lab of **Byron Caughey** at the National Institute of Allergy and Infectious Diseases' Rocky Mountains Laboratories in Hamilton, Montana.

Caughey's lab has made important contributions to the understanding of how prions propagate their shape. He developed an assay (called RT-QuIC) to diagnose prion diseases. He, Vallabh, and Minikel have collaborated to show that mice treated with antisense oligonucleotides (ASOs) against PRNP RNA—either prophylactically or late in the course of disease—have markedly extended survival times (*JCI Insight* **4:**e131175, 2019). Although Caughey is optimistic about the ASO technology, he cautions that a single approach might not be fully effective. Scientists must also find alternate therapies that directly target the misfolded form, he said.

Vallabh and Minikel, who now run an independent lab at the Broad Institute, are determined to find a cure for prion disease. A large pharmaceutical firm is developing an ASO against the human *PRNP* gene and is collaborating to help carry forward the couple's work, said Minikel.

Their love and faith in each other gives the couple the strength to fight, they said. We have heard that love can move mountains. It may be a first when love conquers a genetic disease. ●

To see a videocast of the WALS December 4, 2019, lecture, go to https://videocast.nih.gov/summary.asp?Live=35113&b.

A Pioneer in Vaccines

First Woman to Head a Lab at NIH

BY GORDON MARGOLIN, OFFICE OF NIH HISTORY

CREDIT: NATIONAL MUSEUM OF AMERICAN HISTORY

Margaret Pittman and NIH biologist Sadie L. Carlin are "reading" an agglutination reaction, part of the test for potency of commercially prepared anti-meningitis serum during the meningitis epidemic of 1935-1937 (1937).

Name this NIH luminary: She was an internationally recognized bacteriologist who worked at the NIH from 1936 until she retired in 1971. She was the first woman to head a laboratory at the NIH, becoming the chief of the Laboratory of Bacterial Products in 1958. And she stayed on as a guest worker for another 20 years after retiring, dying in 1995 at the age of 94.

Do you know whom we're describing? **Margaret Jane Pittman**. Had she still been alive this past year, she would have decried the outbreak of measles in the United States and the severe outbreak (resulting in the death of at least 70, mostly children, by December 2019) in Samoa—all because of widespread misinformation about vaccinations. "Miss Information" is what she called herself in her oral history with the Office of NIH History and Stetten Museum, because other vaccine and infectious-disease researchers routinely sought her scientific advice.

Pittman led the field in setting standards for the potency, stability, and sterility of vaccines, all of which assured the appropriate dosing and the safety of the products (the NIH licensed and tested commercial vaccines and sera until the early 1970s, when the Food and Drug Administration took over that responsibility). Her standards are still applied in modern-day vaccine production and have helped millions of people. For example, in the first 10 years after development of the pertussis vaccine, the death rate of children in the United States from this disease dropped from 9,000 per year to less than 20, according to the Centers for Disease Control and Prevention.

Pittman's father, a general practitioner in Prairie Grove, Arkansas, sparked her interest in medicine by involving her in his practice. She was a brilliant student, graduating magna cum laude in 1923 from Hendrix College in Conway, Arkansas, with a double major in mathematics and biology. After teaching those subjects at Galloway College (Atlanta), she attended the University of Chicago, earning an M.S. in 1926 and a Ph.D. in 1929, both in bacteriology.

In 1928, she began working at the Rockefeller Institute of Medical Research (New York) with physician Rufus Cole, the first director of Rockefeller University Hospital, on whether *Hemophilus influenza* caused influenza. This question was one of the perplexing medical problems of that time. She discovered that there was more than one strain of this organism and that this bacterium was encapsulated, and it produced a toxin responsible for its severe clinical symptoms, at times leading to blindness and death in younger children. Developing a vaccine against the meningitis caused by this strain of *H. influenza* earned Pittman an international scientific reputation before she was 30 years old.

During World War II, Pittman investigated the safety of blood and blood products, especially those used on the battlefield. She discovered and eliminated the cause of fever and death attributed to plasma infusions and determined how to keep stored blood from becoming contaminated.

Pittman served as president of the Society of American Bacteriologists (1928) and of the Washington Academy of Sciences (1955). She received many honors for her foundational contributions to public health, including the 1970 Federal Women's Award. The

CREDIT: OFFICE OF NIH HISTORY

Margaret Pittman explains a test for the efficacy of a vaccine to visitors (c. 1960s).

CREDIT: MICHELE LYONS, OFFICE OF NIH HISTORY

A display case on the first floor of Building 60 (aka the Cloister or the Lasker Center) features Margaret Pittman and her laboratory research. The display will be in Building 60 indefinitely before moving to another campus location.

Margaret Pittman Lectureship was created in 1994 by NIH to honor her exceptional research achievements.

Why are we testing your knowledge of Margaret Pittman? We have a new display case on the first floor of Building 60 (aka the Cloister or the Lasker Center) about her. You can see the pathology slides Pittman hand labeled for her Ph.D. classes nearly 100 years ago, as well as other items and photos from her long and impressive career as a vaccine pioneer. The display will be in Building 60 indefinitely before moving to another campus location. ●

The Office of NIH History and Stetten Museum at NIH advances the historical understanding of the biomedical research conducted at NIH by documenting, preserving, and interpreting records and artifacts. The office creates exhibits and other products, and helps scholars and researchers to navigate the rich history of NIH. For more information, go to https://history.nih.gov.

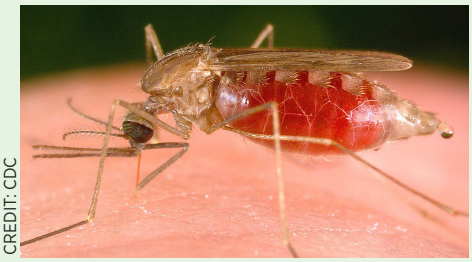
Don't Miss the Next Pittman Lecture

The Wednesday Afternoon Lecture Series has an annual lecture in honor of Margaret Pittman. It is given by a researcher dedicated to advancing and improving the careers of women scientists. Since 1994 when this annual lecture began, every speaker has exemplified the intelligence, scientific excellence, and drive that made Pittman a leader as the first female laboratory chief at NIH. The next Pittman Lecture is scheduled for Wednesday, May 27, 2020, 3:00 p.m. to 4:00 p.m., in Masur Auditorium (Building 10) and will be given by Eve J. Higginbotham, S.M., M.D., Perelman School of Medicine, University of Pennsylvania. (Note: There's a possibility that the lecture could be rescheduled.)

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNIH: Foundation for the NIH
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

Intramural Research Briefs



CREDIT: CDC

Mosquitoes of the genus Anopheles can transmit *Plasmodium falciparum*, the microscopic parasite that causes the disease.

NIAID: FINDING WAYS TO BEAT MALARIA

There's no effective vaccine against malaria, the mosquito-borne disease that affects over 200 million people each year and causes more than 400,000 deaths annually in Africa alone. Mosquitoes of the genus Anopheles can transmit *Plasmodium falciparum*, the microscopic parasite that causes the disease. Children may contract malaria dozens of times before developing immunity in their teens.

Until now, no one understood what gave malaria the strength to evade the immune system. Now NIAID researchers and their international collaborators may have a clue. They found that by altering a single nucleotide in a gene that codes for one transcription factor, *P. falciparum* was much less able to escape the immune systems of mouse models. The researchers suggest that further exploring these genes may help elucidate a target for experimental therapeutics or even a preventative vaccine against malaria.

To watch a video interview with the NIAID researchers who conducted the study, go to https://www.niaid.nih.gov/news-events/malaria-video-snip. (NIH authors: M. Akkaya, A. Bansal, P.W. Sheehan, M. Pena, A. Molina-Cruz, C.K. Cimperman, C.-F. Qi, T. Yazew, D. Sturdevant, S.L. Anzick, G. Thiruvengadam, L.H. Miller, and S.K. Pierce, *Sci Adv* **6**:eaaw6957, 2020; DOI:10.1126/sciadv.aaw6957)

NIEHS: JOINT IMPACT OF PHTHALATE EXPOSURE AND STRESSFUL LIFE EVENTS ON PRETERM BIRTH

Exposure to phthalates and stressful life events in pregnancy have each been associated with preterm birth (PTB), but no study has examined the joint impact of both. NIEHS researchers and collaborators observed an association between the urinary phthalate metabolites concentrations and PTB that was modified by whether a mother was exposed to one or more psychosocial stressors (such as job loss, serious illness, or family death) during pregnancy. Phthalates are chemicals used in personal-care products and plastics. In the study, the researchers used data from The Infant Development and the Environment Study—a prospective birth cohort conducted at four U.S. sites (n=783)—to examine urinary phthalate metabolite concentrations in samples collected from women during their pregnancy. Mothers reported their exposure to stressful life events in each trimester in a questionnaire administered in the third trimester. Additional research to understand the joint impacts of chemical and nonchemical exposures, with an emphasis on timing of exposure, is needed to advance the state of the science on how the environment influences pregnancy. (NIH authors: K.K. Ferguson and E.M. Rosen, *Environ Int* **133**:Part B, 2019; DOI:10.1016/j.envint.2019.105254)

NICHD: PERSISTENT ORGANIC POLLUTANTS IN MATERNAL BLOOD LINKED TO SMALLER FETAL SIZE

Pregnant women exposed to persistent organic pollutants, or POPs, had slightly smaller fetuses than women who hadn't been exposed to these chemicals, according to an analysis of ultrasound scans by NICHD researchers and others. The findings suggest that the chemicals, which are no longer produced in the United States but persist in the environment, may have lasting health effects even at low concentrations. POP chemicals were once used in agriculture (including the pesticide DDT), disease control, manufacturing, and industrial processes. (NIH authors: M. Ouidir, G.M. Buck Louis, J. Kanner, K.L. Grantz, C. Zhang, R. Sundaram, F. Tekola-Ayele, and P. Mendola, *JAMA Pediatr*, 2019; DOI:10.1001/jamapediatrics.2019.5104)

NHGRI, NIAMS, CC, NHLBI: NEW AUTOINFLAMMATORY DISEASE

Over the past 20 years, three families have been unsuspectingly linked by an unknown illness. NHGRI scientific director **Daniel Kastner**, a pioneer in the field of autoinflammatory diseases, and his team discovered the cause of the illness: cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome, which has symptoms including fevers, swollen lymph nodes, severe abdominal pain, gastrointestinal problems, headaches and, in some cases, abnormally enlarged spleen and liver.

The researchers sequenced gene regions and discovered only one gene—*RIPK1*—to be consistently different in all patients. Each affected person had one mutant and one normal copy of the gene, while the unaffected family members had two normal copies of the gene. The *RIPK1* gene encodes for a protein that is involved in the body's response to inflammation and programmed cell death. Cutting *RIPK1* is crucial to controlling cell death and inflammation.

Tocilizumab, which suppresses the immune system, reduced the severity and frequency of CRIA syndrome symptoms in five of seven patients. Researchers are now trying to understand the detailed molecular mechanisms. (NIH authors: S.E. Boyden, G.P. Pinto-M.J. Lenardo, M. Boehm, S.D. Rosenzweig, M. Gadina, D.L. Kastner, and many more, *Nature* **577**:103–108, 2020; DOI: 10.1038/s41586-019-1828-5)

Read more briefs and longer versions of these at: https://irp.nih.gov/catalyst/v28i2/research-briefs.

MERS

CONTINUED FROM PAGE 1

"The finding is very significant because people diagnosed with MERS-CoV develop severe respiratory disease, and one out of three do not survive. Therefore, an effective treatment could make a difference in disease outcome in MERS patients if treated early after diagnosis."

In the study, one group of animals, treated with the drug 24 hours before the virus was introduced, developed no clinical signs of infection. A second group, treated 12 hours after being infected, showed less severe disease than the control group.

"I was worried that a treatment given after infection would not have enough time to limit virus replication," said de Wit. "But we still saw a positive effect of therapeutic remdesivir treatment…and a reduction in damage to the lungs."

The World Health Organization has classified MERS-CoV, which was first discovered in Saudi Arabia in 2012, as a disease with the potential to cause epidemics. Therefore, there is an urgent need for the development of effective antivirals for its treatment and prevention. Remdesivir has previously shown efficacy in the treatment of Ebola virus in monkeys and the severe acute respiratory syndrome coronavirus (SARS-CoV) in mice.

The scientists indicate that the promising study results support additional clinical trials of remdesivir for MERS-CoV and COVID-19. At least two clinical trials of remdesivir for COVID-19 are underway in China, and other patients with COVID-19 infection have received the drug under a compassionate-use protocol. ●

(NIH authors: E. de Wit, F. Feldmann, J. Cronin, T. Thomas, D. Scott, and H. Feldmann, *Proc Natl Acad Sci USA*, 2019; DOI:10.1073/pnas.1922083117)

Highlights of Other Coronavirus Research

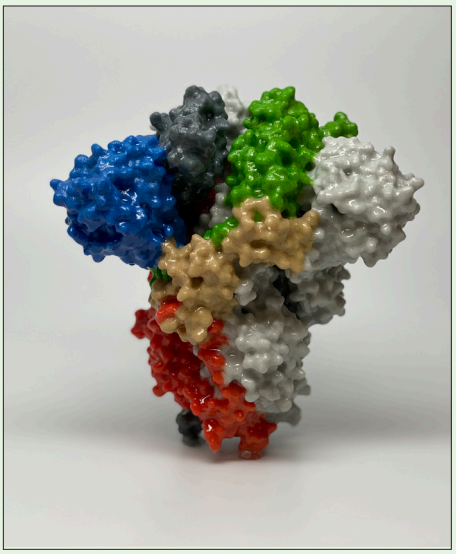
When the new coronavirus disease (COVID-19)—caused by the novel coronavirus severe acute respiratory syndrome coronavirus (SARS-CoV-2)—was first detected in December 2019 in Wuhan, Hubei Province, China, NIAID intramural and extramural scientists mobilized quickly to study the virus. Key areas of investigation include conducting basic research on its origins and how it causes disease, and developing animal study models, new treatments, and vaccines. For more information on the coronavirus, go to https://www.nih.gov/health-information/coronavirus.

COVID-19 A REMINDER OF THE CHALLENGE OF EMERGING INFECTIOUS DISEASES

In a *New England Journal of Medicine* commentary, NIAID Director **Anthony S. Fauci**, NIAID Deputy Director for Clinical Research and Special Projects **H. Clifford Lane**, and CDC Director Robert R. Redfield shared their observations about COVID-19. They pointed to the many research efforts now underway including numerous vaccine candidates proceeding toward early-stage clinical trials as well as clinical trials already underway to test candidate therapeutics, including an NIAID-sponsored trial of the experimental antiviral drug remdesivir that began enrolling participants on February 21, 2020. (A.S. Fauci, H.C. Lane, and R.R. Redfield, *N Engl J Med*, 2020; DOI:10.1056/NEJMp2002387)

NIH CLINICAL TRIAL OF REMDESIVIR TO TREAT COVID-19 BEGINS

In February 2020, a randomized, controlled clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnosed with COVID-19 has begun at the University of Nebraska Medical Center's biocontainment unit (Omaha, Nebraska). NIAID is the trial's regulatory sponsor. This is the first clinical trial in the United States to evaluate an experimental treatment for COVID-19. The first participant is an American who was repatriated after being quarantined on the *Diamond Princess* cruise ship in Japan. For more information go to https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins.



CREDIT: NIAID

3D print of a spike protein on the surface of the novel coronavirus, SARS-CoV-2. Spike proteins cover the surface of SARS-CoV-2 and enable the virus to enter and infect human cells.

STRUCTURAL BIOLOGY POINTS WAY TO CORONAVIRUS VACCINE

Excerpts from the NIH Director's Blog (March 3, 2020; https://directorsblog.nih.gov)

NIH-funded researchers including **Jason McLellan**, an alumnus of the NIAID's Vaccine Research Center (VRC) and now at the University of Texas at Austin, have been studying coronaviruses in collaboration with NIAID investigators for years. McLellan's group recently confirmed that the spike protein on the the new coronavirus is similar to that of its close relative, the SARS virus, but it binds to human cells more tightly, which may help to explain why the new coronavirus appears to spread more easily from person to person, mainly by respiratory transmission. (NIH authors: K.S. Corbett, O. Abiona, B.S. Graham, and J.S. McLellan (NIH alum), *Science* pii:eabb2507, 2020; DOI:10.1126/science.abb2507)

Laskers

CONTINUED FROM PAGE 1

phase, successful scholars either remain as tenure-track investigators in the intramural program, or receive up to three years of NIH support for their research at an extramural research facility. The program's first two scholars (in 2012)—**Nehal Mehta** (National Heart, Blood, and Lung Institute) and **Jessica Gill** (National Institute of Nursing Research)—chose to remain at NIH and have been tenured.

Read more about the people who became Lasker Scholars in 2019.

Sean Agbor-Enoh, M.D., Ph.D.
Lasker Clinical Research Scholar, Laboratory of Applied Precision Omics, National Heart, Lung, and Blood Institute

Sean Agbor-Enoh is developing genomic methods for the early detection and treatment of lung-transplant rejection. His method—which can detect rejection two to three months earlier than the current invasive process of taking a lung-tissue biopsy after rejection has begun—involves a simple blood test that measures cell-free DNA in the bloodstream. "My hope is to bring innovative and cutting-edge approaches to improve survival after lung transplantation," he said. He received his M.D. from the University of Yaoundé (Yaoundé, Cameroon) and a Ph.D. in molecular biology from Georgetown University (Washington, D.C.). He did a postdoctoral fellowship at Georgetown University Medical Center; a residency and chief residency in internal medicine at Johns Hopkins Bayview Medical Center (Baltimore); a fellowship in critical care medicine at the NIH Clinical Center; and a fellowship in pulmonary medicine at Johns Hopkins Hospital (Baltimore). Outside of work he loves to explore nature's treasures with his wife and four children, who range in age from 2 to 17.

Paule V. Joseph, Ph.D., R.N., F.N.P.
Lasker Clinical Research Scholar and NIH Distinguished Scholar, Sensory Science and Metabolism Unit, Biobehavioral Branch, National Institute of Nursing Research; joint appointment at the National Institute on Alcohol Abuse and Alcoholism

Paule V. Joseph is conducting preclinical, clinical, and translational studies to improve the diagnosis, prevention, and management of chemosensory disorders and symptoms—in chronic conditions such as obesity and type 2 diabetes—by examining the role that smell and taste play in those conditions. She is also exploring how the neurological mechanisms underlying taste and smell might be different in individuals with alcohol and substance-use disorders. "The opportunities [at NIH]—especially as an underrepresented minority in science—are unparalleled," she said. "For a junior scientist like me to be able to collaborate with people like **Kevin Hall** [a pioneer in metabolism research at the National Institute of Diabetes and Digestive and Kidney Diseases], **Nora Volkow** [director of the National Institute on Drug Abuse and world pioneer in neuroimaging in addiction], and **Gary Gibbon**s [Director of the National Heart, Lung, and Blood Institute and world-renowned expert in cardiovascular disease], it's a dream come true." After receiving her M.S. in a family nurse practitioner program from Pace University (New York) and a Ph.D. in nursing and genomics from the University of Pennsylvania (Philadelphia), Joseph did a postdoctoral fellowship in NINR. Outside of work, she enjoys spending time with her parents and her younger sister and doing humanitarian work around the world.

Joanna Klubo-Gwiezdzinska, M.D., Ph.D., M.H.Sc.
Lasker Clinical Research Scholar and Acting Section Chief, Thyroid Tumors and Functional Thyroid Disorders, Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Joanna Klubo-Gwiezdzinska focuses on clinical and translational studies to find optimal options for the diagnosis and treatment of thyroid nodules and thyroid cancer. Her work includes identifying the

genetic background of thyroid tumors, novel molecular targets for therapy of thyroid cancer, and a comprehensive analysis of cross-talk between cancer signaling pathways and metabolism. Her lab discovered that the antidiabetes drug metformin can slow the growth of thyroid tumors and other cancers that express high amounts of a certain protein in the mitochondria. She received an M.H.Sc. from Duke University (Durham, North Carolina) and an M.D. and Ph.D. in endocrinology and thyroid cancer from Collegium Medicum, Nicolaus Copernicus University (Torun, Poland). She completed a residency in internal medicine and endocrinology at Nicolaus Copernicus University Hospital (Bydgoszcz, Poland); a postdoctoral fellowship in thyroid cancer at Georgetown University–Medstar Research Institute (Washington D.C.); a residency in internal medicine at Washington Hospital Center–Georgetown University (Washington, D.C.); and a clinical fellowship in endocrinology at NIDDK. Outside of work, she enjoys going to the opera in New York and the Kennedy Center in Washington, D.C.; spending family time with her husband and son, particularly walking their dog together; and reading inspiring biographies.

To learn more about the Lasker Clinical Research Scholars Program, which honors the contributions of Mary and Albert Lasker to the NIH and to the overall biomedical community and the 23 other scholars who have been profiled in the past, go to https://www.nih.gov/research-training/lasker-clinical-research-scholars.

Nirali N. Shah, M.D., M.H.Sc.
Lasker Clinical Research Scholar, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute

Nirali N. Shah is testing novel immunotherapeutic approaches to treat high-risk hematologic malignancies in children, adolescents, and young adults. Her research focuses on chimeric antigen receptor (CAR) T-cell-based strategies and other antibody-based therapies. She leads clinical trials to treat relapsed and refractory pediatric acute lymphoblastic leukemia; serves as an associate investigator on several transplant trials with patients who have primary immunodeficiency; and, in collaboration with investigators in the National Institute of Allergy and Infectious Diseases, is leading an effort on transplantation for children with DOCK8 immunodeficiency syndrome. She received her M.H.Sc. in clinical research from Duke University (Durham, North Carolina)–National Institutes of Health and her M.D. from the University of Illinois, College of Medicine (Chicago). She did an internal medicine residency at Harvard Combined Internal Medicine–Pediatrics Residency Program (Boston); was a fellow in pediatric hematology-oncology at the joint National Cancer Institute–Johns Hopkins Hospital (Baltimore) training program; and served as clinical fellow and staff clinician in NCI's Pediatric Oncology Branch. Outside of work, she is kept busy with three children ages 4 to 11—balancing work, homework, after-school activities, and "having a bossy baby make us all sing *Frozen* songs."

David Takeda, M.D., Ph.D.
Lasker Clinical Research Scholar, Laboratory of Genitourinary Cancer Pathogenesis, Center for Cancer Research, National Cancer Institute

David Takeda uses functional genomic approaches to advance the understanding of prostate cancer in order to provide new insights into potential therapies. He is interested in how prostate cancer becomes resistant to therapy. Using a combination of functional genome editing and epigenomic profiling, his lab recently described an enhancer of the androgen receptor that is activated and amplified in 80% of metastatic castration-resistant prostate cancers. He earned an M.M.Sc. in biomedical informatics, an M.D., and a Ph.D. in medicine and experimental pathology from Harvard Medical School (Boston). He did a residency in internal medicine at Brigham and Women's Hospital (Boston) and a hematology-oncology fellowship at Dana-Farber Cancer Institute (Boston). NIH is "one of the few places where they encourage and support you to come do high-risk, high-impact projects," he said. "I think being able to invest in something like that really attracted me and the fact that the [NIH Clinical Center] is entirely dedicated to research." Outside activities include following Boston sports (when he lived in Boston); now he's on the lookout for new hobbies.

Flow Cytometry Interest Group

Highlights from Winter Meeting 2019

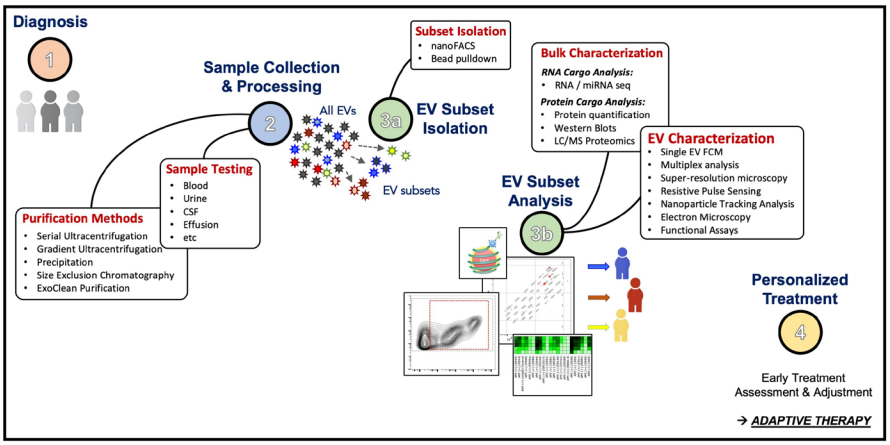
BY RAFAEL VILLASMIL, NEI

Flow cytometry technology, which is constantly evolving, simultaneously analyzes physical and chemical characteristics of thousands of cells (such as blood or bone-marrow cells) as they move through fluid and are excited by a light source. By identifying and quantifying the cells of the immune system, flow-cytometry studies can characterize hematological malignancies and evaluate primary immune-deficiency disorders. Recent advances have enhanced the role of flow cytometry as an important method for characterizing immune function.

Some 150 attendees at the NIH Flow Cytometry Interest Group's (FCIG's) annual meeting (held on December 12, 2019, in Lipsett Amphitheater, Building 10) were eager to hear the latest research advances in the flow-cytometry field. "The meeting was a good educational event on the technological advances of [flow cytometry] and its applications, and an occasion for sound scientific exchange," said **Raul C. Braylan**, senior clinician and chief of the Hematology Laboratory (NIH Clinical Center). It "offered a unique opportunity to learn technical advances of this very useful methodology and its importance in the evaluation and treatment of critical diseases such as immunodeficiencies and hematologic malignancy."

Nine experts gave presentations including four NIH intramural researchers and five guests from biomedical companies.

Siak Jyh Kuen Jay, a visiting scholar at the National Eye Institute (NEI), presented his work on microorganisms that are that are living on the eye and described how he uses flow cytometry to monitor changes in the immune system.



TRANSLATIONAL NANOBIOLOGY SECTION, NCI

Translational Nanobiology Section clinical pipeline development

Flow cytometry can be used to analyze nanoscale extracellular vesicles (EVs) that have been released by tumor cells, immune cells, and irradiated tissue in patients with immunodeficiencies or hematologic malignancies. Shown: An illustration depicting the Translational Nanobiology Section's clinical pipeline, developed to analyze EVs as prognostic biomarkers of cancer therapies. Using EV data may lead to a better understanding of tumor and immune biology and could contribute to the development of personalized treatments.

For example, cells collected from patients who have the autoinflammatory disease cryopyrin-associated periodic syndrome are prepared for cytometry and single-cell RNA sequencing. Jay discussed bioinformatic aspects of data analysis and plans for future use of oligonucleotide conjugates. **Sergio Rosenzweig**, chief of the Clinical Center's Immunology Service, described how flow cytometry is used to diagnose immunodeficiencies by identifying and quantifying immune cells such as in blood, bone marrow, and other body fluids.

Flow cytometry is also used to characterize the quality of the chimeric antigen receptor T cells (CAR-T) and to measure the effectiveness of CAR-T therapy. National Cancer Institute (NCI) Investigator **James Kochenderfer** provided an update on CAR-T therapy clinical trials, which included a long-term follow-up of safety and efficacy for all subjects. Postdoctoral Fellow **Joshua Welsh** (Translational Nanobiology Section in NCI's Laboratory of Pathology) talked about how flow cytometry is used to analyze extracellular vesicles (EVs, which are membrane-bound packages secreted by eukaryotic cells). Tumor cells, immune cells, and irradiated tissue release nanoscale EVs. Using EV data may lead to a better understanding of tumor and immune biology.

Five guest speakers from biomedical companies gave presentations. One spoke about new instrumentation and latest version of software used to analyze flow-cytometry data. Another presented innovative developments on time-resolved cytometry. Others described the spectral analysis technology in an instrument; an innovative fluidics system that generates several sample streams and processes samples at a rate 100 times as fast as typical cytometers can; and new software that relies on machine learning and deep-learning to automatically classify cells. ●

The FCIG provides central information for basic and clinical investigators doing flow and image cytometry. All biomedical researchers with an interest in cytometry (regardless of institutional affiliation) are welcome. Visit https://oir.nih.gov/sigs/flow-cytometry-interest-group to learn more about this group and for instructions on joining the LISTSERV email list.

New SIG: Interspecific Modeling

NIH researchers use a variety of animal models including mice (*Mus musculus*), fruit flies (*Drosophila melanogaster*), zebrafish (*Danio rerio*), chicken embryos (*Gallus gallus domesticus*), frogs (*Xenopus laevis*), and flatworms (*Schmidtea mediterranea*) to study diseases, physiology, and other mechanisms. Animals represent humans well because they are evolutionarily related. Mice and humans have almost the same embryogenesis process. Fruit flies and humans share the same neural-transmission physiology. Fish and humans have very similar blood-vessel formation. From the perspective of evolution, we and animals are all cousins. Scientists commonly use the principle "what is conserved in evolution must be important" to identify key genes, functions, and mechanisms of biological processes.

The new Interspecific Modeling Interest Group (ISMIG) promotes collaboration among researchers who work on developmental and disease models of different species via 1) technical expertise exchange; 2) comparative analysis of multispecies datasets; 3) functional cross-validation; and 4) cross-validation with clinical sets. **Kent Hunter** (acting chief, Laboratory of Cancer Biology and Genetics, NCI) is the advisor for the ISMIG. The ISMIG will organize workshops to teach technologies for interspecific modeling and invite potential collaborators to participate in panel discussions.

Everyone is welcome to attend ISMIG's activities and take part in the brainstorming, exchange of information, and discussions. For more information, go to https://oir.nih.gov/sigs/interspecific-modeling-interest-group. To join the LISTSERV email list and receive event notifications of meetings and events, please contact the chair, **Chi-Ping Day** (daychi@mail.nih.gov).

L. ALEXANDER/THINKSTOCK.COM

Scientific Interest Groups (SIGs)

NIH Scientific Interest Groups (SIGs) are assemblies of scientists with common research interests. These groups engage with their members via a LISTSERV; sponsor symposia, poster sessions and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director of Intramural Research; provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series. Most of these groups welcome interested non-NIH scientists.

For more information about SIGs and a full list of them, go to https://oir.nih.gov/sigs.

PARTIAL LIST OF SIGS

3D Printing and Modeling
Adherence Research Network
Antibody
Artificial Intelligence
Bioethics
Bioinformatics
Biomarkers in Pediatric Therapeutics
Biomedical Instrumentation Development
Breastfeeding and Human Lactation
Cell Cycle
Chemistry
Chronobiology and Sleep
Circulating Nucleic Acids/Liquid Biopsy
Cytokine
Data Science in Biomedicine
Decode Chromatin
Deep Learning in Biomedical Imaging
Developmental Biology
Natural Products
Neuro Infectious Disease
Neurobiology
Neurodevelopmental Disorders
Neuron-Glia Interactions
Neuropharmacology
Neuroscience Clinical Trials
Noninvasive Brain Stimulation
Nurse Practitioner/Physician Assistants
Outcomes and Effectiveness Research
PAIN
Patent Law & Technology Transfer
Pediatric Clinical Research and Outcomes
PET (Positron Emission Tomography)
Single-Cell Genomics
Special Populations Research Forum
Statistics
Stem Cell
Stigma
Structural Biology
Systems Biology
Text Mining and Natural Language Processing
TGF-beta Superfamily
Tobacco and Nicotine Research
Virology
Virtual and Augmented Reality
Washington Area Yeast Club

Improving End-of-Life Care for Dying Children

NIH Researchers Develop an Illustrated Storybook

BY SOFIYA HUPALO, NIGMS

It's devastating when a child is diagnosed with a fatal illness. As parents struggle to absorb complex medical information and make important decisions, they may agonize over how to discuss the illness with their child. Fortunately, palliative-care specialists—who provide holistic care focused on physical, emotional, social, and spiritual issues—can support the families and help them communicate difficult news in culturally informed and developmentally appropriate ways. Open communication about treatments and prognoses can alleviate the anxiety and depression that sick children experience.

Dedicated to improving this communication, palliative-care researchers **Lori Wiener** and **Meaghann Weaver** have written a children's storybook—*The Gift of Gerbert's Feathers*—to help families and caregivers of children with a terminal illness talk about progressive illness, engage children in decision making, and reduce the stigma surrounding the topic of death. The book, written for children 6 to 12 years old, portrays a young gosling who knows he is too weak to endure the next migration. Gerbert lovingly escorts children and families through the seasons and life cycles. The story draws parallels to separation of loved ones and togetherness in times of grief, and it acknowledges changes to the body. It allows children to receive the comfort of conversations in a life-affirming way.

"Books can provide language parents may need to explain and have conversations that are gentle, nonthreatening, and respectful of the child," said Wiener, who is a social worker and heads the Psychosocial Support and Research Program at the National Cancer Institute. Weaver, a former fellow in the NIH Clinical Center's Pain and Palliative Care service, is chief of the Division of Palliative Care at Children's Hospital and Medical Center in Omaha, Nebraska.

The Gift of Gerbert's Feathers is intended to address a shortage of children's literature that helps children reflect on death and cope with end-of-life issues. Wiener and Weaver identified the gap in a 2017 paper (*J Palliat Med* **20:**548–559, 2017) and have noted the scarcity of pediatric palliative-care resources in general. In a recent study, Wiener estimated that fewer than 20% of pediatric-cancer patients who were enrolled on a phase 1 study received palliative care (*Pediatr Blood Cancer* **66:**e27771, 2019). To improve the consistency of palliative-care services, Wiener and colleagues developed evidence-based standards of psychosocial care for pediatric-cancer patients (*Pediatr Blood Cancer* **62:**S419–S424, 2015). These standards push for integration of palliative care earlier in disease treatment even before there's been a terminal diagnosis. Wiener also advocates for implementing a system that would "trigger" the automatic consideration of palliative-care consults for certain diagnoses (*J Palliat Med* **21:**452–462, 2018).

In their book, Wiener and Weaver opted for a story of shared human values that is not specific to any one culture or religion. "We thought about identifying an animal that would represent concepts of family love," said Wiener. "When a goose is down, another stays until it gets better or dies. We felt the idea of flight, and the visual image of the V-formation in the sky representing togetherness of families, would be comforting."

The Gift of Gerbert's Feathers (now available in the FAES Bookstore in Building 10) also includes online resources such as notes for parents and pictures of feathers that can be downloaded for children to draw on. Wiener and Weaver hopes it will be used in hospitals and pediatric hospices and will help providers and families broach uncomfortable topics in ways that are respectful of children's cognitive and emotional capabilities. ●

Blood Test May Point to Timing of Breast-Cancer Diagnosis

BY MARLA BROADFOOT, NIEHS

Shifts in the populations of different types of leukocytes, or white-blood cells, in a woman's bloodstream may signal a later diagnosis of breast cancer according to a study by researchers at the National Institute of Environmental Health Sciences (NIEHS) in Durham, North Carolina. The scientists found that women with higher proportions of B cells experienced a higher risk of breast cancer years later. It also found that women with lower concentrations of monocytes had a higher risk for developing breast cancer in the near term.

"This finding opens up a new avenue for looking at breast-cancer risk," said senior study author **Jack Taylor**, head of the NIEHS Molecular and Genetic Epidemiology Group. "Although we know a lot about how the immune system interacts with a tumor, this is one of the first studies to detail changes in circulating immune cells in the months and years before diagnosis."

Refining risk

The new study is one of a slew of recent findings to emerge from the Sister Study, an NIEHS research initiative that enrolled women who have a biological sister with breast cancer but did not have the disease themselves.

CREDIT (BOTH): STEVE MCCAW, NIEHS

Jack Taylor Jacob Kresovich

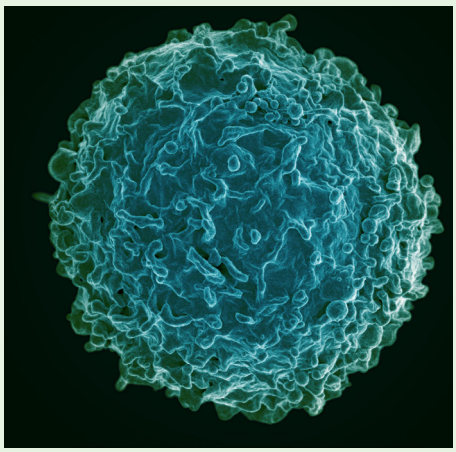
Jacob Kresovich, a postdoctoral fellow in Taylor's lab, said previous research indicated that women with higher numbers of total white blood cells may be at higher risk of breast cancer. "But white blood cells are really diverse and can be further classified based on their subtype and overall function," said Kresovich, who is lead author of the paper. "We believed we could refine some of these associations by looking at the relationship between specific types of cells and the incidence of breast cancer."

Timing is everything

From 53,000 women enrolled in the Sister Study, the researchers selected 2,774 participants to include in this analysis. They used a sophisticated technique called methylation cytometry to estimate the proportions of six different subtypes of white blood cells in each of the women's blood samples.

The researchers found that the composition of white-blood-cell subtypes changed in the years leading up to a breast-cancer diagnosis. The proportion of monocytes, a type of white blood cell that can be activated in the presence of growing tumors, decreased in the bloodstream of women who were diagnosed with breast cancer in the year after blood draw. "Monocytes may be recruited to cancer tissue, which would explain why there would be a drop in blood shortly before the diagnosis of cancer," said Kresovich.

In contrast, the proportion of B cells, which produce antibodies to fight infection and disease, was higher in women who were diagnosed four or more years later. Taylor said although the shift in the profile of these cells seems to be associated with tumors arising in the distant future, this finding needs confirmation.



CREDIT: NIAID

Colorized scanning electron micrograph of a B cell from a human donor. The profile of B cells and other white blood cells in a woman's bloodstream may indicate future risk of developing breast cancer.

"Next, we want to look more broadly at the information we can extract from these profiles and improve our predictions of who will develop cancer," said Taylor. "We would also like to understand whether certain health behaviors alter these profiles."●

(NIH authors: J.K. Kresovich, K.M. O'Brien, Z. Xu, C.R. Weinberg, D.P. Sandler, and J.A. Taylor; *JAMA Netw Open* **3:**e1919536, 2020; DOI:10.1001/jamanetworkopen.2019.19536)

Adapted from an article that appeared in the February 2020 issue of *Environmental Factor*: https://factor.niehs.nih.gov/2020/2/papers/breast-cancer/index.htm.

Recently Tenured


J. ROBERT HOGG, NHLBI


ANDREW D. JOHNSON, NHLBI


VANJA LAZAREVIC, NCI-CCR


VIJAY RAMCHANDANI, NIAAA


SERGIO DAMIÁN ROSENZWEIG, NIH CLINICAL CENTER

J. ROBERT HOGG, PH.D., NHLBI

Senior Investigator, Laboratory of Ribonucleoprotein Biochemistry, National Heart, Lung, and Blood Institute

Education: Haverford College, Haverford, Pennsylvania (B.S in biology with a concentration in biochemistry); University of California at Berkeley, Berkeley, California (Ph.D. in molecular and cell biology)

Training: Postdoctoral training, Department of Biochemistry and Molecular Biophysics, Columbia University–Howard Hughes Medical Institute (New York)

Came to NIH: In 2011 as an Earl Stadtman Investigator

Outside interests: Traveling; photography; exploring DC-area restaurants; watching soccer (Sunderland in England, D.C. United in the USA)

Website: https://irp.nih.gov/pi/robert-hogg

Research interests: My lab studies how cells use RNA-protein interactions to regulate gene expression. In particular, my focus has been on quality control: How does a cell distinguish a beneficial messenger RNA (mRNA) from a deleterious one?

Our favorite system is the nonsense-mediated mRNA decay pathway, which has the difficult task of determining when an mRNA might encode a truncated, and therefore potentially dangerous, protein.

When I joined the field, a lot of great work identifying proteins that promote mRNA decay had been done. So we decided to do the opposite and look for proteins that can shield specific mRNAs from degradation.

We found that two related proteins, polypyrimidine tract-binding protein type 1 (PTBP1) and heterogeneous nuclear ribonucleoprotein L–like protein (hnRNPL), effectively "mark" certain RNAs as beneficial, ensuring that they are not targeted by the RNA-decay machinery.

We think that this mechanism generally allows cells to maintain tight control over gene expression. We were surprised to discover, however, that protection of certain dangerous mRNAs can also promote the development of B-cell lymphoma.

These findings have given us a new perspective and toolkit to understand how RNA decay is regulated in human health and disease. (*EMBO J* **38:**pii:e99128, 2019).

ANDREW D. JOHNSON, PH.D., NHLBI

Senior Investigator and Head, Biomedical Informatics, Population Sciences Branch, National Heart, Lung, and Blood Institute; senior investigator, The Framingham Heart Study, NHLBI (Framingham, Massachusetts)

Education: Pennsylvania State University, University Park, Pennsylvania (B.S. in vertebrate physiology); Ohio State University, Columbus, Ohio (Ph.D. in biomedical sciences)

Training: Postdoctoral fellow, Framingham Heart Study, NHLBI

Came to NIH: In 2007 for training; became NHLBI tenure-track investigator in 2012

Outside interests: Spending time with family and friends; doing puzzles; playing boardgames and pinball; juggling; cycling; skiing; playing "old man's softball"

Website: https://irp.nih.gov/pi/andrew-johnson

Research interests: Platelets are a critical cell type that stops bleeding. Their reactivity, however, is double-edged in that they contribute to cardiovascular disease (heart attacks, clots, and strokes).

My main interests include research on platelet genetics and epidemiology. My laboratory uses population-based

S. CENK SAHINALP, NCI-CCR

approaches to understand how platelets vary across people and whether that variation contributes to disease. I have led the largest studies ever conducted on the genetics of platelet numbers in circulation and how platelets react to stimuli. In these studies my lab found dozens of new genes contributing to platelet variation and cardiovascular disease.

A major goal of the lab is to apply these gene findings to developing potential new drug or lifestyle interventions, or to better personalize antiplatelet treatments in cardiovascular disease. Because smaller studies and basic cell science have suggested that platelets may also play important roles in cancer, diabetes, inflammation, and infectious disease, we also work hard to expand large population studies of platelet measurements to better understand other roles for platelets beyond cardiovascular disease.

If you have been recently tenured, the *NIH Catalyst* will be in touch soon to include you on these pages.

VANJA LAZAREVIC, PH.D., NCI-CCR

Senior Investigator, Immunopathogenesis Unit, Experimental Immunology Branch, Center for Cancer Research, National Cancer Institute

Education: University of Nottingham, Nottingham, United Kingdom (B.S. in microbiology); University of Pittsburgh, Pittsburgh (Ph.D. in molecular virology and microbiology)

Training: Postdoctoral fellow in immunology, Harvard School of Public Health (Boston)

Before coming to NIH: Research scientist, Harvard School of Public Health

Came to NIH: In 2011, tenure-track investigator, Experimental Immunology Branch, NCI

Outside interests: Swimming; traveling; gardening

Website: https://irp.nih.gov/pi/vanja-lazarevic

Research interests: My laboratory is striving to understand how transcription factors and their downstream targets drive the process of autoimmune inflammation in such diseases as multiple sclerosis and rheumatoid arthritis. Dysregulated gene expression due to aberrant activation or inactivation of transcription factors results in the sustained and elevated expression of immune-related genes and leads to chronic inflammation.

In multiple sclerosis, immune cells attack the protective myelin sheath that wraps around neurons in the brain, spinal cord, and optic nerves. Relentless and unchecked immune-system activation in the central nervous system (CNS) leads to irreversible neuronal damage and, ultimately, paralysis.

Most of our understanding of the pathogenesis of multiple sclerosis comes from investigations using an experimental autoimmune encephalomyelitis (EAE) mouse model. In this model, both CD4+ T-helper 1 (Th1) and Th17 cells contribute to the pathogenesis of the disease. Our overall goal is to understand how transcription factors and their downstream targets affect CD4+ T-helper cell differentiation and effector function in the context of autoimmune diseases using this EAE animal model.

Our research has yielded new insights into the T-box transcription factor TBX21 (T-bet)–mediated mechanisms that fuel chronic inflammation in the CNS. We have identified cellular pathways that could be targets of future therapeutic interventions for immune-mediated disorders.

We have demonstrated that the pathogenesis of autoimmune neuroinflammation is dependent on T-bet expression in two immune cell subsets: autoantigen-specific CD4+ T cells and the natural cytotoxicity triggering receptor 1–positive (NKp46+) innate lymphoid cells (ILCs). Targeting T-bet in either subset was sufficient to protect the mice from autoimmunity (*Immunity* **40:**355–366, 2014). These findings suggest that T-bet-targeted therapies hold great potential in the treatment of CNS autoimmunity. The most significant revelation from these studies was the demonstration that T-bet-dependent NKp46+ ILCs could overthrow the immune-privileged status of the CNS by acting as the gatekeepers to autoreactive CD4+ T cells (*Nat Immunol* **18:**1117–1127, 2017).

Although a growing body of literature is focused on T-cell-specific functions of T-bet in the immune system, our findings exemplify how T-bet expression in the *innate* immune system is detrimental in the context of autoimmunity. Our study is also the first unequivocal demonstration of the direct involvement of ILCs in organ-specific autoimmunity.

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Recently Tenured

CONTINUED FROM PAGE 17

VIJAY RAMCHANDANI, PH.D., NIAAA

Senior Investigator and Chief, Section on Human Psychopharmacology, National Institute on Alcohol Abuse and Alcoholism

Education: K.M. Kundnani College of Pharmacy, Bombay University, Bombay, India (B.Pharm.Sc.); Medical College of Virginia–Virginia Commonwealth, Richmond, Virginia (Ph.D. in pharmacy and pharmaceutics)

Training: Visiting research associate, Department of Medicine/Division of Endocrinology and Metabolism, Indiana University School of Medicine (Indianapolis)

Before coming to NIH: Assistant scientist/assistant professor in the Department of Medicine and associate member of faculty of Indiana University Graduate School, Indiana University (Indianapolis)

Came to NIH: In 2003 as staff scientist; became tenure-track clinical investigator in 2010

Outside interests: Reading; listening to music; cooking

Website: https://irp.nih.gov/pi/vijay-ramchandani

Research interests: My lab studies alcohol-use disorder (AUD), which has a tremendous negative individual and global impact. Research on the clinical pharmacology of alcohol is necessary to explain how variability in alcohol response affects the risk of developing AUD. An improved understanding of the genetic, environmental, and neurobiological factors that affect alcohol response in humans could lead to the development of novel treatments.

We are using behavioral, neuroendocrine, electrophysiological, and functional-imaging measures to characterize the pharmacokinetics and pharmacodynamics of alcohol in humans. These studies, conducted in social and high-risk drinkers, enable the evaluation of genetic and environmental risk factors influencing the acute and adaptive responses to alcohol. We are also conducting studies to develop human laboratory paradigms that can be used to screen novel potential treatments for alcoholism for their ability to alter the pharmacological effects of alcohol and/or alcohol self-administration behavior.

Our lab, in collaboration with a colleague at the Indiana University School of Medicine, developed two pharmacokinetic model–based intravenous alcohol-administration paradigms for human research: 1) the alcohol clamp in which alcohol is administered intravenously and 2) computer-assisted self-infusion of ethanol. Both approaches provide exquisite control of brain-alcohol exposures that overcome the substantial (three- to fourfold) variability in exposures seen after oral alcohol administration. These paradigms provide a unique platform for studies evaluating the influence of risk factors including sex, age, drinking history, and genetic polymorphisms on alcohol responses and alcohol-consumption behavior in human laboratory studies.

We conducted a study—in collaboration with colleagues at the University of Louisville and Robley Rex Veterans Affairs Medical Center (Louisville, Kentucky)—that highlighted the relevance of drinking "too much too fast" as a potential marker of risk for alcohol-use disorder (*Am J Psychiatry* **174:**1094–1101, 2017). We used the intravenous alcohol self-administration paradigm in a sample of nondependent drinkers and demonstrated that the rate of consumption of alcohol was associated with measures of risk for alcohol-use disorder such as sex, family history of alcohol problems, impulsivity, and self-reported sensitivity to alcohol.

SERGIO DAMIÁN ROSENZWEIG, M.D., PH.D., NIH CLINICAL CENTER

Senior Investigator, Department of Laboratory Medicine, NIH Clinical Center

Education: School of Medicine, University of Buenos Aires, Buenos Aires, Argentina (M.D.); University of Buenos Aires (Ph.D. in Immunology)

Training: Residency in Pediatrics, National Pediatric Hospital J. P. Garrahan (Buenos Aires); fellow in Pediatric Immunology, National Pediatric Hospital J.P. Garrahan (Buenos Aires)

Before returning to NIH in 2009: Professor of Pediatrics, Microbiology and Immunology, School of Medicine, University of Buenos Aires

Came to NIH: In April–May 1999, as a guest researcher in the National Institute of Allergy and Infectious Diseases (NIAID); visiting scientist, Clinical Pathophysiology Section in NIAID's Laboratory of Host Defenses (LHD; 2000–2003); returned in 2009 as head, Infectious Diseases Susceptibility Unit, LHD; and director, NIAID's Primary Immunodeficiency Clinic; in 2013 became deputy chief of the NIH Clinical Center's Immunology Service, and chief in 2016.

Outside interests: Playing squash; traveling; following international politics; exploring and tasting ethnic foods

Website: https://irp.nih.gov/pi/sergio-rosenzweig

Research interests: I am a pediatrician and clinical immunologist with more than 25 years of experience in the field of primary immunodeficiency (PID). In our lab, we are studying the molecular and functional aspects underlying PID in people with a genetic susceptibility to mycobacteria and fungal infections (*J Allergy Clin Immunol* **133:**1134–1141,

2014); immune-dysregulation diseases in families with autoimmune or autoinflammatory diseases (*J Allergy Clin Immunol* **143:**1676–1687, 2019); and the role of glycosylation in susceptibility to infectious disease (*N Engl J Med* **370:**1615–1625, 2014).

We are also studying the IKAROS transcription factor family in PID (*N Engl J Med* **374:**1032–1043, 2016). We found that heterozygous mutations in the gene for IKAROS can be involved in the most severe forms of PID such as an autosomal dominant form of common variable immunodeficiency (CVID) that is associated with a striking decrease in B-cell numbers. This latter group of proteins, depending on the type of DNA mutation, can be involved in the most severe forms of PID (i.e., severe combined immunodeficiency or combined immunodeficiency) or the most common symptomatic form of PID (that is, common variable immunodeficiency); carriers of these variants can even be completely asymptomatic. The "how" and "why" this could happen (technically known as penetrance and expressivity of genetic diseases), will keep our lab busy for years to come.

Tune in to *Speaking of Science* (https://irp.nih.gov/podcast), an audio show featuring NIH intramural research program scientists who are working at the cutting edge of biomedicine.

S. CENK SAHINALP, PH.D., NCI-CCR

Senior Investigator, Cancer Data Science Laboratory, Center for Cancer Research, National Cancer Institute

Education: Bilkent University, Ankara, Turkey (B.S. in electrical engineering); University of Maryland, College Park, Maryland (Ph.D. in computer science)

Training: Postdoctoral fellow, Bell Labs (Murray Hill, New Jersey)

Before coming to NIH: Professor and associate chair, Computer Science, Indiana University Bloomington (Bloomington, Indiana); professor and Canada research chair, Simon Fraser University and Vancouver Prostate Centre (Vancouver, British Columbia, Canada)

Came to NIH: In 2019

Outside interests: Biking; playing tennis; skiing; traveling with family

Website: https://irp.nih.gov/pi/s-cenk-sahinalp

Research interests: In my research, I apply combinatorial algorithms to analyze cancer genome data. My lab's key focus is the discovery and interpretation of large-scale (especially structural) genomic and transcriptomic variants in tumor samples. Our algorithmic methods were the first that had the ability to handle novel insertions, deletions, inversions, and duplications in repetitive regions of the human genome.

In the past 15 years, my lab has produced many algorithmic tools for analyzing high-throughput sequencing data and in particular for discovering and interpreting large-scale genomic structural alterations in tumors. Our tools—such as VariationHunter, novelSeq and DeStruct—were the first algorithmic methods that could handle novel insertions, deletions, inversions, and duplications in human genomes.

My group has developed many other algorithmic and computational methods, including Cypiripi and Aldy, which can identify structurally variant genes such as those involved in drug metabolism. In addition, we contributed to the identification and quantification of transcriptomic aberrations such as gene fusions, genetic inversions, duplications, and deletions in cancer samples.

I have an additional interest in "algorithmic infrastructure" for genomics; this includes mapping (of reads from repetitive regions of the genome or those with high error rates); compressing genomic data; and secure and privacy-preserving computing with genomic data. Our mapping tools, mrFAST and mrsFAST, are among the best for multi-mapping (identifying all mapping loci for a given read). Similarly, our genomic data-compression methods have been leaders in both compression rate and speed. One recent method, called SkSES (Sketching algorithms for Secure Enclave-based genomic data analysis) is the first computational framework to perform secure and privacy-preserving collaborative genomic analysis (*bioRxiv*, 2018; DOI:10.1101/468355).

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PHOTOGRAPHIC MOMENT

President Trump Visits NIH to Discuss Coronavirus

On March 3, 2020, President Donald Trump visited NIH for a tour of the Vaccine Research Center (VRC), where research is underway to develop a safe and effective vaccine for the novel coronavirus. From left: NIH Director Francis Collins, NIAID Director Anthony Fauci, VRC Director John Mascola (behind Fauci), HHS Secretary Alex Azar, and President Trump. Read more at https://irp.nih.gov/catalyst/v28i2/photographic-moment.

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