

## CHASING VIRUS CHECKMATE Sullivan Describes Long-Range Science Match vs. Ebola

BY CARLA GARNETT

When the first Ebola vaccine to be tested in humans entered phase I clinical trials in fall 2014, it may have seemed like near-perfect timing. After all, West Africa was in the midst of the largest and deadliest outbreak of the virus since 1976, the Clinical Center had just successfully treated a survivor of the illness and many NIH'ers were still heavily engaged in all aspects of containing the epidemic. But time is relative. Vaccine researchers Dr. Nancy Sullivan and Dr. Julie Ledgerwood and their VRC colleagues already had nearly two decades of groundwork invested in



Dr. Nancy Sullivan gives the Chen lecture.

Ebola virus research and, as any investigator involved in it will tell you, crafting a vaccine is long-game science.

"I like to think of it like lightning chess," Sullivan said, "because the host and the

virus—almost irrespective of whatever the virus is—have this interplay where whatever the virus does, the host tries to quell that and then the virus in turn evolves to evade whatever the host is doing to clear the virus. With Ebola, that process is very quick because once there are symptoms observed, subjects can either resolve or suffer the fatal effects within a week or two. So, it really is a very fast process of this battle between the virus and the host."

An NIAID senior investigator in the NIH Vaccine Research Center and chief of the biodefense research section, Sullivan recently delivered "Lightning Chess: How Host Immunity Gains a Winning Position Against Ebola Virus Infection," the 13th annual Philip S. Chen Distinguished Lecture on Innovation and Technology Transfer.

The talk honors longtime scientist, research administrator and overall visionary leader Chen, who retired from the NIH

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Puerto Rico is still recovering. See story, p. 8.

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## SON OF NIH, BETHESDA May Describes Prevalence of Fetal Alcohol's Harms

BY RICH MCMANUS

No matter what country or continent you travel to, people enjoy their alcohol, which can have a harmful effect on a fetus if you happen to be a pregnant woman.

It has been known since the early 1980s that there is no safe level of alcohol consumption if you are pregnant. Nonetheless, women who are pregnant sometimes drink, and in some cultures—for example, in parts of rural South



Dr. Philip May

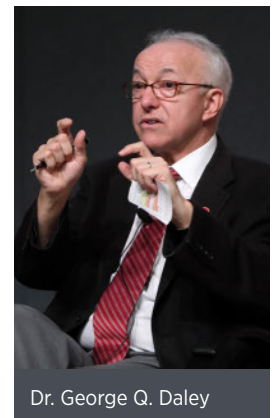
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## NEW BLOOD Daley Discusses Potential to Make Blood in the Lab

BY DANA TALESNIK

Imagine if blood cells could be manufactured, offering an unlimited, universal blood supply for transfusions, transplants and other therapeutic uses. So many would benefit; millions of lives could be saved. It may sound far-fetched, but decades of research have brought us much closer to the possibility.

"After more than 20 years of effort, working doggedly to try to develop human



Dr. George Q. Daley

SEE DALEY, PAGE 6

### 'Intelligent Vending' Comes to Bldg. 37

The NIH Supply Center recently launched a pilot Intelligent Vending Machine (IVM) initiative in Bldg. 37. IVM is a reliable method to deliver supplies convenient to the customer, near labs and offices. It provides on-demand accessibility to essential laboratory products 24/7.

The Supply Center conducted market research with the NIH community, and specifically with NCI and occupants of Bldg. 37, to determine the most frequently used products that could be stocked in the machine. The IVM purchase transaction mimics the process at the Self-Service Supply (SSS) stores in Bldgs. 10 and 31. An SSS store CAN card and an NIH PIV ID card are required to make a purchase from the machine.

The goal of the IVM initiative is to expand the IVMS throughout campus to service additional labs and offices. Also planned are IVMS stocked with office supplies for administrative offices.

The IVM in Bldg. 37 is located on the ground floor, adjacent to the elevators. Customer feedback is encouraged.

Contact the NIH Supply Center customer service at (301) 496-9156 or email [NIHSC-CustomerService@od.nih.gov](mailto:NIHSC-CustomerService@od.nih.gov).



New "intelligent vending" machine in Bldg. 37 is part of a pilot. If it succeeds, there will be IVMS located throughout campus. Also planned are IVMS stocked with office supplies for administrative offices.



At the recent awards ceremony are (from l) APAO's Jimmy Do, Tyrone C. Banks, Dr. Paul Liu, Dr. Rashmi Gopal-Srivastava and Dr. Jianhua Xiong. Not shown is Dr. Kai Ge.

PHOTO: MARY ZHANG

### APAO Presents Annual Awards

The Asian and Pacific Islander American Organization (APAO) recognized individuals for their contributions to the NIH community at its annual awards ceremony held in December.

The Leadership Excellence Award was jointly presented to Dr. Rashmi Gopal-Srivastava and Dr. Paul Liu. Gopal-Srivastava has strengthened collaboration within NIH and with outside institutions in clinical and translational research, especially in rare diseases research activities. In addition to his own research, Liu makes a wider impact through leadership roles in NIH-wide committees and academic societies and by supervision of generations of young scientists.

Dr. Kai Ge received the Scientific Achievement Award, recognizing his work in the field of epigenomic regulation of cell fate transition. His laboratory identified a large molecular complex named PTIP and subsequent work from his lab and collaborators have highlighted its important functions in adipogenesis, cell differentiation and cancer development.

APAO's Young Investigator Award was given to Dr. Jianhua Xiong, whose interest spans cell research to immunology and bioinformatics. He recently received the K22 NHLBI Career Transition Award.

Tyrone C. Banks, recognized for his continuous support to the Asian-American community at NIH, received the KT Jeang Distinguished Service Award. Many APAO members have worked closely with Banks through the years to realize the aims of equity, diversity and inclusion. Among them was the late Kuan-Teh Jeang, for whom the award is named.

NIH Deputy Budget Director Cecile Shaya shared insights and experiences as the ceremony's keynote speaker.



### NIDA Hosts Teleconference to Discuss Teen Drug Use Survey Results

The National Institute on Drug Abuse hosted a press teleconference on Dec. 17 to discuss the findings of the 44th annual Monitoring the Future (MTF) survey.

The 2018 MTF survey of drug use and attitudes among 8th, 10th and 12th graders in schools nationwide showed that teens reported a dramatic increase in their use of vaping devices since last year.

The survey continues to provide encouraging news, with self-reported use of alcohol, cigarettes and many illicit drugs remaining at historically low levels.

The MTF survey, funded by NIDA, is conducted by researchers at the University of Michigan. For more on the 2018 MTF survey, go to <https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future>.



## Senescent Cells Block Cancer, Contribute to Aging

BY ERIC BOCK

A process that prevents damaged cells from dividing also prevents the development of cancer, said NCI director Dr. Ned Sharpless. But as these cells build up over time, they might contribute to diseases associated with advanced age.

"There's an explicit trade-off between aging and cancer," Sharpless said recently at the Florence Mahoney Lecture on Aging, sponsored by the National Institute on Aging and part of the NIH Director's Wednesday Afternoon Lecture Series. "You can do things about aging, but often they'll promote cancer and you can do things about cancer, but often they'll promote aging."

Cells that can no longer divide but continue to function are called senescent cells. They are beneficial in certain situations, suppressing tumor formation and aiding in wound-healing, Sharpless said.

Dr. Leonard Hayflick first observed senescent cells *in vivo* in the early 1960s. He discovered that certain cells stop dividing when they become

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*"You can do things about aging, but often they'll promote cancer and you can do things about cancer, but often they'll promote aging."*

-DR. NED SHARPLESS

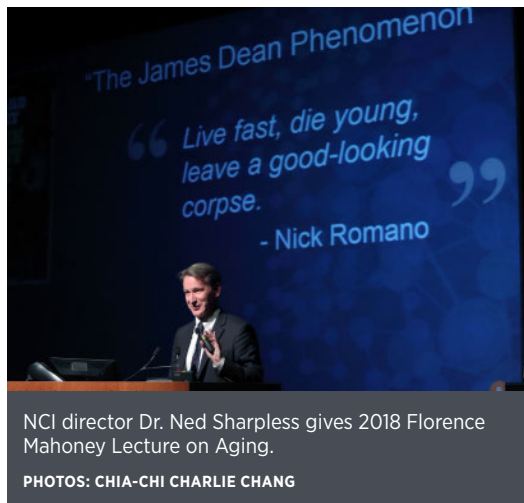
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damaged. The cells don't die; rather, they continue to be metabolically active.

A tumor-suppressor gene called p16INK4a (p16) activates the senescence process once it senses damage to a cell. Sharpless observed that mice lacking the gene didn't age as fast as mice with p16. However, those without the gene got cancer at higher rates.

"We think senescent cells hang around a long time and do stuff that's undesirable and contribute to the pathology associated with advanced age," he said.

Because senescent cells don't divide, they can't regenerate tissue, Sharpless said. They interfere with important functions. For example, senescent cells might get in the way and contribute to the size of atherosclerotic plaques. These cells also make cytokines, which can damage other cells and contribute to chronic inflammation during later life. Although the immune system can clear senescent cells, its ability to do so is limited and may decrease with age.



NCI director Dr. Ned Sharpless gives 2018 Florence Mahoney Lecture on Aging.

PHOTOS: CHIA-CHI CHARLIE CHANG

In mouse studies, scientists are studying several approaches to clearing senescent cells. If researchers can destroy them using "senolytic" drugs, for example, they believe they might be able to reverse some types of age-related pathology.

Sharpless, who in addition to directing NCI is chief of the aging biology and cancer section in NIA's Laboratory of Genetics and Genomics, said chemotherapy can trigger cellular senescence. Although chemotherapy can treat cancers, it also spurs an increase in senescent cells, he said. The amount of senescent cells varies from patient to patient.

"These cells appear to drive some of the long-term toxicities of cancer chemotherapy," he said.

For example, chemotherapy can interfere with the body's ability to produce blood cells, Sharpless explained.

Oncologists who treat cancer patients are not surprised by his results. This suggests DNA-damaging chemotherapy made the marrow biologically older, on the order of 20 years.

Many patients who undergo chemotherapy experience debilitating fatigue for months. Sharpless noted that "chemotherapy-induced fatigue is a limiting toxicity in many patients." He described a means to reduce the toxicity of chemotherapy for cancer patients, in a way to protect their hematopoietic stem cells.

In a footnote, Sharpless mentioned that in early November, the field of geriatric oncology lost a valuable contributor with the death of Dr. Arti

Hurria, director of City of Hope's Center for Cancer and Aging in Duarte, Calif.

Sharpless called Hurria's death "devastating for the field because Arti was a particularly good leader and a really forceful advocate for this topic. She will be sorely missed."

There is "a real shortage," Sharpless concluded, of students who are interested in basic and translational research in geriatric oncology.

"We are thankful to Dr. Sharpless for giving an engaging presentation about his research on tumor suppression and aging," said NIA director Dr. Richard Hodes. "His work in geriatric oncology, in particular regarding tumor suppressor molecules, is relevant and of interest to many NIH institutes. His research has helped show that while senescent cell production is helpful with wound-healing and tumor suppression, this process also contributes to multiple aging-related diseases." **R**



ON THE COVER: Human neutrophil interacts with *Klebsiella pneumoniae* (pink), a multidrug-resistant bacterium that causes severe hospital infections.

IMAGE: NIAID

### The NIH Record

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**Editor:** Rich McManus  
[Rich.McManus@nih.gov](mailto:Rich.McManus@nih.gov)

**Associate Editor:** Carla Garnett  
[Carla.Garnett@nih.gov](mailto:Carla.Garnett@nih.gov)

**Staff Writers:**  
Eric Bock • [Eric.Bock@nih.gov](mailto:Eric.Bock@nih.gov)  
Dana Talesnik • [Dana.Talesnik@nih.gov](mailto:Dana.Talesnik@nih.gov)

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## Alcohol

CONTINUED FROM PAGE 1

Africa—weekend bingeing of perhaps 3 to 8 drinks a night can yield a devastating harvest: up to 10 percent of the children born to drinking mothers in small towns outside of Cape Town were shown to qualify for a diagnosis of fetal alcohol syndrome (FAS) and up to 28 percent for a diagnosis within the full continuum of fetal alcohol spectrum disorders (FASD).

The work was done by a team led by Dr. Philip May, a restless son of Bethesda whose dad, Dr. Everette L. May, had spent 35 years in NIH's intramural program; he worked in the Laboratory of Medicinal Chemistry in the 1960s and 1970s at what was then NIAMD, having begun employment at NIH in 1941.

The son returned to NIH recently to give NIAAA's 23rd annual Mark Keller Honorary Lecture on the prevalence of FASD, a topic May has explored on three continents.

Born and raised in Bethesda and the Shenandoah Valley, where the family had a farm, May had "a yearning to get out and explore...I was fairly independent, and tenacious." He describes himself as a "shoe-leather epidemiologist, which means direct inquiry among the people you are studying. It's not common today, but it's what I specialize in. Taking science to the population."

In a 90-minute talk, May, now at UNC's Gillings School of Global Public Health, described his journey, stopping often to credit the far-seeing leadership at NIAAA, which supported him when "I was an unknown professor at the University of New Mexico."

FAS was first recognized in 1973, and even then, it was known to be a disorder of degree; some babies born to drinking mothers were categorized as suffering "fetal alcohol effects," which means that they might not exhibit the classic dysmorphism of FAS, but did show behavioral and learning problems characteristic of the syndrome.

May had joined the Public Health Service in 1970, and by the time he began a 33-year career as a professor at UNM, he was well-grounded in the conduct of public health. Using "active case ascertainment" methods, he and his team found a prevalence of FASD of 2 percent in some of the heaviest-drinking tribes of the Southwest Plains.

By the time he contributed to a 1996 Institute of Medicine report on FAS, the spectrum nature of the disorder had begun to take shape. It included growth deficiency and its victims were highly dysmorphic, especially if the mother's heaviest drinking had taken place during the first 30 to 90 days of gestation.

Subcategories emerged. PFAS, or partial fetal alcohol syndrome, included more than one facial phenotype; children with PFAS were more normal in their physical growth and development. There was ARND (alcohol-related neurodevelopmental disorder), where there is much less dysmorphia, and ARBD (alcohol-related birth defects), which are rarely seen and where isolated major physical anomalies are present that can be linked to alcohol exposure.

"There's not just one phenotype," May said, "but multiple ones. The signs vary. Children can look very different [from one another] and still have FASD.

"The mother and the fetus have exactly the same blood alcohol concentration" when a pregnant mom drinks, May explained. "The elimination of alcohol and its metabolites from the fetus is much slower, though."

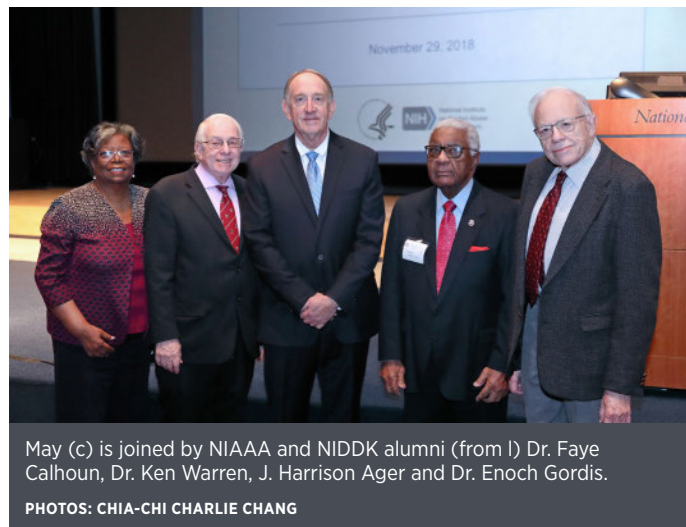
QFT is critical: quantity, frequency and (gestational) timing of the alcohol exposure.

The severity of FAS seems to increase, May said, with advancing maternal age; with each subsequent pregnancy; and with a mother's smaller body mass. It turns out that a high BMI, or obesity, is somehow protective against the syndrome.

Interestingly, twins born to a drinking mother are not equally affected. "We don't know the specific genetic, or epigenetic, mechanism, although concordance is higher with identical (monozygotic) twins," May noted.

May's first RO1 grant enabled him to study FAS in tribes of the Northern Plains. He found that the close personal contact of case management "made for healthier babies, in part because our staff members became their friends and were able to assist them in lowering their drinking."

May went to South Africa in the



May (c) is joined by NIAAA and NIDDK alumni (from l) Dr. Faye Calhoun, Dr. Ken Warren, J. Harrison Ager and Dr. Enoch Gordis.

PHOTOS: CHIA-CHI CHARLIE CHANG

mid-1990s at the government's invitation. One local South African pediatrician had suspected very high rates of FAS, as much as 10 percent. May thought that was impossible.

But in a prevalence study among 450 first-graders conducted between 1997 and 1998, May and colleagues found, to their astonishment, that the South African pediatrician's estimate was true.

"That was absolutely unheard of," he said. "No one thought it was possible."

Subsequent studies of nearly 11,000 first-graders in two South African communities turned up total rates of 24 percent qualifying for a diagnosis within the continuum of FASD. "These are unbelievable rates," May said.

The big challenge is to diagnose a FASD early, to help address the newborns' disabilities, May said. Children with FASD can be diagnosed as early as 9 months, "and for sure by 18 months if a combination of physical dysmorphism and developmental testing is used. It's really going to help a lot of individual cases. Cognitive testing at age 5 and later, if widely implemented, could help a lot of kids' lives."

Interventions include a focus on skills building, including extra tutoring in language and literacy. Exercise and music are important—especially if they can be linked—as a form of cognitive stimulation. Adequate nutrition is also important, although it has yet to be demonstrated whether multivitamins alone are beneficial, or if targeting with particular nutrients such as choline, omega-3 fatty acids and iron is the most efficacious.

Other takeaways included:

- There is an effect of male drinking on fetuses, an issue that will be studied further.

- Kids exposed to alcohol solely via breast milk are also affected—they tend to have lower birthweight, lower verbal IQ and more anomalies.

- FASD affects boys and girls similarly, but girls tend to be in worse shape by age 7, both mentally and physically; it appears that more males miscarry, or are victims of SIDS than females.

- Prevalence studies in the U.S., ongoing since 2006, reveal no particular ethnic or racial distribution of FASD—it's a democratic malady in May's studies to date. "It affects just as many upper-income families as lower-income ones," he noted.

- Contrary to what one might expect, general cognitive abilities in affected children are generally in the normal range. It may not be a major cause of mental retardation as it was previously believed to be, but there are a host of behavioral problems found in children with FASD in the general population of the U.S., including mood regulation, lack of inhibition, aggression and attention problems. "An FAS child would have a real problem with this talk, which is over 1 hour long," May quipped.

- Alcohol use in pregnancy is a principal cause of developmental delay and behavioral problems in children. The U.S. rate of FASD is quite conservatively estimated in May's active case ascertainment studies in 4 regions of the country to be between 2-6.5 percent.

"Most people like alcohol, especially the population in general who are now of child-bearing age. And current norms encourage or allow alcohol use more than in the past two or three generations," said May. "You just don't know—maybe one or a few drinks a night during particularly sensitive times in pregnancy could reduce your child's IQ somewhat. Repeated nights of drinking have been demonstrated to affect not only brain structure and development, but also are linked with a variety of behavioral problems. There is too frequently an attitude-behavior disconnect with a significant number of people today."

He concluded on a hopeful note: "These children with FASD do mature. They can get better with early recognition and remediation." **R**

## 'Intellectual Family Tree' Examined in NINR Lecture

HEART FAILURE

Attendees of the NINR Director's Lecture series are accustomed to learning more about an accomplished nurse scientist's program of research. Less common, however, is an exercise in examining one's "intellectual family tree." Attendees at the recent lecture "Integrative Biobehavioral Research in Heart Failure," featuring Dr. Christopher Lee, were treated to both.

Lee, professor and associate dean for research at Boston College's Connell School of Nursing, described his research in heart failure focused on symptom science and



At NIH for a recent lecture, Dr. Christopher Lee, shown with NINR acting director Dr. Ann Cashion, discussed "a human model of heart failure."

patients' response to symptoms when they occur. The innovative approach to research that Lee calls "biobehavioral profiling" reflects an understanding of biological underpinnings of symptomatology as well as knowledge of advanced statistical techniques, which he uses to better understand differing responses to heart failure and its therapies.

To more succinctly describe his research, Lee quipped that he studies the "human model of heart failure."

He highlighted studies he and his team have conducted on heart failure self-care management, as well as the symptom science and symptom biology of heart failure.

Notably, Lee and his team studied the impact of the patient/caregiver dyad on self-care management, discovering that a mismatch between how patients and caregivers rate the patient's symptoms is associated with an increased risk for a cardiac event. Throughout his research on caregiving dyads, Lee noted that caregivers themselves often have serious illnesses of their own. Because of this, he considers the classifications of "patient" and "care partner" to be arbitrary and encourages research focused on the health of the partnership itself—not the health of one valued over the other.

Lee also discovered that what we know about heart failure may not be as straightforward as it would seem. For instance, an increased left ventricular internal diastolic diameter is associated with worse symptoms among heart-failure patients—but only if those patients are men. For women, the opposite is true. Similarly, the biological underpinnings of symptoms can vary depending on the severity of the illness.

Lee described his own intellectual family tree—the mentors from varied fields who together make up his intellectual lineage, as well as those mentees whose work he has influenced. He encouraged audience members to examine who has influenced their own scientific thinking and advised attendees to consider their roles in mentoring relationships.

The NINR Director's Lecture Series is designed to bring the nation's top nurse scientists to NIH to share their work and interests with a trans-disciplinary audience. Lee's lecture is available on NINR's YouTube channel at <https://www.youtube.com/NINRnews>.—**Jo-Ann Kriebel**



## Daley

CONTINUED FROM PAGE 1

hematopoietic stem cells from a petri dish, we're tantalizingly close to being able to say we've got it working," said Dr. George Q. Daley, a hematologist, professor and dean at Harvard Medical School. He spoke recently as part of NHLBI's 70th anniversary lecture series in Lister Hill Auditorium.

"I started thinking about the possibilities of deriving blood cells from embryonic stem cells even when I was a graduate student in Dr. David Baltimore's lab," said Daley. In the late 1980s, in Nobel laureate Baltimore's lab, Daley linked an oncogene to chronic myeloid leukemia, a type of blood cancer that was fatal without a bone marrow transplant. The discovery paved the way for an effective treatment for CML.

"At that time, the standard of care was a sibling transplant, but there was growing interest in crossing immunologic boundaries using unrelated donors," said Daley.

Early on, his lab was culturing mouse embryonic stem cells, prodding them to differentiate into blood. It proved challenging, though, to customize stem cells to make them rejection-proof.

In 2001, equipped with his first human stem cell grant from NHLBI, Daley began differentiating human embryonic stem cells into blood, and later succeeded in making induced pluripotent stem cells (iPS), which are adult stem cells reprogrammed back into an embryonic stem cell (ESC)-like state so they can develop into other cell types for therapy. Daley made iPS cells from patients with various blood diseases.

Bolstered by advances in gene-editing techniques, Daley took disease models, corrected them *in vitro*, creating a control for diseased iPS cells and a repair stem cell that could be replicated in the petri dish and coaxed into blood lineages. Recently, with NHLBI funding, Daley used disease-specific iPS cells from a patient with diamond blackfin anemia to configure a drug screen that identified a compound that is headed for human clinical trials.

"This is the beginning of what I hope will be an increasing number of drugs that will find their way to the clinic by virtue of having been tested in these iPS systems," said Daley. "It's my longstanding hope—going back those 30 years or so—in thinking about being



able to rescue patients with a curative bone marrow transplant, [to use] human ES or iPS intermediates for that purpose."

ES and iPS cells also potentially could provide a predictable supply of platelets for the millions of units transfused into patients annually. Recipients traditionally rely on blood donations, which can be erratic, especially in Daley's hometown of Boston, where harsh winters sometimes prevent donors from traveling to give blood. Manufactured platelets could help circumvent several challenges of donated platelets, providing an inexhaustible, reliable, pathogen-free supply.

In a recent project, Daley has collaborated with Japanese researchers to convert iPS cells into self-renewing platelet progenitors that become platelets that are structurally and functionally comparable to human platelets. The process, however, is prohibitively expensive for a tiny yield. Daley's lab is now exploiting live cell confocal imaging to identify rare subclones of cells with greatly increased platelet production. This new platform, which is proving much more efficient but still isn't cost-effective for commercial production, will soon go into a first-in-human clinical trial at Boston's Dana-Farber Cancer Institute.

"I predict, in the future—5, 10, 15 years down the road—we will see an increasing dependency on *in vitro* manufactured platelets and red blood cells to replace, and provide advantages over, donor-derived cells," said Daley.

Another research area is cancer immunotherapy. The process of engineering CAR T

cells and re-infusing them into patients to target malignant tumors is labor-intensive and currently costs hundreds of thousands of dollars.

"One appealing alternative is to change a patient-specific strategy into an off-the-shelf strategy," Daley said. Some of his preliminary research has produced robust iPS-derived T cells that hold promise

for enabling wider access to this potentially curative technology.

Daley continues culturing and gene modifying hematopoietic (blood-forming) stem cells toward producing cloneable, immortal stem cells in the lab. "For the many dozens of hematopoietic diseases for which there is still lacking any kind of gene therapy," said Daley, "this would be a single common platform for combined gene and cell therapy."

Hematopoietic stem cells are particularly challenging to manufacture, said Daley, because blood develops in waves. The first wave of embryonic red cells is transient, then lifelong blood formation develops from a second wave. Now, investigators can employ markers for mature stem cell and lymphoid development that can help researchers manipulate stem cells into blood cells for therapy.

Some experiments show great promise. Daley's lab has reached the point where they can generate hematopoietic stem cells from human ES and iPS cells in a petri dish on a small scale. The cell dose is only adequate for a mouse.

"We have to imagine an engineering solution that would allow us to scale up, maybe 1,000-fold, to have a dose of hematopoietic stem cells that could transplant even a pediatric patient," Daley said. "So there's more work to be done. There's still a long way to go before clinical use, but we're motivated to press on." **R**

## AI Approach Outperformed Human Experts in Identifying Cervical Precancer

A research team led by investigators from NIH and Global Good has developed a computer algorithm that can analyze digital images of a woman's cervix and accurately identify precancerous changes that require medical attention. This artificial intelligence (AI) approach, called automated visual evaluation, has the potential to revolutionize cervical cancer screening, particularly in low-resource settings.

To develop the method, researchers used comprehensive datasets to “train” a deep, or machine, learning algorithm to recognize patterns in complex visual inputs, such as medical images. The approach was created collaboratively by investigators at NCI and Global Good, a fund at Intellectual Ventures, and the findings were confirmed independently by experts at the National Library of Medicine. The results appeared in the *Journal of the National Cancer Institute* on Jan. 10.

“Our findings show that a deep learning algorithm can use images collected during routine cervical cancer screening to identify precancerous changes that, if left untreated, may develop into cancer,” said Dr. Mark Schiffman of NCI's Division of Cancer Epidemiology and Genetics, who is senior author of the study. “In fact, the computer analysis of the images was better at identifying precancer than a human expert reviewer of Pap tests under the microscope [cytology].”

The new method has the potential to be of particular value in low-resource settings. Health care workers in such settings currently use a screening method called visual inspection with acetic acid (VIA). In this approach, a health worker applies dilute acetic acid to the cervix and inspects the cervix with the naked eye, looking for “aceto whitening,” which indicates possible disease. Because of its convenience and low cost, VIA is widely used where more advanced screening methods are not available. However, it is known to be inaccurate and needs improvement.

Automated visual evaluation is similarly easy to perform. Health workers can use a cell phone or similar camera device for cervical screening and treatment during a single visit. In addition, this approach can be performed with minimal training, making it ideal for countries with limited health care resources, where cervical cancer is a leading cause of illness and death among women.

## NIH Study Implicates Hyperactive Immune System in Aging Brain Disorders

In a study of fruit flies, NIH scientists suggested that the body's immune system may play a critical role in the damage caused by aging brain disorders. The results are based on experiments in which the researchers altered the activity of Cdk5, a gene that preclinical studies have suggested is important for early brain development and may be involved in neurodegenerative diseases such as ALS, Alzheimer's and Parkinson's disease. Previously, they found that altering Cdk5 sped up the genetic aging process, causing the flies to die earlier than normal

and have problems with walking or flying late in life and greater signs of neurodegenerative brain damage.

In this study, published in *Cell Reports*, they suggested that altering Cdk5 resulted in the death of dopamine-releasing neurons, especially in the brains of older flies. Typically, Parkinson's disease damages the same types of cells in humans. Further experiments in flies suggested the neuron loss happened because altering Cdk5 slowed autophagy, or a cell's waste disposal system that rids the body of damaged cells in a contained, controlled fashion, which in turn triggered the immune system to attack the animal's own neurons. This immune system attack is a much “messier” and more diffuse process than autophagy.

Genetically restoring the waste system or blocking the immune system's responses prevented the reduction in dopamine neurons caused by altering Cdk5. The authors concluded that this chain reaction, in which a breakdown in autophagy triggers a widely destructive immune reaction, may occur in human brain during several neurodegenerative disorders. Researchers may want to look to these systems for new treatment targets and strategies.



An artificial intelligence approach called automated visual evaluation has the potential to revolutionize cervical cancer screening.

IMAGE: CYBRAIN/ISTOCK

## Better Mouse Model Enables Precision-Medicine Research for Alzheimer's

Incorporating genetic diversity into a mouse model of Alzheimer's disease resulted in greater overlap with the genetic, molecular and clinical features of this pervasive human disease, according to a study funded by NIA. The study also suggests that adding genetic diversity may be key to improving the predictive power of studies using mouse models and increasing their usability for precision medicine research for Alzheimer's. This research comes out of the newly established Resilience-Alzheimer's Disease Consortium (Resilience-AD) and was published Dec. 27 in the journal *Neuron*.

“This is the first study to show that you can replicate many of the molecular features of Alzheimer's disease in a genetically diverse mouse model,” said NIA director Dr. Richard Hodes. “It points to a strategy for better use of mouse models for precision medicine research—both basic and translational—for Alzheimer's disease.”



NIH scientists suggested that the body's immune system may play a critical role in the damage caused by aging brain disorders.

IMAGE: JACOB WACKERHAUSEN/ISTOCK

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out simple tasks. As many as 5.5 million Americans ages 65 and older are estimated to be living with Alzheimer's disease, the most common form of dementia.

A key tool among the multiple efforts to find a treatment or cure for Alzheimer's, mouse models allow researchers to explore genetic, molecular and even behavioral aspects of disease that can't be done in humans. The researchers noted that mouse models with Alzheimer's mutations are important for defining high-risk as well as protective genes and disease mechanisms and for efficient testing of new potential interventions and therapeutics.





Three NIMH employees—Karen Bartholomew, Dr. Susan Borja and Dr. Delany Torres-Salazar—responded to post-Hurricane Maria Puerto Rico.

## NIMH Volunteers Help Out in Post-Maria Puerto Rico

BY BETH SHERMAN

On Sept. 20, 2017, Hurricane Maria's 155 m.p.h. winds slammed into Puerto Rico, downing power lines and flattening buildings. Heavy rains caused catastrophic flooding. For the next 6 months, first-response teams worked to feed and house 3.3 million residents and restore basic infrastructure. Following this emergency response period, FEMA and HHS called for volunteers to help restore essential medical and social services. Several NIMH employees answered the call.

"When I got the email that HHS was looking for volunteers, I signed up right away. I was the first volunteer from the NIMH and I was told to be ready to leave within 24 hours," recalls Karen Bartholomew, a supervisory social worker in the psychosis and cognitive studies section, who has been a clinician and administrator for more than three decades.

Within weeks of her arrival in March 2018, Bartholomew was asked to take over as chief of the HHS Puerto Rico Behavioral Health Services Branch, a job she held for both of her two tours (March-May, July-August) as an HHS volunteer. Though the branch had been operating for 3 months, she was the first branch chief to have a background in mental health—not to mention in behavioral health services administration. In her new role, Bartholomew went to universities, hospitals and public agencies, building

relations and finding out about the residents' mental health needs. The bad news was the effects of the hurricane. The good news was that all residents have health insurance, most of the public health clinics that provided psychiatric care had stayed open and the people were remarkably resilient.

During her second tour on the island, Bartholomew was asked by the new field commander, PHS Capt. Elizabeth Hastings, to take charge of the combined Human and Behavioral Health Services Branches. This made her responsible for health and

behavioral health care services in schools and for children, families and seniors.

"Because the next hurricane season was about to start," she explains, "we decided that what each agency and municipality, each school, clinic and hospital needed most was an emergency health preparedness plan—complete with training programs—spelling out what to do to get medical care during hurricanes and their aftermath."

She found that residents were extremely receptive to the plans being designed by branch teams. Teachers, for instance, were



Much that is idyllic about Puerto Rico stands astride ongoing efforts to rebuild the country.

PHOTOS: SUSAN BORJA





Tale of two islands. Images show Puerto Rico's resilience (above) and endurance (below).

eager to know what they could do to prepare while school was out. Added to this, FEMA was hiring—a real boost for the devastated local economy—and local staff were replacing volunteers on FEMA human services teams.

“It is wonderful to work together toward a common goal, with everybody 110 percent dedicated to what they are doing,” said Bartholomew. “It may seem strange from here, but the work was so joyous, and Puerto Ricans are so open and welcoming, it was quite natural for everybody to hug and kiss one another at the end of a meeting.”

After Bartholomew left, NIMH volunteer Dr. Susan Borja, a program officer with the Traumatic Stress Research Program, took over as branch chief.

“While Karen was the first HHS person with a mental health background to go,” she notes, “I was the first with a background in trauma and disasters. I had worked with the HHS assistant secretary of preparedness and response on the development of a conceptual framework for preparedness and the coordination of federal resources for behavioral health needed during the response and recovery periods following disasters and public health emergencies. When confronted with real-world challenges on the ground, it was enlightening to see exactly where advanced planning falls short.”

Borja considers one of her biggest contributions to be translating PTSD Coach (an app for dealing with post-traumatic stress disorder) into Spanish. Developed by the Veterans Administration

and Department of Defense, PTSD Coach includes tools to help with recognizing, managing and tracking symptoms and determining when to seek professional help.

“People often ask me, ‘How was it really in Puerto Rico?’” Borja muses. “A year after the hurricane, power was mostly restored—except where it wasn’t. Even in San Juan, hotels and lovely tourist beaches sit next to homes and schools with no roof. The island is a mix of

beautiful, destroyed, historic, abandoned and rehabilitated. It has a long way to go before recovery is full and sustained.”

from such a devastating disaster and an iron determination to thrive. It felt very special to be a part of it.

“Because Puerto Rico had not been hit by a hurricane for 14 years,” added Torres-Salazar, who worked with the HHS response team in Puerto Rico from mid-September to mid-October 2018, “the island wasn’t ready. People needing medical attention had no idea where to go locally or whom to contact. The result was that after Maria, everybody rushed to the hospitals and the system collapsed.”

As a legacy project, the HHS team created a map of all health care facilities on the island, plus a legend indicating the different services (such as satellite communication, generators, audiology, dialysis, oncology, maternity) each could provide. “Because it can be understood at a glance, this map

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—DR. SUSAN BORJA

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“I will never forget being in Puerto Rico on Sept. 20, 2018—the first anniversary of Maria’s strike,” said Dr. Delany Torres-Salazar, a research fellow in the Laboratory of Molecular and Cellular Neurobiology. “Love for that little island was in the air—along with pride at being able to recover

is a powerful tool—especially for first-responders unfamiliar with an area,” notes Torres-Salazar.

Not long into his stay, Torres-Salazar was, to his surprise, put in charge of one of the two “red teams” set up to put the finishing touches on the HHS regional

preparedness plans. His team was tasked with individualizing the plans to make sure they met the needs of each of Puerto Rico’s seven health department regions.

Although Torres-Salazar was no longer in Puerto Rico when the plans were presented, his team told him they were a resounding success. “The biggest challenge now,” he notes, “is educating the population about these plans. But they are working hard on that and I am confident that next time around, Puerto Rico will be ready.” **R**



## Sullivan

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Office of Intramural Research in 2006 after a 41-year career here.

Known as the scientist who invented a phosphate assay technique still used in labs today, when the administrator established the Office of Technology Transfer at NIH, formulated all of its guiding principles and created the CRADA, or cooperative research and development agreement. Once implemented, his vision opened whole new avenues of research invention, creativity and partnership for investigators at NIH working with like-minded scientists outside the agency.

“Phil was well known for making things better...he made the intramural research program a well-oiled machine,” said NIH deputy director for intramural research Dr. Michael Gottesman, who introduced the



Sullivan describes how the Ebola vaccine evolved through decades of research.

PHOTOS: CHIA-CHI CHARLIE CHANG

chess game. A virus makes the opening move, invading and replicating locally at the site of infection. The host then sends out an innate signal to the immune system, alerting it to the danger. The immune system answers the call on two fronts: A humoral response circulates throughout other tissues, recruiting antibodies to capture the virus; a cellular response

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*“What happens ultimately is if the virus wins this battle of lightning chess, then it’s checkmate...about 50 percent of the people who are infected actually succumb to the lethal effects of the virus.”*

—DR. NANCY SULLIVAN

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lecture and recognized the honoree, who has attended the event every year and sat in the front row with his wife and family.

In her lecture, Sullivan discussed her group’s “two main projects at the VRC—the vaccine and the antibody work.” She began, though, by acknowledging individuals in NIAID’s Technology Transfer and Intellectual Property Office.

“They labor silently behind the scenes and don’t get the recognition that the scientists get and we really rely on them so heavily,” Sullivan said. “They work so hard for us to fulfill the NIH mission of getting these discoveries that we make into people who can benefit from them...You might think they step in at the end after we’ve made discoveries and done clinical developments, but in fact they’re integrally involved from the very beginning. They help us with research collaboration agreements, with patent filing and, of course, CRADAs.”

Sullivan described a typical viral infection

engages—shortly before or just after—to mop up whatever the humoral misses.

“What happens ultimately is if the virus wins this battle of lightning chess, then it’s checkmate and we know in Ebola infections that about 50 percent of the people who are infected actually succumb to the lethal effects of the virus,” Sullivan explained. “In contrast, if the host can mount its responses early enough and with enough strength, then virus replication is controlled and the host wins that battle. We want to understand the interplay of these factors and try to use vaccines and immunotherapies to give the host an advantage in this game.”

Seeking to better equip hosts, Sullivan and her team study prevention—gene-based Ebola vaccines—and treatment—a monoclonal antibody called mAb114 immunotherapy. Their research also helps further define the mechanisms and strategies at work in the game, so that future vaccines

and immunotherapies are more informed for upcoming battles.

Ebola is a tough, persistent opponent, Sullivan said. The earliest experiments with vaccines disappointed scientists; traditional approaches led instead to enhanced disease in animal tests.

“When we began this work, the field was thinking that perhaps this Ebola virus was just too aggressive, too fast and too potent to protect against with a vaccine,” she admitted. “We, on the other hand, wondered whether filoviruses had evolved mechanisms to evade humoral immunity and maybe we’d need other components of the immune response to clear the virus more effectively.”

Looking at pathogen structure and repli-



Former NIH scientist, administrator and visionary Dr. Philip Chen never misses the lecture in his honor.

cation, investigators learned several unique characteristics of the virus. Unlike HIV, for instance, Ebola does not have frequent sequence changes.

“If you compare the glycoprotein sequence from 1976 to the current outbreak, they’re virtually identical,” Sullivan said.

The problem with Ebola is that the virus folds and curls onto itself, making it hard for antibodies to reach, latch onto and vanquish infected cells. Also, the virus reproduces in



large volumes, so the antibody army must be equally robust to overcome Ebola's structure.

In addition, unlike other viruses, Ebola doesn't just choose one type of tissue to infect. It enters the lymph nodes, but then very quickly moves to liver and spleen, circulating to kidneys, lungs and brain.

"Realizing the replication strategy helps us think about how we might approach a vaccine," Sullivan noted. "Our goal when we started with vaccine development was to induce both humoral and cellular immunity, thinking that humoral immunity would not be sufficient."


Sullivan's next quest was to consider how to advance the candidate vaccine in humans via clinical trial.

"It's very difficult for Ebola" for several reasons, she said. Ebola virus outbreaks are sporadic; nearly 20 years separated a 1976 outbreak from the next in 1994. In recent times, infection periods have occurred more frequently: 2014-2016, 2017 and 2018. However, epidemic sites have been geographically distant from each other, even within the same country.

"Even though we see the Democratic Republic of Congo [DRC] has experienced repeated outbreaks, it's a huge country," Sullivan said. "Just the capital alone has 12 million people, so it's difficult to know who you would vaccinate if you wanted to do a randomized control trial. But, more importantly, with lethal pathogens like Ebola virus, it's hard to argue for placebo-controlled trials."

Ultimately, Sullivan's vaccine and several others were developed, mass-produced and dispensed widely. But for a number of reasons, including regional political instability, the current high-risk Ebola epidemic in DRC was not yet contained at the time of Sullivan's lecture.

"It illustrates the continued urgency for therapeutics even if we have vaccines," she emphasized, "because in spite of having [more than 25,000 people vaccinated] we're still having trouble controlling this outbreak."

Sullivan also described her team's work on developing treatments for Ebola infection. Watch the full lecture at <https://videocast.nih.gov/summary.asp?Live=28496&bhcp=1>. 

## Radiation Scientist Doody Retires from NCI

Michele Morin Doody, a staff scientist in NCI's Radiation Epidemiology Branch (REB), retired at the end of December.

Doody joined the Environmental Epidemiology Branch in the Division of Cancer Cause and Prevention in 1980 as a commissioned officer in the Public Health Service. She had received an M.S. in epidemiology from the University of Massachusetts. She transferred to the REB shortly after its inception in 1984, and coordinated several major branch studies.



Michele Morin Doody

Doody managed a case-control study of diagnostic x-ray procedures and risk of leukemia, lymphoma and multiple myeloma in the Kaiser HMO setting. She also investigated the risk of breast cancer in young women with scoliosis who underwent multiple x-ray procedures to monitor their spinal curvature and found a borderline excess risk of breast cancer incidence according to estimated radiation breast dose from diagnostic x-rays.

Doody was project manager of cancer mortality among a large cohort of adult patients treated for hyperthyroidism with an initial follow-up through 1990, and additional follow-up through 2014. She managed the field work for the United States

Radiologic Technologists study cohort of 146,000 U.S. radiologic technologists, in which she oversaw four cycles of questionnaires, a major dosimetry effort to reconstruct occupational radiation doses and collection of biological samples.

Doody helped expand the study in new directions to assess cancer and cataract risks in technologists conducting nuclear medicine and/or fluoroscopically guided procedures and these outcomes in technologists according to their estimated ultraviolet radiation exposure. In 2018, she received an NCI group award for this landmark occupational radiation study.

## VOLUNTEERS

### Healthy Volunteers Sought

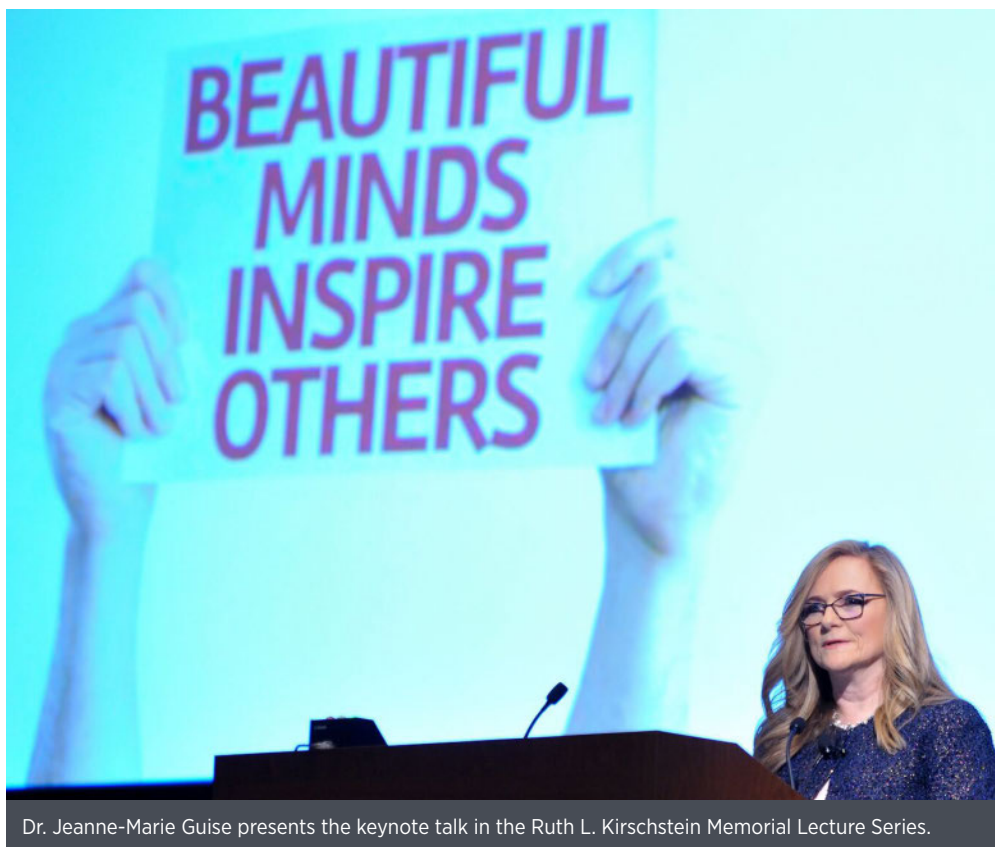
Healthy volunteers at least 18 years old with no history of cardiovascular disease are needed to participate in a research study with NHLBI. Researchers are interested in understanding the effects of diets enriched with palmitoleic acid (omega-7) on decreasing cardiovascular risk and effects on metabolism. All study-related medications, tests or procedures are at no cost. Receive compensation for your participation at the end of the completed study. For more information, call the Office of Patient Recruitment, 1-800-411-1222 (TTY 1-866-411-1010) or visit <https://go.usa.gov/xQq2p>. Refer to study 18-H-0019.

### Post-Transplant Patients Needed

NHLBI researchers are testing whether a mouth rinse containing topical dexamethasone can be used to prevent oral chronic graft vs. host disease in post-transplant patients. If you are 12 years of age or older and have received a stem cell transplant in the last 60 to 90 days, you may be eligible to participate. Study-related tests and procedures are provided at no cost. For more information, call the Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010). Read more at <https://go.usa.gov/xnhak>. Refer to study 07-H-0005.

### NHLBI Study Recruits Volunteers

NHLBI invites volunteers ages 18-80 of African descent with or without sickle cell trait and patients with sickle cell disease to participate in a one-time visit research study. Volunteers will provide blood samples that will be used to look for a link between the PKLR gene and pyruvate kinase protein. The PKLR gene is active in the liver and in red blood cells and helps to create protein called pyruvate kinase that is essential in normal functioning of red blood cells. Compensation is provided. For more information about study 18-H-0146 call 1-866-444-2214 (TTY 1-866-411-1010) or visit <https://go.usa.gov/xP8Hx>.



Dr. Jeanne-Marie Guise presents the keynote talk in the Ruth L. Kirschstein Memorial Lecture Series.

## Meeting Showcases Progress of Women's Health Scholars

The Office of Research on Women's Health recently held the 2018 Building Interdisciplinary Research Careers in Women's Health (BIRCWH) annual meeting. Created in 2000 as one of ORWH's signature programs, BIRCWH connects junior faculty (scholars) and senior faculty with shared interest in women's health and sex-differences research. Through collaborative partnerships with the ICs, BIRCWH has funded 700 scholars since its inception and currently supports 60 scholars through K12 awards to 20 institutions.


Presenting the keynote Ruth L. Kirschstein Memorial Lecture Series talk was Dr. Jeanne-Marie Guise, principal investigator of a BIRCWH K12 awarded to the Oregon Health & Science University. She discussed the importance of mentorship.

"Academic careers are like adolescence," said Guise. As junior faculty progress toward greater independence—and possibly make some missteps along the way—mentors provide necessary guidance and protection, allowing room to learn from those mistakes and other experiences. She stressed

multigenerational research and multidirectional mentoring to promote greater fusion and help address the complexity and scope of problems science faces today. She ended with a discussion of core competencies—including passion, tenacity, civility, connectivity, creativity, courage, diversity and energy—that are needed in science and can be fostered through mentoring.

The keynote address was followed by a panel discussion on curriculum development for training in the consideration of sex as a biological variable (SABV) in research. SABV is important to the reproducibility and rigor of science. In accordance with NIH policy, scientists funded by the agency need to factor sex into the design, analysis and reporting of studies across the research spectrum.

The meeting also included presentations by four BIRCWH scholars and a mentoring and networking session staffed by multiple ICs.

The meeting ended with a poster session featuring research from 46 scholars supported by the BIRCWH program. A videocast of the plenary session is available at <https://videocast.nih.gov/summary.asp?Live=28502&bhcp=1>. —Mark B. Johnson 

## NCI Welcomes Inaugural iCURE Program Scholars

"Commit to conducting innovative, impactful, interdisciplinary research with integrity and sustained excellence," said Dr. Lauren Wood in her keynote address to the inaugural cohort at the recent National Cancer Institute Intramural Continuing Umbrella of Research Experiences (iCURE) welcome ceremony.

Nearly one year after the iCURE program was first announced, the first 15 iCURE trainees—called iCURE scholars—were officially welcomed to NCI during a recent ceremony at Stone House.

iCURE is run by the Center to Reduce Cancer Health Disparities and the NCI Intramural Research Program that supports mentored research experiences in a multidisciplinary environment. It is an extension of the Continuing Umbrella of Research Experiences (CURE) program, which for more than 20 years has used a pipeline approach to promote the progress of its trainees toward research independence as well as enhance diversity in the cancer and cancer health disparities research workforce.

"This is a program that is near and dear to our hearts. It is something that we've envisioned for quite some time and today marks the beginning of a new reality," said CRCHD director Dr. Sanya Springfield.

iCURE scholars were also welcomed by Dr. Tom Misteli, Center for Cancer Research director, and Dr. Ethan Dmitrovsky, president of Leidos Biomedical Research and laboratory director of the Frederick National Laboratory for Cancer Research.

"We are training the next generation of leaders and role models—and that is you—and that is why this program is important," Misteli told the iCURE scholars. The program strongly encourages the participation of individuals from underrepresented populations and is aligned with NCI's interest in diversity.

The 2018 cohort of iCURE scholars includes 6 post-baccalaureate (including post-master's) individuals, 3 graduate students and 6 postdoctoral fellows. The scholars will work closely with scientists on the NCI campuses for the next 1 to 3 years.



The first cohort of iCURE scholars poses with NCI leadership and iCURE staff during welcome ceremony.