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## Doudna Describes Exciting Future for CRISPR

BY ERIC BOCK

CRISPR genome editing is a powerful tool that can treat many genetic diseases. If it's to reach its full potential, scientists must develop new delivery methods, said CRISPR pioneer Dr. Jennifer Doudna during an NIH Director's Lecture in Masur Auditorium.

"Even if we have a great genome editor, we still have to get it into cells," said Doudna, Nobel laureate in chemistry (2020) and professor of biochemistry, biophysics and structural biology at the University of California, Berkeley.

Often described as "genetic scissors," CRISPR is a revolutionary tool that allows scientists to selectively modify the DNA of living organisms. Short for clustered regularly interspaced short palindromic repeats, CRISPR is a defense system that bacteria use to prevent infection. CRISPR technology is based on this system and can be engineered to make targeted changes to a genome.

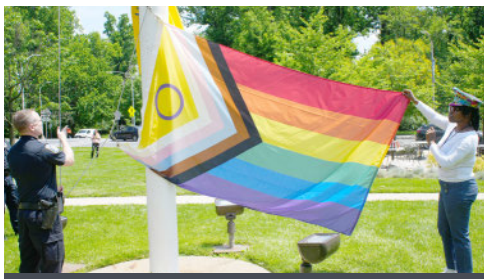
Doudna started out in the field by trying to answer a "fundamental question in biology, namely, how bacteria fight viral infections." She became interested after a colleague at Berkeley, Jill Banfield, theorized that bacteria have an adaptive immune system that uses RNA molecules to protect cells from future infection.

In 2012, Doudna and French scientist Dr. Emmanuelle Charpentier published their seminal paper on Cas9, an enzyme that uses an RNA guide in bacteria to bind to and then cut strands of DNA. Since then, scientists have identified large families of these enzymes in bacteria. They

SEE **DOUDNA**, PAGE 6

CRISPR pioneer and Nobelist Dr. Jennifer Doudna addresses a Masur Auditorium crowd.

PHOTO: CHIA-CHI CHARLIE CHANG



Pride flag rises at NIH. See more images, p. 12.

**ALSO THIS ISSUE**



HIJACKING A PROCESS

## Tisdale Develops New Options for Treating SCD

BY DANA TALESNIK

Dr. John Tisdale
PHOTO: DISCOVERY

People with sickle cell disease (SCD) commonly describe the pain as feeling as though shards of glass are moving through their veins. About 100,000 Americans live with this debilitating disease; millions are afflicted worldwide.

When Dr. John Tisdale arrived at NIH 30 years ago, there was no specific treatment for SCD. He felt compelled to change that.


IMAGE: VCHAL/SHUTTERSTOCK

"I've been interested in

SEE **TISDALE**, PAGE 8

LABS (& COLLIES & TERRIERS) REPORT

## Ostrander Connects Canine, Human Mental Health

BY AMBER SNYDER

Dr. Elaine Ostrander

Children's author Roald Dahl once said, "The greatest secrets are always hidden in the most unlikely places."

That couldn't be more true for National Human Genome Research Institute (NHGRI) Distinguished Investigator Dr. Elaine Ostrander, whose interest in genomics research led her to study an unassuming candidate: *Canis lupus familiaris*, better known as the domestic dog.

Research into dog genetics may have useful applications for human health,

SEE **CANINE**, PAGE 4

## FEVS Open Through July 5

The Federal Employee Viewpoint Survey (FEVS) is an opportunity to confidentially voice your opinion about your work experience, organization and leaders. The 2024 FEVS is open now through July 5. Leaders in each institute, center and office take feedback seriously. FEVS is used to create positive changes throughout the organization. Your feedback also enables managers to find ways to improve your experience in the workplace.

Who is eligible to take the 2024 FEVS? Full- and part-time permanent, non-seasonal employees, onboarded on or before Nov. 30, 2023, will receive an email invitation from the U.S. Office of Personnel Management (OPM) containing a unique link to participate in the survey. Contractors are not eligible.

Eligible federal employees should look for an email from OPM with the following heading:

Source email address: Federal Employee Viewpoint Survey-HE
Subject line: [EXTERNAL] 2024 OPM Federal Employee Viewpoint Survey

OPM administers the survey and does not provide raw data to any participating federal agencies. Therefore, NIH does not have access to any individual's raw data. To learn more, visit https://hr.nih.gov/workforce/fevs.

## Network at the Grad School Fair

**July 17**

The 2024 NIH Graduate and Professional School Fair will be held in-person on Wednesday, July 17 at the Natcher Conference Center. There will be opportunities to connect with school and program representatives at the exhibitor sessions. Also, hybrid panel sessions will provide recommendations for getting into graduate or professional school.

The fair is focused on graduate and professional school applications and networking with representatives from programs across the U.S. It also provides an opportunity for NIH summer interns, especially those in college, and postbacs, as well as other college students in the D.C. area to prepare for the next step in their careers by exploring educational programs leading to the Ph.D., M.D., D.D.S., M.D./Ph.D. and other graduate and professional degrees.

More than 250 colleges and universities from across the U.S. send representatives of their graduate, medical and dental schools, schools of public health and other biomedically relevant programs with the aim of recruiting NIH trainees.

For a list of participating institutions and to register, see https://www.training.nih.gov/me/gfair/.


At left, in new Blood Bank digs are donor Sarah "Sally" Fowler and clinical research nurse Abayneh Alemu. At right, the new location is just off the central corridor of the original CC hospital building.

## NIH Blood Bank Moves to New Location

The NIH Blood Bank has relocated to a new and improved facility. The new location is off the central corridor of the original Warren Grant Magnuson Clinical Center in Rm. 1N224. Parking for blood donors remains available on the first floor of MLP-9.

To get to the new location from Masur Auditorium, make a right turn immediately after walking past the main elevator bank. It is just around the corner from the FAES coffee shop.

There is a great need for O positive and O negative blood donors. Platelet donors are also urgently needed. Donations remain critical to supporting patients. To schedule a donation, visit https://www.cc.nih.gov/blooddonor or call (301) 496-1048.


At left above, Hal Wilkins (l), donor resources recruitment supervisor, and Natasha Hammond, donor centers managing director, show the new spacious accommodations. At right are welcoming faces (from l) Manyahilishal "Manny" Mekonnen, donor resources specialist; donors Edward Byrd and Carl Udler; and Maura O'Rorke, marketing manager. Below, a view of the exterior path leading to the blood bank's new location.

**PHOTOS: CHIA-CHI CHARLIE CHANG**

The Modular Terrace Facility will be used to produce cutting-edge cell and gene therapies for clinical research trial patients.

## CC's Center for Cellular Engineering Unveils New Manufacturing Facility

BY SEAN MARKEY

The Clinical Center's (CC) Center for Cellular Engineering (CCE) recently unveiled its new Modular Terrace Facility.

First conceived in 2017, the custom-designed, 8,000-square-foot structure features four manufacturing clean rooms spanning 3,000 square feet and another 1,000 square feet of support space.

"There's no research space in this building," said CCE Deputy Director Dr. Rob Somerville. "It's all dedicated to manufacturing." Unlike most commercial facilities, which focus production on one or two cell- or gene-therapy products, CCE oversees a broad portfolio.

Somerville said the new Modular Terrace Facility will directly support CCE's mission to produce therapies for patients enrolled in trials.

These range from stem cells for bone marrow transplants and CAR T-cell immunotherapies for cancer patients to CCE's most advanced product, a graft of retinal pigment epithelial cells for patients with macular degeneration.

To produce epithelial cells, CCE staff reprogram blood cells drawn from a patient sample to create induced pluripotent stem cells (iPSCs), a form of lab-generated embryonic stem cell.

"We then select basic cultures of these cells, pick the best one, and then...go through a differentiation process to turn them into retinal pigment epithelial cells," Somerville said.

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*"Rather than designing a facility for where we are now, we've created flexibility...It is forward thinking."*

–DR. ROB SOMERVILLE

• • •

The cells are later transferred to a scaffold used by an ocular surgeon to implant into a patient who has suffered vision loss caused by macular degeneration.

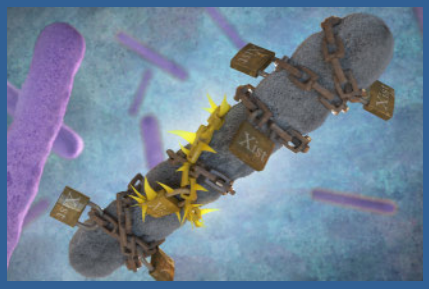
"This is first in human," Somerville explained, noting that the manufacturing process is protracted. "So far only a single patient has been treated with this therapy. It takes multiple months, and we're still just a proof-of-concept stage."

Noting that requested cell and gene therapies for CC patients are constantly in flux, the scientist said CCE's new terrace facility will increase production capacity.

"We can manufacture different products in different rooms, and they won't impinge on whatever is going on in adjacent rooms, which gives us a lot of flexibility," he said.

A key feature of the state-of-the-art facility is that it can be easily cleaned—a crucial requirement to ensure a sterile manufacturing environment to produce patient products free of hospital-acquired infections.

"This facility is a new tool that NIH can use for [many] years looking forward," Somerville concluded. "Rather than designing a facility for where we are now, we've created flexibility...It is forward thinking." R



ON THE COVER: *Xist molecules shut down one of two female X chromosomes to avoid toxic protein levels, but they may also play a role in triggering autoimmune diseases.*

**IMAGE: DONNY BLISS/NIH OCPL**


### The NIH Record

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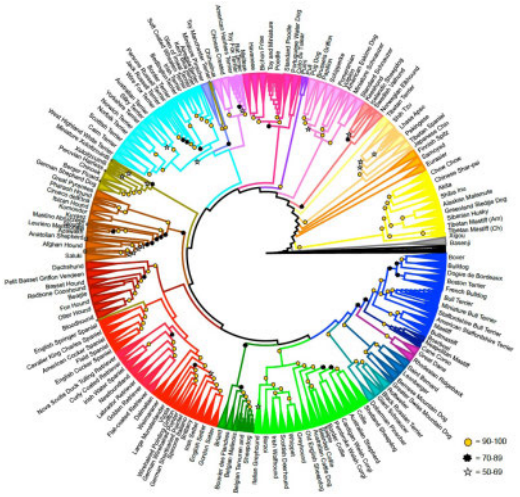


A dendrogram produced by Ostrander's lab shows that all dog breeds can be divided into 23 groups that share a common genetic history.

## Canine

CONTINUED FROM PAGE 1

explained Ostrander and her fellow NHGRI scientist Dr. Philip Shaw in a recent Demystifying Medicine lecture titled "Behavioral Genetics: Man Meets Dog."

The Demystifying Medicine series seeks to bridge the gap between advances in biology and their applications to major human diseases. This edition, host and NHGRI Scientific Director Emeritus Dr. Dan Kastner said, sought to demonstrate "how dog behavioral genetics can help us learn more about ourselves."

What makes dogs so attractive for genetics research?

They are numerous—about 90 million in the U.S. alone—and live in and are exposed to the same environments as their humans. Dogs have shorter lifespans, so researchers can study multiple generations. And owners, veterinarians and breeders are willing to share their dogs' data.

Ostrander's laboratory is a citizen science project; the lab doesn't have any of its own dogs but relies on data provided by its partners. The lab currently has about 40,000 samples.

By analyzing the genomes of individual dogs from 161 breeds, Ostrander was able to organize the breeds into a dendrogram—a branching diagram that shows the relationships of similarity among a group of entities. She used the dendrogram to illustrate the relatedness of the groups that all breeds of dog fall into—such as the herding group or terrier group—and found that they can be divided into 23 distinct clades, or groups that share a common genetic history.

"This is what makes dog genetics so cool," Ostrander explained. Because "dogs come with fantastic labels," (aka breeds) researchers can use those labels to begin to break down conditions that are harder to study in humans due to our lack of clean labels. One example is locus heterogeneity, where mutations in different genes can cause the same disease or condition.

Another helpful data visualization technique Ostrander's lab used was PHATE (potential of heat diffusion for affinity-based transition embedding), which allowed them to view dog lineages in a way that showed unlimited neighbors, rather than a bifurcate way like the original dendrogram.

Basically, Ostrander said, "it gave us more information about what led to what."

Her next goal was to use PHATE to map dog behavior. How? By studying genes that may be associated with stereotypic breed behaviors.

Ostrander's group decided to use the herding dog lineage which, as shown by the PHATE map, included a wide array of breeds with different herding and guarding behaviors. Ostrander focused on the true herders within the lineage.

Her lab conducted an enrichment analysis of the herders' DNA and found that they tended to share similar genetic variants in three types of axon guidance genes, each of which helps shape brain circuitry early in development. Of those genes, many are in ephrin (EPH) pathways. Of particular interest is EPHA5, for which DNA variants are observed in three-quarters of border collies, but less than 10% of non-border collie breeds.

EPHA5 has been implicated in anxiety and maternal pup-herding in mouse models. Could the border collie's herding drive be an augmentation of the anxiety-associated pathways that drive mouse maternal protective behaviors? That's a question for future studies, Ostrander said, but she's excited to investigate it.

Sometimes, though, those anxiety-associated pathways can lead to compulsive behaviors such as pacing or spinning.

"Preliminary genetic analyses have indicated genes that are implicated or associated with human psychiatric conditions [such as autism spectrum disorder, obsessive-compulsive disorder, schizophrenia and attention-deficit/hyperactivity disorder]," explained Ostrander.

Dog breeds that excel in agility competitions are more likely to have variants of a gene called ROBO1.

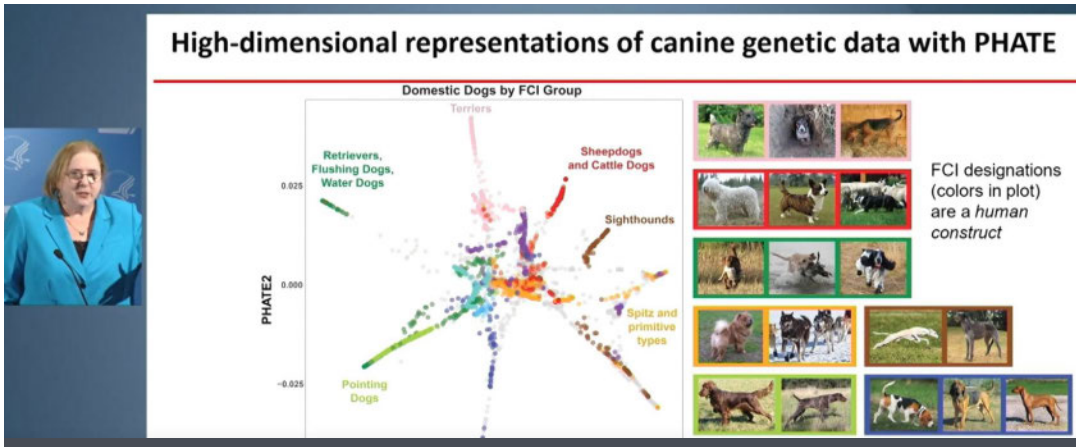
Interestingly, in humans, ROBO1 is associated with developmental dyslexia.

Human children who are affected may learn more effectively through images and diagrams than with written or spoken instruction, because their brains are better at processing visual information.

ROBO1 may help dogs excel at agility by helping them identify and learn environmental information, enabling them to speedily navigate obstacle courses.

These parallels between dogs and humans hold potential for future study, concluded Ostrander, and ultimately may lead to better treatments for both species.

The archived lecture can be viewed at https://videocast.nih.gov/watch=54037.




PHATE analysis is another way to visualize genetic data. Here, it shows that breeds belonging to different groups generally separated into distinct trajectories.

NIH Director Dr. Monica Bertagnolli speaks to graduates of the University of Utah School of Medicine on May 17.

**PHOTOS: UNIVERSITY OF UTAH HEALTH**

## Bertagnolli Delivers Commencement Address at Alma Mater

NIH Director Dr. Monica Bertagnolli returned to her alma mater recently as commencement ceremony guest speaker.

"So many people from so many walks of life are counting on you," Bertagnolli said, addressing graduates of the Spencer Fox Eccles School of Medicine at the University of Utah (U of U) on May 17. "You are the new generation to take on the challenge of caring for everyone with the wellbeing of your patients your highest priority. And I have tremendous confidence in you."

While at the university, she also visited a research laboratory at the Comprehensive Cancer Center at Huntsman Cancer Institute (HCI) and participated in a panel discussion on a documentary film, *dêtetsi vo'i oninjakan Winding Path*.

The movie features Eastern Shoshone medical student Jenna Murray, who attends U of U, describing the summers she spent with her grandfather on an Indian Reservation nd her healing journey from substance use disorder. The movie premiered earlier this year at the Sundance Film Festival and was nominated in the Best Short Program category.

Bertagnolli, Murray and several other panelists met to talk about topics raised in the movie. The panel was moderated by Dr. Maija Holsti, director of the Native American Summer Research Intern program.

A professor in the division of pediatric emergency medicine and department of pediatrics at Primary Children's Hospital, Holsti directs research education for the department, which supports several training programs for students who are under-represented in medicine. She is principal investigator on three NIH grants that support the internship and co-investigator on another NIH grant that supports the Genomics Summer Research Internship for Minorities.

Bertagnolli (second from l) visits a U of U lab with Dr. Martin McMahon (l), Cumming-Presidential chair of cancer biology and senior director of preclinical translation; Dr. Neli Ulrich (second from r), executive director of the Comprehensive Cancer Center at Huntsman Cancer Institute (HCI) and a Jon M. and Karen Huntsman presidential professor in cancer research in the U of U department of population health sciences; and Dr. Sheri Holmen (r), an HCI investigator and co-director of the Melanoma Disease Oriented Research Team, who is also a professor in the U of U School of Medicine surgery department.

**PHOTO: HUNTSMAN CANCER INSTITUTE**

Discussing a documentary film featuring medical student Jenna Murray (second from l), Bertagnolli (c) participated on a panel moderated by Dr. Maija Holsti (l), director of the Native American summer research intern program at the University of Utah School of Medicine. Also on the panel were Wallita Ranger (second from r), administrative program coordinator for the internship, and Dr. Michelle Debbink (r), co-chair of the Diversity, Equity and Inclusive Excellence Task Force in the university's department of obstetrics and gynecology.


Doudna (l) accepts an NIH Director's Lecture certificate from NIH Deputy Director for Intramural Research Dr. Nina Schor.

## Doudna

CONTINUED FROM PAGE 1

protect bacteria from infection or plasmid transformation.

"Amazingly, they can also be harnessed as technologies for manipulating genomes," Doudna said. "That's something we've been working on for over 10 years."

Last December, the FDA approved the first CRISPR therapy to treat sickle cell disease, a group of inherited red blood cell disorders that affect hemoglobin, the protein that carries oxygen through the body.

"What's extraordinary about this type of therapy is it's a one-and-done treatment that can correct a disease-causing mutation—or in the case of sickle cell disease—override the effect of a genetic mutation. This is incredibly motivating," she said. "Yet, we're still at the very beginning of this field and what will be possible with CRISPR."

The treatment uses the same CRISPR enzyme Doudna and Charpentier studied more than a decade ago, Cas9.

Although there are many more enzymes out there now, Doudna said Cas9 is "still one of the very best for manipulating genomes for reasons that we're still working to understand."

While CRISPR-based therapies are very exciting, "we have to grapple with the challenges, including the cost and the difficulty of delivering CRISPR into patients," she explained. Right now, a doctor removes a patient's bone marrow stem cells and edits the cells in a lab. The edited cells are returned after the patient's bone marrow is destroyed.

"We imagine a day where that won't be necessary," she said. "It could be possible to deliver the CRISPR genome editor directly into patients."

Doudna and her colleagues are now focused on improving Cas9 gene editors, even though they are already effective enough to use clinically.

Having enzymes that are robust, stable and very active at low concentrations "will be critical for reducing the amount of enzymes that you need to use in the clinic and for improving the specificity and the kinds of editing efficiencies that we can observe over time," she pointed out.

In 2017, her lab at the Innovative Genomics Institute started studying a protein from a thermophilic bacteria, or microbes that live in high-temperature environments, such as hot springs or deep-sea hydrothermal vents. Called GeoCas9, the high-temp protein has a similar structure—"a classic, clam shell shape that holds onto the RNA guide"—to other Cas9 proteins.

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***"What if we have a mechanism for delivery that would allow us to put these editing enzymes safely and efficiently into just the cells of the body where they could have clinical benefit? It would be transformative."***

-DR. JENNIFER DOUDNA

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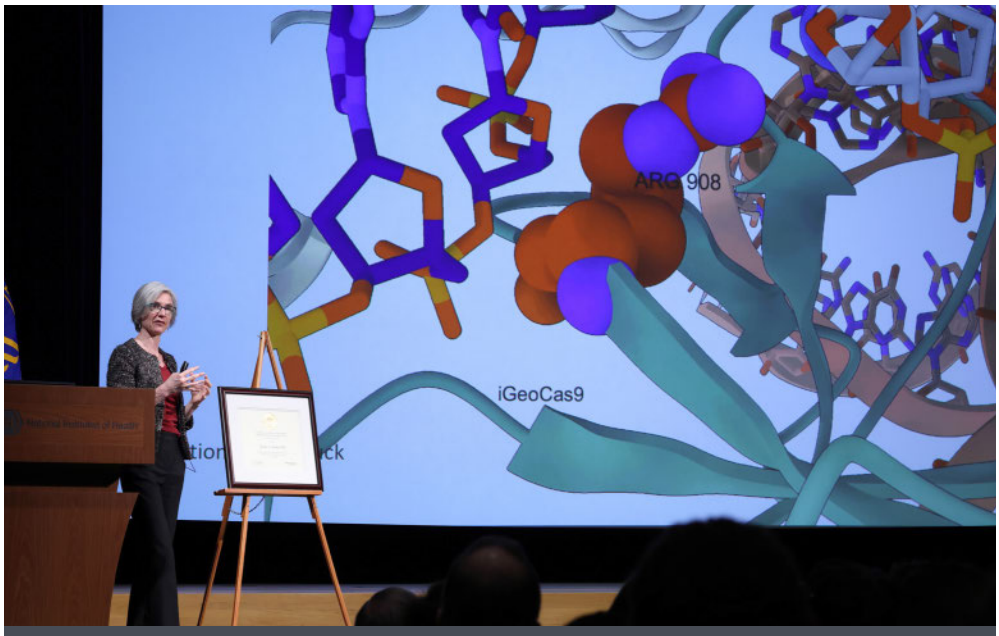
"These proteins work by using their RNA guides to interrogate DNA in a genome and identify sequences that match the RNA guide," she explained.

Compared to Cas9, GeoCas9 remains active at much higher temperatures. Perhaps because of this thermostability, GeoCas9 is highly stable in the presence of human serum, she said. Research is ongoing.

According to Doudna, figuring out how to deliver these treatments in vivo is at the "forefront of the field." Most patients who can benefit from an approved therapy using CRISPR-Cas9 can't access it because of the cost or the lengthy hospital stay as a result of a bone marrow transplant.

"What if we have a mechanism for delivery that would allow us to put these editing enzymes safely and efficiently into just the cells of the body where they could have clinical benefit?" she remarked. "It would be transformative."

Doudna's lab is studying several techniques to deliver CRISPR treatments more efficiently. Research "points in a direction that's very promising." A few years ago, a




Doudna and her colleagues are focused on improving the effectiveness of Cas9 gene editors.

**PHOTOS: CHIA-CHI CHARLIE CHANG**

postdoctoral student, Jenny Hamilton, demonstrated that the exterior envelope of a virus could be emptied and filled with Cas9 for precise gene editing in vivo.

Since then, these enveloped viruses have been altered so much that they are now referred to as enveloped delivery vehicles (EDVs). These EDVs are wrapped up like a virus and have molecular machinery on the surface that can recognize target cells. However, they are not infectious and they don't carry a viral genome.

"We've been working on how these EDVs are put together and how we can make them better," she said.

Improving the accuracy and delivery of CRISPR therapies to reduce the cost will make these treatments "that can be much more widely available ultimately globally," Doudna concluded.


The a capella group Nerds in Harmony present Nobel Laureate Dr. Jennifer Doudna with a t-shirt, making her an honorary member.

## Nerds in Harmony Perform *CRISPR Cas9*

After delivering her NIH Director's Lecture, "The Future of CRISPR: What's Ahead for Genome Editing," in Masur Auditorium, Dr. Jennifer Doudna attended a reception in the NIH Library. There, NIH's a cappella ensemble Nerds in Harmony performed their song *CRISPR Cas9*, sung to the tune of *Mr. Sandman* for the Nobel Prize laureate. The Nerds presented Doudna with a t-shirt, making her an honorary member.

Following her lecture, Doudna joins well-wishers at a reception in the NIH Library.

**PHOTOS: CHIA-CHI CHARLIE CHANG**

First formed by NIH fellows in 2004, the Nerds have a wide repertoire of a cappella renditions, covering barbershop, pop songs old and new, and holiday classics. They perform regularly on NIH's campus and around Bethesda and Washington, D.C.

Watch the live performance at https://sites.google.com/view/nerds-in-harmony.

Students from Bethesda-Chevy Chase High School visit NIH.

## COSWD Welcomes STEM Students from Local High School

Dr. Marie Bernard, NIH chief officer for scientific workforce diversity (COSWD), recently welcomed several students from Bethesda-Chevy Chase High School to NIH.

Before leading a tour of Bldgs. 1 and 10, COSWD staffers Drs. Montessa Mitchell, Glorivee Pagan-Mercado and Pamela Tamez described their journeys to NIH and encouraged the students to pursue their interests in science, technology, engineering and math.

The visit came about after Bernard accepted an invitation from Julia Meddin, president of the school's Minority Women in STEM club, to present on STEM careers at a club meeting last April.

In an email to the COSWD team, Meddin wrote, "It was very cool to see the UNITE hallway. It's amazing how much minorities have already made an impact on STEM and I hope in the future it will be completely normal to see women and minorities be the most successful doctors and scientists in the NIH and the field as a whole."

With the students from Bethesda-Chevy Chase High School are Drs. Montessa Mitchell (l), Marie Bernard (third from r), Glorivee Pagan-Mercado (second from r) and Pamela Tamez (r), all of COSWD.

## Tisdale

CONTINUED FROM PAGE 1

sickle cell disease for a very long time, since the early 1990s, when I found myself on the wards in internal medicine training taking care of patients, with nothing to give them," he recounted.

SCD is the most common single-gene inherited blood disorder in the world. It results from a misspelled beta globin that makes red blood cells rigid and misshapen, which obstructs circulation. When the red blood cells get stuck, areas just beyond are not getting oxygen.

"It can cause severe pain in muscles and bones and also causes organ damage from head to toe from these repeated episodes," said Tisdale, senior investigator in the Cellular and Molecular Therapeutics Branch of the National Heart, Lung and Blood Institute (NHLBI).

### Early Days in the Blood Factory

There is a cure for SCD. It was inadvertently discovered in the 1980s when a child received a bone marrow transplant intended to treat leukemia. By replacing the bone marrow, which produces blood cells, the transplant also cured the patient's SCD.

Back then, massive doses of chemotherapy were required prior to transplant. In adults, Tisdale noted, "the disease has ravaged their organs and made them ineligible for that kind of a transplant."

That spurred Tisdale's team to research whether such a transplant from a matched sibling could work without chemotherapy. Could they outsmart the immune system into accepting the graft using a combination of patient and donor bone marrow? Could the new, healthy red blood cells overtake and replace the sickled cells?

"It worked! That was our first success, where we could transplant adults with a chemotherapy-free transplant regimen," said Tisdale.

But only a small percentage of patients would be eligible. Most SCD patients don't have a fully matched sibling donor who also doesn't have the disease.

### Toward a Gene Therapy

All along, Tisdale's team was also exploring another type of transplant: gene therapy. Instead of relying on a donor, the bone marrow would be engineered from the patient. Their vision was to extract the patient's marrow and use viral vectors to insert the modified gene into the marrow's stem cells.

Tisdale (front row, second from l) and colleagues during a gathering at his house last July

"That way," explained Tisdale, "if we hijacked this virus and put the gene in, that's correctly spelled, we can take the patient's bone marrow, put it into culture in the flask, squirt this vector in, have it stick its DNA into those cells, and then give them back to the patient."

Tisdale recalled conducting such experiments in mice when he first arrived at NIH in 1994 as an NHLBI hematology fellow. The experiments worked in mice but later not in people. The first in-human studies showed gene transfer among the blood cells, but at insufficient levels.

"So we had to work for many years trying to fix the way we make the vectors, the way we cultured the cells, the way we get the patient ready to receive the cells," he said.

### Newly Approved Therapy

In December 2023, the Food and Drug Administration (FDA) approved two cell-based gene therapies for SCD in patients ages 12 and older. The approval came after Tisdale's team submitted results from their clinical trial launched 10 years earlier.

In the study, researchers developed a viral vector, the principal component coming from inactivated HIV, to deliver the gene therapy.

"The first patients had some benefit," Tisdale said. "Their hemoglobin went up. They had fewer pain events. But they still had disease."

They then discovered it was much more efficient getting bone marrow seeds from the blood than directly from the bone marrow. "That gave us a lot more cells to work with," he noted.

Tisdale's team kept honing the process. They became more efficient at inserting the gene into the marrow and they optimized the way they prepped patients for the transplant.

"We do require chemotherapy...so the cells that we give, that we fixed, can take over," he said.

In their final cohort of patients, severe pain events had resolved after the procedure. The treatment results mirrored that of a matched sibling bone marrow transplant, paving the way for FDA approval.

### Major Step on Long Path

The gene therapy treatment is no doubt a milestone; it's also costly and cumbersome.

"Sickle cell is a very expensive disease in general," Tisdale noted, from managing pain to treating strokes and multiple organ damage. "If you can cure it, or mitigate it, even with an expensive strategy, that should pay for itself."

New technologies and techniques are in the works to drive down costs.

"Ultimately, our goal is to try to [treat SCD] not in a flask—where we take the cells out...put the gene in, give cells back and support the patient after transplant," he said. "We'd like to do all of that inside the body, where we use what we know about viral vectors or about genome-editing strategies and put those tools in the patient's vein, direct them to the bone marrow by tagging that tool that, like a zip code, delivers this editing tool or vector to a specific address."

He concluded, "We're hopeful that we can take all of this complicated stuff, put it with an antibody, and just squirt it in the vein."

Tisdale's research continues and its potential is vast.

"Now, we can genetically modify bone marrow stem cells and fix the disease," he said. "It's a step in the direction of developing this into something that's more widely applicable." R

PROMOTE ROADWAY SAFETY

# Drivers, Pedestrians, Cyclists Urged to Practice Caution

As the weather warms and as summer sets in, pedestrian traffic around campus tends to increase. Motorists, cyclists and pedestrians all have a role to play in ensuring everyone's safety on the road. This is especially true during early-morning and late-evening hours.

Last year, Maryland saw 599 roadway fatalities, including 168 pedestrians and cyclists, according to information at https://zerodeathsmd.gov/resources/crashdata/crashdashboard/. Just this year on NIH's Bethesda campus, two pedestrians have been struck by vehicles and several near misses occurred in crosswalks.

Many of these incidents were avoidable. It requires all of us to adopt basic safety measures. The number of vehicles on the roads is increasing and pedestrian traffic is growing, as more NIH'ers return to campus. Practicing caution has never been more critical.

For nearly a year now, the Roadway Safety Working Group with members from across NIH, has been dedicated to this cause. They've made investments in infrastructure to create safer environments.

Over the winter, NIH Police conducted site visits to key intersections across campus to examine roadway behaviors and identify areas of concern, including the pedestrian crossing at the South Drive entrance on Old Georgetown Road, identified by staff as an issue.

In coordination with the Office of Research Facilities (ORF), the group initiated a massive repainting and repair of sidewalks and crosswalks to increase visibility. Nearby hedges and other foliage have been trimmed so motorists can identify pedestrians from greater distances. Campus shuttle passengers may have noticed an audio reminder as they disembark to be mindful of their surroundings and watch for oncoming traffic.

In addition to these situational prompts, NIH Police have also begun greater enforcement of the 25 mph speed limit.

Other initiatives are upcoming. A contract has just been acquired to refurbish the Bethesda campus's Mid-Block Crosswalk Light System, which features a series of flashing lights to alert drivers to a crossing pedestrian.

The working group is also planning a grassroots education campaign to boost vigilance for everyone who enters campus. Moreover, they are working to incorporate roadway safety information into onboarding for all NIH staff.

We all play a role in making our campus a safer place to navigate, and your experience is essential to making that a reality. Are there key areas or intersections that need greater attention? What tactics would ease your experience on NIH roadways?

Staff are encouraged to report issues and share their experience via the Safety Talk Back reporting tool at https://go.nih.gov/1oWuk5f. It only takes a minute to complete and can make a real difference in how we keep our NIH community safe.

Use this QR code to go directly to the Safety Talk Back web page.

However, enhancements in campus infrastructure are not enough. In addition to reporting areas of concern, practicing good roadway safety behavior among motorists, cyclists and pedestrians is critical. Much of this risk mitigation can seem like second nature, but it can be easy to grow complacent and lose vigilance.

Drivers are reminded to uphold safety standards. This includes adhering to speed limits (25 mph across campus, 5 mph in all parking garages), yielding to pedestrians at crosswalks and refraining from distracted or impaired driving.

The Bethesda campus hosts researchers and patients from around the globe; some may be unfamiliar with American traffic patterns. Use caution and discernment.

Similarly, cyclists should obey all posted signage and yield the right-of-way to pedestrians in crosswalks. Adherence to campus speed limits is also relevant for cyclists—some of our hills can vault cyclists to exceed 25 mph.

Those riding bikes and e-bikes on campus should also practice distraction-free navigation to be fully attuned to their environment.

Increasing cyclist visibility can also make the difference for a safe commute. The NIH Fire Department distributes high-visibility safety reflective sashes that can be worn around your body or wrapped around a backpack to help during low-light times for cyclists and pedestrians. To receive a reflective sash, email Fire Chief Stephen Teagarden at Stephen.teagarden@nih.gov.

Above and below, among several crosswalks viewed on the Bethesda campus, one pedestrian is taking advantage of the safety stripes and one is not.

Pedestrians play an equally vital role in maintaining safety on the streets. Small actions like sticking to designated crosswalks, obeying traffic signals and increasing visibility can have a big impact. Practicing situational awareness is also key—never assume flashing lights at a crosswalk will have a desired effect for oncoming vehicles. Put away phones and turn off headphones/earbuds and other distractions when crossing the street. Such actions can also dramatically lower accidents on NIH roadways.

Fostering a culture of safety requires ongoing public awareness and education. By nurturing a collective commitment to responsible road behavior, communities can significantly reduce the incidence of accidents.

As roadways continue to evolve, a combination of education, enforcement and infrastructure improvements can create environments where accidents are minimized and lives are preserved. Ultimately, practicing caution and mutual respect on the roads will pave the way for a safer and more enjoyable campus for all.

## Endurance Exercise Affects Every Tissue

A large research project in young adult rats has found that all bodily tissues tested respond to exercise training. More than 35,000 biological molecules respond and adapt to endurance exercise over time, including tissues from organs not usually associated with exercise.

Researchers also found differences in responses between male and female rats that were more widespread than anticipated, highlighting the importance of including animals of both sexes in preclinical research.

IMAGE: PANUMAS YANUTHAI/SHUTTERSTOCK

The NIH-funded effort used data from thousands of analyses of 19 tissue types and identified molecular changes in genes, proteins and metabolites. Findings are published in a group of papers in *Nature*.

While molecular changes were seen in all tissues, the way in which each tissue responded was unique. For example, effects on the functions of mitochondria—cellular hubs for energy production and metabolism—were observed across the body yet the specific changes observed differed depending on the tissue.

Mitochondria in the adrenal gland responded substantially to endurance training, including a change in regulation of nearly half the mitochondria-associated genes. This was surprising; adrenal glands had not been previously explored in detail for their role in exercise.

Additionally, differences were found in molecular responses to endurance exercise between young male and female rats in most tissues tested, including the brain, adrenal gland, lung and fat tissue. The findings could play a role in researching how exercise interventions could be recommended for men or women experiencing conditions such as obesity.

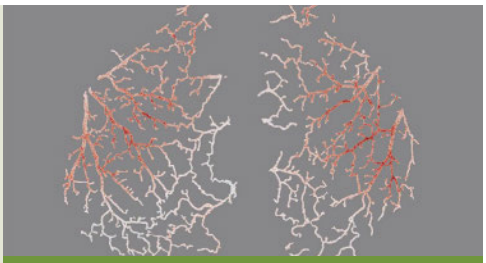
The data is helping scientists create a map of molecular changes in the body following exercise. Studies in rats allow for analysis of a wider range of tissue types compared to human studies. The resulting knowledge will guide researchers in analyzing the human data.

Researchers are currently conducting an exercise study in humans to better understand why the body responds to exercise and how much the response varies for people of different ages, sexes, body compositions and fitness levels. This research was funded by the NIH Common Fund in collaboration with NIA, NIAMS and NIDDK.

## Blood Flow Makes Waves Across Surface of Mouse Brain

Researchers have, for the first time, visualized the full network of blood vessels across the cortex of awake mice, finding that blood vessels rhythmically expand and contract leading to "waves" washing across the surface of the brain. These NIH-funded findings improve understanding of how the brain receives blood, though the function of the waves remains a mystery.

A network of elastic and actively pumping vessels carrying oxygenated blood span the surface of the brain before entering the cortex. There, they feed into a second network of capillaries that supply oxygen deeper into the tissue. In addition to the pulses of blood flow that occur with each heartbeat, there are slower waves of blood flow changes that sweep across the brain and occur about once every ten seconds. The change in blood flow that occurs with these slow waves was up to 20% of the entire brain blood supply. Surprisingly, this phenomenon was only weakly tied to changes in brain activity.



Blood flows in ripples across the brain. Red color shows blood vessels expanding as blood flow increases.

IMAGE: NINDS

The waves produced visible bulges in the blood vessels, which will aid in mixing the fluid around the brain's cells. This mixing activity could aid in removing misfolded proteins and other components from the brain into the cerebrospinal fluid that surrounds it. This process is considered an important protective mechanism for a variety of neurological disorders, such as Alzheimer's disease and other related dementias, and is more active during sleep.

Findings may also affect current approaches to interpreting fMRI scans, which measure changes in blood oxygenation within brain structures as they are activated. This research was funded by NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, NINDS, NIMH and NIBIB.

## Acetaminophen Shown Beneficial in Patients with Sepsis

An NIH-supported clinical trial found that intravenous acetaminophen reduced sepsis patients' risk of having organ injury or developing acute respiratory distress syndrome, a serious condition that allows fluid to leak into the lungs. Sepsis is the body's uncontrolled and extreme response to an infection.

IMAGE: THAIVIEW/SHUTTERSTOCK

While the trial did not improve mortality rates in all patients with sepsis regardless of severity, researchers found that acetaminophen gave the greatest benefit to the patients most at risk for organ damage. With the therapy, those patients needed less assisted ventilation and experienced a slight, though statistically insignificant, decrease in mortality. The study was published in *JAMA*.

In sepsis, red blood cells become injured and die at abnormally high rates, releasing "cell-free hemoglobin" into the blood. The body becomes overwhelmed and can't remove this excess hemoglobin; this can lead to organ damage. Previous work from Dr. Lorraine Ware at Vanderbilt University, first author of the current study, showed that acetaminophen, in addition to relieving pain and reducing fevers, can block the harmful effects of cell-free hemoglobin on the lungs, which are at major risk of injury during sepsis.

To test the therapeutic potential of acetaminophen more fully in a mid-stage clinical trial, researchers enrolled 447 adults with sepsis and respiratory or circulatory organ dysfunction at 40 U.S. academic hospitals from October 2021 to April 2023. Patients were randomized to receive either acetaminophen or a placebo intravenously every six hours for five days. The researchers then followed the patients for 28 days to see how they fared.

Researchers found that intravenous acetaminophen was safe for all the sepsis patients, with no difference in liver injury, low blood pressure or other adverse events compared to the placebo group. Among secondary outcomes, they also found that organ injury was significantly lower in the acetaminophen group, as was the rate of acute respiratory distress syndrome onset within seven days of hospital admission.

More research is needed to uncover the mechanisms and validate these results.

## New NIH Tree Honors Career of NINDS's Fischbeck

BY SHANNON E. GARNETT

On May 1, the Kennedy's Disease Association (KDA) joined with members of the Division of Intramural Research (DIR) at the National Institute of Neurological Disorders and Stroke (NINDS) to plant a tree on the NIH campus honoring the research and achievements of Dr. Kenneth "Kurt" Fischbeck, one of the nation's leading scientists in the field of neurogenetics—the study of genetics in the nervous system.

The commemorative tree celebrates the distinguished career of Fischbeck who served as chief of the Neurogenetics Branch in the NINDS DIR from 1998 until his retirement in December 2023. Fischbeck dedicated his career to advancing the understanding and treatment of hereditary neurological and neuromuscular diseases, such as Kennedy's disease.

Also known as spinal bulbar muscular atrophy (SBMA), Kennedy's disease is a rare inherited neuromuscular disorder that causes muscle weakness and atrophy. Currently, there is no cure or specific treatment. Therapy is symptomatic and supportive.

Dr. Kenneth Fischbeck holds the golden shovel during the tree planting.

"It's fitting that it is such a beautiful day when we are commemorating the work of Kurt's branch with something living that will take root and grow," said Kathy Thompson, KDA corporate secretary. "This symbolizes his contributions to the KDA and Kennedy's disease research. He has built this effort into something larger than it was when it started out."

Fischbeck joined NINDS in 1998 as chief of the newly formed Neurogenetics Branch. In that role, he oversaw and coordinated intramural research programs related to neurological disorders that have a genetic component. His laboratory focused on identifying the causes and studying the mechanisms of hereditary neurological and neuromuscular diseases with the goal of developing effective treatments for the disorders.

"Kurt has been with us since the beginning," said KDA President Terry Thompson. "He has become the face of SBMA research for the KDA membership, listening to patients and their families and providing advice on their situations. He's really great at spending the time to listen and understand the impacts of this disease on their lives."

The sugar maple tree (shown at right) was planted on the side of the PNRC facing Old Georgetown Rd.

PHOTOS: ERIN BRYANT/NINDS

The sugar maple tree, which was specifically selected by Fischbeck, was planted on the side of the Porter Neuroscience Research Center (Bldg. 35) facing Old Georgetown Rd. In a few weeks, a brass plaque will be placed at the site with the inscription "In appreciation to the NINDS Neurogenetics Branch from the Kennedy's Disease Association."

"The location for this tree was intentional," Terry Thompson explained. "It is adjacent to the Neurogenetics Branch lab so you can look out the window and be reminded of the great leadership Kurt provided for the past 25 years. In the spring, when the tree begins to leaf out, you can think of the promise your work is providing for so many Kennedy's disease patients. In summer, you can take a break in the shade and reflect back on how far you've come in understanding this disease. And in the fall, when the tree is at its peak of brilliant color, you can think of the world-class contributions you are making towards the goal of finding a cure for this devastating disease."

Fischbeck earned both his bachelor's degree in biochemical sciences and his master's degree in biology from Harvard University, and his medical degree from Johns Hopkins University. He later trained at the Case Western Reserve University Hospital in Cleveland and at the University of California, San Francisco. In 1980, he served as a research fellow in neurology at the University of Pennsylvania. Before coming to NIH, he was a professor of neurology at the University of Pennsylvania (UPenn) from 1982 to 1998. And in 1992, he served as a Boerhaave visiting professor at the University of Leiden in the Netherlands.

Representatives from the Kennedy's Disease Association join with members of NINDS's Division of Intramural Research to honor the career of Fischbeck.

"Kurt's work on Kennedy's disease goes back even further (than NIH)," said KDA's president. "He was lab director at UPenn in 1990 when one of his graduate students discovered the gene mutation causing the disease. Since that time, Kurt has mentored and developed SBMA researchers in many countries. He has been the major influence in the SBMA research effort around the world."

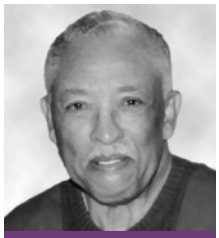
Throughout his career, Fischbeck has received numerous awards and accolades including the Cotzias Award from the American Academy of Neurology and the Jacoby Award from the American Neurological Association. In 1999, he was elected to the Institute of Medicine of the National Academy of Sciences.

"Congratulations on your retirement, Kurt," said Terry Thompson. "We should all meet back here when a cure for Kennedy's disease is finally discovered."

## Former NIH Mail Manager Arnwine Is Mourned

Bill Arnwine, retired NIH mail manager and former chief of the Travel and Administrative Services Branch, passed away Apr. 19 at age 89.

Born in Jacksonville, Tex., and raised in St. Louis, Mo, Arnwine graduated from Lincoln University of Missouri in 1958. Afterwards, he began a decorated career in the U.S. Army including both active duty and reserves, serving in Vietnam where he earned the Bronze Star and two Purple Hearts.



Retired NIH'er Bill Arnwine
Below, a 1982 *NIH Record* story announced his Army command appointment.

Following active duty, Arnwine began a long federal career working in a variety of capacities at NIH and the Department of Defense. At NIH, he was responsible for announcing and overseeing mail handling and postal service management procedures, specifically those involving bulk mailings.

In 1982, an *NIH Record* item noted that he had been appointed commander of the 7th Psychological Operations Battalion, U.S. Army Reserve. Lt. Colonel Arwine's headquarters for this 450-man reserve unit was located in Prince George's County, Md. The batallion had a strategic psychological operations mission in support of U.S. military European forces.

Arnwine is survived by six children, seven grandchildren and two great-grandchildren. R

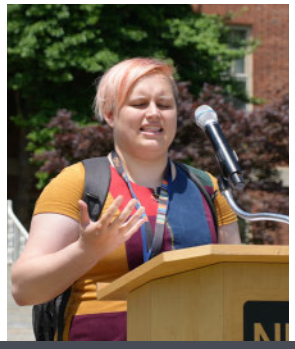
## NIH Kicks Off Pride Month with Flag Raisings

Members of the NIH community gathered June 4 on Bldg. 1's front lawn to raise the Pride flag in honor of Pride Month. A ceremony featured speakers from NIH's Office of Equity, Diversity and Inclusion, LGBTQ+ Fellows & Friends and Salutaris, an employee resource group that promotes health and inclusivity for the LGBTQIA+ community.

The Pride flag also hangs at NIAID's Rocky Mountain Laboratories visitor center in Hamilton, Mont.

The theme for Pride Month 2024 is "Pride in Belonging," which embodies the ongoing journey of recognizing, embracing and uplifting LGBTQIA+ people across NIH and beyond.

Raising the Pride flag signifies that LGBTQIA+ people are welcome and celebrated at NIH, while also demonstrating the agency's commitment to elevating these communities' voices and perspectives.



At the flag-raising ceremony on the Bethesda campus are (from l) Monique Robinson, principal strategist for the Sexual & Gender Minority portfolio in NIH's Office of Equity, Diversity and Inclusion (EDI); Danny Dickerson, director of EDI's Division of Inclusion and Diversity; Milo Taylor of NIH LGBTQ+ Fellows & Friends; and Dr. Jordan Gladman, outgoing chair of Salutaris.

**PHOTOS: ERIC BOCK**

Above, Staff Scientist Dr. Audrey Chong (l) and Associate Director for Scientific Management Dr. Marshall Bloom raise the Pride flag shown below at NIAID's Rocky Mountain Laboratories visitor center in Montana.

**PHOTOS: NIAID**

Robinson (r) and Sgt. Matt Mehlhaff of the NIH Police unfurl the Pride flag before raising it.