

## THERMOSTAT FOR SLUMBER?

### Optogenetics Pioneer Reports Progress on Deciphering Sleep

BY CARLA GARNETT

Researchers have wondered for decades why and how we fall asleep. To solve several age-old questions about slumber, investigators are using a relatively young scientific technique—optogenetics—to study fruit flies hooked to treadmills.

“Sleep is one of the great biological mysteries—each night we disconnect ourselves from the world for 7 or 8 hours, a state that leaves us vulnerable and unproductive,” explained Oxford’s Dr. Gero Miesenböck in an NIH Neuroscience Seminar Series lecture



Oxford’s Dr. Gero Miesenböck talks about configuring the brain for sleep.

held recently. “Despite these risks and costs, we do not know what sleep is good for.”

Miesenböck pioneered optogenetics, a technique scientists can use to manipulate nerve cells—neurons—that have been genetically altered to be sensitive to light. In 2010, the technique was named “Method of the Year” by journals across scientific

disciplines and *Science* magazine called it “Breakthrough of the Decade.”

The Waynflete professor of physiology and founding director of the Centre for Neural Circuits and Behaviour at Oxford University, Miesenböck illustrated the power of optogenetics in a talk titled “Light Sleep.”

“Most of us in this room have used techniques he designed,” said NICHD senior investigator Dr. Mark Stopfer, introducing the speaker. He said that in Miesenböck’s case, necessity must be the father of invention because he’s capable of developing the precise tools he needs to tackle large scientific puzzles.

“This ‘big question’ approach is what I like best about his work,” Stopfer said.

At NIH to discuss “neural control of sleep as an illustration of what optogenetics has enabled us to do,” Miesenböck recalled his first goals for the method.

SEE **SLEEP**, PAGE 4

### Excess Growth Hormone Increases Risk of Heart Disease, Diabetes

BY ERIC BOCK

Diseases of excess growth hormone, such as gigantism and acromegaly, may initially



Dr. Andrew Demidowich

present with a variety of signs and symptoms, including diabetes, said Dr. Andrew Demidowich during a recent Grand Rounds lecture in Lipsett Amphitheater. “The terms gigantism and acromegaly

get thrown around together, but they’re not equivalent; they’re a little different,”

SEE **GIGANTISM**, PAGE 8

### NIDCR’s Boehm Travels to Africa for CDC Fellowship

BY DANA TALESNIK

Karina Boehm enjoys a good challenge. A lifelong interest in other languages and cultures inspired her to apply for a CDC-led global health training program. Once accepted, she eagerly awaited news of her country assignment.



Karina Boehm

Fluent in French, Boehm expected to be heading to a French-speaking African nation for the summer. While she did end up in Africa, much to her surprise, she was assigned to one of the world’s poorest

SEE **BOEHM**, PAGE 6



A patient’s journey from Puerto Rico, p. 12.

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## NIH To Host Rare Disease Day Event, Twitter Chat

Rare diseases affect an estimated 25 million Americans. On Mar. 1, NIH will host an event to raise awareness about these disorders, the people they affect and current research collaborations.

Sponsored by the National Center for Advancing Translational Sciences and the Clinical Center, Rare Disease Day at NIH will take place from 8:30 a.m. to 4 p.m. in Masur Auditorium, Bldg. 10. The event will



**RARE DISEASE DAY** at NIH  
March 1, 2018 | #RDDNIH

feature presentations, interactive panel discussions, posters, exhibits and tours of the Clinical Center. Admission is free and open to the public. In association with Global Genes, participants are encouraged to wear their favorite pair of jeans.

Learn more about Rare Disease Day at NIH at <https://ncats.nih.gov/rdd>. Visit [https://events-support.com/events/NIH\\_Rare\\_Disease\\_Day](https://events-support.com/events/NIH_Rare_Disease_Day) to register and view the agenda. Be sure to follow the event on social media at #RDDNIH.

Prior to the event, NIH is hosting a Twitter chat on rare diseases on Friday, Feb. 23 from 1 to 2 p.m. The chat will feature NIH director Dr. Francis Collins and NCATS director Dr. Christopher Austin as well as representatives from the rare diseases advocacy community. Join in the conversation via #NIHChat.

## New Web Page Offers 'Hope'

NIH has created a new web page—[www.nih.gov/hope](http://www.nih.gov/hope)—aimed at advancing NIH's mission of hope. The page provides quick links to various things that people from all walks of life can do to help NIH. Such actions range from speaking up about the positive impacts of biomedical research to enrolling in clinical trials to pursuing careers in science. The web page was developed by NIH OD's Office of Communications and Public Liaison, based on input from NIH scientific and administrative leadership. To spread the word about this new resource, NIH director Dr. Francis Collins plans to feature the page in many of his presentations to groups across the country in 2018.

## DASH Ranked Best Diet Overall

For the 8th consecutive year, *U.S. News and World Report* ranked the NIH-developed DASH Diet "best overall" diet among nearly 40 it reviewed. The announcement came just as new research suggests that combining DASH, or Dietary Approaches to Stop Hypertension, with a low-sodium diet has the potential to lower blood pressure as well as or better than many anti-hypertension medications.

With its focus on vegetables, fruits, whole grains, low-fat dairy and lean proteins, DASH tied this year for "best overall" diet and was ranked No. 1 in the "healthy eating" and "heart disease prevention" categories.



On hand at the dedication of the William E. Paul Conference Room are NIAID director Dr. Anthony Fauci (l), VRC deputy director Dr. Richard Koup (second from l), VRC director Dr. John Mascola (fifth from l) Paul's widow, Marilyn, and his sons and granddaughter.

PHOTO: CHIA-CHI CHARLIE CHANG

## NIAID Dedicates Conference Room to Paul

NIAID recently honored the memory of Dr. William E. Paul by dedicating a conference room in his name at the Vaccine Research Center. Paul served as chief of NIAID's Laboratory of Immunology from 1970 until his death on Sept. 18, 2015. He was also director of NIH's Office of AIDS Research from 1993 to 1997.

Paul is remembered annually through an NIH Director's Wednesday Afternoon Lecture Series talk named in his honor. The lecture recognizes outstanding contributions to the immunology field. The 2017 William E. Paul WALS lecture was given by NCI's Dr. Thomas Waldmann, NIH distinguished investigator and co-chief of the Lymphoid Malignancies Branch.




According to the World Health Organization, hypertension, more commonly referred to as high blood pressure, is the most common chronic condition worldwide. It is a major risk factor for heart disease, affects 1 billion people and accounts for 1 in 8 deaths each year.

Researchers funded by NHLBI developed DASH to prevent and treat high blood pressure, but the diet also has proven highly effective in lowering blood cholesterol.

"The consistent high rankings of DASH over the years bode well for the way the diet is received and adopted, not just by health professionals, but also by the public at large," said Janet de Jesus, registered dietitian and program officer

at NHLBI's Center for Translation Research and Implementation Science. "This is especially gratifying now that new research underscores the significant blood-pressure lowering effects of a reduced intake of sodium in combination with the DASH diet."

## Now Online, On Demand: Principles of Clinical Pharmacology Course

This past November, the NIH Principles of Clinical Pharmacology course relaunched online. It is a free lecture series covering the fundamentals of clinical pharmacology as a translational scientific discipline. The course consists of approximately 50 lectures by thought-leaders from around the world. Topics covered in the course include pharmacokinetics, drug metabolism and transport, drug therapy in special populations, assessment of drug effects, drug discovery and development, pharmacogenomics and pharmacotherapy. Registration is now closed, but mark your calendar for the 2018-2019 course, which is targeted to open registration in September. There is no continuing education credit offered for the course. However, a certificate of completion is awarded to registered participants who achieve a passing score on the final examination. For more information on the course, visit <https://www.cc.nih.gov/training/training/principles1.html> or contact the course coordinator at [cc-od\\_clinp@mail.cc.nih.gov](mailto:cc-od_clinp@mail.cc.nih.gov). 

## NIGMS Hosts High School Career Day

Many students dream of becoming scientists and making the next great discovery, but they don't always know the best way to get there. NIGMS recently welcomed six juniors from Bethesda-Chevy Chase High School as part of B-CC's annual High School Career Partnership Day.

The students had an opportunity to explore what it means to be a scientist at NIH while also receiving career and college advice. They were all thinking about scientific careers before arriving on campus, but they left realizing there are even more opportunities and paths than they had imagined.

The students were greeted by NIGMS director Dr. Jon Lorsch, who gave an overview of the institute and the importance of basic biomedical research. He noted that NIGMS has funded the cutting-edge basic research of 87 Nobel laureates over the years.

NIGMS postdoctoral fellows then took the students on tours of their labs. The



Students from Bethesda-Chevy Chase High School meet with NIGMS director Dr. Jon Lorsch and other NIGMS staff as part of the school's Career Partnership Day.

PHOTO: SALLY LEE

scientists do have to use math, the youngsters seemed relieved to hear that calculators are allowed after high school.

In a tour of the Clinical Center, the students saw firsthand how research moves from the lab to the bedside. They learned about clinical trials at NIH and how clinicians do important research as well.

Like most juniors, they were thinking about colleges, research opportunities and what majors they should declare if they want to be scientists. They spoke with a range of NIGMS staff—postdocs, program officers, Lorsch and NIGMS Executive Officer Sally Lee. Everyone in the room had a different major, college and experience that led them to NIGMS.

The biggest takeaway from the day was that there isn't just one path to becoming a scientist.

The day offered students reinforcement and motivation to pursue careers in science and expanded their view of what scientists do and how they can contribute.

In an evaluation form at the end of the day, one student said the career day "helped me figure out what I want to do in the future and work at NIH." Inspiring future scientists and NIH employees is always a good day's work at NIGMS.—Ashley Swanson **R**

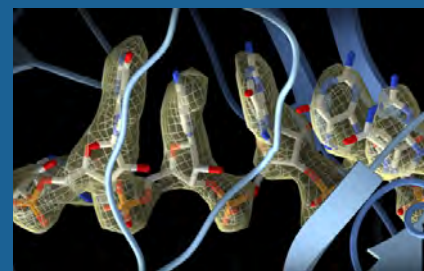


NIGMS PRAT fellow Erin Wall (r) shows B-CC students how to streak a petri dish to grow bacteria.

PHOTO: ASHLEY SWANSON

students got to hear about research in engineering, microbiology, biophysics and immunology and see what a typical day is like for a scientist working in the lab.

Uppermost in students' minds was, "Do you have to do a lot of math?" While



ON THE COVER: RNA incorporated into the CRISPR surveillance complex is positioned to scan across foreign DNA. Cryo-EM density from a 3Å reconstruction is shown as a yellow mesh.

IMAGE: NATIONAL RESOURCE FOR AUTOMATED MOLECULAR MICROSCOPY

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Miesenböck gives a Neuroscience Seminar Series lecture at NIH's Porter Bldg.

## Sleep

CONTINUED FROM PAGE 1

Almost 20 years ago, he hoped technologies such as optogenetics would accomplish three things: First, “pinpoint the neural causes of behavior and cognition in a way that had previously been inaccessible.”

As a young scientist in training, he said he remembers one mantra being drilled into him daily—“reconstitution, reconstitution, reconstitution.” In order to understand a biological system, Miesenböck was taught, an investigator has “to be able to take it apart and put it back together.”

“As a biochemist,” he explained, “that means you have to purify the enzymes that you think are responsible for a particular biological process and then reconstitute the process from the purified components.”

What would be the equivalent approach for a neuroscientist?

“Metaphorically speaking, you have to purify the electrical activity patterns that underpin our mental lives and play them back into the nervous system,” he said. “And if you can do that—and in this way recreate perception, action, memory and emotion—then you will have a credible claim that you really understand the causes of neural events.”

The other doors he hoped optogenetics would help open included the search for connections between key neurons and the dissection of mechanisms at work within specific systems.

All three goals were realized over the past two decades. In recent years, his team

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*“The answer to the mystery of sleep will probably be found in understanding the sleep homeostat [which] measures something...that happens in our brains while we are awake. When that something reaches a threshold, we fall asleep.”*

-DR. GERO MIESENBOECK

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has turned its attention to another, more elusive quest.

Quoting renowned sleep research pioneer Dr. Allan Rechtschaffen, Miesenböck said, “‘If sleep did not have an absolutely fundamental purpose, then it would probably be the biggest mistake that evolution has ever made.’ But the question is, what is that purpose?”

Scientists know that two systems govern slumber—the circadian clock and what’s known as the “sleep homeostat.”

Studies of fruit flies back in 1971 gave the first clue of what determines a basic 24-hour wake/rest cycle that reigns over most organisms with nervous systems. This cycle anticipates predictable occurrences in the environment—darkness, for example—caused by Earth’s rotation and ensures we sleep when it suits our lifestyle best.

“Turns out, we know a lot about the mechanics of the circadian clock,” Miesenböck explained. Then, showing a blank screen, he quipped, “This slide summarizes much of what we know about the sleep homeostat.”

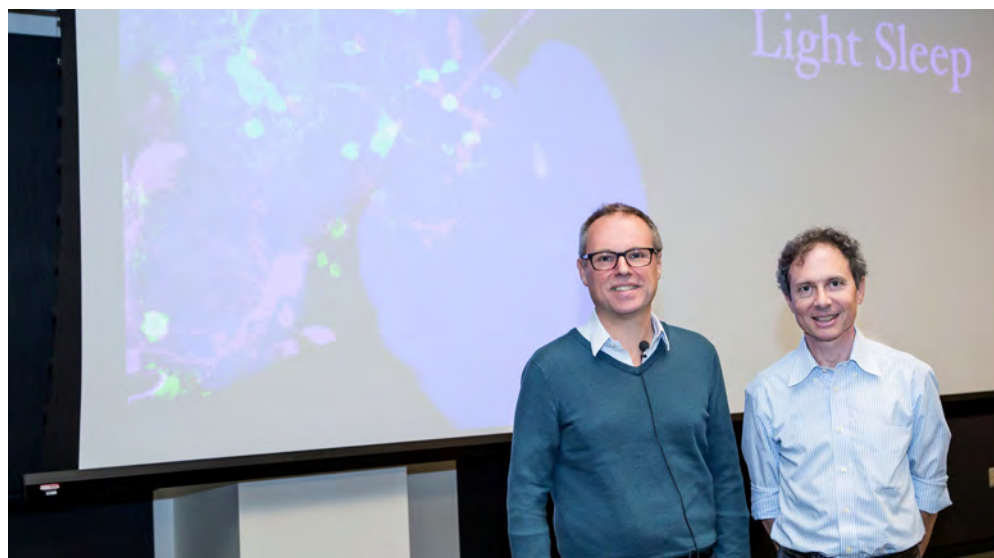
“The answer to the mystery of sleep,” he continued, “will probably be found in understanding the sleep homeostat [which] measures something—and we don’t know what that something is—that happens in our brains while we are awake. When that something reaches a threshold, we fall asleep.” The cycle resets itself as we rest.

“If we knew what that something is that accumulates or depletes to threshold,” Miesenböck said, “then we would have a very, very important piece in the puzzle of sleep.”

To try to understand why the brain turns itself off at night, the investigators returned to the simple nervous system of *Drosophila*, the fruit fly.

Each fly contains a couple dozen sleep-promoting neurons in a cell cluster that Dr. Jeff Donlea, a former member of Miesenböck’s team who is now at UCLA, identified when he was a graduate student in Dr. Paul Shaw’s group. Other animals, including humans, are thought to have neurons playing similar roles in inducing sleep.

“Optogenetics has shown us that these neurons exert a powerful influence on



Miesenböck with NICHD senior investigator Dr. Mark Stopfer, who introduced the speaker

PHOTOS: CHIA-CHI CHARLIE CHANG



Miesenböck and company devised an apparatus that lets them monitor fruit flies running on tiny treadmills or Styrofoam rollerballs.

IMAGE: MIESENBOECK GROUP

sleeping and waking.” The neurons have nothing to do with the circadian cycle, but convey the output of the sleep homeostat.

Miesenböck and company devised an apparatus that lets them monitor fruit flies running on tiny treadmills or Styrofoam rollerballs. Because fruit flies aren’t known to walk in their sleep, he joked, the investigators surmise that when the rollerball stops spinning, the flies have fallen asleep.

The scientists were able to put the flies to sleep optogenetically by stimulating the sleep-inducing cells with a short burst of light. Reacting to the optical signal, the neurons ramp up their work and the flies go to sleep.

Over time, the researchers learned to reverse the effect—also optogenetically—by signaling release of dopamine to the neurons, which short-circuits the sleep-inducing neurons’ electrical work and wakes the flies.

Miesenböck’s group had successfully deconstructed and rebuilt the brain’s process of slumber. They published their most recent findings about this on/off switch in 2016.

“What I’ve described is a mechanism that you’re familiar with, because you have it on the walls of your living room,” Miesenböck said.

Much like the thermostat that controls a room’s temperature, your brain has a sleep homeostat that regulates your shuteye. **R**

## AT NIEHS

### Fast-Paced Ethics Day Informs, Educates

The 8th annual NIEHS Ethics Day featured a fast-paced review of ethics topics in science and government. Led by NIEHS Ethics Office Director Bruce Androphy, the recent event included guest speakers, a roundup of the year’s ethics offenders and required training. This was the second year that Ethics Day participation was an accepted alternative to the online course.

Dr. Eric Juengst, director of the Center for Bioethics at the nearby University of North Carolina at Chapel Hill and a former ethicist at NIH, addressed the rapidly evolving field of gene editing.

Dr. Elise Smith, a postdoctoral research fellow in Androphy’s office, made a surprising finding while studying misbehavior in scientific research. Her survey reached more than 6,000 researchers worldwide to study factors—such as seniority, power and gender—that influenced authorship in published research papers. Among the responses she received were several reports of sabotage by fellow lab members. Some actions—including slowing down the research process, limiting access to equipment and harsh peer review of papers—did not fall under the definition of misconduct used by the NIH Office of Research Integrity.

Looking into predictors to discover ways to prevent such sabotage, Smith found that conditions such as lack of autonomy, perception of injustice and frustration with an organization appeared to contribute. “We need to find a way to disagree in an ethical manner that doesn’t push individuals to need or want to retaliate or to sabotage another’s work,” she said.

Attorney Justina Fugh, senior ethics counsel for the Environmental Protection Agency, shared examples from the Volkswagen emissions control scandal to highlight the nuances of determining ethical bounds.

NIEHS bioethicist Dr. David Resnik invited the audience to identify photos of 2017’s ethics baddies, as he called them. Images ranged from the journal *Tumor Biology*, which retracted 107 papers, to leaders at VW.—Kelly Lenox



Dr. David Resnik was recently elected fellow of the American Association for the Advancement of Science, underscoring the importance of scientific ethics.



Justina Fugh said VW software shifted operations to reduce emissions when the engines were being tested. Other times, it bypassed controls to improve fuel efficiency. Bruce Androphy developed the popular Ethics Day format, which attracts a larger audience every year.

PHOTOS: STEVE MCCAWE



Above, Boehm with Mozambique chief dental officer Dr. Marta Mapengo Domingos (c); below, a typical daily commute in Maputo

## Boehm

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countries, Mozambique, where the official language is Portuguese.

Director of NIDCR's Office of Communications & Health Education, Boehm did her 3-month stint abroad last year as part of the International Experience & Technical Assistance (IETA) program. The program, run by CDC's Center for Global Health, is primarily for CDC employees but staff at other HHS agencies are also eligible to apply.

"This opportunity put me in my happy place—at the intersection between language, culture, science and health," said Boehm.

Coming from an immigrant family, Boehm studied language and culture in college before pursuing an M.P.H. in health behavior. Yet despite her affinity for linguistics, the language barrier was a challenge during her time in Mozambique. She took Portuguese language classes when she arrived in Maputo, the capital, and the local staff was eager to help her learn. But she had a hard time understanding what was said during meetings with the Ministry of Health and sometimes struggled with reports written in Portuguese.

"Rather than try to translate every word in my head, I tried to take it all in and see what I could get, and each week I understood a little more," she said. "It also helped that Mozambican Portuguese is a bit more rolling, slower and more



relaxed [than European Portuguese]."

Another challenge was being apart from her husband and two teenage children. The weeks seemed to fly by at work, but time dragged outside the office. "I think I really underestimated how hard it would be to be away from my family for 3 months," she said.

Boehm's husband is a teacher and had the flexibility to take on family obligations

during his summer break while she was away. Her family did get to visit her, at the end of her assignment, just as she finally had gotten acclimated to the country, the CDC Mozambique office and her work.

While in Mozambique, Boehm worked on health communication projects related



*"This opportunity put me in my happy place—at the intersection between language, culture, science and health."*

—KARINA BOEHM



to HIV/AIDS. She found the work personally gratifying, a fulfilling way to honor her father's memory.

"My father died of AIDS in the early 1990s," said Boehm. "So it made me happy to be working with a group that had HIV prevention and treatment as its main goals."

New HIV infections and AIDS-related deaths have decreased dramatically over the past decade, but the prevalence of HIV remains high in Mozambique at over 10 percent. The HIV/AIDS epidemic has contributed to a reduced life expectancy of 55

years and in 2015 there were approximately 34,000 AIDS deaths and more than half a million children orphaned by AIDS.

Boehm's assignment was to provide technical assistance to CDC Mozambique's prevention, maternal and child health and care and treatment branches and to train staff on how to develop effective health communication programs.

"We had some really great conversations about the need to make a conceptual shift from developing informational materials to developing broader community-based social and behavior change initiatives," said Boehm. "We also talked about the importance of engaging the audience from the start and understanding what they see as barriers to behavior change."

During her stay, she also advocated for oral health, presenting information to local staff about the global burden of oral disease and inviting Mozambique's chief dental

officer to talk about the oral manifestations of HIV.

Boehm also learned that working abroad requires more than just intellect and technical skills.

"In Mozambique, you can't get anything done unless you're also culturally and socially adept,"

she said. "I also learned the importance of bringing my whole self to the table." When she shared with colleagues there that her father had died of AIDS, it helped them understand that her interest in the disease was both personal and professional.

Despite the language barrier, Boehm accomplished a great deal in her short time abroad. It was often disheartening seeing the poverty and disparity, but that made the work all the more meaningful, she said. And although some of her pre-trip training included intense security awareness preparation, Boehm was grateful she never needed to shoot a rifle or use the other self-defense tactics she learned; Mozambique, she discovered, is a relatively safe country.

In the end, Boehm had a fulfilling IETA experience. She enjoyed observing how the U.S. government operates abroad and how different agencies work together.

"It gave me a unique perspective on what it means to be a public servant," she concluded. **R**



Dr. Fred Tyson (c) met with students during the speed mentoring session and participated on the career panel.

PHOTOS: STEVE MCCAWE

## Bennett Students, Faculty Launch New NIEHS Connection

BY JOHN YEWELL

A dozen students and faculty from Bennett College, a historically black college in Greensboro, N.C., launched new connections with NIEHS recently. The visitors enjoyed a tour of the facility, career panel discussion, speed mentoring with NIEHS staff and grants advice for faculty. The director of NIEHS's Office of Science Education and Diversity (OSD) provided an overview of diversity in research and training.

Visiting school groups are typically treated to



NIH and Bennett College participants mark the event with a group photo.

a tour and career panel organized by John Schelp, OSD special assistant for community engagement and outreach. For the Bennett College visit, OSD and the NIH Office of Equity, Diversity, and Inclusion (EDI) built on that model by adding elements such as mentoring and grants sessions.

"Mentors can help you figure out what you want to do and what you're actually qualified to do," said Dr. Fred Tyson of the NIEHS extramural program. "They are great people to bounce ideas off of." He spoke as part of a career panel that included Robbie Majors, a

grants management specialist, and Dr. Mercedes Arana, a biologist in the DNA replication fidelity group. Arana encouraged students to pursue a career they love.

"Always think about your passion and let that be your driving force," she advised.

During the speed mentoring event, students rotated through brief meetings with more than a dozen staff from across the institute. Sophomore Aariella Houston, a chemistry and chemical engineering major, said she was inspired. "I felt encouraged to keep pursuing my academic and career goals," she said. "I couldn't be more thankful for this amazing opportunity."

"Coordinating this event with NIEHS has been a great experience," said Gerard Roman of EDI. "NIEHS has a solid diversity program in place and we wanted to showcase their success." The institute works closely with surrounding school systems, historically black colleges and universities (HBCUs) and other higher education institutions.

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*"Mentors can help you figure out what you want to do and what you're actually qualified to do."*

-DR. FRED TYSON

• • •

"We are honored and pleased to provide access and opportunity to students and faculty from nearby colleges and universities," said OSD director Dr. Ericka Reid. EDI complements the effort by providing further partnership and networking opportunities. Roman, who is based at NIEHS, collaborated with Victoria Gross from the Bethesda EDI office. "We hope to showcase this successful example of a collaborative effort with other NIH institutes and centers," he added.

According to Gross, data shows that NIH has a lower than expected representation of black scientists, including tenured and tenure track researchers. So Gross seeks opportunities to build connections with students at HBCUs. "Our goal is to go beyond a one-time visit," she said. "We

want to encourage relationships that foster information sharing, networking and collaboration."

The power of networking was evident in the origins of the event, which arose from the suggestion of Alexis Branch, an intern in Gross's office. "She was a Bennett graduate and she thought it would be great to arrange a visit to NIEHS," Gross explained.

"I know we're going to have at least 10 students applying for [summer and academic-year] research internships," said Michael Cotton, associate professor of biology at Bennett and a co-organizer of the event. "We are looking forward to developing and sustaining this relationship."

"I think our students are very excited," added Dr. Willietta Gibson, also an associate professor of biology at Bennett. OSD already facilitates an exchange effort with Fayetteville State University, another HBCU, and the University of North Carolina, Greensboro. **R**

## Gigantism

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explained Demidowich, an assistant research clinician in the Office of the Clinical Director at NICHD. He went on to clarify that gigantism results when excess growth hormone is produced before the growth plates of long bones (e.g., arms and legs) close. Consequently, people with gigantism are very tall.

In acromegaly, conversely, the growth excess begins after puberty, when the growth plates have already closed. As a result, those with acromegaly may have large skulls, jaws, nose, ears, palms and feet, but not the extremely tall height seen in gigantism.

Demidowich said the pituitary gland produces growth hormone after it receives a signal from the hypothalamus. Normally, the hormone stimulates bone and muscle growth, cell reproduction and regeneration. The hormone “isn’t secreted constantly, but rather comes in pulses or bursts,” especially when we sleep.

In one case, an otherwise healthy teenager visited a local hospital complaining of nausea and vomiting. Doctors ran a battery of tests and diagnosed him with diabetic ketoacidosis, a life-threatening condition that develops when a person’s body doesn’t produce enough insulin. Doctors treated him with insulin, but a day later the ketoacidosis returned.



Dr. Constantine Stratakis



Dr. Prashant Chittiboyna explains that surgery is complicated because cranial nerves and carotid arteries surround the pituitary gland, which is “nestled at the base of the brain.”

PHOTOS: CHIA-CHI CHARLIE CHANG

The patient was 6’9” and had to change his shoes every 3 months because he had grown so fast. He had frequent headaches, had a deep voice and developed skin tags around his neck. Upon reexamination, the doctors realized that his diabetes was probably the result of a different disease: gigantism. He was referred to the CC for further work-up.

well recognized by clinicians or endocrinologists, Demidowich said, the condition “is seen in about 25 percent of individuals with acromegaly.” When there’s too much IGF-1, it hampers the body’s ability to deal with glucose. Patients may be given insulin to control the diabetes.

Typically, gigantism and acromegaly are treated by removing the adenoma, followed

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*“There are a lot of genes to find in acromegaly and our lab is actively working to find them.”*

-DR. CONSTANTINE STRATAKIS

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Usually, the cause of excess growth hormone is a benign, noncancerous tumor called a pituitary adenoma, Demidowich said. Excess growth hormone spurs the liver to produce high levels of insulin-like growth factor 1, or IGF-1. Elevated levels of IGF-1 cause many of the symptoms of acromegaly, including increased risk of heart failure and diabetes.

Although the connection between diabetes and growth hormone excess isn’t

by drug therapy. If remnants of the tumor survive surgery and medication, doctors may recommend radiotherapy.

The surgery is complicated because cranial nerves and carotid arteries surround the pituitary gland, which is “nestled at the base of the brain,” said Dr. Prashant Chittiboyna, assistant clinical investigator in the neurosurgery unit for pituitary and inheritable diseases at NINDS. Surgeons approach the tumor through the nasal cavity.



When the tumor is large, “it’s not uncommon to see that the surgeon is unable to remove all the tumor tissue. Post operatively, individuals are put on medications to ensure long-term remission,” Demidowich said.

In the case of the patient treated at the CC, surgeons were able to remove most of the tumor. After the procedure, the patient was given medication, which brought down IGF-1 and his insulin requirements. The medication had significant side effects, so he opted for radiotherapy to destroy any remnants of the tumor. Most likely, he won’t have to take the acromegaly medication for the rest of his life.

“We’re treating a patient, not just a disease,” Demidowich said. “Our patient, understandably, had difficulty coping with a significant diagnosis and impact on his life, and he was just a kid—still in high school.”

Dr. Constantine Stratakis, director of the Division of Intramural Research and head of the section on genetics and endocrinology at NICHD, said that gigantism and acromegaly are frequently the result of genetic defects that may be inherited or occur within the tumors that cause the disease. Indeed, there are several genetic mutations that are present in patients with growth hormone excess that Stratakis and his laboratory have studied.

The teenager with gigantism did not have any of these mutations; it is likely that his disease was caused by a defect that has not yet been discovered.

“There are a lot of genes to find in acromegaly and our lab is actively working to find them,” Stratakis concluded. **R**

### Sailing Association Open House, Mar. 8

The NIH Sailing Association invites everyone to its open house on Thursday, Mar. 8 from 5 to 8 p.m. at the FAES House at the corner of Old Georgetown Rd. and Cedar Ln.

Explore your interest in learning to sail and discover opportunities for sailing with NIHSA. There will be information about 6-week basic training classes, the club’s racing program and social activities offered by NIHSA.

A fee of \$5 at the door includes pizza, drinks and snacks. Cash bar for beer and wine—\$2 each. Look for NIHSA posters and flyers around campus. For more information, visit [www.nihsail.org/](http://www.nihsail.org/).



The warehouse features south-facing office space for solar heating. Louvers admit winter light and shade the hot summer sun.

### NIEHS Opens Net-Zero Energy Warehouse

The new environmentally friendly NIEHS warehouse was dedicated recently in a ceremony attended by some two dozen dignitaries and NIEHS staff and watched by many more via webcast. Known as a net-zero energy building because of its ability to produce at least as much energy as it uses, the facility is the only one of its kind in the Department of Health and Human Services.

“I’m proud that NIEHS can be a leader and a role model for thoughtful, environmentally friendly design,” said NIEHS and National Toxicology Program director Dr. Linda Birnbaum.



On hand at the ribbon-cutting are (from l) NIEHS executive officer Chris Long, Research Triangle Foundation president and CEO Scott Levitan, Rep. David Price, NIEHS/NTP director Dr. Linda Birnbaum, N.C. department of environmental quality secretary Michael Regan, Durham mayor Dr. Steve Schewel, ORF senior architect Dan Cushing and ORF project engineer Victor Stancil.

PHOTOS: STEVE MCCAWE

“To some people, dedicating a warehouse might not seem too exciting,” said U.S. Rep. David Price, whose district includes NIEHS. “But this is not an ordinary warehouse.”

The warehouse was designed to meet standards for LEED Platinum certification from the U.S. Green

Building Council. Certification involves evaluation of construction practices and operations and should be completed by May. Net-zero certification is a separate process and should be completed within a year.

The new warehouse will help keep pace with the institute’s needs, Birnbaum explained, especially for specialized IT equipment storage. It eliminates the need to continue leasing offsite storage space and can be expanded should more space be needed.

The remote site, a short distance north of the main campus, once housed temporary offices for NIEHS. “The environmental footsteps began

before construction,” NIEHS executive officer Chris Long pointed out. “We recycled almost 400 tons of material, including Freon, and cleared out mercury.” The location provides security advantages, with one access road and no connection to the rest of the campus.

“Everyone working in this facility has been trained on its features and their role in keeping it net-zero, healthy and green,” Long said. “That includes simple things like turning off computers and printers. Our behavior is really the key to our success.”

Presenters noted the building’s use of advanced environmental technology and the institute’s leadership by example in protecting health through

environmentally sustainable operations.

“Our commitment to this project goes well beyond just building a new warehouse,” said Long. “We built a sustainable facility that can serve as a model for healthy building in the future.”—John Yewell **R**



An experimental treatment developed from cattle plasma for Middle East respiratory syndrome coronavirus infection shows potential.

IMAGE: IVONNEW/THINKSTOCK

## MERS Antibodies Produced In Cattle Safe, Treatment Well Tolerated in Trial

An experimental treatment developed from cattle plasma for Middle East respiratory syndrome (MERS) coronavirus infection shows broad potential, according to a small clinical trial led by NIH scientists and their colleagues. The treatment, SAB-301, was safe and well tolerated by healthy volunteers, with only minor reactions documented. The results were reported in *The Lancet Infectious Diseases*.

The first confirmed case of MERS was reported in Saudi Arabia in 2012. Since then, the MERS coronavirus has spread to 27 countries and sickened more than 2,000 people, of whom about 35 percent have died, according to the World Health Organization. There are no licensed treatments for MERS.

SAB-301 was developed by SAB Biotherapeutics of Sioux Falls, South Dakota, and has been successfully tested in mice. The treatment comes from so-called “transchromosomal cattle.” These cattle have genes that have been slightly altered to enable them to produce fully human antibodies instead of cow antibodies against killed microbes with which they have been vaccinated—in this case the MERS virus. The clinical trial, conducted by NIAID, took place at the Clinical Center.

In the study, 28 healthy volunteers were treated with SAB-301 and 10 received a placebo. Six groups of volunteers given different intravenous doses were assessed 6 times over 90 days. Complaints among the treatment and placebo groups—such as

headache and common cold symptoms—were similar and generally mild.

The researchers believe they may be able to use transchromosomal cattle to rapidly produce human antibodies against other human pathogens as well, in as few as 3 months. This means they could conceivably develop antibody treatments against a variety of infectious diseases in a much faster timeframe and in much greater volume than currently possible.

## Stem Cell Transplant for Severe Scleroderma Improves Survival, Quality of Life

New clinical trial findings show that a therapeutic regimen involving transplantation of a person’s own blood-forming stem cells can improve survival and quality of life for people with severe scleroderma, a life-threatening autoimmune disease.

The regimen, known as myeloablative autologous hematopoietic stem cell transplant (HSCT), includes chemotherapy and total body radiation to destroy the bone marrow followed by transplantation of the person’s own blood-forming stem cells to reconstitute the marrow and immune system.

The study, funded by NIH, found myeloablative HSCT to be superior to treatment with the immune-suppressing drug cyclophosphamide.

The findings appeared in the Jan. 4 issue of the *New England Journal of Medicine*.

Scleroderma is characterized by hardening of the skin and connective tissues. Diffuse systemic sclerosis is a severe, often fatal form of the disease that also involves the internal organs. Treatment options are limited. People with the disease may take anti-rheumatic drugs and immune-suppressing drugs such as cyclophosphamide to help manage symptoms, but none of these medications has been proven to provide long-term benefit.

The clinical trial, called Scleroderma: Cyclophosphamide or Transplantation (SCOT), compared the safety and potential benefits of the 2 treatment regimens among 75 people with diffuse systemic sclerosis who had lung or kidney involvement.

Compared with cyclophosphamide, transplantation offered significantly greater long-term benefits, but also carried known

short-term risks such as infections and low blood cell counts.

“We need effective therapies for scleroderma and other severe autoimmune diseases, which can be not only debilitating to the patient but also difficult to treat,” said NIAID director Dr. Anthony Fauci, whose institute sponsored the study. “These results add to the growing evidence that stem cell transplants should be considered as a potential treatment option for people with poor-prognosis scleroderma.”



By tagging bone marrow cells of mice with a genetic label, or barcode, researchers were able to track and describe the family tree of individual blood cells as they form in their natural environment.

THINKSTOCK IMAGE: MEDIOIMAGES/PHOTODISC

## Cellular Barcoding Helps Scientists Understand Behavior Of Stem Cells

By tagging bone marrow cells of mice with a genetic label, or barcode, researchers were able to track and describe the family tree of individual blood cells as they form in their natural environment. The scientists discovered that these cells regenerate differently than their counterparts do after a blood cell transplant, according to a study published Jan. 3 in *Nature* and funded by NHLBI.

“The findings of this research, if applicable to humans, will have implications for blood cell transplantation and for clinical and research methods using blood cells such as gene therapy or gene editing,” said Dr. John W. Thomas, stem cell and cell-based therapy coordinator at NHLBI.

This study moves research a step further towards the development of blood regeneration therapies, but the researchers believe it is also applicable to a variety of cells and will yield insights about regenerating diseased or damaged tissues.

“Our results show that stem cells and their less pluripotent descendants, blood progenitors, behave somewhat differently when studied without removing them from their native environment versus when studied in a laboratory or in transplantation, leading to differences in the type of blood lineages they make,” said the study’s first author Dr. Alejo Rodriguez Fraticelli of Harvard Stem Cell Institute at Boston Children’s Hospital.

Due to the lack of appropriate tools to study how blood forms in the natural environment of the body, the majority of studies about where individual blood cells come from have been done after a transplant. In that context, the transplanted cells would have been “perturbed,” or removed from their natural environment. According to the researchers, the current models are more likely to represent a roadmap of lineage potential for the blood cells’ natural offspring.

For Rodriguez Fraticelli, this highlights the importance of studying blood regeneration in its native context. “Moving forward, we need to come up with methods to better predict what types of cells will be the most optimal for therapy, for instance in reprogramming cells and editing,” he said.

## Iodine Deficiency May Reduce Pregnancy Chances

Women with moderate to severe iodine deficiency may take longer to achieve a pregnancy, compared to women with normal iodine levels, according to a study by researchers at NIH. The study is the first to investigate the potential effects of mild to moderate iodine deficiency—common among women in the United States and the United Kingdom—on the ability to become pregnant. It appears in the latest edition of *Human Reproduction*.

Iodine is a mineral used by the body to regulate metabolism. It also helps regulate bone growth and brain development in children. It is found in seafood, iodized salt, dairy products and some fruits and vegetables. Severe iodine deficiency has long been known to cause intellectual and developmental delays in infants.

“Our findings suggest that women who are thinking of becoming pregnant may need more iodine,” said Dr. James Mills, who conducted the study along with colleagues at NICHD and the New York State



Findings suggest that women who are thinking of becoming pregnant may need more iodine.

IMAGE: THINKSTOCK

department of health in Albany. “Iodine requirements increase during pregnancy and the fetus depends on this mineral to make thyroid hormone and to ensure normal brain development.”

The researchers analyzed data collected from 501 U.S. couples who were planning pregnancy from 2005 to 2009. The couples were part of the Longitudinal Investigation of Fertility and the Environment (LIFE) study, which sought to examine the relationship between fertility, lifestyle and environmental exposures. When the women enrolled in the study, they provided a urine sample from which their iodine levels were measured. Each woman was also given a digital, at-home pregnancy test.

Of the 467 women analyzed for the current study, iodine status was sufficient in 260 (55.7 percent), mildly deficient in 102 (21.8 percent), moderately deficient in 97 (20.8 percent) and severely deficient in 8 (1.7 percent).

Although the study population was not a representative sample of the U.S. population, the authors note that the percentage of women in the study having insufficient iodine (44.3 percent) is close to that seen in population-wide studies. For example, a previous study estimated that 30 percent of U.S. women of childbearing age had insufficient levels of iodine.

The authors concluded that if their findings are confirmed, public health officials in countries where iodine deficiency is common may want to consider programs to increase iodine intake in women of child-bearing age. **R**

## Asthma Research Volunteers Needed

Individuals 18 years or older with asthma are sought to participate in a 1- to 2-day research study in the Cardiovascular and Pulmonary Branch at the National Institutes of Health. A thorough medical evaluation and monetary compensation will be provided. If interested, call (301) 402-1553.

## Healthy Volunteers Needed

NIAID researchers seek healthy volunteers, 18-50 years old, for an investigational vaccine study targeting respiratory syncytial virus (RSV). Compensation is provided. For more information, call 1-866-833-5433 (TTY 1-866-411-1010). Email [vaccines@nih.gov](mailto:vaccines@nih.gov) or visit <http://bit.ly/2nOkOvY>.

## Flu Vax Study Recruits Healthy Vols

Vaccine Research Center researchers seek healthy volunteers, 18-70 years old, for an investigational influenza vaccine study. Scientists are testing new vaccines to determine whether they are safe and effective in preventing the flu. Compensation is provided. For more information, call 1-866-833-5433 or email [vaccines@nih.gov](mailto:vaccines@nih.gov). Read more at <https://go.usa.gov/xNH7U>. Refer to study VRC316.

## Diagnosed with Stomach Cancer?

Have you been diagnosed with stomach cancer? NCI researchers need volunteers 18 or older with stomach cancer that has spread to the abdomen for a study at the Clinical Center combining surgery with heated chemotherapy as a potential new treatment for stomach cancer. For more information, call the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Learn more online at <https://go.usa.gov/xXnqK>. Refer to study 17-C-0070.

## Study Needs Healthy Children

NICHD seeks healthy children 7 to 11 years old to join in a research study. Researchers want to learn if breaking up sitting with short periods of activity improves children’s metabolism and attention. Six outpatient visits on consecutive days of about 3 hours each (Monday-Friday, early evening and Saturday morning) are required. Compensation will be provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010). Read more at <https://go.usa.gov/xRPAg>. Refer to study 17-CH-0130.

## Study Needs Overweight Adults

NICHD seeks adults who are overweight, have high blood pressure and/or pre-diabetes to participate in a study. Researchers are examining the effects of the medication colchicine on the complications of obesity. Compensation is provided. For more information call 1-866-444-2214 (TTY 1-866-411-1010) *Hablamos español*. Refer to study 14-CH-0119.

## AFTERMATH OF STORM

**A Patient's Journey from Puerto Rico to NIH**

BY CHLOE GANSEN

Jesus Garces-Soto and his wife Lysette Santiago never expected to travel from Puerto Rico to NIH.

In 2013, Garces-Soto underwent an operation for bladder cancer in Puerto Rico. Although the operation was initially considered successful, doctors confirmed his cancer had recurred in April 2017 after he began to feel sick again.

Last fall, on the same day that Hurricane Maria, a storm with 150 m.p.h. winds, made direct landfall on Puerto Rico, Garces-Soto returned to the hospital to address an infection related to his cancer.

The timing of the infection could not have been worse. The hurricane immensely damaged the hospital and surrounding infrastructure. While the destruction made it difficult to provide adequate care, many patients had no choice but to stay in the facility as their homes had been severely damaged in the hurricane.

"The hospital didn't have electricity and there was no working generator or air conditioning," recalled Garces-Soto.

He and his wife were on a floor with other cancer patients, many of whom were in need of electricity to run the equipment they relied on for survival.

"The patient rooms were unbelievable—it was terrible," Santiago said. "But we couldn't return to our house because of the damage. We wouldn't have had water."

As a sportscaster and former reporter in Puerto Rico, Santiago was keen to use her talents to get word out about the devastating conditions and need for aid. "I used to write for the media, so I began writing to let people know what was going on and hopefully get attention from someone that could help us."

Santiago's efforts did not go unheard; she eventually connected with members of the American Cancer Society (ACS) Puerto Rico, who were eager to help. Garces-Soto was soon discharged from the hospital and transferred to the ACS Puerto Rico Hope Lodge in San Juan. The lodge, which provides free lodging for adults and children undergoing cancer treatment in Puerto Rico and surrounding islands, offered the couple



Jesus Garces-Soto and his wife Lysette Santiago chat with Dr. Andrea Apolo, investigator and Lasker clinical research scholar in NCI's Genitourinary Malignancies Branch in the Clinical Center.

PHOTO: CHLOE GANSEN

temporary relief from the sweltering heat and dire conditions while they awaited news from ACS about where they could go next.

Members of ACS Puerto Rico worked with other ACS members in the mainland United States to coordinate travel plans for Garces-Soto and Santiago to leave Puerto Rico. Initially, the couple heard they would travel to Moffitt Cancer Center in Florida. The good news, however, came with a major caveat: although Garces-Soto's health plan included a category for costs associated with catastrophes, because he was in Puerto Rico, the funds could not be applied to a health care facility in the continental United States. The couple was devastated to learn they would need to cover the treatment expenses out-of-pocket.

"We looked at each other and we began to cry," said Santiago. "But then, there was another phone call from the American Cancer Society."

It was then that the couple was delivered a lifeline. Members of ACS and the National Cancer Institute were calling to tell the couple that Garces-Soto could receive treatment while enrolled on a clinical trial at NCI free of charge. Less than a week later, Garces-Soto and Santiago were on their way to Bethesda.

"We feel so blessed and thankful for all that you're doing for us," said Santiago, fighting back tears. "Our people are

hurting. Really hurting. We appreciate all that you're doing for the Puerto Rican people that come here."

The couple is able to stay at the Edmond J. Safra Family Lodge at NIH while Garces-Soto receives treatment at the Clinical Center. Currently, he is being treated by Dr. Andrea Apolo, investigator and Lasker clinical research scholar in NCI's Genitourinary Malignancies Branch.

"The health tragedies and emergencies that Puerto Ricans have endured and are still enduring due to Hurricane Maria are heartbreaking," said Apolo. "It is wonderful that many cancer organizations, including the NCI, are able to help cancer patients continue to receive treatment despite overwhelming difficulties. I feel fortunate to be involved in this effort. Mr. Garces-Soto and his family have maintained such a positive attitude throughout these difficult times—a reflection of the strength and perseverance of the people of Puerto Rico."

When asked about the best part of staying at NIH, both Garces-Soto and Santiago emphasized the impact the staff have had on their stay. "The staff are the best—so caring and lovely," said Santiago. "They even tried to speak Spanish!"

"That's the best part—the people," offered Garces-Soto. He smiled as he added, "And the menu." **R**