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Barbra Streisand Talks Up Women's Heart Health

BY BRANDON LEVY, OIR

Barbra Streisand knows how to command an audience, whether she's behind a microphone, a camera, or a podium. After a storied career beguiling theater-goers, Streisand's new goal is not just to warm hearts but to save them from disease as well.

The Broadway and Hollywood star, a lifelong advocate of health and gender equity, graced the stage of NIH's Ruth Kirschstein Auditorium (Building 45) on May 15 to give the annual J. Edward Rall Cultural Lecture named for former Deputy Director for Intramural Research **Joseph "Ed" Rall**. As this year's invited speaker, Streisand is in good company; over its 30-year history, the event has featured a variety of celebrities from writer Maya Angelou, to musician Yo-Yo Ma, to doctor and news correspondent Sanjay Gupta. Streisand took the opportunity to highlight an issue that is—literally—near and dear to her heart: women's cardiovascular health.

Streisand's quest to reduce gender disparities in cardiovascular medicine began with her 1983 film *Yentl*. The movie—which Streisand directed, co-produced, co-wrote, and starred in—tells the story of a young woman living in Eastern Europe in the early 1900s who disguises herself as a man in order to pursue an education. Eight years after the movie's 1983 debut, the *New England Journal of Medicine* published an editorial written by cardiologist and former

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Machine Learning

Teaching Computers to Think

BY SUSAN CHACKO, CIT

ALEXLMX, THINKSTOCK.COM

Enter Richard Leapman's lab at the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and you'll find a serial block-face scanning electron microscope, the size of a lab freezer, busily slicing and scanning pancreatic tissue, blood platelets, or other biological matter. In 12 hours, there will be 20,000 images of 25-nanometer-thick slices of each sample.

Before the microscope arrived four years ago, Leapman had a team of postbacs manually delineating features of the objects in the images. Such work is labor-intensive, taking a hardworking postbac a few hours to trace the outline of a single platelet in an image

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Creating a More Diverse and Inclusive NIH

BY MICHAEL GOTTESMAN, DDIR, HANNAH VALANTINE, AND ROLAND OWENS

Evidence indicates that heterogeneous groups of talented individuals, with experience in managing diversity, are better equipped to tackle complex problems than are homogeneous groups. It is also well documented that medical conditions are multidimensional and influenced by many factors such as race, genetics, gender, geography, socioeconomic status, and community values. Tackling these complex multivariable scientific and biomedical problems requires a vibrant culture of inclusive excellence that draws from a diversity of perspectives and experiences. As a testament to fostering such an environment, the NIH intramural research program (IRP) is recruiting talented scientists who also have experience in promoting and mentoring individuals from groups underrepresented in biomedicine.

There have always been individual NIH principal investigators (PIs) who have gone out of their way to make opportunities accessible to highly innovative biomedical researchers from underrepresented groups. To date, however, these PIs often worked in isolation and were therefore limited in their ability to promote an NIH-wide environment of inclusive excellence. This year, the IRP has begun a multi-year pilot, called the Distinguished Scholars Program (DSP), to create such an environment. The DSP is designed to create an annual cohort of 10 to 15 recently hired PIs (primarily at the tenure-track level) who have a commitment to promoting diversity and inclusion in the biomedical research workforce and trainee pool. The DSP scholars will become the focal point of a new mentoring and networking initiative led by the Office of Intramural Research (OIR) and the Scientific Workforce Diversity office (SWD). All NIH Institutes and Centers (ICs) with IRPs have contributed funds to help fund the DSP scholars.

> Tackling complex multivariable scientific and biomedical problems requires a program that draws from a diversity of perspectives and experiences and fosters those who foster diversity.

This spring, the first cohort of 10 tenure-track investigators (TTIs) and three assistant clinical investigators (ACIs) representing seven ICs were selected as DSP scholars. All of them are expected to be on board by the end of September. These individuals were selected for the DSP because of their scientific accomplishments and because they have demonstrated a desire to be change agents. Each DSP cohort will have a year-long program of monthly activities designed to promote career development as well as interactions among DSP scholars, between DSP scholars and other IRP PIs, and between DSP scholars and NIH senior leaders. Embedded in the program will be four to five highly accomplished senior investigators, recruited to serve as mentors and sponsors for the DSP scholars.

In addition to these activities designed to strengthen relationships among cohort members, DSP scholars will participate in a curriculum of professional development and skill-building activities. These professional-development activities will be open to all TTIs and ACIs.

The next deadline for applications will be early in Spring 2019. To assist with identification of DSP candidates in the future, the IRP will have language in its PI-recruitment advertisements requesting applicants to include in their CVs a description of their mentoring and outreach activities, especially those involving women and individuals from groups underrepresented in biomedical research.

The success of the DSP program will be measured not only by the scientific success of the DSP scholars, but also by how they contribute to the transformation of the NIH IRP into an environment in which inclusive excellence is the norm, rather than the exception. We welcome your ideas about how to make the DSP program the best it can be, and we hope you participate fully by helping to recruit and make welcome scientific colleagues who will help us create a diverse and inclusive community that maintains NIH's status as a top-tier biomedical research institution. ●

Hannah Valantine is the Chief Officer for Scientific Workforce Diversity, Office of the Director; Roland Owens is the Director of Research Workforce Development, in the Office of Intramural Research.

NEW SIG: Metals in Biology Scientific Interest Group

Metals are critical to a dizzying array of biological functions. Up to one-third of cellular proteins contain a bound metal cofactor, yet only a minority of these cofactors have been identified. Metal ions also bind and modulate the structure and function of RNA in an equally intriguing number of ways. By virtue of their variable coordination properties and redox behavior, metal ions often carry out unique functions in biology. However, metal ions such as copper and iron can be double-edged swords because, when unsequestered, they can generate toxic radical species that can damage proteins, nucleic acids, and lipids. Consequently, cellular systems devote a considerable amount of resources to the trafficking, chaperoning, and homeostasis of essential metal ions.

Malfunctions of one or more elements (pun intended!) of this metal-ion machinery cause many devastating human diseases such as hemochromatosis, Friedreich ataxia, Wilson disease and Menkes disease. In addition, metal ions have proved valuable in medicine including serving as magnetic-resonance contrast-imaging reagents and anti-cancer therapeutics. The Metals in Biology SIG unites several active intramural research groups whose interests span one or more aspects of the biology of metals. The new SIG facilitates interactions among NIH researchers at the forefront of metallobiology and exposes trainees to a wider spectrum of problems, approaches, and techniques. The SIG plans to host one seminar every two months and continue the biweekly journal clubs. For more information, contact **Anirban Banerjee** (anirban.banerjee@nih.gov). ●

SGHD SIG: Sex Differences in Sleep

BY JOANNA CROSS, NIMH

Fruit flies may hold the secret to helping scientists understand sleep. The little critters share many of the characteristics relevant to sleep in humans—they sleep mostly at night, stimulants can interfere with their sleep, and sleep deprivation can wreak havoc on their memory. In humans, sleep deprivation can lead to impairments in learning and memory, neurological diseases, cardiovascular problems, hypertension, and other disorders. Scientists can use fruit flies (*Drosophila melanogaster*) to study how genetic traits affect sleep, too. And some scientists like **Susan Harbison** are investigating something rarely studied: how sex differences may play a role in sleep.

Harbison, who joined NIH in 2012 and is a Stadtman tenure-track investigator in the National Heart, Lung, and Blood Institute, gave a presentation on her research at the May 22, 2018, gathering of the Sex and Gender in Health and Disease (SGHD) Scientific Interest Group (SIG).

But how do you measure sleep in a creature as tiny as a fly? You use an infrared-based Drosophila activity-monitoring system: Each fly is placed in a three-inch long glass tube; when it is awake and active, its movements disrupt an infrared beam; and the data can be used to decipher sleep.

Some of us require more sleep than others. To investigate this trait in flies, Harbison genetically engineered 19 long-sleeping and 20 short-sleeping lines. The long-sleeping flies slept for 17.8 hours in a 24-hour period, while the short-sleeping flies slept for only 3.3 hours. That's a staggering 14.5 hours difference.

Harbison induced sleep deprivation by disturbing the flies mechanically via a custom-mounted vortexer. The device was programmed to deliver a shaking stimulus once a minute for 12 hours during the night. Harbison observed the flies' rebound response (making up for lost sleep) the following morning. "Flies don't have a job, so they can sleep in!" Harbison said during her talk. She found that short-sleepers lost less sleep (up to 412 minutes) than long-sleepers (up to 709 minutes) but the rebound response was similar (up to 260 extra minutes of sleep). However, there was a fair amount of variability among the lines, suggesting that the amount of rebound sleep is more dependent on genotype than sex. Preliminary data also showed that intermittent disruptions also affected sleep; short-sleeping males had a decreased arousal threshold (it takes less stimulus to awaken them) compared to females.

SARAH NEEDLE, NHLBI

NHLBI researcher Susan Harbison has found that male and female fruit flies have different sleeping habits.

As with humans, flies have a 24-hour circadian rhythm pattern. Using a rhythmicity index (the extent to which activity patterns are similar from day to day), the scientists determined that male flies have more rhythmicity within their circadian patterns compared to females.

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Special from NIGMS

Advice from an Early Career Investigator

BY JENNIFER SIZEMORE, NIGMS

CHIA-CHI CHARLIE CHANG

University of Kentucky biologist Jeramiah Smith (left) offered career advice to undergraduate students from Morgan State University at the NIGMS Director's Early Career Investigator Lecture hosted by NIGMS Director **Jon Lorsch** (right).

"Embrace being wrong." Rather than feeling discouraged when an experiment yields unexpected results, try to understand what happened and why. That's how science advances.

Jeramiah Smith gave this and other career advice to the undergraduate students from Morgan State University (Baltimore, Maryland) who attended his lecture on April 17, 2018. Smith, a biologist from the University of Kentucky (Lexington, Kentucky), delivered the third annual National Institute of General Medical Sciences (NIGMS) Director's Early Career Investigator Lecture. NIGMS established this lecture series three years ago to highlight the achievements of early-career grantees and to encourage undergraduates and other students to pursue biomedical research careers.

After his lecture, Smith answered questions from the students about pursuing a career in laboratory research.

AMONG SMITH'S OTHER TIPS:

- If you're interested in doing lab research, don't wait until your senior year in college. It takes a while to learn the lab techniques, so if you start as a freshman or sophomore, you'll have more time to actually do your own research.
- Before asking a professor or lab chief whether you can work in his or her lab, do some homework: Read one or more articles by the research group. Have an idea of relevant research questions. "If a student has read your work and has an idea, especially something they would be interested in pursuing, even if it needs to be further shaped, that means a lot in terms of my perception."
- Make an appointment to see the lab chief. Show up. On time.
- Keep asking questions. "You tend to be more limited by your ability to address questions than by the number of questions there are to address. It's great, it's job security in a sense." ●

The archived videocast includes the entire lecture and the Q & A session afterwards: https://videocast.nih.gov/launch.asp?23827.

CHIA-CHI CHARLIE CHANG

Smith (left) offered more career advice to the Morgan State students as he chatted informally with them.

Let's Talk Microbes

The Big Read at NIH Featured Author Ed Yong

BY ALLISON CROSS, NCI

Let's talk microbes! This is what members of the NIH community were doing this spring as they came together to discuss science journalist Ed Yong's 2016 book *I Contain Multitudes: The Microbes Within Us and a Grander View of Life* as a part of the second annual Big Read at the NIH. Then, on June 5, the award-winning author visited NIH for an informal conversation about the book in Masur Auditorium (Building 10) with NIH Director **Francis Collins**.

The Big Read, a nationwide event initiated by the National Endowment for the Arts, aims to foster collaboration and community across the NIH through the discussion about a single book over several months. This is our second year participating in a local Big Read event. To promote book conversations, the NIH Library made an eBook version of *I Contain Multitudes* available through its collection, held three discussion groups, and offered training sessions to guide individuals in organizing their own book groups. These Big Read activities brought together a wide range of people from across the NIH.

Scientists have been studying the microbiome for centuries, but research in this area has picked up dramatically in the last few decades. The idea that bacteria cause disease, the well-known germ theory, has misled many people to believe microbes need to be eradicated to cure disease. However, it is now understood that most microbes do not make us sick. In his book, Yong explains the complex relationships between bacteria and animals, the benefits of these partnerships, and what happens when these partnerships go awry.

Yong spent six months researching and reporting for his book and interviewed more than 100 people in the process.

CHIA-CHI CHARLIE CHANG

The second annual Big Read at NIH featured Ed Yong and his book *I Contain Multitudes: The Microbes Within Us and a Grander View of Life*. Yong visited NIH for an informal conversation about the book with NIH Director Francis Collins.

During his conversation with Collins, he explained that in deciding what to include in the book, he "gravitated toward things that would provide really good stories [and] would illuminate some of the broader themes about how the microbiome works." In structuring the book around the particular relationships between microbes and their hosts, Yong wanted to create something that "would stand the test of time even as new papers and discoveries were continuing to be published." He hopes that people who read his book will understand that "microbes are not just things to go 'eww' over or to fear [but] are a dominant life from of the planet."

Although this is his first book, Yong is a prolific science writer and currently reports for *The Atlantic*; his work has been featured in *National Geographic*, the *New Yorker*, *Scientific American*, and other publications. It was with "an urge to explain, to describe, to tell stories" that he first began science writing in 2006. He described the experience of writing his first book as a joy. It has become a *New York Times* best seller and earned him a spot in the best-of-2016 lists by the *NYT*, National Public Radio, the *Economist*, the *Guardian*, and several others.

"Do you have any advice for scientists about their own responsibilities and opportunities to communicate what they do?" Collins asked near the end of the program.

"I think good science writing and good science communication is not just about… explaining it in lay language," Yong said. "It is also about explaining how that science came to be, like the stories behind it and the stories of the people behind it. That's what I tried to get across in the book [and] in all the pieces I write." ●

The Big Read was sponsored by the Foundation for Advanced Education in the Sciences. To watch a videocast of Yong's June 5, 2018, presentation, go to https://videocast.nih.gov/launch.asp?23932.

Elisabeth Murray, Ph.D.

Investigating the Role of Different Brain Regions in Memory and Decision-Making

BY CLAIRE E. MCCARTHY, NCI

JULES ASHER, NIMH

NIMH Senior Investigator **Elisabeth Murray**, who studies the neural basis of learning, memory, emotion, and response, is holding a 3-D model of Patient H.M.'s brain. In 1953, the surgical removal of his medial temporal lobe helped stop his epileptic seizures but left him unable to form new memories.

When you walk into Elisabeth Murray's office, you can see a 3-D model of the brain belonging to Patient H.M. (Henry Gustav Molaison), a man well known by students in psychology and neuroscience. In 1953, surgeons removed his medial temporal lobe in an attempt to stop his epileptic seizures. Although the surgery helped, there was an unfortunate side effect: He was unable to form new memories about individuals, objects, or events. He did, however, retain most of his memories formed prior to the procedure and could carry on a normal conversation, solve math problems, and write sentences. Based on this evidence, the prevailing dogma when Murray began her postdoctoral training in 1979 with **Mortimer Mishkin** at the National Institute of Mental Health (NIMH) was that specific areas within the medial temporal lobe—the hippocampus and amygdala—were the seeds of memory formation for previously encountered objects and people.

But when Murray began investigating the neural substrates of this recognition memory in the 1990s, she showed that the amygdala and hippocampus were not the key for object-memory formation, but that two other regions within the medial temporal lobe—the entorhinal and perirhinal cortex—were. Her studies overturned long-standing theories about neurobiology at the time.

Murray continues to challenge existing theories and explore new frontiers in neuroscience. During this year's Anita B. Roberts Lecture held on May 17, 2018, she described her current research examining the role of the orbitofrontal cortex (OFC, the area of the brain directly above the eyes), which is important for learning and decision-making. In one set of studies with macaque monkeys (*Macaca mulatta*), she tested and rejected the established theory that the OFC itself plays a role in cognitive flexibility (the ability to adapt one's thinking to changing circumstances). Instead, she and her team were surprised to find that a fiber bundle connecting the temporal lobe to the frontal lobe—passing near the OFC—was involved.

In other studies, she is attempting to gain a deeper understanding of how the OFC and the adjacent ventrolateral prefrontal cortex (VLPFC) work to guide behavior. For example, she and her lab have investigated the OFC's role in the devaluation of rewards (when the value of something is reduced in a person's mind and influences their actions). In her talk, Murray used the example of the hardboiled-egg-eating contest in the 1967 movie *Cool Hand Luke*. Luke, played by Paul Newman, sets out to win an impromptu bet that he could eat 50 eggs in an hour. Although he succeeds—the scene is

agonizing to watch—he goes from valuing (liking) eggs to devaluing (hating) them. The eggs have become devalued because he doesn't want to eat any ever again.

Similar to Luke, monkeys will typically devalue a food if they eat as much of it as they can during one sitting. Normally in behavioral tests, the monkeys would choose objects that would reward them with a more desirable food, avoiding objects yielding the devalued food. But Murray found that OFC-damaged monkeys continued to choose objects that rewarded them with the devalued food. This research showed that the OFC is involved in decision-making based on desirability.

Murray also explored the impact of the OFC and the VLPFC on credit assignment, the ability to link an outcome with the choice or action that produced it. In monkeys, this behavior can be tested by having them press images on a touch-sensitive screen to receive a piece of food. The monkeys learn to touch the images yielding the most rewards, all while the "best" image is changing over the test session. Murray and her team discovered that damage to the VLPFC—not damage to the OFC as expected—impaired credit-assignment and the ability of monkeys to track the best image. The VLPFC, therefore, is important for determining the value of an outcome based on the probability of reward and credit assignment. Thus, unlike OFC, the VLPFC guides decision making based on the history of rewards, which relates to availability.

To further tease out how the OFC functions, Murray's lab used a drug that temporarily inactivated parts of it. They determined that the loss of neural activity in the back of the OFC impaired the monkeys' value-updating abilities; loss of activity in the front interfered with goal selection (linking knowledge of outcome value to image choice).

Overall, Murray has improved the understanding of brain-behavior relationships by showing that the OFC contains distinct functional regions for determining the value of things and selecting goals. Her research may lead to new insights about neuropsychiatric and mood disorders that are associated with OFC dysfunction.

In addition to conducting research, Murray strives to be a good mentor—just as **Anita Roberts** was—by helping junior scientists. "I have been the beneficiary of many efforts of the NIH Women Scientist Advisors (WSA) and received good advice from a handful of female role models who were able to mentor me in my own career development," she said during the lecture. Now, she passes on the lessons she has learned by supporting trainees in her lab, participating in the WSA, and having discussions with young tenure-track scientists at NIH to help them navigate the complexities of NIH while they work toward achieving tenure. ●

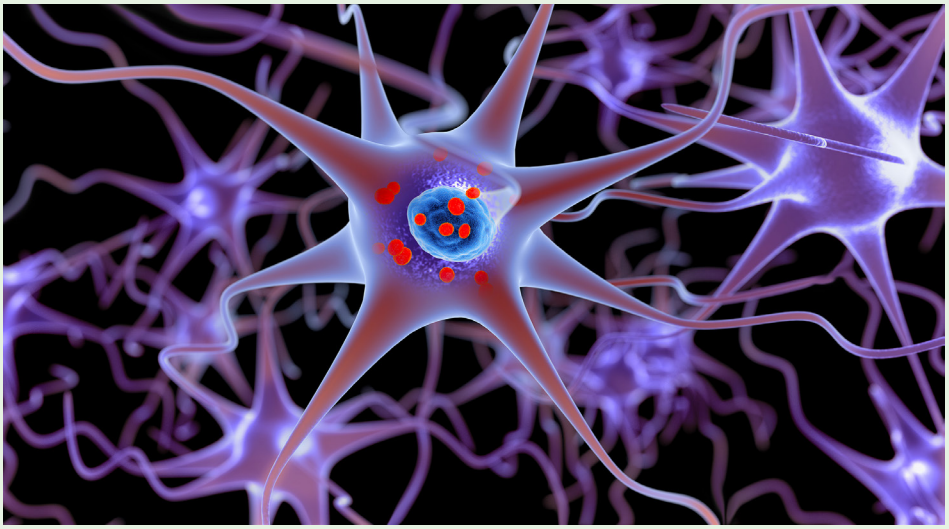
The "Anita B. Roberts Lecture Series: Distinguished Women Scientists at NIH" honors the research contributions Roberts and other female scientists have made. Roberts, who spent 30 years at NCI before her death in 2006, was known for her groundbreaking work on transforming growth factor-beta. To watch a videocast of her May 17 lecture, "Specializations for Decision Making in Primate Prefrontal Cortex,", go to https://videocast.nih.gov/launch.asp?23894.

MORE ABOUT ELISABETH MURRAY, PH.D.

Senior Investigator and Chief, Section on Neurobiology of Learning and Memory, and Chief, Laboratory of Neuropsychology, National Institute of Mental Health

Born and grew up: In Syracuse, New York
Research Interests: Understanding the neural basis of learning, memory, emotion, and decision making. Her laboratory has pioneered the use of MRI-guided stereotaxic surgery, a method that has for the first time allowed the examination of the selective mnemonic contributions of various medial temporal lobe structures.
Education: Bucknell University, Lewisburg, Pa. (B.S. in biology); University of Texas Medical Branch, Galveston, Texas (Ph.D. in physiology)
Training: Postdoctoral training in NIMH's Laboratory of Neuropsychology with Mortimer Mishkin
Came to NIH: In 1979 for training in neuropsychology and behavior; became a NIMH staff fellow in 1982, senior staff fellow in 1984, a research physiologist in 1989, chief of the Section on the Neurobiology of Learning and Memory in 1996, and chief of the Laboratory of Neuropsychology in 2015
What excites her about research: "There's something new every day and often it is something unexpected."
Outside interests: Hiking and birding
Little known fact: "When I was applying to graduate school, I wanted to study dolphins. I was fascinated with the work of John Lilly, who was studying communication between man and dolphins."
Interesting fact about her family: "I recently learned that my great-aunt was one of the early female graduates of the Columbia University College of Physicians (New York). Childhood psychotherapy was her specialty and she practiced in Ithaca, New York."
Website: https://irp.nih.gov/pi/elisabeth-murray

Intramural Research Briefs



LARS NEUMANN, THINKSTOCK.COM

NIDDK: An NIDDK researcher was part of an international team that designed the first potentially therapeutic photoactive drug—MRS7145—to fight Parkinson disease. Shown: A 3D illustration showing neurons containing Lewy bodies (small red spheres), which are deposits of alpha-synuclein proteins accumulated in the brain cells.

NIDDK: FIRST PHOTOACTIVE DRUG TO FIGHT PARKINSON DISEASE

An NIDDK researcher was part of an international team that designed the first potentially therapeutic photoactive drug—MRS7145—to fight Parkinson disease (PD), a neurodegenerative disorder caused by a loss of dopamine, which in turn causes a gradual loss of motor control. Although there is no cure, there are drugs (such as levodopa) and treatments (such as deep-brain stimulation) to treat symptoms, which include tremors, stiffness, slowed body movements, and poor balance. But the action of conventional drugs can be limited because they can't precisely target the areas of the brain involved in PD, their effects diminish over time and the dosage may have to be increased, and newer drugs have unwanted side effects such as uncontrolled body movements. But scientists have found that they can use certain wavelengths of light to control the precision of light-sensitive drugs and thereby avoid adverse effects.

The researchers in the current study developed MRS7145, a photo-sensitive adenosine receptor (A2AR) antagonist. A2A receptors play a role in controlling movement. The MRS7145 is activated by violet light in a wavelength that is non-toxic to neurons. In the current study, which involved rodent models of PD, the researchers implanted optical fibers in the striatum (area of the brain that controls motor activity), then used a remote-control device to trigger the release of light. The light activated the MRS7145, which blocked the A2A receptors, allowing dopamine to be released and reducing the PD symptoms. Although this photo-sensitive drug has only been tested in laboratory animals so far, the researchers hope their work will lead to new therapeutic solutions for treating PD. (NIDDK researcher: K. Jacobson, *J Control Release*, **283**:135-142, 2018, DOI: 10.1016/j.jconrel.2018.05.033)

NICHD: POSSIBLE LINK BETWEEN GESTATIONAL DIABETES AND EARLY-STAGE KIDNEY DAMAGE

Researchers may have uncovered a potential link between women who have had gestational diabetes and early stage kidney damage. According to the study led by NICHD investigators and other institutions, women who had gestational diabetes were more likely to have a high glomerular filtration rate (GFR), which is an estimate of how much blood passes through the glomeruli (the tiny filters within the kidneys that extract the waste) per minute. Researchers believe that a very high GFR rate can be a sign of early kidney damage. The work was conducted as part of the NICHD-funded Diabetes and Women's Health Study. Researchers collected and analyzed blood and urine samples from Danish women who had pregnancies from 1996 through 2002. The data included results from tests for diabetes and kidney functioning an average of 13 years later. The group included 601 women who had gestational diabetes and 613 who did not.

Results showed that women who had gestational diabetes and later developed diabetes were approximately nine times more likely to have an elevated GFR later in life compared to women who did not have gestational diabetes. In addition, women who had gestational diabetes and later-life diabetes were also more likely to have elevated urinary albumin to creatine ratio (UACR), an indicator of kidney disease. Although the study could not prove that gestational diabetes is a direct cause of kidney damage, more research needs to be conducted in order to confirm these findings. The authors noted, however, that women who have had gestational diabetes may benefit from periodic checkups to monitor for early-stage renal damage so clinicians can initiate treatment to prevent or delay further disease progression. (NIH Authors: S. Rawal, S.N. Hinkle, J. Wu, E. Yeung, J.L. Millis and C. Zhang, *Diabetes Care* **41**:1378-1384; DOI 10.2337/dc17-2629)

[BY LESLIE REVOREDO, NIDCR]

NCI: ENHANCING TUMOR RESPONSE TO RADIOTHERAPY

Radiotherapy plays a significant role in the management of non–small cell lung cancer (NSCLC), but recurrence after treatment remains problematic. In a recent study, investigators at NCI found a novel

combination-therapy approach to treat NSCLC. The researchers used a CDK4/6 inhibitor, abemaciclib, and combined it with ionizing radiation (IR) to enhance radiosensitivity of NSCLC cells and tumor xenografts in mice. CDK4/6 inhibitors are are a class of drugs designed to interrupt the growth of cancer cells. The drug inhibited phosphorylation of the retinoblastoma (RB) protein and effectively blocked cell proliferation in cells as well as in mouse tumors. This combination therapy resulted in significant inhibition of IR-induced DNA-damage repair. Several NSCLC cell lines with varied genetic backgrounds were tested for the effect of this novel drug and IR combination.

The study identified enhanced radiation-induced cell killing with this combination to be more effective in cells with functional RB protein. Interestingly, the researchers found an unexpected role of abemaciclib in inhibiting radiation-induced vasculogenesis (the process of blood vessel formation). Tumor vasculogenesis is a backup pathway to restore tumor vasculature that may contribute to recurrence of a tumor after radiotherapy. The study found that abemaciclib, when administered during and after IR treatment, inhibited vasculogenesis thus delaying tumor regrowth. Abemaciclib unexpectedly inhibited vasculogenesis by reducing the activation of tumor hypoxia inducible factor-1 and the recruiting of bone-marrow derived immune cells to the tumor. The findings suggest that abemaciclib in combination with IR could provide a novel biomarker-driven combination therapeutic strategy for patients with NSCLC. (NCI authors: S. Naz, A.L. Sowers, R. Choudhuri, M.F. Wissler, J. Gamson, A. Mathias, J.A. Cook, J.B. Mitchell, *Clin Cancer Res*, 2018; DOI: 10.1158/1078-0432.CCR-17-3575)

[BY SARWAT NAZ, NCI]

NIEHS, NCI: OBESITY ASSOCIATED WITH LOWER BREAST CANCER RISK

Young women with high body fat have a decreased chance of developing breast cancer before menopause, according to NIH scientists and an international team of researchers in the Premenopausal Breast Cancer Collaborative Group. The international team pooled data from 19 different sites comprising more than 750,000 women (ranging in age from 18 to 54) from around the world. The researchers evaluated questionnaires, filled out by study volunteers, that included height, weight, and other health-related factors. It was determined that the relative risk of premenopausal breast cancer was reduced 12 to 23 percent for each five-unit increase in body mass index (BMI). The strongest effect was seen in relation to BMI at ages 18-24, with very obese women in this age group being 4.2 times less likely to develop premenopausal breast cancer compared to women with low BMI at the same age. The NIH researchers are unsure why young, premenopausal women with a high BMI appear to be protected against breast cancer and caution that young women should not intentionally gain weight to lower breast-cancer risk as there are so many health risks associated with being overweight or obese. Understanding the biological mechanisms underlying the association of BMI and the risk of breast cancer could have important implications for breast-cancer prevention. (NIH authors: D.P. Sandler , C.M. Kitahara, M.S. Linet, K.M. O'Brien, *JAMA Oncol*; DOI: 10.1001/jamaoncol.2018.1771)

NCATS, NCI: STOPPING CANCER METASTASIS

NIH researchers and collaborators at Northwestern University (Evanston, Illinois) have identified a compound that blocks the spread of pancreatic and other cancers in various animal models. The team identified a compound, which they named metarrestin, that stopped tumor metastasis in multiple animal models. Mice treated with metarrestin also had fewer tumors and lived longer than mice that did not receive treatment. Metarrestin breaks down an incompletely understood component of cancer cells called the perinucleolar compartment (PNC). PNCs are found only in cancer cells, and in a higher number of cells in advanced cancer when it has spread to other sites in the body. The Northwestern scientists had shown earlier that the more cancer cells with PNC in a tumor, the more likely it would spread. Those findings suggested that reducing PNCs might translate to less cancer progression and better outcomes in patients. To test these ideas, the Northwestern scientists relied on NCATS's expertise in screening, chemistry, and compound development and testing to evaluate more than 140,000 compounds for their potential effectiveness in eliminating PNCs in cells in advanced cancer. The investigators identified one compound, metarrestin, that could effectively break down PNCs in advanced prostate cancer cells. The NCI researchers evaluated the effects—including toxicity—of metarrestin in pancreatic cancer mouse models. The scientists found that the compound prevented the further spread of pancreatic cancer by disrupting the protein-making machinery of cancer cells, and that mice treated with metarrestin lived longer than mice without treatment. The NCI and NCATS scientists are working together to collect the preclinical data on metarrestin needed to further its development as a candidate drug. The scientists plan to file an Investigational New Drug (IND) application in the fall with the FDA. (NIH authors: Udo Rudloff (NCI), Juan Jose Marugan (NCATS), and 15 others, *Sci Trans Med* **10**:eaap8307, 2018; DOI: 10.1126/scitranslmed.aap8307)

Read more research briefs online at https://irp.nih.gov/catalyst/v26i4/research-briefs.

Machine Learning

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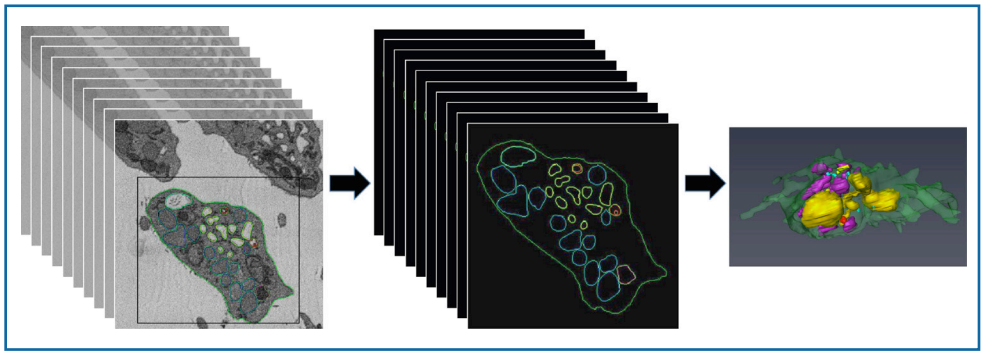


NIBIB

A mouse blood platelet has been sliced into 80-some 25-nanometer-thick layers (left) by a serial block-face scanning electron microscope. It takes a person a full day to manually trace the organelles through all the slices of one platelet (center). On the right is the resulting 3-D model of the platelet's subcellular organelles. With machine learning, computers can be taught to do the job in minutes. The sample was provided by Brian Storrie, University of Arkansas for Medical Sciences (Little Rock, Arkansas); data were analyzed by postbaccalaureate students **Michael Tobin** and **Rohan Desai** in **Richard Leapman's** laboratory in NIBIB.

set. Small wonder, given that a platelet that measures two to three micrometers across would be contained in about 80 image slices. It soon became clear that even the most zealous postbac would spend a lifetime working through the volume of data being produced by the microscope. When **Matthew Guay** joined Leapman's lab as a postdoc data scientist, he suggested they use new developments in machine learning to speed up the process.

Machine learning is by no means new. It's been around for decades. But thanks to big data and more-powerful computers, it has evolved into an amazing tool that has helped to advance—and often speed up—scientific research. In machine learning, computer systems automatically learn from experience without being explicitly programmed. A computer program analyzes data to look for patterns; determines the complex statistical structures that identify specific features; and then finds those same features in new data. For Leapman's platelet images, a machine-learning program would start with the platelet structures that had been painstakingly outlined by the postbac team, learn the features that identify the structures, and then use computer algorithms to demarcate platelets and organelles in new sets of similar images at high speed.

A more recent outgrowth of machine learning is deep learning, which takes advantage of the availability of massive amounts of data and powerful computers to train large and complicated artificial neural networks. For supervised deep learning, each element of the training data is labeled according to whether or not it contains an object of interest; however, the researcher doesn't specify to the computer which features uniquely identify that object. The computer learns to deduce the most-predictive features of the object from the dataset and then develops computational rules to identify labeled objects. This process is akin to pointing out cats to a small child, who will eventually figure out the features that identify a cat without needing to be told about ears or whiskers or tails.

Reliability, reproducibility, standardization, increased throughput, and decreased cost of data processing are among the benefits of machine learning. If larger datasets are available, deep learning can be used, and it is often more accurate than older machine-learning methods and less biased by human input.

Unsupervised machine or deep learning goes a step further: Objects or features are not labeled at all and the program searches for common characteristics to organize the data. This process offers the additional possibility of finding subtle patterns in large multivariate datasets such as genetic, imaging, and neurological data and biomarkers from patients.

Machine learning supports much of the technology around us. Smartphone cameras recognizing faces; online translating and captioning; credit-card fraud detecting; personalized online marketing; and providing newsfeeds. In the NIH intramural program, machine-learning techniques are being used in several research areas: image processing; natural-language processing; genomics; drug discovery; and studies of disease prediction, detection, and progression.

IMAGE PROCESSING

Analyzing X-rays and other images. **Ronald Summers'** group in the Clinical Center has been using machine learning for two decades so that computers could examine and analyze X-rays, computed tomography scans, and magnetic resonance images (MRIs). The goal is to improve the accuracy and efficiency of the image analysis to enable earlier detection and treatment of diseases. A few years ago, Summers and his group began using deep learning. "It has been the most accurate technique, a significant performance jump," he said. His group recently released a curated set of 120,000 anonymized chest X-rays (CXRs) to the scientific community. Researchers around the world can use this publicly available dataset to develop automated techniques for disease detection and diagnosis.

Screening for diseases. At the National Library of Medicine's (NLM's) Lister Hill Center (LHC), **Sameer Antani** and **George Thoma** are developing deep-learning-based diagnostic methods that will improve disease testing, decrease its cost, and produce more accurate, reliable, and standardized results. Antani is using

CXRs to automatically screen for tuberculosis (TB) and other pulmonary diseases, with a special focus on sub-Saharan Africa regions where medical facilities are limited and people have to travel long distances to hospitals. Ideally, sick people there need to be tested and treated close to home. A truck containing an X-ray generator and Antani's software has been travelling around rural Kenya since 2015, allowing more Kenyans to get tested easily and treated early.

Thoma's group is applying deep-learning models to screen for other diseases such as cardiovascular diseases, malaria, and the human papillomavirus (HPV). **Sema Candemir** is using deep learning—with CXR collections from international sources as well as from Ron Summers—to detect cardiomegaly (abnormal enlargement of the heart). **Stefan Jaeger** is applying a deep-learning algorithm to classify and count malaria parasites in blood-smear images faster and more accurately than humans can. Malaria affects millions worldwide, and inadequate diagnosis is one of the hurdles to overcome in reducing mortality. Jaeger developed a system on a smartphone attached to a microscope and is field testing it in Bangladesh and Thailand.

Screening for HPV is important because, if not prevented or caught early, it can develop into cervical cancer. Antani and his colleagues **Zhiyun Xue** and **Rodney Long** are working with **Mark Schiffman**, **Nicolas Wentzensen**, and their team at the National Cancer Institute (NCI) and collaborators at other organizations (including Global Good, which is supported by Bill Gates and the invention expertise of Intellectual Ventures) to develop and validate an automated visual-evaluation (AVE) algorithm that will identify precancerous lesions during visual inspection of the cervix. This AVE algorithm outperforms human interpretation and provides sensitive screening with minimal clinical training or cost. Installing AVE on camera phones or similar devices, combined with available low-cost treatments, could permit unprecedented dissemination of high-quality, point-of-care cervical screening, especially in developing countries where medical resources are scarce.

Thoma considers the results from applying deep learning to this automated screening "nothing short of a revolution." LHC Scientific Director **Clement McDonald** concurs. McDonald was initially chary of the claims for this technique but now says that the results of deep learning have been truly impressive.

Analyzing complex brain activation patterns. The National Institute of Mental Health's (NIMH's) functional MRI (fMRI) Core Facility, led by **Peter Bandettini**, supports structural MRI and fMRI for 70 clinical protocols including for schizophrenia, autism, anxiety disorders, multiple sclerosis, epilepsy, and stroke. Traditionally, fMRI studies compared scans from a patient group with those from a control group to identify specific differences related to a disease. Now, machine-learning and deep-learning methods can be used to analyze more complex and subtle brain-activation patterns as well as many other sources of information such as electroencephalograms.

"Deep learning is more of an adaptive model that allows scientists to find subtle connections without imposing a structured model on the data," said Bandettini. "There's a push to get more information from the research, have it translate to patients, and there's also this overwhelming increase in data because of newer imaging techniques."

Bandettini has recently started new collaborative teams within NIMH for data science and machine learning. The data-science team, headed by **Adam Thomas**, will share data across protocols so that intramural researchers can have access to well-curated image datasets and be able to mine data from public repositories. The machine-learning team, led by **Francisco**

CONTINUED ON PAGE 12

SAMEER ANTANI

A truck containing an X-ray generator and **Sameer Antani's** software (developed via machine-learning) has been traveling around rural Kenya, where medical resources are scarce and hospitals are often far away, since 2015, allowing more Kenyans to be screened for TB and other pulmonary diseases and treated early.

Machine Learning

CONTINUED FROM PAGE 11

Pereira, will use various techniques—and train researchers to use them—including multivariate analyses to extract individual differences from fMRI data to predict which drugs may help treat particular conditions.

Screening for eye diseases. Machine learning is proving useful in detecting eye diseases such as age-related macular degeneration (AMD), the leading cause of incurable blindness in people over 65. National Eye Institute (NEI) scientist **Emily Chew**, whose research focuses on AMD and other retinovascular diseases, is collaborating with **Zhiyong Lu** at NLM's National Center for Biomedical Information (NCBI) to classify 60,000 retinal images and calculate risk factors for AMD. In their most recent work, the automated deep-learning technique was consistently more accurate than human ophthalmologists.

Chew is also working with **Jongwoo Kim** in Thoma's group to develop deep-learning models that will improve screening for glaucoma. Drawing from thousands of images from NEI and international open-access sources, the model has learned to detect and classify features in specific regions of retinal images.

NATURAL LANGUAGE PROCESSING

In natural-language processing (NLP), researchers program computers to understand, interpret, and manipulate human language. Some of the ways that NLP is being used at NIH is for PubMed searches, dealing with medical questions that come from the public, and helping to improve the grant-application process.

Making PubMed searches better. Each day, some 2.5 million people use PubMed, NLM's search engine that provides free access to over 28 million biomedical and life-sciences publications. Few are aware, however, of the machine-learning technology (developed by NCBI) behind it. PubMed traditionally sorts search results by date with the latest papers listed first. Zhiyong Lu points out that this method may not be ideal for satisfying various kinds of user information needs. In early 2017, his machine-learning work allowed PubMed users to search for relevance-based results by choosing the new sort option "Best Match."

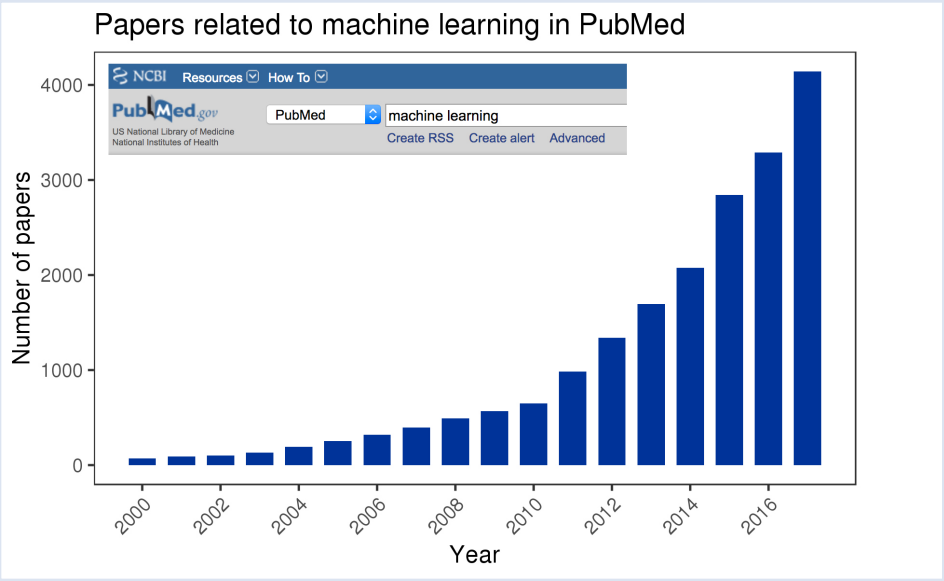
Lu's training dataset was developed by mining tens of thousands of past PubMed searches in an aggregated fashion. Dozens of features are used to rank PubMed results, the most important being past usage (access statistics) of an article, publication date, relevance score, and type of article. Some papers might not contain the precise words in a query or even synonyms of those words but may still be relevant. Deep learning offers great promise here: It can identify related articles by analyzing words in context. And PubMed users, when responding to tests that present both the date-sorted and relevance-sorted ("Best Match") results, have indicated that the relevance-based results are more useful to them.

Responding to medical questions. Streams of medical questions come in to NLM every day from people looking for advice and treatment options. An NLM team responds with suggestions pointing to accurate health information for patients and families at NLM's MedlinePlus health-information website, but this process is both slow and expensive. **Dina Demner-Fushman** in Thoma's group has developed prototype systems using NLP and deep learning to analyze incoming questions, extract question topics, and identify or generate precise answers.

Improving the grant-application process. The NIH Center for Scientific Review is the gateway for NIH grant applications and their review. To improve the grant-application process, **Calvin Johnson's** group at the Center for Information Technology (CIT) has developed a tool that uses machine learning to analyze the text in the application and recommend an appropriate study section.

DISEASE DETECTION, GENOMICS, AND DRUG DISCOVERY

Detecting diseases early. Parkinson disease (PD) is characterized by a wide variation in age of onset, duration until death, symptoms, and rate of progression. Until now, early detection and individualized



A PubMed search for machine learning shows the explosive growth of published research in this field since 2000.

predictions have been based on clinical observations. **Andrew Singleton's** group at the National Institute on Aging is using deep learning to examine multidimensional data—clinical reports, imaging data, blood tests, genetic data, and results of neurological tests over time—from large cohorts of patients with PD.

Singleton points out that humans are very good at identifying patterns in 2-D or 3-D data, but only computers, using the latest techniques, can find subtle differences and patterns in 130 dimensions. The predictive models built by Singleton's group allow for phenotypic clustering on a massive scale and indicates how patterns are related. The group recently used deep learning to identify the natural subtypes of PD as well as identify and predict the progression rates of each subtype. Singleton's group is also collaborating with **Sonja Scholz** (National Institute of Neurological Disorders and Stroke) on a deep-learning project that analyzes genomic data to predict and differentiate among dementia syndromes.

Detecting gene-gene interactions. **Joan Bailey-Wilson** at the National Human Genome Research Institute (NHGRI) has been collaborating for decades with **James Malley** (retired from CIT and now a special volunteer at NHGRI) to develop open-source software and methods for statistical machine learning, with particular interest in detecting gene-gene interactions. They have been applying machine-learning methods to find genetic variants that increase the risk of complex traits such as childhood-onset schizophrenia and several hereditary cancers.

Accelerating drug discovery. Scientists at the National Center for Advancing Translational Sciences (NCATS) are collaborating with researchers at NIH and beyond to accelerate the discovery of therapeutic medications. In an effort led by NCATS Director **Christopher P. Austin** and Scientific Director **Anton Simeonov**, NCATS is developing and applying machine-learning models across a broad spectrum of drug-discovery projects including antiviral drugs, anti-infection medications, epigenetic targets and deubiquitinating enzymes, and medications for rare diseases.

NCATS researchers also use machine-learning to guide the optimization of new drugs for adsorption and metabolism, select the best clinical candidate for efficient and safe clinical trials, and develop better toxicity-assessment methods. The models are available to other NIH institutes and centers and can be used, for example, to design RNA- and DNA-based nanoparticles with desired immunomodulatory activity as well as to predict toxicity, measure estrogen-receptor activity, and determine whether the stability of certain compounds depends on specific human cytochromes.

CHALLENGES

Although deep learning holds huge potential in several biomedical areas, its success depends on getting large training datasets. Small training datasets can result in the program's defining functions that do not generalize well to real-life data. Large annotated datasets can be difficult to obtain, however, so machine learning is a more practical approach for projects with small numbers (of patients, for example). In validating machine-learning methods, McDonald stresses how important it is to do a good statistical analysis of the datasets to avoid subtle biases.

Deep learning can be a black box. A scientist cannot easily tell why the algorithm comes up with a particular result. Singleton is sanguine: At the start "much technology appears [to be] a black box," he said. "But if the results are reliable, that's good enough to be getting on with [deep learning]."

The sensitivity of deep learning also means that the algorithms may not generalize well. A deep-learning program trained on, say, PubMed abstracts might not work well on full-text papers because the nature of the data is different.

In some cases, the algorithm can produce the "right result for the wrong reasons," said Antani. His program once correctly identified a patient as having TB due to an abnormality in the X-ray that was actually not TB-related. To find the cause of such errors, **Siva Rajaraman** (NLM) is investigating the way in which the layers in a multilayer deep-learning structure process the input images.

What are the prospects for using deep learning in clinical diagnosis? Lu believes that physicians may have more trust in a traditional computer program with rules that can be understood and modified. An incorrect deep-learning prediction that is corrected by a physician might not change the next diagnosis: The algorithms learn from thousands of examples, so modifying a single sample may not change the way an algorithm works.

The heavy computational requirements mean that the training phase of deep learning takes longer than traditional methods. Once training has been completed, however, deep learning can be applied very rapidly.

Despite the challenges, machine learning is likely to produce impressive results in the future. "Previous methods limited the questions that could be asked," said Bandettini. "But machine learning is exciting because it's taking all of the data to the next level, [and] trying to make it usable for individual patients, as well as pulling even more subtle information out of it." ●

For a list of resources and to read about how other intramural researchers are using machine learning or deep learning in their work, go to https://irp.nih.gov/catalyst/v26i4/machine-learning.

Barbra Streisand

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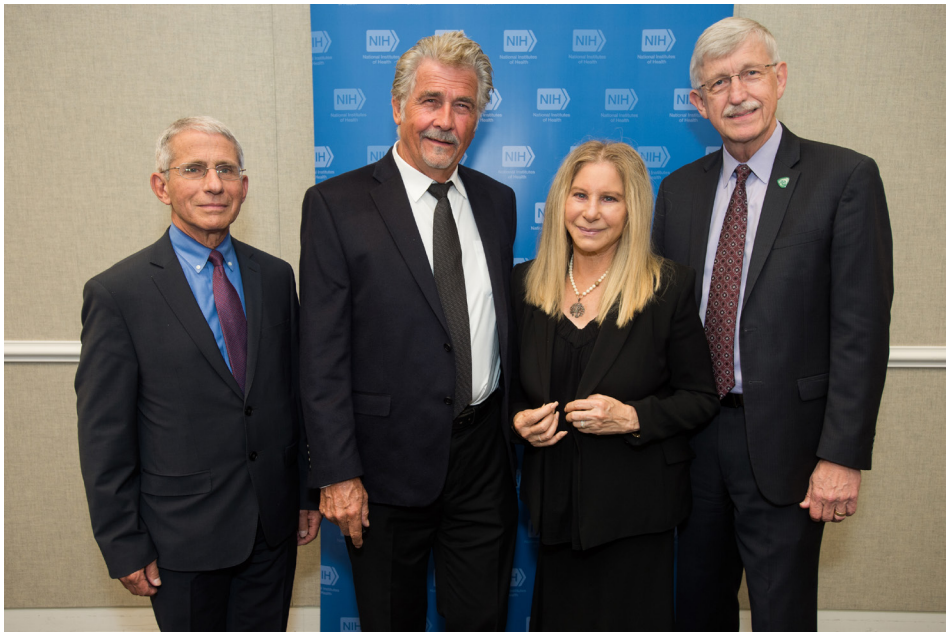


AARON CLAMAGE

As the featured guest at the annual J. Edward Rall Cultural Lecture, Barbra Streisand took the opportunity to highlight an issue that is near and dear to her heart: women's cardiovascular health. Her lecture was followed by an on-stage conversation with NIH Director **Francis Collins** and, later a tour of an NIAID lab at the Clinical Center. From left: NIAID Director **Anthony Fauci**, Streisand's husband, the actor James Brolin, Streisand, and Collins.

NIH Director **Bernadine Healy** titled "The Yentl Syndrome." The piece detailed a woefully under-recognized disparity in how physicians treated men and women with cardiovascular disease (CVD). Women admitted to the hospital with signs of a heart attack or other severe cardiovascular ailment were significantly less likely than men to receive the standard tests and treatments. "The problem is to convince both the lay and the medical sectors that coronary heart disease is also a woman's disease, not a man's disease in disguise," Healy wrote.

Given its relationship to her film, the editorial unsurprisingly piqued Streisand's interest, prompting her to learn more about the issue of women's heart health. She was "astonished and upset" to discover the stark gaps in the awareness and diagnosis of CVD in women, as well as the dramatically lower levels of treatment and needlessly inflated death toll that result from them. Much like Healy, Streisand attributed the problem partly to mistaken cultural beliefs and attitudes toward heart disease.

"I think women are embarrassed to talk about heart disease because there is a stigma attached to it," Streisand said. "It is known as an old man's disease in a sense, so many people think it just affects older men, but that is not true." In fact, heart disease is the leading cause of death for both men and women. Moreover, even after adjusting for age, women are 25 percent more likely than men to die, develop heart failure, or experience a stroke within five years of their first heart attack.

In 2008, Streisand helped raise $22 million dollars—including a $10 million donation of her own—for the Women's Heart Center at Cedar Sinai Medical Center in Los Angeles, which was subsequently renamed after her. Six years later, she co-founded the Women's Heart Alliance, a non-profit group that advocates for increased research into gender differences in cardiovascular health and medical treatment.

Promisingly, the rise of organizations like the Women's Heart Alliance and advocates like Streisand have led to considerable progress in closing the gender gap in cardiovascular care. Recent NIH policies encourage, and in some cases require, that NIH-funded research include members of both sexes. These directives pertain not just to human studies but also preclinical studies in which scientists have often limited their experiments to male animals and cells. Streisand specifically highlighted an NIH-funded endeavor called the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), launched in 2015, citing its goal to recruit a diverse cohort in order to examine differences in outcomes between men and women.

Despite these developments, Streisand said, more work remains to be done. She called for increased research funding for the study of sex differences in heart health. The Women's Heart Alliance is also taking steps to eliminate gender disparities in the quality of cardiovascular care and to educate women about lifestyle changes that reduce the risk for CVD.

"We start from the recognition that, biologically, women and men are not the same," Streisand said. "We have different equipment, we have different plumbing. And we advocate for funding and research so we can understand even more and apply those breakthroughs to provide prevention, care, treatment, and outcomes for everyone. As we like to say, we want to make sure women's hearts are on everyone's minds." ●

This article is adapted from a May 29, 2018, "I Am Intramural Blog" post (https://irp.nih.gov/blog/post/2018/05/barbra-streisand-talks-up-women-s-heart-health). To watch a video of Barbra Streisand's presentation at the May 15, 2018, J. Edward Rall Cultural Lecture, go to https://videocast.nih.gov/launch.asp?23875.

The SIG Beat

CONTINUED FROM PAGE 3

Sex differences were also detected when social interaction was a factor. Previous studies had shown that a fly had increased daytime sleep if it was exposed to 30 same-sex flies for five days compared to being kept in isolation. Harbison discovered that males were more sensitive to this paradigm than females; almost all the males in social groups had increased daytime sleep whereas the female response was more varied.

Harbison's studies established that there are indeed differences in sleep between male and female fruit flies. Genome-wide association studies (GWAS) have investigated 1.9 million variants for association with sleep in flies; three studies have found thousands of genes. But if only one sex was focused on, 17-35 percent of genes would have been missed! She did note that she would like to investigate gene expression in the fly brain to determine if the same differences occur there as at the whole-body level.

Fruit flies are invertebrates and therefore not covered by the NIH policy that requires sex as a biological variable to be factored into research using vertebrate animals and in human studies. But Harbison urged that unless there is a compelling reason to not look at both sexes, it should be done…even in fruit flies! ●

The SGHD SIG promotes information exchange and interaction among NIH and other scientists who work on or are interested in aspects of sex-based research in any segment of the research continuum or in sex differences research relevant to health and disease as approached via a wide variety of scientific disciplines. For more information, visit https://oir.nih.gov/sigs/sex-gender-health-disease or contact the co-chairs: **Elena Gorodetsky** (egorod@mail.nih.gov) or **Katrina Serrano** (katrina.serrano@nih.gov).

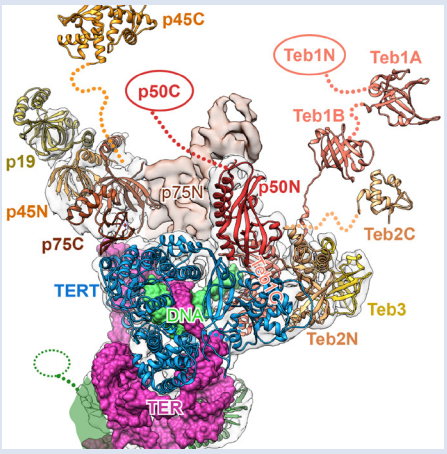
MPIG and SBIG: Determining Molecular Structures

BY MANJU BHASKAR, NINDS

The Membrane Protein Interest Group (MPIG) and the Structural Biology Interest Group (SBIG) are science hubs for brainstorming interactions among scientists who strive to determine molecular structures by applying the principles of computational biology and biophysics and using experimental tools such as X-ray crystallography, electron microscopy (EM), mass spectrometry, nuclear magnetic resonance (NMR), cryo-electron microscopy (cryo-EM), and computational approaches.

The SBIG/MPIG Student and Postdoc Symposium, held at the NIH Cloisters (Building 60) on May 24, showcased the novel discoveries and significant contributions made by the research groups from several institutes.

Many of the researchers in the SBIG/MPIG use cryo-EM, an EM technique in which a sample is cooled to extremely low temperatures. Cryo-EM helps scientists decipher and visualize the structural properties of a variety of protein molecules including the human anion exchanger 1, the major membrane protein in red blood cells that plays a key role in carbon dioxide exchange in the blood; tubulin isoform composition and microtubule dynamics; Ton, a multi-subunit membrane protein complex and molecular engine found in the inner membrane of gram negative bacteria; voltage-activated potassium channels in lipid nanodiscs (synthetic model membrane systems); particles of virus-associated RNA-I/protein kinase RNA-activated PKR inhibiting; transposons widely used for genomic engineering; the outer mitochondrial membrane sorting and assembly machinery complex; and a membrane enzyme that serves as a basis for designing in silico inhibitors.



JIANSEN JIANG, NHLBI

In his keynote talk, Jiansen Jiang (NHLBI) described how cryo-EM revealed structures of telomerase and provided new insights into telomeric DNA synthesis. Shown: A map of the ribbon structure of a telomerase complex.

The symposium's keynote speaker, **Jiansen Jiang** (National Heart, Lung, and Blood Institute, NHLBI) spoke about how cryo-EM structures of telomerase, a critical determinant of human health—affecting aging, cancer, and stem-cell renewal—can reveal new insights into telomeric DNA synthesis.

Structural biology has also paved way for phenomenal contributions in the discovery of novel therapeutics. One such noteworthy discovery is how proton pump inhibitors—traditionally used to treat gastrointestinal tract bleeding, stomach ulcers, and acid reflux—could be also used as inhibitors of HIV-1. NHLBI postdoc **Madeleine Strickland** explained how her group used NMR to determine the high-resolution structure of one of the inhibitors that plays a role in the pathogenesis of HIV.

Read more online at https://irp.nih.gov/catalyst/v26i4/the-sig-beat/. ●

For more information on the MPIG, contact Reinhard Grisshammer (reinhard.grisshammer2@nih.gov). For more on the SBIG, contact Antonina Roll-Mecak (Antonina.roll-mecak@nih.gov) or Anirban Banerjee (anirban.banerjee@nih.gov).

Recently Tenured

BIBIANA BIELEKOVA, NIAID

STEPHEN GILMAN, NICHD

RAPHAELA GOLDBACH-MANSKY, NIAID

NASSER RUSAN, NHLBI

HUMPHREY HUNG-CHANG YAO, NIEHS

BIBIANA BIELEKOVA, M.D., NIAID

Senior Investigator and Chief, Neuroimmunological Diseases Section, National Institute of Allergy and Infectious Diseases

Education: Comenius University School of Medicine, Bratislava, Slovakia (M.D.)

Training: Medical internship, SUNY Downstate Medical Center (Brooklyn, New York); neurology residency, Boston University School of Medicine (Boston); neuroimmunology fellowship in NINDS's Neuroimmunology Branch

Came to NIH: In 1997 for training; staff clinician in NINDS (2000-2005); left NIH to be a tenured associate professor of neurology and director, Waddell Center for MS, University of Cincinnati (Cincinnati, Ohio); returned to NIH in 2008 as an investigator in NINDS

Selected professional activities: Elected fellow of the American Academy of Neurology; elected fellow of the American Neurological Association; reviewer for several journals; co-organizer of a multiple sclerosis (MS) biomarker workshop, a Center for Human Immunology workshop, and the Spinal Fluid Consortium for MS

Outside interests: Taking photographs; hiking; volunteering on medical missions in developing nations

Website: https://irp.nih.gov/pi/bibiana-bielekova

Research interests: My laboratory is studying the mechanisms of immunoregulation and immune-mediated central nervous system (CNS) tissue injury in multiple sclerosis (MS) and other neuroimmunological diseases. Our long-term goal is to develop effective therapies for these diseases. Because observational studies cannot determine causal relationships, we use proof-of-principle interventional trials supported by biomarker/mechanistic studies and mathematical/statistical modeling to investigate major hypotheses about the pathophysiology of MS.

Because immunomodulatory treatments do not work well for progressive MS, it was believed that progressive MS is mainly a neurodegenerative disease. We demonstrated that the levels of CNS inflammation are the same for patients with progressive MS and those with relapsing-remitting MS. The multiplicity of potential pathogenic processes in progressive MS makes it unlikely that a single therapeutic agent will have major clinical efficacy. Effective therapy will require combinations of therapeutics that target patient-specific drivers of disability.

To produce such combination treatments, we must reliably measure the diverse CNS pathophysiological processes in living people and thereby define process-specific biomarkers to use as outcomes in Phase 2 trials. Indeed, using cerebrospinal fluid (CSF) biomarkers and statistical learning we have defined (and validated in an independent cohort) molecular signatures that differentiate MS from other CNS diseases and predict rates of MS progression. Our goal is to formulate (and validate) a framework in which CSF biomarker-based models provide reliable diagnostic, prognostic, and therapeutically-predictive information that will empower neurologists to practice precision medicine.

Among my lab's scientific achievements is the development of a CSF-based test that identifies and quantifies compartmentalized CNS inflammation specific for T cells, B cells, and monocytes/macrophages without the need for a brain biopsy. In addition, we used statistical learning to develop a CSF-based molecular diagnostic test that can differentiate MS from other CNS diseases (including inflammatory). We also developed much more sensitive measures of clinical outcomes and a MS disease severity scale (MS-DSS) that can be used to predict the progression of the disease.

If you have been recently tenured, the *NIH Catalyst* will be contacting you soon about including you on these pages. It's a great way for your colleagues to get to know about you and your work.

STEPHEN GILMAN, SC.D., NICHD

Senior Investigator, Social and Behavioral Sciences Branch, Division of Intramural Population Health Research, National Institute of Child Health and Human Development

Education: Tufts University, Medford, MA (B.A., social psychology); Harvard School of Public Health, Boston (Sc.M. and Sc.D. in health and social behavior)

Training: Postdoctoral fellowship in behavioral medicine, Brown Medical School (Providence, Rhode Island)

Before coming to NIH: Associate professor, Department of Social and Behavioral Sciences and Department of Epidemiology, Harvard School of Public Health

Came to NIH: In 2015

Selected professional activities: Adjunct professor, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health; elected fellow and councilor, American Psychopathological Association; member, Education Committee, Society for Epidemiologic Research; associate editor, *Nicotine & Tobacco Research*

Website: https://irp.nih.gov/pi/stephen-gilman

Research interests: Common mental disorders—depression, anxiety, and substance-use disorders—account for a substantial portion of the global burden of disease. My group investigates the life-course epidemiology of common mental disorders with an emphasis on understanding their developmental origins. Given that there are substantial social inequalities in common mental disorders, we also seek answers to the question "Why do social inequalities in common mental disorders emerge early in the life course, persist into adulthood, and become transmitted to the next generation?"

We are investigating the mechanisms for the link between disadvantaged childhood environments and the onset and recurrence of mood and substance disorders in childhood and adulthood. Discovering the mechanisms that produce social inequalities in psychopathology is integral to advancing our understanding of the developmental origins of psychiatric disorders.

This research has directed our focus on neurodevelopment as a key underlying pathway. For example, in a recent study, we found that neurologic abnormalities in infancy were more likely to occur in the context of socioeconomic disadvantage; in part the abnormalities were associated with lower concentrations of the proinflammatory cytokine interleukin-8 in prenatal serum during mid to late gestation. This work suggests that stress-immune mechanisms are one potential pathophysiologic pathway involved in the early origins of population-health inequalities. Other work involves examining neurodevelopmental and other early childhood risk factors for suicide, a leading cause of death among young people.

RAPHAELA GOLDBACH-MANSKY, M.D., M.H.S., NIAID

Senior Investigator and Chief, Translational Autoinflammatory Disease Studies Section, National Institute of Allergy and Infectious Diseases

Education: Universität Witten/Herdecke Medical School, Witten, Germany (M.D.); Duke, Durham, North Carolina (M.H.S.)

Training: Postdoctoral research fellow, Memorial Sloan-Kettering Cancer Center (New York); combined residency in internal medicine and pediatrics, Case Western Reserve University, MetroHealth Medical Center (Cleveland, Ohio); and rheumatology fellowship at NIAMS

Came to NIH: In 1997 for training; became staff clinician in 2001 and tenure-track investigator in 2008; in 2016 became tenure-track investigator in NIAID

CONTINUED ON PAGE 18

Two Elected to NAS

Michael Gottesman and Clare Waterman have been elected to the National Academy of Sciences (NAS) for 2018. Together they join more than 40 active NIH scientists in the NAS.

In addition to being the Deputy Director for Intramural Research, Gottesman leads the National Cancer Institute's (NCI's) Laboratory of Cell Biology. His interests have ranged from how DNA is replicated in bacteria to how cancer cells elude chemotherapy. Collaborating with **Ira Pastan**, chief of NCI's Laboratory of Molecular Biology, and others, Gottesman identified the multi-drug resistant gene (MDR1) responsible for resistance of cancer cells to many of the most common anticancer drugs and showed that this gene encodes a protein that acts to pump anticancer drugs out of drug-resistant human cancers.

Waterman is a Distinguished Investigator in the National Heart, Lung, and Blood Institute's Laboratory of Cell and Tissue Morphodynamics. She has made pioneering discoveries into the complex and dynamic mechanical interactions among organelle systems within cells that are required for directed movement. She has made key contributions to our understanding of the cellular cytoskeleton, including how integrin, microtubules, and filamentous actin work together to produce movement. She has also created cutting-edge technologies such as quantitative fluorescent speckle microscopy that have enabled new studies and insights into these systems. ●

Recently Tenured

CONTINUED FROM PAGE 17

Selected professional activities: Founder of the trans-NIH Translational Autoinflammatory Research Initiative; editorial board member of *Rheumatology*, *JCI Insight*, and *Frontiers in Immunology*

Outside interests: Reading about and studying world and art history; hiking; gardening; and listening to classical music

Website: https://www.irp.nih.gov/pi/raphaela-goldbach-mansky

Research interests: My translational autoinflammatory research focuses on children who have early-onset autoinflammatory diseases (immune dysregulatory diseases with excessive sterile inflammation that cause organ dysfunction and damage). My research team conducts pathogenesis and treatment studies in patients who have interleukin-1 (IL-1)-mediated autoinflammatory diseases—including neonatal-onset multisystem inflammatory disease (NOMID) and deficiency of the IL-1 receptor antagonist (DIRA)—and in patients with the type I interferon (IFN)-mediated autoinflammatory diseases, CANDLE and SAVI. Furthermore, we evaluate and study patients with undifferentiated autoinflammatory diseases that respond poorly to treatment.

We apply a diagnostic approach that includes careful clinical, genetic, and immune evaluations. We are part of the NIAID Clinical Genomics Program and aim to identify novel genetic variants that cause or modify inflammatory disease phenotypes.

With the goal of translating clues from early pathogenic and genetic studies into novel treatments, we develop treatment studies for our patients. Past studies using treatments that block IL-1 signaling confirmed a key role for the proinflammatory cytokine IL-1 in causing the disease manifestations of NOMID and DIRA. Our work led to the FDA's 2012 approval of the IL-1-blocking agent anakinra for the treatment of NOMID. More recently we identified diseases presenting with chronically elevated blood IFN signatures suggesting excessive IFN signaling (in CANDLE and SAVI). Treatment in a compassionate program using a JAK inhibitor that blocks IFN signaling confirmed a key role for IFN in causing the disease.

Many genetically defined autoinflammatory diseases have become models for understanding the pathogenesis of more common inflammatory diseases and are providing models for treatment.

Our work benefits from the NIH Clinical Center's help in phenotyping patient; conducting interventional studies; and providing inpatient- and outpatient-care facilities, laboratory services, and first-class imaging modalities. My active collaborations with specialists in many NIH institutes and the NIH Clinical Center's radiology and physical therapy department are crucial in our studies and in supporting our patients.

NASSER RUSAN, PH.D., NHLBI

Senior Investigator, Laboratory of Molecular Machines and Tissue Architecture, National Heart, Lung, and Blood Institute

Education: University of Massachusetts, Amherst, Massachusetts (B.A. in biology and Ph.D. in molecular and cellular biology)

Training: Postdoctoral training, University of North Carolina (Chapel Hill)

Came to NIH: In 2011 as an Earl Stadtman Investigator in NHLBI

Selected professional activities: Editorial board member of *Molecular Biology of the Cell* and of *Frontiers in Developmental and Cell Biology*; chair of the Drosophila Image Award

Website: https://irp.nih.gov/pi/nasser-rusan

Research interests: My lab studies the role of centrosomes during animal development. The centrosome is a non-membrane bound organelle that serves as the main microtubule organizing center of most animal cells. Centrosomes help build mitotic spindles, which are the molecular machines required for chromosome separation during cell division. Given the importance of cell division for proper development and tissue maintenance, it is not surprising that defects in centrosome function lead to a wide range of failures at the cellular level, which in turn, lead to tissue defects and many human diseases.

My lab is trying to determine how centrosomes are properly constructed from their individual parts and how they function in a wide range of cell types to avoid human diseases such as polycystic kidney disease, microcephaly, cancer and many others. We have streamlined a system to investigate multifunctional centrosome proteins and figure out how they play unique roles in different developmental stages, cell types, and cell-cycle stages. Using Drosophila genetics, cell biology, super-resolution microscopy, biochemistry, and modern molecular biology, we have uncovered unexpected new roles for centrosome proteins including in interphase neural stem cells during embryogenesis and spermatogenesis.

We have found that diversity in protein-protein interactions networks is responsible for the diversity of centrosome functions across cell types and cell-cycle stages. In other words, not all centrosomes are made equally. Understanding this centrosome diversity is a priority because it could help explain why different mutations in centrosome proteins affect specific cell types and manifest different diseases.

My laboratory is also venturing into developmental neurobiology. This direction started as a project aimed at investigating centrosomes as microcephaly-suppressor organelles. We have now expanded our research well beyond the centrosome, taking a hardcore cell-biology approach to understanding brain development using all the latest imaging technologies.

HUMPHREY HUNG-CHANG YAO, PH.D., NIEHS
Senior Investigator, Reproductive Developmental Biology Group, National Institute of Environmental Health Sciences

Education: Fu-Jen University, Taipei, Taiwan (B.S. in biology); University of Illinois at Urbana, Urbana, Illinois (M.S. in animal science; Ph.D. in reproductive biology)

Training: Postdoctoral fellow in developmental biology, Duke University (Durham, North Carolina)

Before coming to NIH: Associate professor, Department of Comparative Biosciences, University of Illinois at Urbana

Came to NIH: In 2010

Selected professional activities: Chair for the 2018 Gordon Research Conference on Mammalian Reproduction; associate editor, *Biology of Reproduction*; editorial board member, *Sexual Development and Endocrinology*

Outside interests: Playing tennis and golf; cooking; being a public-speaking coach; and translating English literature to Chinese

Website: https://irp.nih.gov/pi/humphrey-yao

Research interests: My lab is defining the normal process of how gonads and reproductive tracts form during embryogenesis. We are investigating whether this process is susceptible to in utero exposure to endocrine disruptors.

Compelling animal evidence and human epidemiological data have revealed that impairments in the development of fetal organs have profound consequences on adult health. The concept of "fetal origins of adult diseases" also applies to the reproductive systems—defects in the formation of reproductive organs manifest as disorders of sex development. However, minor abnormalities often go undetected and become a potential cause of fertility problems and neoplasia when the affected individual reaches adulthood.

My group uses organogenesis of the gonads and reproductive tracts as a model for understanding the basic process of organ formation. We are trying to determine how exposure to endocrine disruptors affects the formation of reproductive organs in fetuses and fertility in adults. Reproductive organs exhibit a dramatic sex-specific pattern of dimorphic development. This unique pattern of development provides us with opportunities to understand not only the basic mechanism of sex determination, but also how progenitor cells make the decision to differentiate into tissue-specific cell types, the fundamental concept of embryology.

Disorders of sex development, which affect one in 4,500-5,500 newborns, are major birth defects with significant health and psychological impacts on patients and their families. By using genetically modified mice to model human disorders of sex development, we hope to identify the potential causes of these disorders. We hope that our research will, one day, enable doctors to make appropriate diagnoses and treatments. ●

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

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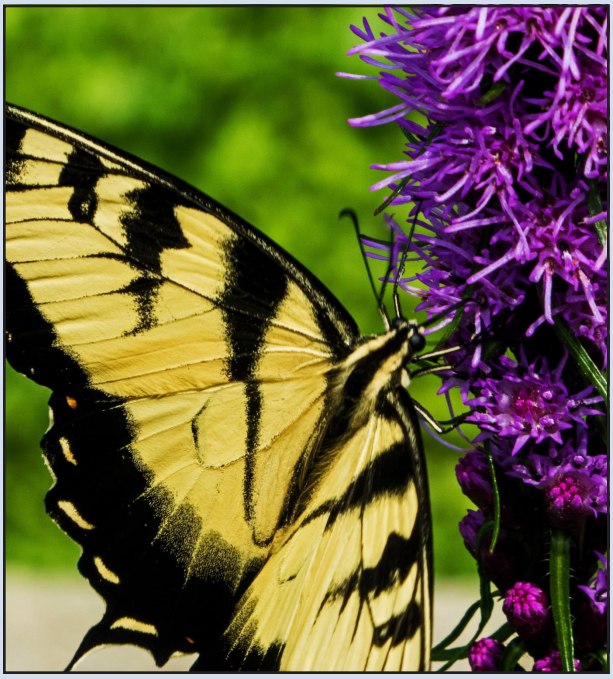
PHOTOGRAPHIC MOMENT

Butterfly Effect

This male Eastern Tiger Swallowtail butterfly (*Papilo glaucus*) is feeding on a *Liatris spicata*, a plant commonly known as blazing star or dense blazing star, on the NIH Bethesda campus. The photo was taken by **Joanna Cross**, a visiting fellow studying the genetics of neuropsychiatric disorders in the National Institute of Mental Health. In addition to working in the lab, she's an accomplished nature photographer and is especially good at macrophotography. "I love to take walks through the countryside or woods whenever possible, often taking my camera with me," said Cross. "Macro shots are fascinating as they show the level of detail contained within the multitude of tiny things that make up the world in which we live." She used a Panasonic Lumix TZ60 camera to take a photo of this butterfly right on the Bethesda campus. ●



JOANNA CROSS, NIMH

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