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The NIH Big Read

A Review of Inaugural Event With Writer Siddhartha Mukherjee

BY HAYLEY RAQUER, NIAID

Excitement built throughout NIH this spring when NIH's inaugural Big Read program had dozens of people reading and discussing Siddhartha Mukherjee's new book, *The Gene: An Intimate History*. Then, on April 17, the Big Read culminated with an appearance by the Pulitzer-Prize-winning author himself to discuss his book and meet his fans. It was his second book visit to NIH, the first being in 2011 to talk about *The Emperor of All Maladies: A Biography of Cancer*, the bestseller that won him the Pulitzer Prize and was the basis of a PBS film on cancer.

Although he carries obvious credentials within literary circles, Mukherjee's background is rooted firmly in the biomedical sciences. In 1992, he graduated from Stanford University (Standford, California) with a B.S. in biology. He had undergraduate research experience in the lab of Nobel Prize winner Paul Berg. After completing his Ph.D. at Oxford University (Oxford, England) as a Rhodes scholar, Mukherjee matriculated to Harvard Medical School (Boston) where he received his M.D. in 2000. Now an assistant professor of medicine at Columbia University in New York City, he splits his time as an oncologist, researcher, and science writer.

Given his extensive curriculum vitae and contributions to science, medicine, and

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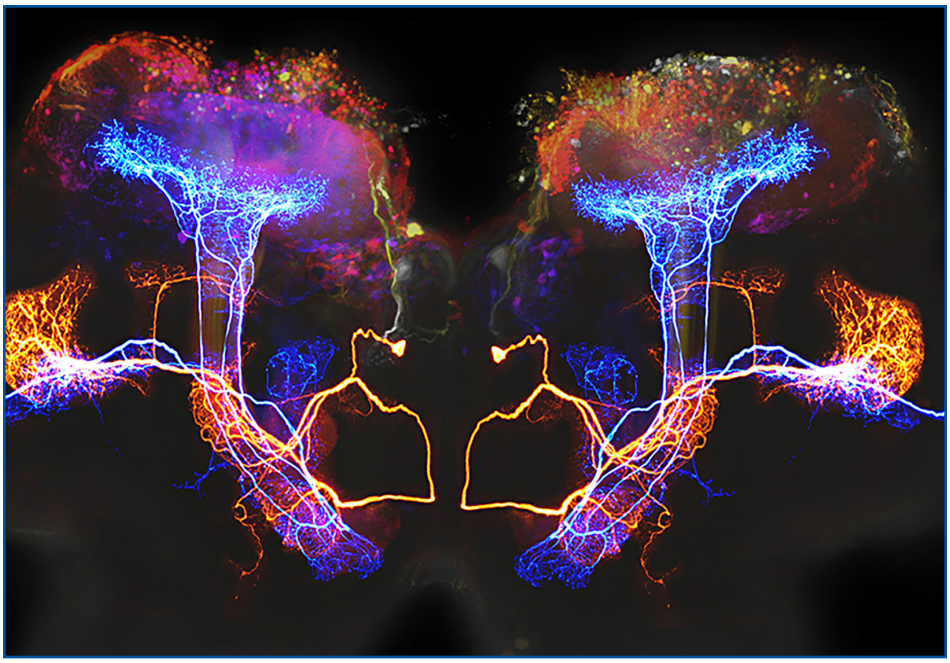
Microscopy as Masterpiece

A Beautiful Way to Study Neurons

BY LAURA STEPHENSON CARTER



MARK STOPFER, NICHD

This composite image shows two neurons, in the locust brain, that process olfactory information.

Perhaps only a scientist can find the beauty within a locust brain. An image—looking like mirrored, psychedelic-colored mushrooms—captured by **Mark Stopfer**—reveals the intricacies of neurons in the brain of the *Schistocerca Americana* locust. The image is one of several included in the "Microscopy as Masterpiece" digital exhibit at the Strathmore arts center in North Bethesda, Maryland. NIH and the Strathmore partnered to develop the exhibit, which complements the "Arts and the Brain" lecture series, and features beautiful brain microscopy images and videos created by NIH-supported researchers.

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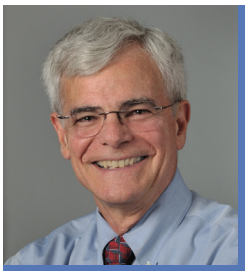


Population-Based Research Improving Public Health

BY MICHAEL GOTTESMAN, DDIR

In the past I have pointed out how laboratory-based research at the NIH has changed the practice of medicine. An even greater impact on public health can be attributed to the epidemiological studies done by NIH scientists or as collaborations between intramural and extramural investigators. Such population-based intramural programs have been established in about half of the institutes and centers, including the NCI, NICHD, NIAID, NIEHS, NIMH, NHLBI, NHGRI, NEI, NIA, NIDDK, and NIMHD.

Epidemiologic studies provide rigorous statistical evidence of the association between human behavior or environmental circumstances and disease that may motivate more detailed mechanistic studies to enhance prevention or suggest other interventions to ameliorate disease and disability. Such studies use a wide range of research designs, often involve multidisciplinary and multi-investigator collaborations, and may generate mechanistic data that support findings from laboratory-based studies.

By way of example, allow me to cite studies that have led to changes in the practice of medicine and have made obvious improvements in the public's wellbeing. These studies represent a tiny percentage of the population-based studies done at the NIH and have been chosen only to illustrate how powerful such studies can be.

The focus of NCI's Division of Cancer Epidemiology and Genetics (DCEG), founded more than 50 years ago by **Joseph Fraumeni Jr.** (who has just retired but will continue as a scientist emeritus at the NIH; congratulations, Joe!), has been on genetic and environmental factors that increase the incidence of cancer. NCI scientists have discovered a substantial percentage of the human genetic syndromes that predispose one to cancer, including the eponymous Li-Fraumeni syndrome that is due to inherited p53 mutations that lead to cancers in multiple organ systems. People who carry mutations that predispose them to cancer can be counseled to undergo earlier and more frequent screening to improve the likelihood that cancer can be discovered in an earlier, more treatable stage.

DCEG scientists also did many of the early epidemiological studies that showed the relationship between human papillomavirus (HPV) infection and cervical and oropharyngeal cancer. Their work pointed to the need for an HPV vaccine, which was developed by **John Schiller** and **Douglas Lowy** in NCI.

NCI has also demonstrated associations between environmental exposures, such as medical X-rays and computed-tomography scans, and an increased incidence of cancer. These studies have resulted in changes in medical practice that should reduce the incidence of radiation-associated cancers.

Another distinguished population-health program at the NIH is NICHD's Division of Intramural Population Health Research, which will be celebrating its 50th anniversary soon. Epidemiologists in this program study human populations across the lifespan. Twenty-five years ago, NICHD scientists in collaboration with researchers in Ireland found an association between neural-tube defects and folate deficiency.

Today, expectant mothers take folate supplements, and bread is supplemented with folate to ensure adequate maternal concentrations for normal fetal development. As a result, there has been a dramatic drop in neural-tube defects in the United States and several other countries.

NICHD epidemiologists have made other important contributions. They were the first to show an association between maternal diabetes and poor fetal outcomes.

They also showed that participation in formal swimming lessons was associated with an 88 percent reduction in the risk of drowning in children aged one to four years old. (Drowning is a common cause of death in childhood in many parts of the world.) That demonstration has influenced the advice that pediatricians give parents and will, we hope, lead to universal swimming lessons.

Some studies have been reassuring; for example, NICHD epidemiologists have shown that children conceived by assisted reproductive technologies have the same growth and developmental trajectories as children conceived without treatment.

NIEHS has also contributed to studies of pregnancy and human development. The observation that up to 25 percent of embryos fail to survive six weeks (before women know they are pregnant) came from an NIEHS study, as did the finding that by age 50 up to 80 percent of black women and 70 percent of white women have uterine fibroids. For black women, especially, the earlier development of fibroids has significant public-health implications.

For NHLBI, the iconic Framingham Study represents a comprehensive effort to

enumerate the risk factors that contribute to the development of atherosclerotic cardiovascular disease. Most of the seminal observations about the association among smoking, high blood pressure, lipid abnormalities, obesity, and diabetes and heart disease came from the rigorous population-based studies conducted by the intramural leaders of the Framingham study and their many extramural colleagues who contributed. Additional studies to test the role of these factors in more diverse populations are underway, but the primary methodology came from the Framingham study.

With three generations of study participants, decades of clinical data, and a treasure trove of molecular and DNA-methylation data from thousands of participants analyzed by whole-genome sequencing, gene-expression profiling, microRNA profiling, proteomics, and metabolomics, the Framingham study is at the forefront of a burgeoning new field of molecular epidemiology that will provide insights into the next generation of risk factors for cardiovascular and many other diseases.

There are many other examples of profoundly important observations made by NIH population scientists that have improved public health. The ones cited here give you a flavor of the important contributions that the NIH has made to this field.

Although different from laboratory- or clinic-based mechanistic studies, population-based research has had a substantial effect on public health. And, it's important to note, that the work is not possible without a team-science approach. Research teams often include biostatisticians, health behaviorists, and clinicians.

The celebration, this May, of a half-century of studies on population health at NICHD provides us with an occasion to take stock of our many successes and to ensure that we will support rigorous and vigorous population studies at the NIH in the future. ●

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

LIGHT MICROSCOPY

The Light Microscopy Interest Group (LMIG), which aims to build a bridge between NIH biologists and microscopists, informs the NIH community about cutting-edge research in light fluorescence microscopy and about available resources, both extramural and intramural.

NIH researchers are at the leading edge of this fast-growing field. Do you want to learn about madSTORM, the super-resolution technique multiplexed antibody size–limited direct stochastic optical reconstruction microscopy developed in NCI's Center for Cancer Research and applied to localization of 25 proteins simultaneously in activated T cells? Or how about innovative dyes for single-molecule imaging permitting bright, stable, and reliable labeling of protein fusions to HaloTag, SNAP tag, and CLIP tag; a new antibody-based drug-delivery method based on "uncaging" of biologically active molecules by near-infrared light; or genome organization and its cell-to-cell variation revealed by high-throughput fluorescence in situ hybridization?

If you are interested, come to the LMIG seminars to learn about innovative microscopy techniques and their application to biomedical research. The aim is to demonstrate applicability of the state-of-the art microscopy to tissue- and cell-biology problems. Presentations include biological data and in-depth description of appropriate microscopy techniques.

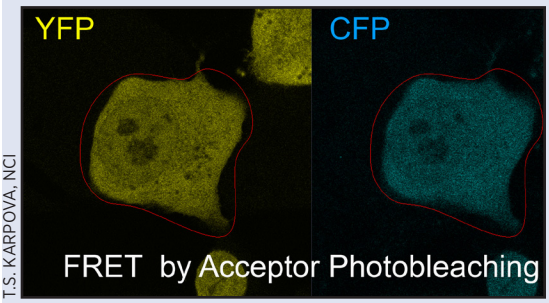
To get the mailings, join the LISTSERV at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=light_micro_interestl&A=1. For more information, contact the LMIG moderators **Christian Combs** (combsc@mail.nih.gov) and **Tatiana Karpova** (karpovat@mail.nih.gov).

NEW SIG: SCIENTIA ET PHILOSOPHIA

The Scientia et Philosophia Interest Group seeks to foster and expand the knowledge and understanding of the NIH research community and staff of the philosophical foundations of the scientific endeavor. In an interdisciplinary, open, and inclusive environment, the group promotes an exchange of knowledge in a diversity of fields and topics including the philosophy, origins, and foundations of science; logic and rationalism; cosmology and cosmogony; biology and biogeny; ethics, meta-ethics, and metaphysics; and history of philosophy (classical to modern).

The group stresses how our current empirical scientific projects in basic and clinical research are inseparably tethered to these philosophical underpinnings and are strengthened when clearly grounded on a strong philosophical foundation. A good working knowledge of the philosophical foundations of science and the limits of rationalism allow for better formulation of scientific experimental design, model construction, and parsimonious extraction of inferred conclusions.

This SIG is open to intramural investigators, staff, and trainees as well as to extramural affiliates and academic scientists and clinicians outside the NIH. Activities will include regular discussion meetings, internal and external speakers, and webinars. To join the SCIENTIA_ET_PHILOSOPHIA LISTSERV, go to https://list.nih.gov/cgi-bin/wa.exe?A0=SCIENTIA_ET_PHILOSOPHIA-L.For more information, contact the group moderator, **Peter Leeds** (leedsusa@mail.nih.gov).



T.S. KARPOVA, NCI

The Light Microscopy Interest Group focuses on innovative microscopy techniques and their application to biomedical research. Shown: A technique called Förster resonance energy transfer (FRET) reveals mammalian cells transformed with the fusion protein cyan fluorescent protein (CFP)–yellow fluorescent protein (YFP) before and after acceptor (CFP) photobleaching.

Lasso Your Data

Consider Adding Data-Science Skills to Your Biologist's Toolbox

BY CRAIG MYRUM, NIA

Think back to when you still had a basic cell phone. You could make calls, you could text, you could play some games. It got the job done. When you got your first smart phone, its capabilities probably seemed endless. How could you possibly go back to your "dumb" phone now?

For day-to-day data organization and analysis, we are all probably quite comfortable with Excel. But biology's complexity is now being reflected in complex sets of data, so computational analyses that require coding skills are becoming the norm. With any hope, we biologists will soon look back at Excel in the same way we do old cell phones.

Learning coding sounds like a daunting task to many of us. Our excuses for not learning a coding language often resemble justifications for not learning a foreign language: "I get by without," "I don't have time," or "I'm not good at those kinds of things." But enhancing your data-science skills (machine learning, data visualization, and especially coding) can be your ticket to better personal and professional opportunities. Biomedical scientists' ability to work with model organism databases, structural data, clinically relevant variation data, omics data, or any other publicly available set of "big data"—a virtual treasure trove—can help answer important research questions. Although most basic biological graduate programs do not require coding classes, the demand for data-science training has not gone unnoticed at the NIH.

"All [intramural] trainees have quite a few resources at their disposal if they want to start to tip-toe into the computational space," said **Andy Baxevanis**, head of the National Human Genome Research Institute's Computational Genomics Unit. "Classes range from the hands-on training available through the NIH Library and Foundation for Advanced Education in the Sciences to the 'Current Topics in Genome Analysis' series." (For the latter, check out those lectures at http://genome.gov/CTGA2016). Online coding classes are growing tremendously in popularity. Many of them are free or at least reasonably priced for the quality of content you receive.

NIH scientific interest groups (SIGs) and LISTSERV electronic mailing lists are also valuable resources. "One of the best things about the Bioinformatics SIG is that people can post specific questions on the LISTSERV. Questions are usually answered within the hour," said **Ben Busby**, genomics outreach coordinator at the National Center for Biotechnology Information.

Efforts are underway to set up a related interface for general data science. Busby and colleagues are also establishing an NIH-wide data-science mentorship program to facilitate one-on-one mentorship and training. Several NIH institutes and centers have their own bioinformatics cores that offer similar training and mentoring opportunities.

For example, **Supriyo De**, staff scientist at the National Institute on Aging, and colleagues recently launched the Biomedical Data Science Initiative, which offers seminar-type overview training, hands-on training for smaller focus groups, and integrated one-on-one teaching for fellows analyzing data from their own projects.

All trainees can also reach out to Intramural Research Program faculty members who use computational approaches in their own work. "Many of us very much enjoy mentoring," said Baxevanis. "People should feel free to reach out when they need some advice and guidance regarding their projects."

So should *all* trainees learn a coding language? "Familiarity with a command-line interface such as Linux is a basic literacy skill in any technical field because a large and increasing proportion of modern data and tools are intractable with GUI [graphical user interface] tools," explained Busby. (For coding-illiterate folks out there, GUI is the graphical display, rather than purely textual, that allows us to use the computer hardware in a user-friendly way.)

Whether or not you should learn coding may depend on the types of data that you want to analyze and your overall career trajectory. "It certainly is advantageous to have these skill sets to facilitate data analysis," said Baxevanis. "But in many instances, what is more important is being able to use the analysis resources that are out there in an intelligent fashion, taking the time to understand what these predominantly Web-based resources can do and how they do it—and that they should never treat these resources as a 'black box'! The same way it's important to understand the underpinnings of any laboratory-based method, the same applies for all things computational." ●

RESOURCES

- **NIH Library:** https://nihlibrary.nih.gov/resourcetraining/Pages/default.aspx
- **LISTSERVS & SIGs:** https://datascience.nih.gov/community/datascience-at-nih/sigs#title3
- **Computational Biology Scientific Focus Area:** https://irp.nih.gov/our-research/scientific-focus-areas/computational-biology
- **More online at:** https://irp.nih.gov/catalyst/v25i3/the-training-page-news-everyone-can-use

Lights, Camera, Mouse Action

NIH Develops New Mouse-Behavior Monitoring System

BY SWAGATA BASU

GHADI SALEM, CIT

SCORHE video (center) is analyzed automatically to produce a per-frame 3D-pose estimate (right) and behavior label (left). The pose estimates (estimates of the mouse's position) and behavior labels are used to generate full circadian-cycle profiles of activity and behavior.

Automated video-based monitoring of laboratory mouse behavior is getting more efficient thanks to a team of NIH researchers led by **Ghadi Salem**, a staff scientist in the Signal Processing and Instrumentation Section (SPIS) at NIH's Center for Information Technology. The new "System for Continuous Observation of Rodents in Home-cage Environment" (SCORHE) is composed of custom video-acquisition and analysis tools that can quantify mice activity and behavior for short and long (multi-day) durations while the mice are housed within a typical home-cage. The specialized hardware is space efficient, compatible with vivarium cage racks, and animal-facility-user friendly. The advanced software algorithms output animal-behavior measures.

Video monitoring of animals in their home cages is noninvasive and provides more information about behavior than observations of mice using running wheels or tripping photobeam detectors. SCORHE—which can monitor the day-to-day health of mice, provides advanced behavioral screening, assesses the short- and long-term effects of experimental treatments—avoids disrupting circadian rhythms, does away with the need for mice to become acclimated to test environments, and allows for night-time measurements. Commercially available systems can be expensive and, unlike to SCORHE, do not integrate with vivarium cage-racks.

"SCORHE was designed to demonstrate the feasibility of integrating large-scale, video-surveillance methods in animal facilities by means of efficient mechanical design leveraging a nontraditional camera configuration," according to the group's publication in *Behavioral Research Methods* (*Behav Res Methods* **47:**235–250, 2015).

"This [system] eliminates issues with moving the mice from their home cage to the testing environment, which can be stressful for them," said principal investigator **Alexxai Kravitz** (National Institute of Diabetes and Digestive and Kidney Diseases), who is validating SCORHE's ability to analyze obesity-related behaviors such as locomotion and feeding.

Lights: To obtain both daytime and night-time measures of behavior, SCORHE uses near-infrared illumination, which provides consistent image quality without disturbing the animals' light and dark cycles.

Camera: The SCORHE units employ inexpensive Raspberry PI digital cameras fitted with fisheye lenses. Although the fisheye lenses cause images to be distorted, they are key to the compact design and ventilated-rack integration. SPIS engineers developed software for continuous high-frame-rate capture of digital video from multiple cameras over long durations. The software comes with a Python-based Graphical User Interface (GUI) which allows the user to preview video streamed from the cages and set up multi-cage experiments.

Action: The most advanced feature of SCORHE is its ability to extract measures of mouse activity and behaviors. The SCORHE team has developed algorithms to accurately estimate the 3D position of the mouse despite the fisheye-lens distortion. The algorithms also measure bouts of predefined behaviors including walking, grooming, food-interaction, drinking, climbing, and resting. The measures provide detailed time-resolved locomotion and behavior profiles for the mouse over multiple circadian cycles.

The system can be used for phenotypic characterization of animal models, behavioral and activity profiling, circadian and sleep-pattern monitoring, and therapeutic trials. "Since behavior is an expression of overall health, our system can demonstrate improvements in health and quality of life, said SCORHE team member John Dennis, who is the director of the Division of Veterinary Services at the FDA Center for Biologics and Evaluation Research (Silver Spring, Maryland). "And it can make animal studies more humane by identifying and reporting humane endpoints automatically."

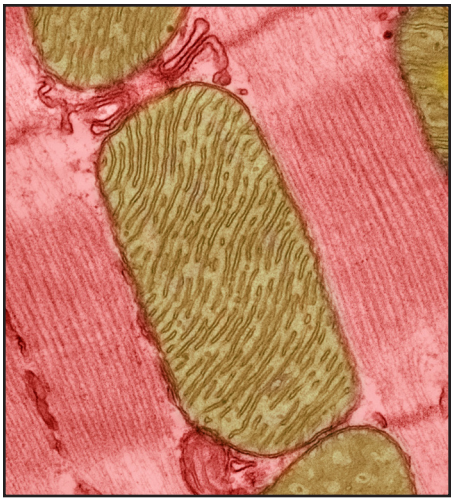
As work is underway to produce the latest set of prototypes, the SCORHE team is preparing for NIH intramural researchers to collaborate on beta testing (on their specific application) to produce a more refined and capable system. The development will be kept open-source to widely serve the NIH intramural program and the greater scientific community. ●

More information can be found at the project website: https://scorhe.nih.gov.

NIEHS Team Reports How Oxidative Stress Kills Cells

A Key to Understanding the Origins of Some Human Diseases

BY ROBIN ARNETTE, NIEHS



THOMAS DEERINCK, U. OF CALIFORNIA, SAN DIEGO

Mitochondria are specialized energy-producing machines that fuel cells, but they also produce reactive oxygen species (ROS) molecules that harm cellular DNA and proteins. Shown: mitochondria (with diagonal striations) from the heart muscle cell of a rat.

HUMANS NEED ENERGY TO FUNCTION, so it might be hard to imagine how a naturally occurring process that generates power for the body can also harm its cells. But it does, noted **Samuel Wilson** and members of his DNA Repair and Nucleic Acid Enzymology Group, in the National Institute of Environmental Health Sciences (NIEHS).

Based on work done by Wilson's research fellow **Melike Caglayan**, the team determined more details about how this particular type of damage leads to DNA strand breaks and, ultimately, cell death. The scientists used biochemical and cell-biology methods, along with X-ray crystallography, to uncover the inner workings of cells. Their recent findings, published in the journal *Nature Communications,* may help scientists better understand the origins of some human diseases (*Nat Commun* **8:**14045, 2017; doi: 10.1038/ncomms14045).

Breaking DNA: Wilson said that cellular mitochondria, which are specialized energy-producing machines that fuel cells, also produce molecules that harm cellular DNA and proteins. These harmful molecules, known as reactive oxygen species (ROS), can alter the chemical composition of the compounds used to build DNA, as well as DNA itself. If the DNA building blocks are not restored to their original shape, or if DNA is structurally modified due to ROS, the DNA can break, triggering the cell to self-destruct.

"When ROS-modified compounds are incorporated into a DNA strand, they cause frayed ends that can't be properly glued together during DNA repair," Wilson said. "This gap or break in DNA can initiate cell death."

Double-edged sword: The pressure that ROS places on cells is called oxidative stress, and it happens all the time. The body takes advantage of the killing power of ROS in a series of steps known as innate immunity, which is the natural immunity a person is born with.

For example, Wilson explained that when a bacterium enters the body, a white blood cell activates a special immune cell called a macrophage. The macrophage douses the bacterium with ROS. Just as ROS causes breaks in human cellular and mitochondrial DNA, it will go to work breaking the bacterium's DNA. That way, the macrophage kills the bacterium before engulfing it.

The scheme is a resourceful way to kill living things that could make a person sick, but what happens when the invader is not alive? Take, for example, the particles in cigarette smoke or smog. When these small pieces of matter enter human lung cells, they trigger a similar ROS response by macrophages.

The macrophages use the same mechanism to get rid of invaders. But in this case, the oxidative stress eventually leads to fibrosis, which is the thickening or scarring of tissue seen in chronic lung disease. Wilson mentioned other conditions, such as cataracts, cardiovascular disease, and some neurodegenerative disorders, that are also linked to the effects of oxidative stress.

Understanding the mysterious mitochondria: Wilson said the research described in the new paper demonstrates a subtle way cells can accommodate the damage ROS inflicts on them. The self-destruction of an individual cell as a result of oxidative stress is a less extreme outcome than the result of exposure to a strong oxidizing agent, such as bleach. In that case, all of the cells in the mix—both the body's cells and the pathogens—would die.

"We know that the mitochondria probably produce the majority of ROS in a cell," said NIEHS mitochondrial expert **Bill Copeland**, who was not involved in this research. "So fully understanding their function may lead to the root of human illness." ●

This article is adapted, with permission, from the March 2017 issue of *Environmental Factor*: https://www.niehs.nih.gov/news/newsletter/2017/3/feature/feature-2-oxidative/index.htm.

More photos at https://irp.nih.gov/catalyst/v25i3/niehs-team-reports-how-oxidative-stress-kills-cells.

Delayed Walking Associated with Gene Anomalies in Autisms

Distinct Behavioral Profiles Linked to ASD Risk Genes

BY JULES ASHER, NIMH

A team of National Institute of Mental Health (NIMH) intramural and grant-supported researchers has discovered a pattern of behavioral and genetic features seen in some cases of autism spectrum disorder (ASD) that could ultimately lead to identification of subgroups and improved treatment.

Children diagnosed with ASD who had spontaneous, noninherited changes in autism-linked genes showed "muted" core autism symptoms related to social behavior and language compared with sex-, age-, and IQ-matched children with ASD without known genetic abnormalities. A key clue was that children with the spontaneous glitches—abnormal numbers of copies of genes or other mutations linked to functional impairments—tended to start walking later than usual, which is not typical of children with ASD. In fact, the odds of a child in this sample having a spontaneous abnormal gene finding increased by 17 percent for each month of delay in walking.

"Identifying individuals whose ASD is associated with a specific type of genetic abnormality may lead us to distinct processes ultimately traceable to specific causes, which could be targeted by more personalized interventions," explained NIMH intramural researcher **Audrey Thurm**. "In the meantime, our results can increase awareness that among children with an ASD diagnosis, certain characteristics [such as] late walking are associated with genetic abnormalities."

Thurm, NIMH grant–supported researcher Somer Bishop of the University of California at San Francisco, and colleagues reported their identification of an emerging cluster of developmental, behavioral, and genetic markers in ASD on March 3, 2017, in the *American Journal of Psychiatry* (*Am J Psychiatry*, DOI:10.1176/appi.ajp.2017.16101115).

Before the study, the estimated 10 to 15 percent of children with ASD who have noninherited, or de novo, gene-copy-number variations or suspected disrupting, severe mutations had not been found to show specific patterns of ASD-related symptoms or delays in developmental milestones. The new discovery was made possible through advances in genomics technology, allowing for a large number of "high-confidence" suspect genes to be identified, as well as more rigorous matching of children with and without genetic abnormalities than in previous studies. For example, the new study controlled for the potentially confounding effects of IQ, which has been previously found to be lower in children with ASD with de novo mutations.

Results showed that children with de novo mutations tended to be less impaired on core ASD symptoms than their peers with more typical ASD and no known genetic abnormalities. Children with de novo mutations also tended to have stronger verbal, language, and social-communication abilities, and clinicians involved in assessing the children were less confident in their ASD diagnoses for the subgroup with de novo mutations. Yet children with de novo mutations began walking, on average, at 19 months, compared with 13.6 months for children with typical ASD, when controlling for differences in nonverbal IQ.

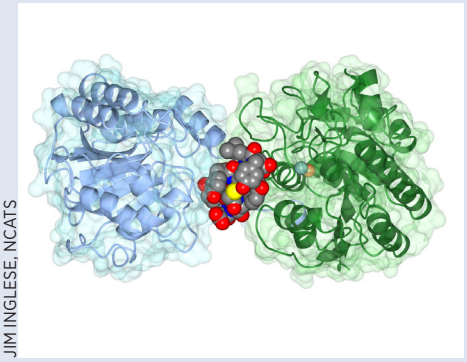
"While all children in this study met diagnostic criteria for ASD, those with genetic abnormalities showed subtle, yet potentially important, differences in their behavioral profiles when compared to appropriately matched children with no such abnormalities," said Bishop. "These findings are in line with previous assertions that, as a group, de novo mutations may be best understood as conferring risk for neurodevelopmental problems more generally, rather than ASD core symptoms specifically." ●

SOURCE: ADAPTED FROM GORDON, FLIKR

A pattern of behavioral (such as delayed walking) and genetic features seen in some cases of autism spectrum disorder (ASD) could ultimately lead to identification of subgroups and improved treatment.

This article first appeared on the NIMH science news website at https://www.nimh.nih.gov/news/science-news/2017/delayed-walking-may-signal-spontaneous-gene-anomalies-in-autism.shtml.

Intramural Research Briefs



JIM INGLESE, NCATS

NCATS, NHLBI: The cyclic peptide ipglycermide binds to and blocks the activity of a cofactor-independent phosphoglycerate mutase (iPGM) enzyme, which is essential for glycolysis in disease-causing parasites and bacteria.

NCATS, NHLBI: INTERNATIONAL SCIENTIFIC TEAMS FIND POTENTIAL APPROACH AGAINST PARASITES

Parasitic nematode infections cause many devastating infectious diseases around the world. Researchers from NCATS and NHLBI and the University of Tokyo (Tokyo) identified the first inhibitor of an enzyme long thought to be a potential drug target for fighting disease-causing parasites and bacteria. After sorting through more than 1 trillion small-protein fragments (cyclic peptides), the scientists found two potential inhibitors of the enzyme. The target enzyme—cofactor-independent phosphoglycerate mutase (iPGM)—exists in both parasites and bacteria and is essential for glycolysis. The team collaborated with structural biologists at the University of Kansas (Lawrence, Kan.) to determine the structure of the iPGM-cyclic peptide arrangement and how it prevented the enzyme from working properly. Next, the researchers will look for ways for cyclic peptides to enter cells. This study could inform developments of broad-spectrum antiparasitic and antibacterial agents. (NIH authors: P. Dranchak, R. MacArthur, N.J. Baird, and J. Inglese, *Nat Commun* 8:14932, 2017; DOI:10.1038/ncomms14932)

[WRITTEN BY ALIA SAJANI, NIAID]

NHGRI: SELFIES COULD HELP DIAGNOSE A RARE GENETIC DISEASE

Taking selfies may one day help physicians diagnose genetic diseases such as DiGeorge syndrome, which is also known as 22q11.2 deletion syndrome and is caused by a defect in chromosome 22. Those with the syndrome exhibit certain facial features—such as an underdeveloped chin, low-set ears, wide-set eyes, or a narrow groove in the upper lip—and may have congenital heart disease; poor immune-system function; and delays in growth, development, and speech. The disorder is commonly underdiagnosed, especially in diverse populations. NHGRI scientists used digital facial-detection analysis on 101 photos—from consenting individuals with the syndrome—from 11 countries to determine 126 distinct geometric and textural facial features that serve as markers of the syndrome. The facial-recognition technology accurately diagnosed the syndrome 96.6 percent of the time across diverse populations. The prevalence of smartphones in areas of the world that lack molecular- and cytogenetic-testing facilities means that facial diagnostic capabilities of handheld devices can enhance early detection and treatment of 22q11.2. (NIH authors: P. Kruszka, Y.A. Addissie, J. Duncan, A.A. Adeyemo, and M. Muenke, *Am J Med Genet* 173:879–888, 2017)

[WRITTEN BY ALIA SAJANI, NIAID]

NIBIB: NOVEL RADIOTRACER MAY IDENTIFY PROSTATE CANCER

There is no single imaging technique or test for diagnosing, monitoring, and staging prostate cancer. NIH researchers, however, are taking steps to develop a single method that, in one scan, can identify the cancer in its early stages as well as after metastasis. Using a novel radiotracer that recognizes two biomarkers normally found in prostate cancer–gastrin-releasing peptide receptor and integrin alpha-V beta-3–the researchers successfully identified 75 percent of primary prostate tumors and 100 percent of metastatic lymph nodes and bone lesions in the study cohort (five healthy volunteers and 13 patients with various stages of prostate cancer). The probe (gallium-68–bombesin–arginylglycylaspartic acid) was well tolerated and outperformed prostate biopsy, magnetic resonance imaging, and positron-emission tomography using fluorine-18-labeled fluorodeoxyglucose in detecting prostate cancer and metastatic lesions. Combined with other imaging tools, this new technique could provide tumor-staging information and monitoring response to therapy and could serve as a guide for delivering internal radiation therapy. Larger-scale clinical studies are needed to confirm the findings. (NIH authors: J. Zhang, G. Niu, L. Lang, X. Yan, X. Chen, *J Nucl Med* 58:228–234, 2017)

[WRITTEN BY ALEJANDRO CHIBLY, NIDCR]

NIAMS, NHLBI, OD: TREATING LUPUS WITH TOFACITINIB

Tofacitinib, a drug already approved for the treatment of rheumatoid arthritis, prevented the onset of lupus in lupus-prone mice, NIH researchers found. Lupus is a chronic autoimmune disease that causes widespread inflammation and eventually leads to cardiovascular and renal damage. It is thought that high concentrations of cytokines, especially interferons, are associated with the progression of the disease. Tofacitinib, which was discovered and developed at NIH, blocks the inflammatory response pathway Janus kinase–signal transducers and activators of transcription. When administered to mice that had already developed lupus, tofacitinib reversed kidney damage, skin inflammation, and blood-vessel abnormalities. In mice that had not yet developed lupus, the drug prevented onset of the disease. Further studies are needed to determine the efficacy and safety of using tofacitinib to control lupus symptoms in humans.

(NIH authors: Y. Furumoto, C.K. Smith, L. Blanco, W. Zhao, S.R. Brooks, S.G. Thacker, A. Zarzour, G. Sciumè, W.L. Tsai, A.M. Trier, L. Nunez, L. Mast, V. Hoffmann, A.T. Remaley, J.J. O'Shea, M.J. Kaplan, and M. Gadina, *Arthritis Rheumatol* **69**:148–160, 2017)

[WRITTEN BY ALEJANDRO CHIBLY, NIDCR]

NCI: THYROID CANCER ON THE RISE

The incidence of thyroid cancer has increased by 211 percent in the United States over the past 40 years, according to an NCI-led study. Researchers at NCI and Duke University Medical Center (Durham, N.C.) analyzed data from more than 77,000 thyroid-cancer patients diagnosed during 1974–2013 and from more than 2,000 thyroid-cancer deaths during 1994–2013. Although some investigators have thought that the increase was due to improvements in diagnostic technology that picked up small tumors that would have never required treatment, the current study challenges that notion. Additional research is needed, however, to determine whether environmental factors—such as endocrine-disrupting chemicals or changes in obesity and smoking prevalence—may be associated with the increase. (NIH authors: H. Lim, S.S. Devesa, D. Check, and C.M. Kitahara, *JAMA* **317**:1338–1348, 2017)

NIAMS: MECHANISMS TO IMPROVE NUCLEAR REPROGRAMMING

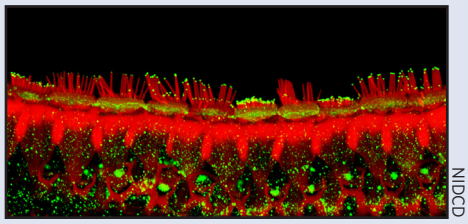
NIAMS researchers conducted high-throughput RNA sequencing of transplanted oocytes to uncover the mechanisms that cause some genes to resist reactivation. The findings will help improve the success of nuclear reprogramming. (NIH authors: S. Wang and V. Sartorelli, *Molec Cell* **65**:873–884, 2017)

NIDCD: GENE THERAPY FOR HEARING LOSS AND DIZZINESS DISORDER

Using gene therapy, scientists from NIDCD and Johns Hopkins School of Medicine (Baltimore) have corrected defective structures in the inner ears of newborn mice, with long-term benefits. The study is one of the first to use gene therapy successfully to improve hearing and restore balance in mice with a type of inherited deafness, called Usher syndrome, also found in people. The findings support growing evidence that gene therapy could be an effective treatment for inherited types of hearing loss, deafness, and balance disorders. The experimental gene therapy used in the study targets hair cells, which are sensory cells in the inner ear. These cells have hair-like projections called stereocilia that help detect and process incoming sound and information about movement to guide a person's sense of balance. Stereocilia need the protein whirlin to fully grow and function properly. In one type of Usher syndrome, the gene that encodes whirlin, *Whrn*, is mutated. This causes the stereocilia to be abnormally short and disorganized, making them dysfunctional. As a result, the sensory hair cells cannot detect sound and information about movement to guide the sense of balance, leading to dizziness and to hearing loss or deafness. Read full article on NIDCD webpage at https://www.nidcd.nih.gov/news/2017/gene-therapy-usher-syndrome. (NIH authors: K. Isgrig, J.W. Shteamer, I.A. Belyantseva, M.C. Drummond, T.S. Fitzgerald, A.J. Griffith, T.B. Friedman, L.L. Cunningham, and W.W. Chien, *Mol Ther* **25**:780–791, 2017)

NICHD: SCREENING TESTS FAIL TO PREDICT PRETERM BIRTH IN FIRST-TIME PREGNANCIES

Two screening methods that once seemed promising for predicting premature deliveries in first-time pregnancies may not be so helpful after all. NICHD researchers screened more than 9,000 women throughout their pregnancies by evaluating routine ultrasound examination of the uterine cervix (a short cervix early in pregnancy could be a warning sign of preterm birth) and testing for fetal fibronectin (some studies have suggested that the presence of this gluelike protein in the vagina early in pregnancy could signal early labor). But the screenings failed to identify most of the women who would go on to give birth prematurely. The researchers concluded that, alone or together, the methods did not identify enough preterm births to support using them for routine screening of first-time pregnancies. (NIH author: U.M. Reddy, *JAMA* **317**:1–10, 2017) ●



NIDCD

NIDCD: Gene therapy with *Whrn* restores stereocilia bundles (red spikes) in the inner ear of a *Whrn* mutant mouse to normal length and position. Even after four months, stereocilia continue to produce whirlin protein (green speckles), helping to maintain the structure and function of the stereocilia and improving the mouse's ability to hear and maintain balance.

Read longer versions of the above briefs and others online at https://irp.nih.gov/catalyst/v25i3/research-briefs. The following are online only:

- NHGRI: AFRICAN-SPECIFIC GENOMIC VARIANT ASSOCIATED WITH OBESITY
- NICHD: EXTREME TEMPERATURES MAY INCREASE RISK FOR LOW BIRTH WEIGHT
- NICHD, NHGRI: ORIGINS OF BLOOD-BRAIN BARRIER "SENTRY CELLS"
- NIAID, CC: NIH STUDY OF EBOLA PATIENT TRACES DISEASE PROGRESSION AND RECOVERY
- NIAID: NIH SCIENTISTS ADVANCE UNDERSTANDING OF HERPESVIRUS INFECTION

The Big Read

CONTINUED FROM PAGE 1

Pulitzer-Prize-winning author Siddhartha Mukherjee visited NIH to discuss his new book, *The Gene: An Intimate History*, which was featured in NIH's inaugural Big Read event.

scientific communication, it is not surprising that Mukherjee returned to the NIH to a packed auditorium. This visit and the successful turnout were thanks to the tireless efforts of the NIH Library, who partnered with FAES, to bring literature and discussion to the NIH through this Big Read program.

One of the core pillars of the Library is to "foster collaboration and community across NIH," said **Kathleen McGlaughlin**, the librarian who oversaw the planning and preparation for the entire Big Read event. The biggest hope of the project was to create a forum in which diverse members of the NIH community could weigh in on *The Gene* and its discussion of the latest technologies in human genetics and their inevitable social, ethical, and moral implications.

Anyone who follows the latest in biomedical research knows that the past few years have seen an explosion of potential in terms of genome editing—led by the speeding bullet that is the Crispr/Cas9 gene-editing system. Mukherjee, as a physician-scientist, has seen these breakthroughs and recognizes their great and terrible potential. And members of NIH's workforce—technicians, administrators, trainees, professors, physicians, counselors, nurses, and others—recognize that potential, too, and were eager to discuss the ideas and concerns reflected in Mukherjee's book.

For a two-month period, more than 70 individuals came together for hour-long book-discussion sessions, hosted by the Library. Interest was so strong that a fourth discussion group had to be opened to accommodate the lengthy waitlist. Unlike participants in some proctored events who require prodding and pointed questions, the book-club participants needed little incentive to share their thoughts on the book, its historical context, and the ethical implications of the past few years of research. What was remarkable was the obvious time and depth of thought both scientist and nonscientists had given to many of the ethical issues raised in the final chapters of *The Gene*. As one participant pointed out, "We can't afford to stick our heads in the sand and not think about these issues."

Although the Big Read sought to include the entire NIH in a discussion of genetics history, medicine, and biomedical ethics, Mukherjee had a larger goal for his book. He stated that the book, and the coming documentary by Ken Burns, was meant to reach an audience wider than "laboratories and scientific institutions" and to explore "the extent [to which] these technologies [such as gene editing] will transform human beings and human culture."

His motivation for writing *The Gene* stemmed from three sources. The first was his desire to write a prequel to his previous book, *The Emperor*; the second, to explore the latest advances in genetics and medicine; and the third, to chronicle his own personal familial relationship with genetic diseases. During the question-and-answer session that followed Mukherjee's talk, NIH Director **Francis Collins** asked him how he set about writing a book of the depth and scale of *The Gene*.

The most "complicated thing is not what you put in, but what you leave out," Mukherjee said. He was wary of overwhelming his audience with too much scientific information because he did not want to lose the "most important readers," the non-scientists, with whom he hoped to spark a discussion and invite into the conversations surrounding the history and future of genetics.

The question is no longer "Can we?" said Mukherjee. We must now ask, "Should we?" and determine "the limits and constraints, both scientific and social. . .ethical that [these technologies] have to be tempered with." Later, he elaborated on this perspective when asked what role bench scientists who are developing the technologies should play in these often highly charged conversations. "They absolutely should" play a role, he said. "And they definitely are."

From the size of the audience and the successful book clubs, it appears that the NIH has heard *The Gene*'s rallying cry and is prepared to listen to and reflect on the implications that have arisen with our entrance into this new age in genetics. As our community has learned over the last few hundred years, the ethical implications are just as important as the scientific questions. The NIH Library has done an excellent job of creating a space for discussion and community; Mukherjee provided a strong framework and context; and it is now up to us to continue the conversation. ●

The NIH Big Read was inspired by the National Endowment for the Arts Big Read program and sponsored by the NIH Library and the Foundation for Advanced Education in the Sciences. To watch a videocast of Mukherjee's April 17, 2017, presentation (NIH-only), go to https://videocast.nih.gov/launch.asp?23226.

Microscopy as Masterpiece

CONTINUED FROM PAGE 1

Stopfer, a senior investigator at the National Institute of Child Health and Human Development, uses simple animal models such as locusts to study basic questions in neuroscience. He is identifying and analyzing the properties of neurons that process information about odors. He places an intracellular electrode into a locust neuron to record responses when odors are puffed onto the animal's antennae. The neurons respond with vigorous spiking when odors are presented; when the odor changes, the spiking patterns change, too.

Stopfer had the following to say about how the image was produced:

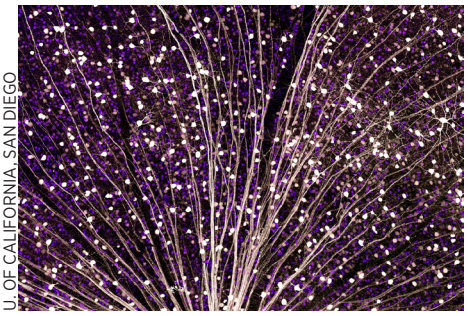
"The image is a composite of several micrographs illustrating two kinds of olfactory neurons in the locust brain. In the background, in gray, is an outline of the locust brain. Superimposed on that, in [an] assortment of colors, is a confocal microscope image of the 'mushroom bodies,' brain areas that process sensory stimuli and form memories. The image was made by injecting large amounts of dye into the mushroom bodies and then imaging them such that parts closer to the brain surface are more red and parts deeper in the brain are more blue.

"Finally, the image includes two olfactory neurons. In the intact animal, each neuron was studied by placing an intracellular electrode into it to record its responses when odors were puffed onto the animal's antennae. (Both neurons respond with vigorous spiking when odors are presented; the spiking patterns change when the odor is changed.) Then, dye was injected into the neuron, and later the neuron was imaged on a confocal microscope. One cell here is colored blue and one orange. These colors were selected artificially in Photoshop when the composite image was assembled. Overall, the image shows the locations, enormous size, and complex branching patterns of neurons that process olfactory information."

Arts and the Brain Lecture Series

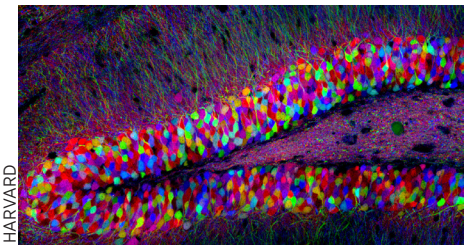
Strathmore's "Arts and the Brain" lecture series engages teachers, scholars, and artists working at the intersection of arts and health to present innovative, practical strategies for harnessing the arts to alleviate suffering and strengthen vitality. The final lecture, titled "Medical Avatar," will take place on Thursday, June 1, at 7:30 p.m., in the Mansion at Strathmore. For information, go to https://www.strathmore.org/education/programs-for-adults/arts-the-brain-package. Tickets cost $25 for each lecture, but you can view the "Microscopy as Masterpiece" exhibit for free. ●

More images from exhibit:



U. OF CALIFORNIA, SAN DIEGO

The pinpricks of light in this starry night sky are actually green fluorescent protein, marking specific cells in a mouse retina. This detailed image was made using large-scale mosaic confocal microscopy, a technique that, like Google Earth, computationally stitches together many small, high-resolution images.



HARVARD

Random mixing of fluorescent dyes created this psychedelic slice of a mouse brain. Known as "brainbow," the technique allows scientists to distinguish nearby cells by color and has helped advance the NIH Human Connectome Project.s.

Yasmine Belkaid Elected to NAS

Congratulations to Yasmine **Belkaid** who has been elected to the National Academy of Sciences (NAS) for 2017. She explores the field of immune regulation and has defined fundamental mechanisms that regulate tissue homeostasis and host immune responses. She has uncovered key roles for the commensal microbiota and dietary factors in the maintenance of tissue immunity and protection against pathogens, demonstrating that commensals play a major role in the control of host-defense in both the skin and the gastrointestinal tract. The NAS announced in May that it had elected 84 new members and 21 foreign associates in recognition of their distinguished and continuing achievements in original research. Election to the academy is considered one of the highest honors in the fields of health and medicine. Including the newly elected, the total number of active members is 2,290 and the total number of foreign associates is 475. ●

Researchers in the Intramural Research Program have won hundreds of significant professional awards in the last several years, far too many to list comprehensively. For highlights, go to https://irp.nih.gov/about-us/honors.

WALS Superstars

NIH's Wednesday Afternoon Lecture Series Features Nobel Laureates and Other Science Stars

BY VIVIANNE CALLIER, NEI; ALEJANDRO CHIBLY, NIDCR; AND LAURA S. CARTER

The 2016–2017 NIH Director's Wednesday Afternoon Lecture Series (WALS) has featured a parade of science superstars on most Wednesdays (and occasionally other days), from 3:00 to 4:00 p.m., in Masur Auditorium (Building 10).

Each season includes some of the biggest names in biomedical and behavioral research. An added treat is the annual J. Edward Rall Cultural Lecture, which features top authors and other cultural icons. This season's Rall guest was none other than world-renowned cellist Yo-Yo Ma on December 5, 2016 (see the *NIH Catalyst* article in the January–February 2017 issue).

WALS speakers are nominated by the NIH community. To check out the rest of the season, which ends on June 28, go to https://oir.nih.gov/wals/current-lecture-season. The 2017–2018 season begins in September. Here's a taste of what 2016–2017 season had to offer.

HOLLIS CLINE: BUILDING A BRAIN THAT SEES

BY VIVIANNE CALLIER, NEI

New research is revealing how visual activity guides the development of brain circuits that support vision.

The findings may help researchers understand the origins of diseases such as amblyopia, explained Hollis Cline, president of the Society for Neuroscience and professor at the Scripps Research Institute (San Diego, California), at the January 18 WALS. Amblyopia is when the vision in one of the eyes is reduced because the brain is favoring the other eye. Cline imaged developing tadpoles, whose brains are clearly visible through their skin, and found that retinal ganglion axons send out exploratory branches before forming synapses with other neurons. During this process, neurons that fire together in response to a common stimulus strengthen their connections and, over time, terminate their branches at the same location.

She also found that neurons firing in response to the same stimulus at slightly different times terminated in slightly offset positions in the brain. In short, neurons that fire in sequence wire in sequence. The wiring rule ensures that information about retinal inputs spread across the entire target area in the brain.

Read more in the April 7, 2017, issue of the *NIH Record*. To see a videocast of the Cline's WALS lecture, "Building Circuits to Process Visual Information," go to https://videocast.nih.gov/launch.asp?21087.

GEORGE CHURCH: THE FUTURE OF GENETIC CODES

BY ALEJANDRO CHIBLY, NIDCR

On February 8, geneticist George Church (Harvard Medical School, Boston) delivered the annual Marshall Nirenberg Lecture, which recognizes 1968 Nobel Laureate Nirenberg for his work deciphering the genetic code.

Church himself was a major contributor to one of *Science's* Top 10 Breakthroughs of 2013—the CRISPR-Cas method of gene editing. He is also widely recognized for his innovative contributions to genomic science and his many pioneering contributions to chemistry and biomedicine.

In 1984, Church developed the first direct genomic sequencing method, which resulted in the first commercial genome sequence (the human pathogen *Helicobacter pylori*). He helped initiate the Human Genome Project in 1984 and the Personal Genome Project in 2005. He invented the broadly applied concepts of molecular multiplexing and tags, homologous recombination methods, and array DNA synthesizers.

Much of the latest progress in genomic engineering has happened thanks to the research in Church's lab. Undoubtedly, one of his more influential contributions has been the development of the CRISPR-Cas9 gene-editing system, which allows for site-specific, programmable DNA cleavage in single cells or whole organisms. Currently, the system is being used for a vast array of biomedical and research applications, from controlling transcription of specific genes to alleviating genetic disorders in animals.

Church has also exploited the advantages of this system to trace the cause and effect of point mutations in patient-derived and genetically engineered induced pluripotent stem cells, to provide insight into the pathophysiology underlying the cardiomyopathy of Barth syndrome (*Nat Med* **20:**616–623, 2014).

Furthering the advancement of medicine with the CRISPR method is one of Church's goals. He believes, for example, that we can overcome the shortage of organs for transplantation by using CRISPR gene editing to inactivate endogenous retroviruses that can create problems in pig-to-human xenotransplants. Beyond medical applications, Church also discussed the potential (and concerns) of altering wild populations to address ecological problems.

One shortcoming of the CRISPR-Cas9 technology is what Church referred to during his presentation as the double-strand-break dilemma: "When you make a double-strand break, it's a race between the cell fixing it and getting your donor DNA to fix it how you want," he explained.

To overcome this efficiency limitation, Church's lab is working on CRISPR-Cas9 alternatives that would allow gene editing while avoiding double-strand breaks. With this new approach, Church and his team have successfully performed the largest and most radical genome engineering to date, altering the genetic code in *Escherichia coli*. The end result is an organism that depends on nonstandard amino acids to survive and thus is easily biocontainable, and it possesses a unique synthetic genetic code that prevents horizontal gene transfer and confers resistance to almost any virus. This work provides a foothold for developing safer genetically modified organisms (*Nature* **518:**55–60, 2015; *Science* **342:**361–363, 2013).

The CRISPR-Cas9 gene-editing technique has opened the door for developing therapies that remained somewhat unthinkable until recently. For instance, the possibility of engineering one's own genome has attracted fans since the advent of CRISPR-Cas9—so much so that do-it-yourself gene-therapy kits are available in the market for reversing aging.

Church cautions that there hasn't been extensive testing of these approaches but agrees that veterinary preclinical trials, which his group is working on, place human studies in the foreseeable future.

To watch a videocast of George Church's WALS lecture, "The Future of Genetic Codes and BRAIN Codes," go to https://videocast.nih.gov/launch.asp?21127.

LINDA BUCK: UNRAVELING SMELL

Not only does WALS have named lectures in honor of Nobel laureates, but also some of the lecturers are Nobel laureates themselves. Linda Buck (Fred Hutchinson Cancer Research Center, Seattle), who won the 2004 Nobel Prize in Physiology or Medicine (with Richard Axel) for her discoveries of odorant receptors and the organization of the olfactory system, presented the annual Margaret Pittman Lecture on March 29.

Pittman was the first woman to be a laboratory chief at NIH (1957–1971) and is recognized for her work on an improved and standardized pertussis (whooping cough) vaccine; the isolation of the influenza strain responsible for most childhood meningitis; the identification of the cause of epidemic conjunctivitis; and her key observations that led to the development of a Salmonella vaccine.

In her lecture, Buck talked about her pioneering work that has shed light on how thousands of odor molecules are detected in the nose and translated by the brain into perceptions and instinctive behaviors.

A videocast of her lecture, "Unravelling Smell," will be available soon at https://videocast.nih.gov/PastEvents.asp (search "past lectures" for March 29, 2017).

THOMAS CHRISTIAN SÜDHOF: SYNAPSE FORMATION IN THE BRAIN (COMING IN 2018)

Another Nobel laureate, Thomas Christian Südhof (Stanford School of Medicine, Stanford, California), was originally scheduled to give a WALS lecture this year, but will coming on Wednesday, January 31, 2018, instead.

Südhof is interested in how synapses form and function in the developing and adult brains. His work focuses on the role of synaptic cell-adhesion molecules in establishing synapses and shaping their properties, on pre- and postsynaptic mechanisms of membrane traffic, and on impairments in synapse formation and synaptic function in neuropsychiatric and neurodegenerative disorders. He shared the 2013 Nobel Prize in Physiology or Medicine with James E. Rothman and Randy W. Schekman "for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells."

If you can't make the talk in person, you can watch a videocast at http://videocast.nih.gov.

ATUL GAWANDE (TUESDAY, JUNE 13, 2017)

Surgeon, writer, and public health researcher Atul Gawande (Harvard Medical School) will give a talk on Tuesday, June 13. He practices general and endocrine surgery at Brigham and Women's Hospital (Boston). He is a professor in the Department of Health Policy and Management at the Harvard T.H. Chan School of Public Health and the Samuel O. Thier Professor of Surgery at Harvard Medical School (Boston).

Gawande has been a staff writer for T*he New Yorker* magazine since 1998 and has written four *New York Times* bestsellers: *Complications, Better, The Checklist Manifesto*, and most recently, *Being Mortal: Medicine and What Matters in the End*. He is the winner of two National Magazine Awards, Academy Health's Impact Award for highest research impact on health care, a MacArthur Fellowship, and the Lewis Thomas Award for writing about science.

The Gwande lecture will be videocast to NIH only at http://videocast.nih.gov.

Going the Distance

Teresa Przytycka: Driven by Curiosity and Big Dreams

BY KATHRYN MCKAY, NLM

If you ask computational biologist **Teresa Przytycka** where she's from, and she's likely to quip, "Do you mean geographically or scientifically?"

Both answers cover long distances for her. Her journey, which began in Poland many years ago, brought her to NIH where she's a senior investigator in the National Library of Medicine's National Center for Biotechnology Information (NCBI).

The geographical journey

Przytycka was born and raised in Myszków, Poland, a small city with three factories surrounded by a rural area. Although her parents were educated, they "came from a village where…people typically ended their education at basic reading and writing skills," she said. "In fact, since they grew up during the war, a good chunk of my parents' schooling was within the Polish underground education system—very brave but not very rigorous."

Despite growing up under unassuming circumstances, Przytycka considers herself fortunate. She was lucky enough to have a group of curious friends in school. "I think we inspired each other in dreaming big," she said. Her curiosity and big dreams have stayed with her.

She studied at the University of Warsaw (Warsaw, Poland), earning a master's degree in mathematics with a concentration in computer science. After graduating, she stayed at the university, working as a research and teaching assistant in the Department of Mathematics, Mechanics, and Informatics. It was there she met her husband, Jozef, who had a Ph.D. in mathematics from Columbia University (New York). Shortly after they married, Jozef was offered a postdoctoral position at the University of British Columbia (UBC) in Vancouver, Canada.

So she applied to a Ph.D. program in computer science at the same university. Again, Przytycka felt fortunate—UBC accepted her. Plus, she was accepted without having to take an English test.

"[A] Slovak professor recognized the names of some of the mathematicians who taught me [from] the so-called 'Polish School of Mathematics,' [which] had international recognition," she explained. "UBC had faith in me."

It was only after arriving in Vancouver that Przytycka had to take English exams. Even though she hadn't taken English in school, her knowledge of German and a friendship with an American journalist proved to be helpful.

"The journalist wanted to learn about life under communism, so we spent lots of time together," she said. "I was a member of 'Solidarity'—an underground anticommunist movement. Sometimes, I helped translate texts from underground newspapers for her."

Przytycka planned to get her Ph.D. and return to the University of Warsaw. But by the time she had earned her degree in computer science in 1990, she also had two sons—a toddler and an infant. She decided not to go back to Poland after all. She knew she wouldn't be able to work because there was a "lack of support for children this young and social pressure to be a stay-at-home mom [and] very few day-care centers," she said.

With her two boys in tow, she chased down opportunities in the departments of computer science at University of Southern Denmark at Odense (Odense, Denmark) and the University of California, Riverside. Her husband followed when he could, but often she was on her own with the children.

She was also many times the only female member of the computer-science faculty.

BILL BRANSON

She remembers receiving an invitation to a faculty barbecue that read, "Wives are welcome." She joked, "Can Jozef come?" But most of the time she says she didn't think very much about being the only woman (and later one of two) in the department.

The beginnings of a new direction

In the mid-1990s, she told her husband, "Next time you find a position, I'll follow you." Unbeknownst to her at the time, she would be doing more than following her husband. She would be forging a new career.

When her husband secured a position at George Washington University (Washington, D.C.), Przytycka, as promised, followed him, starting with a visiting position at the University of Maryland (College Park, Maryland).

At the same time, while her research was still focused on the theory of algorithms, she began working on questions that were motivated by biology.

"There were some nice mathematical questions that arise in the context of evolution and other interesting, biologically motivated mathematical problems. How would you construct evolutionary trees? How to measure an agreement between two evolutionary trees constructed with different methods?" she explained. "Those are very mathematical questions, and while they don't require biological understanding, they started my interest in biology."

Her interest was piqued even more when she learned from the *Notices of American Mathematical Society* that the Department of Energy and the Sloan Foundation had announced a new fellowship in computational biology. Before she could apply, she needed to find a mentor in biology. With the help of a computer science colleague, she found one: George Rose, a professor at Johns Hopkins University (Baltimore) and a well-known biophysicist working on protein folding.

With this fellowship in hand, she crossed the line from working on computer-science questions that are motivated by biology to biological questions that require computer science.

The road to NCBI

A few years later, in 2003, she was hired as a principal investigator at NCBI. Not only was it a dream position scientifically, but hers and Jozef's "two-body" problem—two researchers trying to find jobs in the same geographical area—was finally solved.

She was officially working toward a career in biology. "Biology has [become more] mathematical, more quantitative, and, from my perspective, far more exciting," she said. "It's fair to say that I was amongst the first group of computer scientists that made their way to biology."

Through the years, she has built her team of men and women thoughtfully—albeit unconventionally.

"Often people come to my group without any knowledge of biology," Przytycka said. "You are well-served if people in your group are strong in computer science, and since this is the field where I'm coming from, it's easier for me to work with people who think mathematically. I am able to see where their strengths are and can help them navigate biology, so they can direct their talents toward solving biological questions."

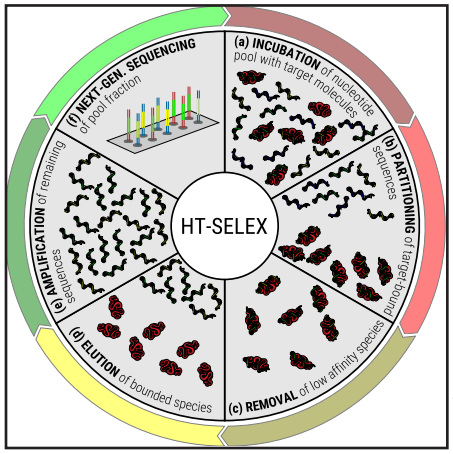
Three areas

Przytycka's team works in three basic areas: cancer and diseases, gene regulation, and algorithms for the efficient utilization of large datasets.

In the context of disease studies, her group develops computational methods advancing systems-level understanding of cancer, the emergence of complex phenotypes, and the detection of causal genetic mutations and their interactions.

As for gene regulation, she collaborates with **Brian Oliver**'s group (National Institute of Diabetes and Digestive Diseases) to work on fruit flies and is developing methods for constructing condition-specific regulatory networks. She also work with **David Levens** (National Cancer Institute), on non-B DNA structures and their role in gene regulation, mutagenesis, and diseases.

The third area relates to analysis of big data. For example, they developed novel clustering and motif-finding algorithms. Her team developed a software tool called AptaTRACE that could help drug developers and scientists identify molecules that bind with high precision to targets of interest.



JAN HOINKA, NIBIB

Schematic of one selection cycle of HT-SELEX (high-throughput systematic evolution of ligands by exponential enrichment), which is used to identify aptamers.

"This research is an excellent example of how the benefits of 'big data' critically depend upon the existence of algorithms that are capable of transforming such data into information," she said.

Driven by curiosity

Whatever she's working on, Przytycka appreciates the opportunities at NIH.

"Researchwise, I'm working on a large spectrum of problems. I think that working for NIH particularly helps me do that," she explained. "I am surrounded by experts working on diverse biological inquiries," she said. "Exposure to this variety of biological questions and the realization that they can be helped with novel computational methods makes it is hard to resist and not give them a try."

For this mathematician computer scientist who works in biology, curiosity is a large part of what drives her. And when that curiosity can be helped with an elegant computational algorithm, this is the best combination. ●

This article was adapted from one that appeared in NLM In Focus: https://infocus.nlm.nih.gov/2017/02/06/teresa-przytycka-goes-the-distance.

Recently Tenured


TERRI S. ARMSTRONG, NCI-CCR


ANIL K. CHATURVEDI, NCI-DCEG


PETER DOBBS CROMPTON, NIAID


THEO HELLER, NIDDK


ZHIYONG LU, NCBI

TERRI S. ARMSTRONG, PH.D., NCI-CCR

Senior Investigator, Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute

Education: University of Akron, Akron, Ohio (B.S.N.); Ohio State University, Columbus, Ohio (M.S. in oncology; post-master's nurse practitioner); University of Texas Health Science Center, Houston (Ph.D. in nursing)

Before coming to NIH: Professor and John S. Dunn Distinguished Professor at the University of Texas Health Science Center–School of Nursing; adjunct professor, Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center (Houston)

Came to NIH: In 2016

Selected professional activities: Associate editor of *Neuro-Oncology* and of *Neuro-Oncology Practice*; vice president, Society of Neuro-Oncology; board of directors of the Collaborative Ependymoma Research Foundation; quality-of-life representative to the Neuro-Oncology Committee of NRG and Brain Tumor Committee of Alliance Oncology

Outside interests: Adopting and caring for rescue dogs; cooking; traveling

Website: https://irp.nih.gov/pi/terri-armstrong

Research interests: Although there have been many advances in neurosurgery, radiation oncology, and imaging of the nervous system, the treatments for patients with malignant brain and spinal cord tumors rarely result in a cure. In my research program, we are developing measures to accurately assess symptoms of cancers of the central nervous system (CNS) and the impact of the disease and therapy on patient outcomes.

Our efforts have included the development, psychometric evaluation, and assessment of the utility of instruments as well as the use of patient-reported outcomes (PRO) in multicenter clinical trials. We are also exploring the clinical and genomic predictors of risk of symptoms and toxicity and investigating the underlying pathophysiology to develop approaches to care and symptom management. Our work has focused on myelotoxicity and vascular toxicity associated with chemotherapeutic agents as well as fatigue and hypersomnia (excessive daytime sleepiness) associated with cranial radiation.

We are focusing on four areas. In one project, we are developing the Neuro-Oncology Branch (NOB) Patient Outcomes Program, which will combine research and clinical care for patients with CNS cancers. We will be interrogating disease and therapeutic correlates of select PROs and other clinical-outcome assessments (COAs) measures as well as developing innovative approaches to assessment (such as electronic data capture and use of in-home and wearable technology).

In a second project, done jointly with NOB clinical investigators, we will be incorporating COAs into brain-tumor clinical trials. We will gauge the utility of including COAs in early-phase and precision-medicine clinical trials; evaluate innovative approaches to assessment; and apply these findings to improve the understanding of the natural history of common and rare CNS malignancies as well as the survivorship and palliative-care needs.

In a third project, we are identifying clinical and genomic predictors of treatment-related toxicities in CNS cancers, tumor-associated symptoms, and complications. We will also study alterations in circadian rhythms in fatigue and sleep and evaluate select medical and neurologic complications such as seizures and thrombosis.

Our fourth project involves patient education, outreach, and outcomes. Much of the patient-outcomes data will be generated by patients' participation in the NOB natural-history study. We will have an unprecedented opportunity to integrate clinical-outcomes data with COAs and genomics, but we need to establish the applicability to the general CNS-cancer patient population. Therefore,

an educational and outreach effort, particularly for the rare CNS cancers, will be critical for validating the data and disseminating information about the disease trajectory. We will incorporate patient education into the research component and provide patients and their caregivers with important information about the illness, treatment, and possible clinical outcomes. In addition, we will test novel educational tools, a task made difficult because of the neurologic complications from CNS cancer or its treatment.

Our findings will be shared with other groups that deal with brain tumors, other neurologic disorders, or cancer.

ANIL K. CHATURVEDI, PH.D., NCI-DCEG

Senior Investigator, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: Andhra N.G.Ranga Agricultural University, School of Veterinary Medicine, Hyderabad, India (B.S. in veterinary sciences and animal husbandry); Tulane University, New Orleans (M.P.H. and Ph.D. in epidemiology)

Training: Postdoctoral training at NCI's Infections and Immunoepidemiology Branch; became a research fellow in 2007 Came to NIH: In 2005 for training; was appointed as a tenure-track investigator in 2009

Selected professional activities: Member, Oral Cancer Screening Guidelines Panel, American Dental Association; external advisor, Scientific Advisory Board, Catalan Institute of Oncology/International Agency for Research on Cancer HPV Information Center (Barcelona, Spain)

Outside interests: Cooking; playing and watching tennis

Website: https://irp.nih.gov/pi/anil-chaturvedi

Research interests: I study the molecular epidemiology of head and neck cancers and lung cancers.

Head and neck cancers, which are the eighth most common cancer worldwide, occur in the oral cavity (lips and mouth), oropharynx (base of tongue back through tonsil area), other parts of the pharynx (part of throat leading from the oral and nasal cavities to the esophagus and larynx), and the larynx (voice box). Risk factors include tobacco and alcohol use; poor oral hygiene; low fruit and vegetable consumption; and human papillomavirus (HPV) infection. HPV has been found to be an etiologic agent for oropharyngeal cancers, but it rarely causes oral cavity and larynx cancers. I am using population-based studies to investigate the epidemiology, the natural history, and the unique anatomic, histopathologic, and molecular characteristics of HPV-positive oropharyngeal cancers.

Cancers of the oral cavity are easy to detect visually, making them ideal candidates for early detection and secondary prevention. But we don't understand enough to be able to develop guidelines for screening, treatment, or follow-up of patients with oral-cancer precursor lesions. I am using a combination of retrospective and prospective cohort studies to address key questions about to the natural history and molecular predictors of oral-cancer precursor lesions and how they progress to cancer.

Lung cancer, the leading cause of death from cancer in the United States, is usually caused by cigarette smoking (80 to 90 percent of cases). But there are other risk factors, too, such as chronic inflammation. I am studying the role of chronic inflammation in lung cancer by measuring circulating immune and inflammation marker concentrations in case-control studies nested within large prospective cohorts.

I am collaborating with NCI-DCEG colleague **Hormuzd Katki** to develop, validate, and apply lung-cancer risk-stratification tools. In 2011, the landmark National Lung Screening Trial (NLST) showed a 20 percent decrease in mortality from lung cancer in the low-dose CT group as compared with the group that received standard chest X-rays. On average, over three rounds of screening exams, 24 percent of the CT scans were positive compared with 6.9 percent of the X-rays. Most positive screens led to additional tests. Based on these results, LDCT screening is currently recommended for the highest-risk smokers who meet the NLST entry criteria.

I am researching the potential utility of lung-cancer risk-prediction tools to improve the population-level effectiveness of LDCT screening. Additionally, I study minimally invasive lung-cancer biomarkers for improved risk stratification.

PETER DOBBS CROMPTON, M.D., M.P.H., NIAID

Senior Investigator, Laboratory of Immunogenetics, and Chief, Malaria Infection Biology and Immunity Section, National Institute of Allergy and Infectious Diseases

Education: Boston University, Boston (B.A. in biochemistry and molecular biology); Johns Hopkins School of Medicine, Baltimore (M.D.); Johns Hopkins School Public Health, Baltimore (M.P.H.)

Training: Clinical fellow and resident in internal medicine at Massachusetts General Hospital, Harvard University (Boston); clinical and research fellow in infectious diseases at NIAID; diploma in tropical medicine and hygiene, London School of Hygiene and Tropical Medicine (London)

Came to NIH: In 2004 for training; in 2010 became a tenure-track investigator and chief of NIAID's Malaria Infection Biology and Immunity Unit

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

Selected professional activities: Board of consulting editors, *Journal of Clinical Investigation*; guest editor, *Proceedings of the National Academy of Sciences* and *PLoS Pathogens*; co-chair, Malaria Gordon Research Conference 2017 and 2019; member, American Society for Clinical Investigation

Outside interests: Enjoys spending time with his wife and three daughters—biking, hiking, cooking, singing, and playing musical instruments

Website: https://irp.nih.gov/pi/peter-crompton

Research interests: Malaria caused by *Plasmodium falciparum* remains a major cause of morbidity and mortality worldwide. A limited understanding of the interaction between malaria and the human immune system hinders the development of malaria vaccines. Clinical immunity to malaria can be acquired but only after years of repeated infections, and immunity wanes rapidly without ongoing malaria exposure. The mechanisms and targets of protective malaria immunity and the factors underlying its inefficient acquisition remain unclear. In the Malaria Infection Biology and Immunity Section, we aim to accelerate malaria-vaccine development and gain fundamental insights into human immunology by addressing these knowledge gaps.

We apply advances in basic immunology and functional genomics to clinical data and biospecimens obtained through intensive longitudinal cohort studies conducted at our field sites in Mali and elsewhere. Recently, we have determined key features of the specificity, function, and kinetics of the antibody response to malaria, identified mechanisms by which B-cell and T-follicular-helper-cell responses contribute to the inefficient acquisition of protective antibodies, defined mechanisms by which malaria-induced inflammation is regulated, and gained insights into fundamental aspects of malaria epidemiology, including the relationship between chronic asymptomatic *P. falciparum* infection and malaria risk.

Our studies in Mali are made possible through a collaboration with an experienced team of clinicians and scientists at the Malaria Research and Training Center at the University of Bamako (Bamako, Mali). Through this collaboration we also facilitate the expansion of research capacity in Mali by training scientists, improving laboratory infrastructure, and enhancing information technology. Our field studies in Mali are supported by the NIAID International Centers for Excellence in Research program. We hope that our work not only contributes to a better understanding of malaria immunity but also provides insights into the mechanisms at play in human immune responses to infectious diseases more generally.

THEO HELLER, M.D., NIDDK

Senior Investigator and Chief, Translational Hepatology Section, Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Education: University of Cape Town, Cape Town, South Africa (B.Sc. in experimental biology and zoology; B.Sc. in immunology); University of the Witwatersrand Medical School, Johannesburg, South Africa (M.D.)

Training: Residency in internal medicine, Georgetown University Hospital (Washington, D.C.); research associate, Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases; fellow in gastroenterology, University of Maryland School of Medicine (Baltimore)

Came to NIH: In 1999 as a clinical associate in NIDDK; became a staff clinician in 2003; became a tenure-track investigator in 2011

Selected professional activities: Several positions in the American Association for the Study of Liver Diseases: chair, Technology and Social Media Committee; elected vice-chairman, Portal Hypertension Special Interest Group; Hepatitis C Virus Guidance Panel; and member of the Ethics Committee

Website: https://irp.nih.gov/pi/theo-heller

Research interests: Liver disease presents a unique confluence of many disciplines in both the basic science and the clinical realms. There are many unanswered questions in basic hepatic biology and the development of liver disease. Our laboratory is interested in testing hypotheses in clinical situations that can be translated into laboratory projects, which in turn might lead to fundamental biologic insights and improved disease management. Clinical observations can sometimes be best explained at the bench, and human-disease investigation is in many ways better than a model—it is a direct study of authentic biology. Human disease is a window into biology, and by studying diseases, researchers may be able to extrapolate from some rare, derived concepts to a far broader understanding of biologic principles.

We focus on the connections between the innate immune system and liver-related damage and repair. Our clinical focus is on non-cirrhotic portal hypertension. We also study people with chronic granulomatous disease, sickle-cell disease, Turner syndrome, sporadic nodular regenerative hyperplasia, hepatitis D, acute hepatitis C, and congenital hepatic fibrosis.

Liver disease disproportionately affects people during their most productive working years. We hope that our research will result in more effective treatments and fewer people dying of the disease.

ZHIYONG LU, PH.D., NCBI

Senior Investigator, National Center for Biotechnology Information, National Library of Medicine

Education: Nanjing University, Nanjing, China (B.S. in computer science); University of Alberta, Edmonton, Alberta, Canada (M.S. in computer science); University of Colorado School of Medicine, Aurora, Colorado (Ph.D. in bioinformatics)

Came to NIH: In 2007 as a staff scientist; became an associate investigator in 2009; became a Stadtman investigator in 2011

Selected professional activities: Associate editor, *BMC Bioinformatics* and *Journal of Healthcare Informatics Research*; Editorial board member, *Database*; Steering committee member, BioCreative; PI, PubMed Labs

Outside interests: Playing with his three young children; swimming

Website: https://irp.nih.gov/pi/zhiyong-lu

Research interests: I am directing text-mining research and lead the new overall efforts to improve and rebuild PubMed. (Our current development is an innovative system called PubMed Labs in which we are experimenting with new ways to improve search quality and usability for biomedical literature.) Text mining involves going through digitized and unstructured text to find useful, high-quality information. Text analysis includes retrieving relevant documents; identifying named entities (such as gene and disease names); and extracting relationships between entities and other natural language processing tasks. The technology is now applied to a broad range of government, research, and business and marketing needs, and it is used in a wide variety of real-world applications (such as automatic spam filtering or predicting flu trends). In the health-care industry, text mining is essential in helping to find important information that's buried within tens of millions of biomedical articles.

My research group is developing new computational methods and software tools to analyze and make sense of free text data in scholarly publications and other biomedical texts such as elesctronic medical records. We apply text-mining research to improve biomedical literature search; assist in the manual curation of biological databases; and predict new uses of existing drugs. Our text-mining software tools and web services, such as PubTator, have been widely used (over 100 million requests since 2015) by scientists from around the world and has also been integrated into PubMed, PubChem, and many other NCBI web resources.

I also co-organize international scientific conferences and community-wide challenges such as BioCreative, the longest-running international event for evaluating text-mining and information-extraction systems applied to the biomedical domain. ●

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.

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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Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

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https://irp.nih.gov/catalyst/v25i3

BACK PAGE

More Cajal on Campus

This drawing of an olfactory bulb is one of seven newly arrived original drawings by Spanish scientist Santiago Ramón y Cajal, who shared the 1906 Nobel Prize in Physiology or Medicine in recognition of his work on the structure of the nervous system. This drawing and six others are on loan from the Cajal Institute (Madrid) and on display on display on the first floor of the Porter Neuroscience Research Center (Building 35) until the end of 2017. Two previous installations were on display for six months. Cajal, known as the father of modern neuroscience, was a prolific medical artist and produced hundreds of drawings depicting the organization of nerve cells in the brain. Read more online at https://irp.nih.gov/catalyst/v25i3/back-page.

SANTIAGO RAMÓN Y CAJAL

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