THE NIH CATALYST

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Using 3-D Printing to Assess Radiation Exposure

BY CORA A. HERSH, NCI

Three-dimensional (3-D) printing has been used in medicine since the mid-1990s, primarily in the planning of complicated surgical procedures, rapidly evolving to include 3-D-printed prosthetic limbs, skin, airway splints, and ears. In the past 10 years, the cost of consumer-grade 3-D printers brought the technology within reach of a far wider audience and research applications, including epidemiology.

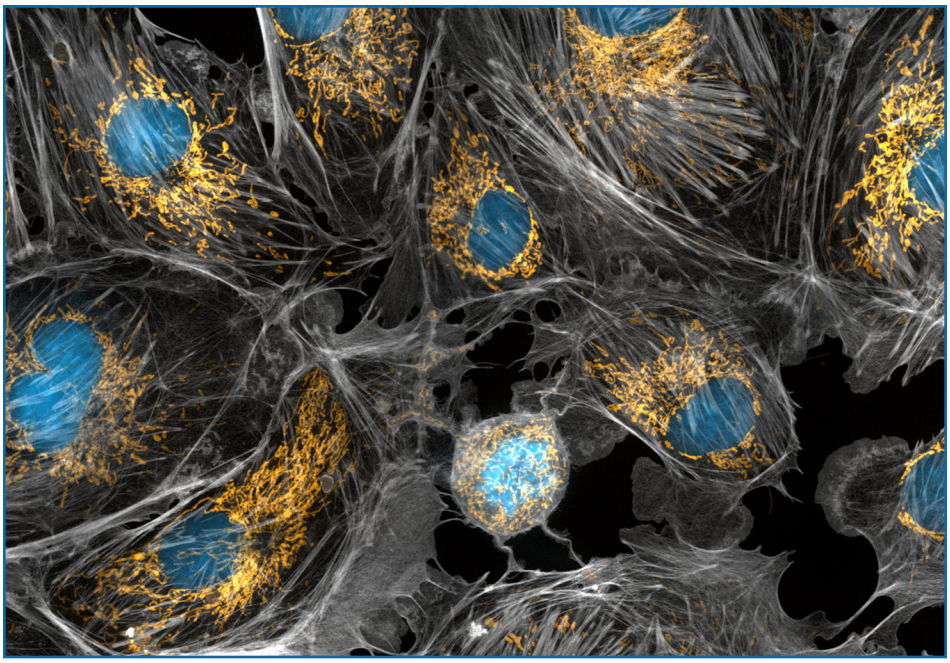
In a lab at the National Cancer Institute (NCI), a 3-D printer about the size of a coffee maker sits atop a table, periodically whirring away as its heated nozzle extrudes plastic in precise patterns. This printer is brewing up tools for health physicists to improve their estimates of radiation dose for epidemiological studies. **Choonsik Lee**, senior investigator in NCI's Radiation Epidemiology Branch (REB) and head of the Dosimetry Unit, and REB postdoctoral fellow **Matthew Mille** are pioneering these techniques as part of the NCI-Division of Cancer Epidemiology and Genetics (DCEG) dosimetry program.

Modeling Radiation Dose: A Two-pronged Approach

Dosimetry, in the fields of medical physics and radiation protection, refers to the calculation of radiation dose received by the human body. Absorbed dose is a measure of the amount of energy deposited per unit

CONTINUED ON PAGE 12

Middle-Age Weight and Fitness Changes: Blame Your Enzyme



TORSTEN WITTMANN, UNIVERSITY OF SAN FRANCISCO

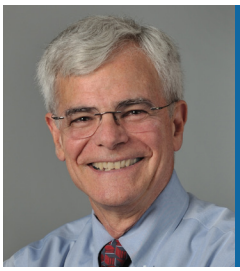
As people age, the DNA-PK enzyme becomes overactive, causing a decrease in the number of mitochondria and promoting weight gain. Shown: Mitochondria stained bright yellow, cell nuclei in blue, and the cell cytoskeleton in gray.

Researchers have long known that losing weight and maintaining the capacity to exercise tend to get harder beginning between ages 30 and 40—the start of midlife. Scientists have developed new therapies for obesity, including fat-fighting pills. However, many therapies have failed because of a lack of understanding of the biological changes that cause middle-aged people to gain weight, particularly around the abdomen.

Jay H. Chung, an endocrinologist at the National Heart, Lung, and Blood Institute (NHLBI), was always puzzled by the aging weight-gain paradox. An average adult in America gains 30 pounds from age 20 to 50, even though food intake usually decreases

CONTINUED ON PAGE 11

CONTENTS



IRBs at NIH Revisited:

Serving the Interests of Patients and Clinical Investigators

BY MICHAEL GOTTESMAN, DDIR , AND RICHARD WYATT, DEPUTY DIRECTOR, OIR

The NIH Clinical Center (CC) pioneered institutional reviews boards (IRBs) more than 60 years ago in recognition of the need for analyzing the risks versus the benefits of clinical protocols. IRBs are fundamental to the scientific integrity of the protocols and the protection of the human subjects involved in the research. As IRBs evolved at NIH and elsewhere, so did the federal policies and regulations that govern federally funded research today.

Academic, pharmaceutical, and government institutions have developed a range of IRBs. The need for consistency and uniformity in procedures led to the formation of a national accrediting body 16 years ago: The Association for Accreditation of Human Research Protection Programs (AAHRPP). NIH sought and achieved AAHRPP accreditation in 2014 and received full re-accreditation in 2017.

At NIH, the IRB evolved from a central entity with subpanels to 12 individual IRBs, based in institutes and centers (ICs) today. Some 20 years ago, then–NIH Director **Harold Varmus** and other leaders questioned why there were so many IRBs at NIH and recommended consolidating them. But nothing happened. During AAHRPP's rigorous accreditation process, that theme re-emerged: Why does NIH have so many IRBs that function largely as IC-based entities rather than having the kind of centralized IRB system that exists in many major medical centers?

NIH's decentralized system has created an unwieldly process with three different information technology (IT) systems; some inconsistencies in review processes across multiple IRBs; lack of standardized application forms, consent templates, and protocol templates; duplication of effort between scientific reviews and IRB reviews; and inefficiencies in the conduct and operation of individual IRBs.

We need a well-functioning, centrally managed IRB system to improve efficiency and ensure consistency. The system must allow NIH investigators to move forward expeditiously and efficiently with their clinical-trial protocols in the interest of patients for whom effective treatments are lacking. The urgency of these compelling clinical-research efforts at the NIH CC is portrayed well in an exciting three-part Discovery Channel series, "First in Human," scheduled to air beginning on August 10, 2017 (9:00–11:00 p.m. EDT).

So, with the best interests of our patients and clinical investigators in mind and based on thoughtful recommendations made by many professionals, NIH has set out to revise and centralize our IRB system. The following action steps were proposed:

1. Implementation of one NIH-wide Integrated Risk Information System (iRIS) to manage all protocols. This IT system will replace the two iRIS systems and the Protocol Tracking and Management System (PTMS).

2. Use of standard protocol templates for scientific and IRB reviews. The proposal clarifies that the ICs, not IRBs, are responsible for the scientific and conflict of interest (COI) reviews. A future goal is to integrate a protocol-authoring tool, data management, and protocol resource requirements into a relational database using Biomedical Translational Research Information System (BTRIS) resources.

3. Creation of a centralized IRB Operations Office and six NIH IRB panels, each with seven to 13 members. The central office will assign protocols and track progress for reviews by the panels, which will meet weekly. (Note: The first of the new IRBs is being established as a pilot under the leadership of NHLBI senior investigator **Richard Cannon**. The new IRB will review all protocols from NHLBI, NCI, and NIAID institute leaders as well as from NHGRI and NHLBI staff.)

4. The other five proposed IRB panels will be generic (medicine and pediatrics) or thematic with possible special panels as needed (for example epidemiology or oncology). New protocols will be assigned to the next available panel with attention to subject-matter expertise as needed.

5. Expedited reviews will be evaluated and approved by the IRB Operations Office staff, IRB chairs/vice-chairs, or the chairs' designees. Panel review remains an option.

6. A centralized Office of Research Support within the CC will assure that all NIH clinical investigators will have access to protocol navigators.

There are many other fine details in the proposed centralization plan, but it is important to point out that we can't fully implement it until the action steps are achieved. At the conclusion of this process, a more efficient IRB system will serve both research patients and clinical investigators in ways that will enhance the research environment in the NIH Intramural Research Program. ●

NIH Director Francis Collins Reappointed

"I received word today that President Trump has made it fully official: He wants me to continue in the role of NIH Director," wrote NIH Director **Francis S. Collins** in an e-mail to NIH staff on June 6, 2017. "I am truly grateful for the President's vote of confidence, and I will be honored to continue to serve this noble institution. This is a time of unprecedented scientific opportunity in biomedical research, as we seek together to advance health and relieve suffering. It will be my distinct pleasure to continue working with you, my valued colleagues at NIH—as well as with our counterparts at the Department of Health and Human Services, the White House, the Congress, and the broader community, including universities, philanthropy, industry, and patient groups. There is much work to do! Finally, I want to thank all of you who dedicate yourselves so passionately to the goals of NIH. I will continue to rely on your brilliance and dedication as we move forward." ●

NIH Director Francis Collins.

A Discovery Channel camera crew filmed in the Clinical Center for the "First in Human" documentary set to air in August.

Clinical Center Documentary

When Emmy-award-winning actor Jim Parsons visited the NIH Clinical Center in February, it wasn't to film an episode of the TV sitcom "The Big Bang Theory." He was onsite to record some of the narration for the Discovery Channel's three-part documentary series "First in Human." Discovery Channel camera crews, who were allowed to film in Building 10 during 2015 and 2016, have provided a behind-the-scenes look at doctors, researchers, and patients and their families while patients underwent experimental treatments.

"The NIH Clinical Center's more than 60-year history has resulted in remarkable medical advances, from the first use of chemotherapy to treat cancer, to the development of the technique to keep the blood supply clean and safe from viruses," said NIH Director **Francis S. Collins**. "For millions of patients around the world, it is known as the National Institutes of Hope."

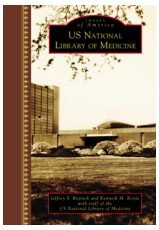
The first episode of "First in Human," is set to air on Thursday, August 10, 9:00–11:00 p.m. EDT. ●

Congressional Staff Visits

A bicameral, bipartisan group of 11 Congressional staffers and a representative from the Department of Health and Human Services (HHS) visited the National Cancer Institute (NCI) in early June to learn about NCI's childhood-cancer research efforts. The group met with several intramural scientists from the NCI Center for Cancer Research Pediatric Oncology Branch, as well as with leaders of key programs within NCI's extramural childhood-cancer research portfolio. The visitors also toured the NIH Children's Inn and met a family whose child participated in an NCI clinical trial. ●

New Illustrated History of NLM

A new illustrated history of the National Library of Medicine (NLM) recently made its debut: *The Images of America: U.S. National Library of Medicine* (Arcadia Publishing), co-edited by **Jeffrey S. Reznick** and **Kenneth M. Koyle**, chief and deputy chief of the NLM History of Medicine Division. A digitial version of the book is available for free download from NLM Digital Collections: https://collections.nlm.nih.gov/ext/pub/ImagesofAmericaNLM.pdf. A hardback verson is also available from booksellers. ●



Read more online at at https://irp.nih.gov/catalyst/v25i4/news-briefs.

From the Fellows Committee

Knowing How and Where to Look for Training Opportunities

BY CRAIG MYRUM, NIA

Postdoctoral fellows provide much of the muscle behind the research output in many labs. With peer-reviewed journal articles as the currency in the world of research and academia, it's no surprise that publishing is where most of our efforts go.

While most fellows also continue to cultivate their depth and breadth of knowledge in their area of expertise, some are so intensively focused on their research that adequate time is not given to strategically planning for life beyond the lab. Regardless of your post-fellowship plans, more time is usually warranted on addressing additional skills that are required for the next step in your career. Although the NIH Office of Intramural Training and Education (OITE) and the NIH Fellows Committee (FelCom) are invaluable resources for career-development programming for all intramural fellows, it is equally important to be proactive in seeking out additional training opportunities … but where?

Network: This word might induce the flight-or flight response in some of us, but "networking" can mean that you just strike up an informal conversation with someone. Maybe you ask them about their job; maybe you ask them about their project. Whether you're looking for a new collaboration, a new job, or nothing at all, those conversations can lead to unexpected, valuable opportunities.

"Almost everyone I know gets a job through informal networking (myself included!)," said **Lori Conlan**, director of Postdoctoral Services and Career Services at OITE. "Almost all NIH alumni talk about the importance of networking."

Look to your neighbors: In the rich life-sciences community within Research Triangle Park in North Carolina, three entities—the National Institute of Environmental Health Sciences (NIEHS) and two neighboring universities—established the Enhancing Local Industry Transitions Through Exploration (ELITE) Consortium which helps fellows explore industry-career options through site visits with industry partners (http://bit.ly/2tqRRsK).

> Regardless of your post-fellowship plans, take the time to work on additional skills that are required for the next step in your career.

"A number of fellows have been hired by companies that they visited through ELITE," said **Tammy Collins**, director of the Office of Fellows' Career Development at NIEHS. "This program is truly a win-win for both the fellows and the companies."

Similar events take place in Baltimore, where NIH and University of Maryland postdocs are invited to participate in Johns Hopkins University's Postdoc Symposium and other networking events.

Professional associations: Find the most suitable organizations for your interests. These are often the best resources to find employment opportunities, insight into preferred skills, and opportunities to network with people in your field. The National Postdoctoral Association (NPA) is also a useful resource; its mission is to enhance research training and professional growth for postdocs. **Didier Chalhoub**, postdoctoral fellow at the National Institute on Aging (NIA), serves as the FelCom liaison for NPA. "NPA allows postdocs to improve and expand their repertoire of soft skills," he said. "They have several subcommittees, including resource development, advocacy, and outreach, all of which postdocs could benefit from to kickstart their careers." All NIH postdocs are granted free affiliate membership with NPA (http://www.nationalpostdoc.org).

Take the reins: Postdocs sometimes find that certain training components are not readily available. For example, NIH's Visiting Fellows Committee (VFC) recognizes that it is often difficult for fellows to navigate through issues such as career transition, immigration, and funding opportunities. In response, the VFC established the Brown Bag series of lunchtime talks to address those very issues.

Another good example, highlighted in the May–June 2017 issue of *The NIH Catalyst,* is how several data-science classes are emerging across NIH in response to fellows' interest and need for such skills (http://bit.ly/2uqZu2p).

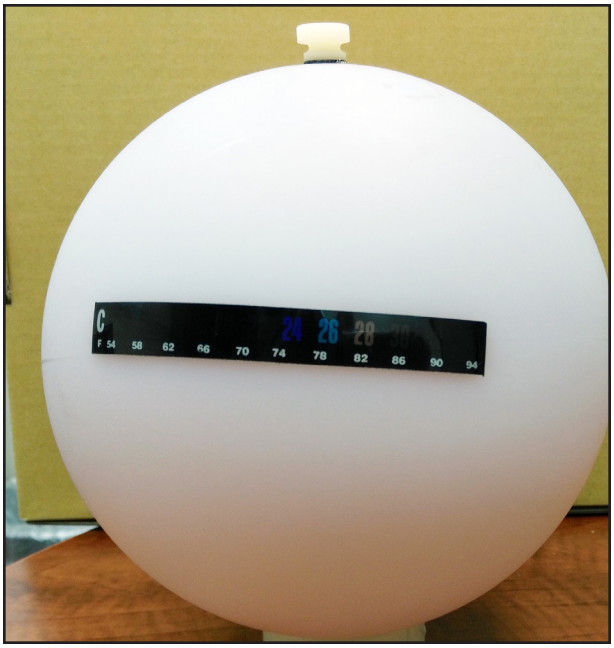
If you recognize a gap in training opportunities, act on it. Both you and your colleagues could benefit from your initiative, and you are also likely to also expand your leadership skills in the process.

Know what's readily available: Are you looking to learn more about specific skills or subjects? One option is to check out the impressive list of courses available at the Foundation for Advanced Education in the Sciences (FAES) at https://faes.org. Alternatively, the ever-improving and expanding options of massive open online courses such as Coursera and EdX can be excellent resources for your individual needs, too. ●

NICHD Medical-Imaging Device Awarded U.S. Patent

Device Calibrates MRI Scanners to Improve Image and Data Quality

BY LINDA HUYNH, NICHD



NIH

The diffusion MRI phantom can be as simple as a hollow plastic sphere, about the size of an adult brain, that contains a substance, polyvinylpyrrolidone (PVP), that can mimic the imaging properties of tissues and organs, such as the brain.

A calibration device for medical imaging developed by researchers at the National Institute of Child Health and Human Development (NICHD) received U.S. Patent approval on March 28, 2017. The device, a diffusion magnetic resonance imaging (MRI) phantom, calibrates MRI scanners that perform diffusion MRI methods, such as diffusion tensor imaging, or DTI. Reliable calibration standards help ensure the quality and accuracy of these images, which can help diagnose stroke, brain disease, and cancer. A patent also can help accelerate development of promising technology so it can reach health-care providers and patients more quickly.

DTI—invented by NICHD senior investigator **Peter Basser** and others in 2000—relies on the diffusion of water to generate images and allows researchers to make detailed maps of neural pathways in the brain, as well as of the muscles, heart, and other soft tissues.

The inventors of the calibration device are Basser, **Ferenc Horkay** (NICHD), and **Carlo Pierpaoli** (National Institute of Biomedical Imaging and Bioengineering, formerly of NICHD). The invention uses a substance, polyvinylpyrrolidone, or PVP, to calibrate MRI scanners. PVP is a stable and nontoxic substance used as a food additive.

"We designed the phantom for use in a clinical setting," said Horkay. "The polymer inside the phantom, PVP, has diffusion properties that can be tailored to match those of the target human tissue."

DTI visualizes important features of brain anatomy and can aid in the diagnosis of many diseases and disorders of the brain, such as stroke and different cancers. Moreover, DTI data provide neurosurgeons with information about the location of sensitive regions of the brain that they need to avoid during brain surgery.

"We and many other researchers are now evaluating whether DTI can be used to diagnose diseases in which changes in brain tissue structure are subtler, such as mild traumatic brain injury," said Basser. "In these cases, proper scanner calibration is essential to obtain high-quality, quantitative diffusion MRI measurements."

The device had been under continuous development and testing by NIH scientists for nearly a decade, and the properties of PVP as a standard for diffusion MRI measurements have been extensively tested by Pierpaoli and collaborators in NICHD. Today, many scientific and clinical research groups use PVP-based diffusion MRI phantoms to ensure data quality, primarily for studies performed across multiple sites.

"This invention will help advance quantitative imaging efforts, which are central to the success of accurate clinical diagnoses, as well as support ongoing clinical studies in which volunteers are imaged at different study sites," said Pierpaoli. ●

This article is adapted, with permission, from one that appeared on the NICHD website (http://bit.ly/2sHMjNk)

U.S. Patent: F. Horkay, C. Pierpaoli, and P. Basser, Phantom for Diffusion MRI Imaging. Pat. No. 9,603,546, March 28, 2017 (http://bit.ly/2tr6NqL).

Share Your Story

We welcome ideas for stories; photos or other graphics that reflect an aspect of life at NIH (including laboratory life); quotations or confessions that scientists might appreciate; "letters to the editor" for publication; and your reactions to anything in *The NIH Catalyst*. If you would like to submit something to be considered for publication, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

Bryon Adinoff, M.D.: Addiction Scientist

Understanding How Thought Processes Work

BY GÜLCAN AKGÜL, NICHD

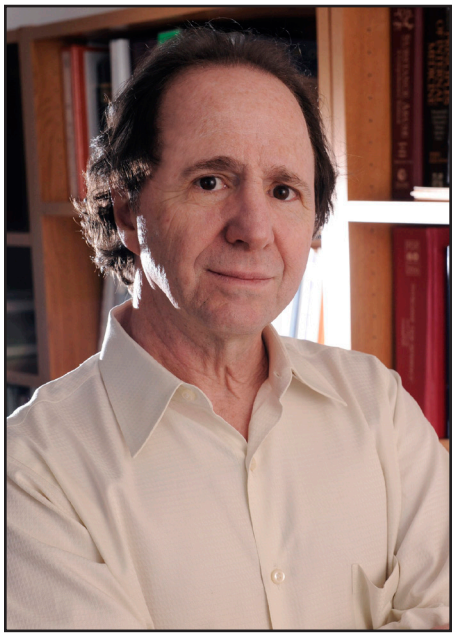
NIH alum Bryon Adinoff visited NIH on April 26, 2017, to give a talk on "Biological Stress Reactivity and Alcohol-use Disorders–From Early Intramural NIAAA to the Present," at the Psychoneuroendocrinology Scientific Interest Group's inaugural meeting. *The NIH Catalyst* had the opportunity to chat with Adinoff about his career and research interests. The following has been lightly edited.

CATALYST: How did you first get involved with research and NIH?

ADINOFF: I was always interested in substance use and brain chemistry. When I was a sophomore in college, I worked in a lab using primates to study drug use. In medical school, a colleague showed me a booklet about a psychopharmacology rotation at NIH. I didn't even know the word back then. I applied and, as a fourth-year medical student, did a two-month rotation with **Steven Paul**'s group at the National Institute of Mental Health (NIMH). I had great time, learned a lot, and decided to become a psychiatrist. I wanted to come back to NIH and do more research. After my residency, I was contacted by **Peter Martin** at the National Institute on Alcohol Abuse and Alcoholism, which was about to open an inpatient unit. I served as a psychiatrist for five years, and my research focused on stress-hormone reactivity and alcohol dependence during withdrawal and abstinence.

CATALYST: How did you decide to pursue science when you already had a career as a medical doctor?

ADINOFF: It was always the science that excited me. I do enjoy working with patients and talking with them. However, a student who sat with me in interviews once pointed out that I was always trying to figure out what was going on inside their heads. Other doctors might be thinking about what they could do to help this person. I was apt to be thinking about how the patient's thought process was working.



DAVID GRESHAM, UT SOUTHWESTERN

Bryon Addinoff, M.D., did a rotation as a medical student in NIMH in 1979 and later worked in NIAAA from 1983 to 1988.

CATALYST: How has the field of psychiatry evolved since you were in medical school in the 1970s?

ADINOFF: Psychiatry was evolving fast, especially around mental disorders like schizophrenia. There was a fierce fight between psychiatrics who believed in the analytic model, in which mental disorders were perceived as due solely to developmentally based emotional processes, and those who ascribed to the biologic model, which presumes biological causes for emotional problems. When I was in medical school, psychiatrists based their treatment of people with schizophrenia on the analytic model and were doing family-intervention studies. It helped, but it didn't cure the disease. Eventually the analytic model gave way to the biological model. But the transition wasn't easy. I remember fights among the faculty when I was doing my residency. You had to decide which side you were on. Now we know both models have their place and are useful.

CATALYST: What do you find fascinating about addiction?

ADINOFF: Abstinence, from the substance being abused, and an addicted person's inability to sustain it. Addicts would say they were never going to use again. And yet, even after suffering through the bad things that happened when they were using the drug and going through the excruciating experience of withdrawal, they would use again. What's happened to the circuitry in their brain? It looks like they never learned from experience. That's the definition of an addict—somebody who uses a substance persistently in spite of bad things that happen to them. That's why there is such a judgmental approach to addiction. But we don't judge people who have a second heart attack in the same way. We don't say, "Why didn't they exercise?" We don't put them in jail.

CATALYST: Does substance abuse trigger neurological disorders or is it the other way around?

ADINOFF: My perspective is that addiction is an independent process. Earlier, the opinion was that addiction is the result of depression or something else. But, really, the root problem is the addiction, which may then explain why a person is depressed. The first step of a 12-step program for recovery from alcohol addiction hits

right at the target by recognizing: "I am powerless over the effects of alcohol." Now we know that there is also a high rate of comorbidity between drug addiction and other psychiatric disorders such as post-traumatic stress disorder and schizophrenia.

CATALYST: You've studied all kinds of addictions, including tanning. Can people really become addicted to that?
ADINOFF: Tanning addiction is not an official psychiatric diagnosis, but some people cannot stop going to tanning salons even when they know that excessive tanning is bad. If they stop, they have withdrawal symptoms. We did experiments with and without ultraviolet (UV) light filters in tanning beds and found that exposure to UV light increases dopamine levels and activates the reward centers in the brains of frequent tanners. The effect is similar to what you'd see in other addictive disorders such as gambling. Half of the frequent tanners get addicted and no one has ever tried treating them.

CATALYST: What's the biggest problem in the substance-abuse arena right now?
ADINOFF: Opioids. It is the largest man-made epidemic and was created [in the 1990s] by very progressive medical schools and doctors like me who thought that patients with chronic pain were undertreated. With big pharma on board, we started prescribing opioids liberally. We thought the risk of addiction was very low in people without a history of addiction. But that was an incorrect notion. Now when the supply of prescription opioids is cut off, those patients who became addicted are looking to heroin as a cheap replacement.

CATALYST: What are your other interests?
ADINOFF: Drug-policy reform.

Bryon Adinoff, M.D.

Current position: Professor and Distinguished Professor of Alcohol and Drug Abuse Research, Department of Psychiatry, University of Texas Southwestern Medical Center (Dallas); Director of Research, Mental Health, Veterans Affairs (VA) North Texas Health Care System (Dallas)
Education: University of Michigan, Ann Arbor, Mich. (B.G.S., 1974); Michigan State University, East Lansing, Mich. (M.D., 1979)
Training: Psychiatry residency (1979–1983), Tulane University Affiliated Hospitals, New Orleans
At NIH: Rotation as a fourth-year medical student in the National Institute of Mental Health (1979); medical staff fellow, National Institute on Alcohol Abuse and Alcoholism (1983–1986); ward administrator, Alcohol Unit, Clinical Center (1983–1986); senior staff fellow, Laboratory of Clinical Studies, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism (1986–1988)
Research interests: Biology of and treatment of addiction

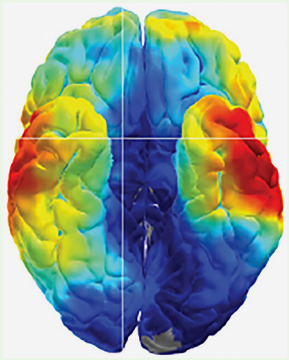
CATALYST: Can you elaborate?
ADINOFF: Drug use among whites and minorities is about the same, but the legal consequences for African-Americans and Hispanics are far more severe than for most white Americans. For example, minority individuals are more likely to be incarcerated for marijuana possession or addiction-related crimes because they cannot afford to post bail. Once they are in jail, the problem multiplies because they lose their cars and then lose their jobs. When they get out of jail, they have a criminal record and can't get new jobs or student loans. It's easier for them to go back to using drugs. One of the ways to stop this problem from snowballing is to pardon as many people convicted of drug-related offenses as possible. I recently gave testimony in Texas to turn marijuana possession from a criminal offense to a civil crime.

CATALYST: What are your plans for the future?
ADINOFF: I want to continue to mentor young trainees and faculty and get more involved in drug-policy reform so I can have a bigger impact on the issues I care about. I will also continue as editor-in-chief of the *American Journal of Drug and Alcohol Abuse*. And I want to spend more time with my family. We travel as much as we can. My wife loves to spend time in Colorado.

CATALYST: What do you like to do outside of science?
ADINOFF: I'm an art docent at the Modern Art Museum of Fort Worth [Fort Worth, Texas]. I love modern art because there are so many ways to interpret it. I have always been drawn to modern art from a very young age. As a docent, I try to engage with people when I show them a piece of art. I like to hear what they take from it and I like to show them how to think about it in a different way. I'm also a bass guitarist in an an R.E.M tribute band. ●

Read more online at at https://irp.nih.gov/catalyst/v25i4/alumni-news-bryon-adinoff.

Intramural Research Briefs



K.A. ZAGHLOUL LAB, NINDS

NINDS: Cracking the brain's memory codes: Scientists at NINDS used electrical recordings to study how the human brain remembers.

NINDS: NIH SCIENTISTS TRY TO CRACK THE BRAIN'S MEMORY CODES

In a pair of studies of patients with drug-resistant epilepsy, scientists at NINDS explored how the human brain stores and retrieves memories. One study suggests that the brain etches each memory into unique firing patterns of individual neurons. The second study suggests that the brain replays memories faster than they are stored.

To help locate the source of the patients' seizures, the team surgically implanted a grid of electrodes into the patients' brains and monitored electrical activity for several days while testing the patients' memories. The patients were shown hundreds of pairs of words, such as "pencil and bishop" and later were shown one of the words and asked to remember its mate. The results showed that the brain replays memories on fast forward. In the other study, the researchers implanted a high-density microelectrode array to monitor the activity of dozens of individual neurons during the memory tests. That study supported the idea that each memory is encoded by a unique firing pattern of individual neurons in the brain. [(1) NIH authors: R.B. Yaffe, J. Arai, S.K. Inati, and K.A. Zaghloul, *J Neurosci* DOI:10.1523/JNEUROSCI.3810-16.2017 (2) NIH authors: A.I. Jang, J.H. Wittig, Jr., S.K. Inati, and K.A. Zaghloul, *Curr Biol* **27**:1700–1705e5, 2017; DOI:10.1016/j.cub.2017.05.014]

NIAID: REAL-TIME IMAGING IN MICE A PROMISING INFLUENZA STUDY TOOL

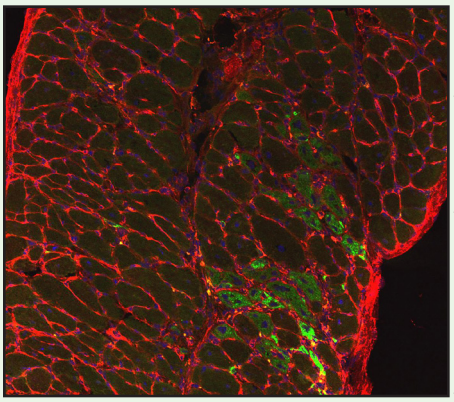
NIAID scientists have found a noninvasive method—real-time imaging—to track and monitor viruses, bacteria, and various types of cells and genes. The promising new method will also make it possible to evaluate whether candidate vaccines and treatments are effective in an animal model.

For the current study, NIAID scientists infected mice with a "reporter" virus after the mice had been immunized against influenza or treated with anti-influenza antibodies either before infection or three days after. The reporter virus, developed with collaborators at the University of Wisconsin at Madison, included a gene that made the virus "light up" in all infected mice. The researchers then injected the mice with a substance that would recognize the luminescent gene in an optical imaging system, allowing them to monitor infection in real time. The group used the imaging system to assess how well the experimental vaccines and antibodies protected the mice from infection and to differentiate between the interventions used, providing clues about how these prevention strategies conferred protection.

They also offered advice to researchers who are considering live imaging as an evaluation tool. For example, how the reporter virus is designed could affect its virulence, and host factors, such as inflammation, could affect detection of the luminescent signal. (NIH authors: R. Czakó, E.W. Lamirande, K.W. Bock, I.N. Moore, and K. Subbarao, *mBio* DOI:10.1128/mBio.00714-17, 2017)

NIAAA: STUDY FINDS TENS OF MILLIONS OF AMERICANS DRINK ALCOHOL IN DANGEROUSLY HIGH AMOUNTS

Nearly 32 million adults in the United States (13 percent of the U.S. population aged 18 and older) consumed more than twice the number of drinks considered binge drinking on at least one occasion within a year, according to a 2013 survey that asked about past-year drinking. This higher level of drinking is associated with increased health and safety risks. The study was conducted by researchers at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). They analyzed data from two waves of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which is a series of large epidemiologic surveys that examine alcohol use and its co-occurrence with drug use and related psychiatric conditions. Comparing data from the 2001–2002 and 2012–2013 NESARC waves, the researchers found that the prevalence of drinking at twofold or threefold—or even greater—the standard binge thresholds in the past year was significantly higher in the most recent NESARC wave, suggesting that more adults are engaging in extreme binge drinking now than a decade earlier. The researchers noted that their findings highlight the need to identify interventions to reduce extreme binge drinking and its negative consequences. Additional research is needed to determine how questions about peak alcohol consumption amounts can be valuable in screening for alcohol misuse as well as in assessing gender-specific risk factors and harms for drinking at extreme levels. (NIH authors: R.W. Hingson, W. Zha, and A.M. White, *Am J Prev Med* **52**:717–727, 2017; DOI:http://dx.doi.org/10.1016/j.amepre.2017.02.014)



D.J. BURKIN, U. OF NEVADA, RENO SCHOOL OF MED.

NCATS: Diaphragm muscle from SU9516-treated dystrophin-deficient mouse showing nuclei (blue), myofibers (outlined in red), and regenerating muscle fibers (green).

NCATS: REPURPOSING EXPERIMENTAL CANCER THERAPY TO TREAT MUSCULAR DYSTROPHY

Researchers at NCATS and the University of Nevada, Reno School of Medicine have demonstrated that a drug originally targeted unsuccessfully to treat cancer may have new life as a potential treatment for Duchenne muscular dystrophy (DMD). DMD is a genetic disorder characterized by progressive muscle degeneration and weakness. The candidate drug, SU9516, ramps up the muscle-repair process, helping to reinforce muscle structure. The team screened more than 350,000 compounds to find SU9516, which had been previously developed as a treatment for leukemia. The research demonstrated that this compound improved muscle function in both laboratory and animal DMD models. The results may provide a promising approach against DMD and other muscle-wasting conditions. (NIH authors: L.A. Mathews Griner, A.E. Dulcey, A. Wang, X. Xu, C.Z. Chen, X. Hu, W. Zheng, N. Southall, M. Ferrer, and J. Marugan, *Mol Ther* **25**:1395–1407, 2017)

NIEHS: PHTHALATE EXPOSURE LINKED TO POLYDACTYLY IN MICE

Phthalates, a group of compounds that soften plastic products yet also disrupt endocrine function in animals, appear in a variety of products, such as cosmetics, perfume, plastic wrap, and shampoo. An NIEHS research group found that embryos from a particular strain of mice have a higher incidence of birth defects after in utero exposure to di-(2-ethylhexyl)-phthalate (DEHP), the most widely used phthalate in the world.

H. YAO, NIEHS

DEHP exposure in utero produced three additional digits in this mouse hind limb.

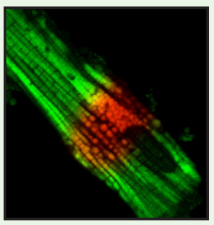
The team was studying the development of sperm and testes using a genetically modified mouse strain engineered so that the male germ cells fluoresce bright green. Male and female mouse pups born to mothers given DEHP exhibited polydactyly, and the male pups produced abnormal-looking germ cells. Polydactyly (having extra fingers or toes) is the most common birth defect in humans. The team noted that phthalates have not previously been linked to severe limb malformations such as polydactyly, and more research is needed to determine whether human polydactyly is related to these findings. (NIH authors: E. Ungewitter, E. Rotgers, T. Bantukul, G.E. Kissling, and H.H. Yao, *Toxicol Sci* **157**:8–19, 2017; DOI:10.1093/toxsci/kfx019)

[BY ROBIN ARNETTE, NIEHS]

NHLBI, NCI: MITOCHONDRIAL "CIRCUIT BREAKER" MAY PROTECT HEART FROM DAMAGE

NIH scientists discovered biological mechanisms that appear to prevent damage to the heart muscle's "power grid," the network of mitochondrial circuits that provide energy to cells. One of those mechanisms, the researchers found, acts much like a circuit breaker, allowing energy to continue moving throughout the heart-muscle cells even when individual components of those cells—the mitochondria—have been damaged. In 2015, members of this same NIH research team announced the discovery of the so-called mitochondrial power grid in skeletal muscle. Since that pivotal discovery, some scientists have raised questions about how such a grid would protect itself from damage to the muscle cells.

This new finding offers some key insights. Using high-resolution 3-D images and special light-activated probes, the scientists revealed a two-part system protecting the heart muscle's power grid from disease-related damage. Instead of being organized as one large, grid-like network such as in skeletal muscle, the mitochondrial circuits in the heart are arranged in parallel rows that form several smaller subnetworks, the researchers found. Each subnetwork acts as a mechanism to prevent damage by limiting the spread of electrical dysfunction to smaller regions. The researchers compared the newly discovered circuit-breaker mechanism to lightning striking a city power grid: Lights may flicker over the whole city, but once the circuit breaker activates, only part of the city loses power. (NIH authors: B. Glancy, L.M. Hartnell, C.A. Combs, A. Fenmou, J. Sun, E. Murphy, S. Subramaniam, and R.S. Balaban, *Cell Reports* **19**:487–496, 2017; https://doi.org/10.1016/j.celrep.2017.03.063)



NHLBI

NHLBI: Microscopic image of mitochondria within a single heart cell. Mitochondria highlighted in red were exposed to ultraviolet light.

Read longer versions of the above briefs and others online at https://irp.nih.gov/catalyst/v25i4/research-briefs. The following are online only:

- NICHD: MOLECULE THAT MAY HELP CONTROL SLEEP AND WAKE CYCLES
- NIAID, FDA: GLUTAMINE SUPPRESSES HERPES IN MICE AND GUINEA PIGS
- NIEHS: AN ANTIDEPRESSANT MAY ENHANCE DRUG DELIVERY TO BRAIN
- NICHD: KEY REGULATOR OF FETAL GROWTH IN MICE
- NIAID: IMMUNE RESPONSES DRIVING OBESITY-INDUCED LIVER DISEASE
- NICHD: CELL PARTICLES MAY HELP SPREAD HIV INFECTION

Science In Space!

Astronaut Kate Rubins Visits NIH

BY EMILY PETRUS, NINDS

Most scientists do experiments in controlled environments, with unlimited access to electricity, air, and gravity. Then there are other scientists who find ways to do research in extreme conditions where everything is compact, suspended, and unknown. Kate Rubins, a molecular biologist turned NASA astronaut, knows how to work in controlled as well as extreme environments—from the remote regions of central Africa to the even more remote regions of outer space. On April 25, 2017 (National DNA Day), she visited NIH to talk about her experiences on Expeditions 48 and 49 to the International Space Station (ISS) and participate in a question-and-answer session with NIH Director **Francis Collins**.

During her 115 days in space (July–October 2016), Rubins performed two space walks and conducted more than 275 experiments. She was the first person to sequence DNA in the microgravity of space.

At NIH, she showed a video of herself—blonde hair floating wildly—in space doing experiments and even using a cordless power drill as a centrifuge. The science was punctuated with breathtaking images of Earth taken from space (NASA collects the images to study weather patterns). Collins and Rubins then sat on stage for a conversation with questions submitted by NIH employees as well as by online viewers who were participating in a chat on NIH's Facebook page. Following are selected questions, lightly edited (more online).

NASA astronaut Kate Rubins.

COLLINS: One application for being able to sequence DNA in space might be to survey the health of the astronauts. For example, by measuring RNA expression in peripheral blood cells of somebody who's not feeling well, we could determine whether it's a viral or bacterial infection. How far along do you think we are with that?

RUBINS: We can draw blood on board, we can make peripheral-blood mononuclear cells, and we can take serum and plasma. So it would be technically feasible to take human-physiology samples, not only to diagnose disease but to also watch processes like bone loss, fluid changes, and cardiovascular effects. We could look for how the biomarkers of those processes evolve over time.

COLLINS: What about the health implications of long-term weightlessness such as if we send humans to Mars?

RUBINS: There are a number of risks to astronaut health for long-duration space flight. High among those is the radiation exposure. We can protect astronauts from that either through shielding of the spacecraft or by giving them a countermeasure such as a radioprotective pill. We also need to work on bone and muscle health, the neurovestibular effects of the microgravity environment, and nutrition. We have the technology to figure out how to keep people safe. So there's no big showstoppers that are absolutely going to prevent us from going to Mars.

COLLINS: Do you think it's possible that there are identifiable genetic differences between individuals that are predictive of how well they will do in space? If so, will this play some role in astronaut selection?

RUBINS: Certainly, as precision medicine improves our understanding of human health, we're going to start using this to understand what would be protective from radiation. We've got some early results from studies about nutrition and DNA health and how that might be influencing factors in space flight. I think we'll continue to look at [individual differences] and try to understand how we can select the best performers in this environment. ●

You can view this April 25 event, which took place in Masur Auditorium (Building 10), at https://videocast.nih.gov/launch.asp?23239 (NIH and HHS only). In addition, you can read an *NIH Catalyst* article (November-December 2016 issue) about Rubins's October 2016 space chat with Francis Collins at https://irp.nih.gov/catalyst/v24i6/news-briefs.

Read more questions online as well as about how NIH and NASA have worked together: https://irp.nih.gov/catalyst/v25i4/science-in-space.

Enzyme Drives Weight Gain

CONTINUED FROM PAGE 1

during this period. Chung and his team of researchers—from NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, and five universities—thus searched for biochemical changes in middle-aged animals (human equivalent of 45 years old). Their study appeared on May 2, 2017, in *Cell Metabolism*.

The team focused on an enzyme called DNA-dependent protein kinase (DNA-PK), which is activated by a specific kind of DNA damage. Evidence has been mounting, however, that DNA-PK has functions beyond DNA repair and can even affect metabolism.

The scientists looked at levels of DNA-PK activity in the skeletal muscles of rhesus macaques (*Macaca mulatta*), mice, and rats. Activity was low over time until middle age, when it rose significantly. Further experiments showed that DNA-PK activity promotes the conversion of nutrients to fat and decreases the number of mitochondria, the tiny organelles in cells that turn fat into energy to fuel the body.

Mitochondria can be found in abundance among young people, but the numbers drop considerably in older people. Researchers know that fewer mitochondria can promote obesity as well as loss of exercise capacity.

The researchers theorized that reducing DNA-PK activity might increase the number of mitochondria and promote fat burning. They tested their theory in mice with a drug that inhibits DNA-PK. Mice that received the inhibitor gained 40 percent less weight when fed a high-fat diet. The drug boosted the number of mitochondria in the skeletal muscle, increased the fitness of obese and middle-aged mice, and reduced the incidence of obesity and type 2 diabetes.

The team also examined the role of DNA-PK activity in calorie restriction and aerobic fitness, both of which can delay aging and protect against chronic diseases in animal models. Rhesus macaques on a calorie-restricted diet had lower DNA-PK activity in skeletal muscle. Rats selectively bred to be strong runners also had three-fold lower DNA-PK concentrations in their skeletal muscle than did the poor runners.

"Our society attributes the weight gain and lack of exercise at midlife—approximately 30–60 years—primarily to poor lifestyle choices and lack of willpower," said Chung. "But this study shows that there is a genetic program driven by an overactive enzyme that promotes weight gain and loss of exercise capacity at midlife."

These findings could lead to the development of a new type of weight-loss medication. However, DNA-PK inhibitors have yet to be tested for this purpose in humans. Middle-aged people who are fighting obesity should continue to reduce calories and boost exercise, according to the researchers. ●

This article is adapted from one that appeared in *NIH Research Matters* on May 12, 2017 (http://bit.ly/2uz7j6k).

Reference: NIH authors: S.J. Park, O. Gavrilova, A.L. Brown, J. Kim, X. Xu, S. Yang, J.H. Um, M.K. Kim, and J.H. Chung, *Cell Metab* 25:1135-1146.e7. DOI:10.1016/j.cmet.2017.04.008)

ABBREVIATIONS

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
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

3-D Printing & Radiation Exposure

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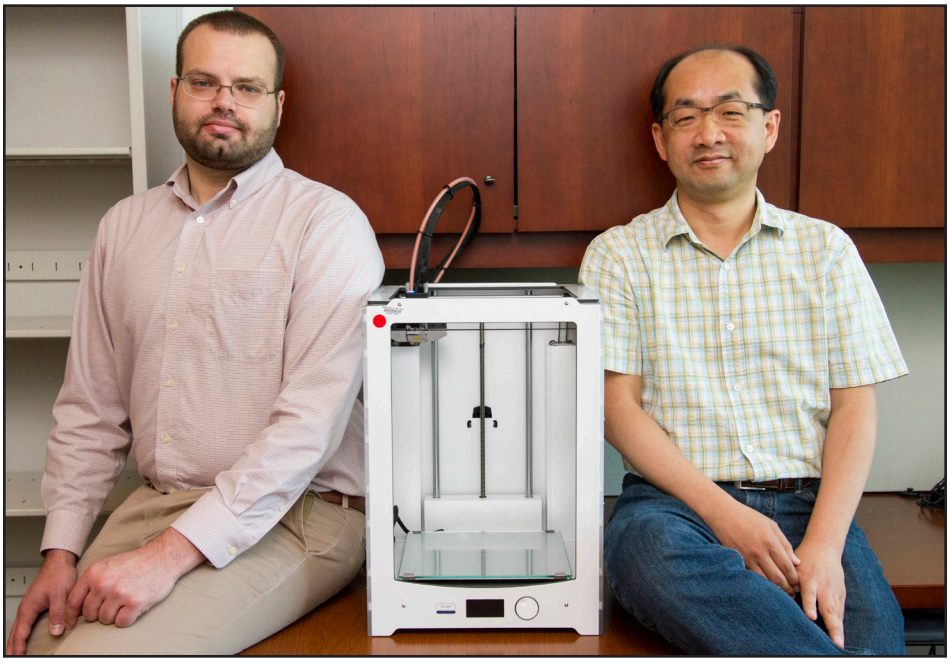


DANIEL SONE, NCI

Choonsik Lee (right) and Matthew Mille with their coffee-machine-size 3-D printer that brews up tools for health physicists to improve their estimates of radiation dose.

of mass. This estimate is a necessary input for risk assessment for exposed individuals as well as for epidemiological investigations that evaluate the associations between radiation and adverse health effects such as cancer. Medical procedures, ranging from X-ray computed tomography (CT) scans to proton therapy, are a common source of ionizing radiation.

The absorbed dose for specific organs ("organ dose") depends on many factors, including the depth of the organ in the body, the density of the surrounding tissues, the size of the patient, and the specifics of the procedure. To make sense of this complexity, Lee's group uses "phantoms," or models of the human body, that absorb radiation in a similar way to an actual patient. These phantoms can be purely computational, existing as lines of code and images within a computer, or they can be physical mannequins, custom-made of plastic and other materials. Each type has strengths and weaknesses; the investigators need both to accurately assess the radiation dose received by an individual.

Physical phantoms are made of stackable layers, each one dotted with a grid of holes in which tiny radiation sensors called dosimeters are inserted. A sensor-packed physical phantom exposed to a radiation source (such as a CT scanner) can provide very reliable dose measurements, but doing so is expensive and time-intensive. Furthermore, the measured doses are constrained by the limited variety of physical phantoms available for purchase.

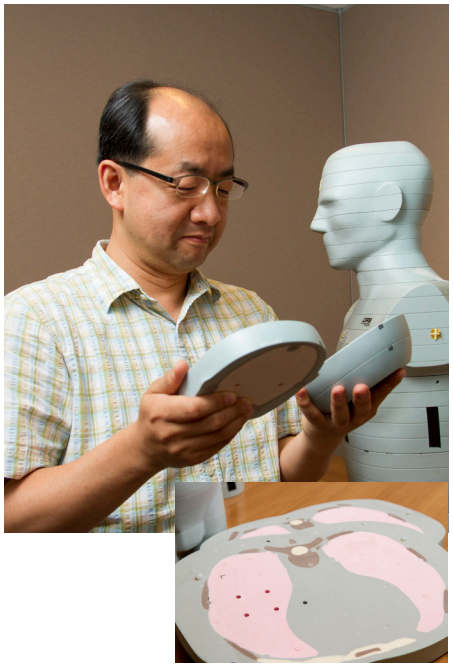
Computational phantoms used in computer simulations fill in the gaps, accounting for doses to a wider range of body characteristics and machine settings. Because they are virtual, these models are cheaper to test (they don't require time in the CT scanner), and the calculations can be accelerated using high-performance computing clusters. The computer models still depend, however, on some measurements from physical phantoms to provide realistic benchmark measurements and validation.

Customization of the Phantoms

Mille became interested in the possibility of using 3-D printing to build phantoms early in his graduate studies. The project gained momentum once he found an enthusiastic mentor in Lee. Although life-size physical phantoms are available for purchase from a few manufacturers, they are very expensive and their relatively simple designs have not changed for decades.

"Our goal is to use 3-D-printing technology to customize phantoms and make them more realistic and versatile," said Mille. "For instance, the two physical models the [DCEG] has now are both male. To simulate exposure to breast tissue, we can print prostheses to be attached to the male phantom to estimate radiation doses from breast-cancer treatment." In addition to reducing costs, the researchers hope to create physical phantoms that more closely resemble their sophisticated computational models and are more anatomically accurate and customizable.

Lee is also experimenting with how to incorporate patient body size into dose estimates. "There are no obese physical phantoms," he said. A recent study he led, published in the *American Journal of Roentgenology,* showed that using a normal-weight reference phantom to assess dose to an obese patient using particular CT machine settings can lead to overestimating the organ dose by as much as 200 percent (*AJR Am J Roentgenol* **208:**1082–1088, 2017). The team developed an ingenious solution: Printing layers of "body fat" that can be attached to an existing phantom.



DANIEL SONE, NCI

Lee examines layers of one of his commercially produced phantoms. Physical phantoms are composed of stacked layers into which radiation sensors are inserted for testing. Inset: Different colors in the layer approximate various body tissues such as bone or muscle. Small holes for sensors dot the slice; when not in use, the holes are filled with plugs.

"The presence of extra body fat effectively shields organs from external sources of radiation," said Mille. "Consequently, technical parameters in CT imaging must be altered for obese patients to maintain good image quality. This [alteration] can result in higher doses for obese patients compared [with] those with a normal [body mass index]."

As part of this work, the team is exploring how 3-D printing materials can be used to mimic the radiation attenuation characteristics of human tissues with different mass density, such as fat, soft tissue, lung, and bone. To ensure that the printed phantom parts appropriately simulate human tissue, Mille images them on a CT scanner and compares the resulting images with those taken of real patients. Through this work, the researchers hope to create physical phantoms that respond to radiation in the same way as a patient.

Adapting to New Technologies

Innovation in the use of radiation in medical practice requires invention on the part of dosimetrists as well. For example, existing physical phantoms are inadequate for evaluating exposure to secondary neutrons produced inside the body during proton therapy, an emerging type of cancer treatment. **Gleb Kuzmin**, a predoctoral fellow in REB who also works with Lee, is spearheading research to estimate organ doses from such treatments. Step one addresses a simple, yet stubborn, problem: The holes in each layer of the commercial phantoms are too small to fit a neutron detector. The obvious solution—drilling larger holes—is not an option, because modifying the expensive phantom for this test would make it less effective with the smaller dosimeters. Instead, the team will print copies of select slices of the human body with larger openings to accommodate the neutron detectors. Once the patchwork phantom is put back together, Kuzmin can validate his simulations by testing it in a proton treatment system and measuring the absorbed dose.

Emphasis on Collaboration

"These phantoms have truly been an 'NIH family' effort," said Lee. Many individuals have contributed their time and ideas, including Jacob Oshinsky, a 12-year-old 3-D-printing whiz and son of DCEG staff scientist **Stephanie Weinstein**. On Take Your Child to Work Day in 2016, Jacob visited the 3-D-printing lab and introduced the dosimetry team to a range of different printing materials.

Through a collaboration with **Roberto Mass-Moreno**, of the Radiology and Imaging Sciences Department at the NIH Clinical Center, REB investigators have access to the center's state-of-the-art imaging equipment with which they can test the printed phantoms.

The partnerships extend to the National Institute of Standards and Technology (NIST) in Gaithersburg, Maryland, where some initial CT scanning was performed. Staff at the NIST Research Reactor are also helping to test novel printing materials. They expose the materials to a low-energy neutron beam emanating from the reactor to determine their elemental composition and, by extension, their radiation-absorption properties.

"DCEG has always been at the forefront of efforts to increase the public-health impact of epidemiology by improving tools and methods," said REB chief **Amy Berrington de González**. "The 3-D-printed dosimetry phantom project by Drs. Lee and Mille is a perfect example of this cutting-edge work."

Working together, these scientists aim to build more realistic human phantoms that will help to improve our understanding of the risks of medical radiation. There remain many challenges to overcome, but the researchers are optimistic. "Our research so far has found that, with some resourcefulness, much can be accomplished despite limitations of current 3-D printing technology," said Mille. "It is only a matter of time until a life-size human phantom can be printed with the push of a button. We think we'll clone Dr. Lee first!" ●

From NCI-DCEG Research News and Highlights:
http://bit.ly/2uemrs1

A Conversation with Atul Gawande

Surgeon, Writer, and Public-Health Researcher

BY MANJU BHASKAR, NINDS

"Better is possible. It does not take genius. It takes diligence. It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try."—Atul Gawande, Better: A Surgeon's Notes on Performance

Surgeon. Writer. Public-health researcher and one of the most prolific commentators on the state of medicine and health care. Atul Gawande has definite ideas on how a more systematized health-care system will go a long way toward eliminating medical errors and improving patient care. He visited NIH recently for a conversation with NIH Director **Francis Collins** about "Systems Science and Innovation in Health-Care Delivery."

Gawande, who's based in Boston, is a surgeon at Brigham and Women's Hospital, a professor at Harvard School of Public Health and at Harvard Medical School, and founder and executive director of Ariadne Labs, a center for health-systems innovation. He has been a staff writer for *The New Yorker* since 1998 and is the author of four *New York Times* best-sellers: *Complications: A Surgeon's Notes on an Imperfect Science* (2002); *Better: A Surgeon's Notes on Performance* (2007); *The Checklist Manifesto: How to Get Things Right* (2009); and *Being Mortal: Medicine and What Matters in the End* (2014), which was also featured in a *Frontline* documentary.

The following is an edited transcript of the conversation that took place between Collins and Gawande on June 13, 2017, in Masur Auditorium (Building 10). Some questions were submitted by NIHers in advance and some came via Facebook and Twitter.

CHIA CHI CHARLIE CHANG

A crowd of NIHers gathered in Masur Auditorium recently to watch NIH Director Francis Collins (left) and public-health commentator Atul Gawande (right) discuss "Systems Science and Innovation in Health-Care Delivery" Gawande is also a surgeon and the best-selling author of several books about improving the health-care system.

COLLINS: How do we reduce errors and address the failure in health-care delivery?

GAWANDE: We don't apply science to the delivery of medicine the same way we do for scientific breakthroughs. Instead, we impose mandates such as pay-for-performance programs and malpractice regulations, but they only have modest effects. What we need to do is systematize, and that requires applying science to the follow-through in what we do.

COLLINS: How do you systematize discovery and delivery?

GAWANDE: In my book *The Checklist Manifesto*, I described how we designed a surgical safety checklist based on the critical components of care. In a study in South Carolina, we found that high-performing teams performed better surgeries because they made sure that they had a verbal checklist before the operation to take on the big killers like infection, management of bleeding, and unsafe anesthesia. This model was piloted locally and later tested in eight sites globally—from the most impoverished region of the world to the University of Seattle. In every hospital, there was an average reduction in complications of 36 percent and an average reduction in deaths of 47 percent. Hence, we can apply science to systematize discovery and delivery.

COLLINS: NIH's "All of Us" research program will have an unprecedented million-strong longitudinal cohort of Americans. What kind of information will be most helpful in moving from precision medicine to precision delivery, and what can NIH do to help manage the transition?

GAWANDE: Applying science to the system is key. A huge amount of data on biologic, genomic, and laboratory results are being collected from a million people. It's important to see the interconnections such as what kind of care patients have received; how it affects their physical, cognitive, and emotional functions; what level of well-being they are getting from the care; how much does their well-being fluctuates and change over time. All such information collated together truly represents precision medicine and its delivery. Where the system is most organized, care is better and costs less.

COLLINS: How do we tackle the opioid epidemic in this country? In the late 1990s, the medical profession recommended that no patient should be allowed to have pain, and it was thought that treatments with Oxycontin would not lead to addiction.

GAWANDE: About six to 10 percent of patients put on opioids after surgery will become addicted to opioids later. We didn't know in the 1990s that the addiction rate was that high. And we did not know how few opioids were needed for good pain control. In a recent study, it was demonstrated that mastectomy patients on average used less than 10 pain pills, and that 80 percent could be covered with a prescription for 15 pills. But the prescriptions for opioids, on average, were many times that. Knowing that data, then, has led people to shrink the number of pills they are using. Another problem is that we tend to give longer prescriptions because we don't want to leave our patients in pain. If a patient runs out of pills, they are required to go back to the doctor for a paper prescription. But what if you are calling after hours?

There are systematic steps that can be taken to address this problem. New York State, for example, has successfully implemented an electronic-prescription approach that tracks every prescription and gives the physicians an efficient and controlled method of ordering narcotics.

CHIA CHI CHARLIE CHANG

If you prescribed too few, the patient could call you and you could order five more pills and they would be ready at the pharmacy for pickup. I think there is an incredible role for NIH being able to support the innovators who are developing those kinds of systems.

COLLINS: In your *New Yorker* article "Big Med," you wrote about a central ICU-monitoring facility that's not in an ICU. Is that kind of technology catching on?

GAWANDE: We know that having a dedicated ICU intensivist-trained person in a critical-care unit leads to substantially better outcomes for patients. But there aren't enough intensivists to go around. A central ICU-monitoring facility provides a hub where an intensivist can consult with nurses and physicians at multiple sites. The newest area in technology is doing hospital-at-home care—monitoring from a distance for people who have acute illnesses such as pneumonia.

COLLINS: Do you think people are beginning to recognize that maybe we're spending vast amounts of money on the last few days of someone's life and it's not what the person wants?

GAWANDE: My book *Being Mortal*, when it was published in 2014, was considered a death-panel work. The belief was that it was forbidden to even to have discussions about what kind of care would be better for people as they come to the end of their life.

In doing the journalistic investigation for my book, I learned that research has demonstrated how people, including the seriously ill and the frail, have goals besides just survival. They have goals for the quality of life, their purpose, and what a full life looks like. And they want our medical capabilities to enable those core goals. The most reliable way to find out people's goals is to ask them.

Our research shows that having such conversations is incredibly powerful. We've distilled into a checklist what the conversation from highly skilled palliative-care and geriatric physicians looks like and how to bring it to non-palliative-care physicians. We're deploying the system across the country and learning how to drive it into practice.

COLLINS: Any advice for young scientists, medical students, and physicians-in-training?

GAWANDE: The cool thing is that we're in a transition around our science and our policies. The power of the past century in science has come from reductionism—focusing on a single area and understanding a component of what happens; and identifying the gene, the neuron, the molecule, the drug, the device, and the specialized operation. What we are now recognizing is that it's the interconnection among these that you need to understand—how the genes connect to create a disease and interact with the environment; how the neurons connect to produce consciousness or dementia; and how the drugs and devices and the specialists fit together successfully to produce better outcomes. In the future, we're switching from the century of molecule to the century of the system. And it's becoming the science of the interconnections, whether it's at the molecular level, at the physiologic level, or at the population level. The biggest insights and biggest gains in health and understanding are going to come from those interconnections. ●

To watch a videocast "Systems Science and Innovation in Health-Care Delivery," which took place on Tuesday, June 13, 2017, go to https://videocast.nih.gov/launch.asp?23354.

Read more online at at https://irp.nih.gov/catalyst/v25i4/a-conversation-with-atul-gawande

Recently Tenured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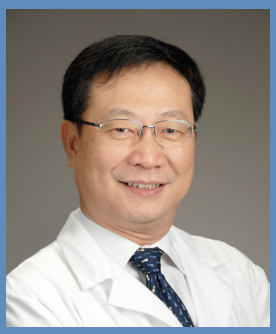
ZENAIDE (ZENA) QUEZADO, CC


JOSHUA N. SAMPSON, NCI-DCEG


ZHENGPING ZHUANG, NCI-CCR

CLAUDIA KEMPER, PH.D., NHLBI

Senior Investigator and Chief, Complement and Inflammation Research Section, Laboratory of Molecular Immunology, National Heart, Lung, and Blood Institute

Education: University of Hamburg, Hamburg, Germany (B.Sc. in biology); Bernhard Nocht Institute for Tropical Medicine, Hamburg (Ph.D. in immunology)

Training: Postdoctoral fellowship, Department of Internal Medicine, Washington University School of Medicine (St. Louis)

Before coming to NIH: Professor of innate immunology, Division of Transplant Immunology and Mucosal Biology, King's College London (London)

Came to NIH: In 2014–2015 as a visiting scientist in NHLBI's Laboratory of Molecular Immunology; returned to NHLBI in February 2017

Selected professional activities: Member, Grant Review Board, Wellcome Trust; senior editor, *Molecular Immunology*; visiting professor of innate immunology at King's College London; adjunct professor of translational complement research, University of Lübeck (Lübeck, Germany)

Outside interests: Reading; running; visiting museums

Website: https://www.nhlbi.nih.gov/research/intramural/researchers/pi/kemper-claudia

Research interests: The complement system is a critical part of the innate immune system and consists of about 50 serum and cell-expressed proteins (in the blood, lymph, and interstitial fluids) that provide protection against pathogens through direct cell lysis and the mobilization of innate immunity.

Before coming to NIH, I helped discover that the complement system plays other physiological roles such as instructing adaptive T-cell responses. At NIH, my lab is trying to understand the unexpected additional roles of the complement system in regulating key basic processes of the cell.

The complement system affects human T-helper type 1 (Th1) immunity by controlling both the induction and contraction of Th1 CD4+ T cells. Further, we discovered that the activation of the key complement components—glycoproteins C3 and C5—is not, as always thought, confined to the extracellular space but also occurs in intracellular areas. We named this intracellular complement system "the complosome."

Intracellular C3 and C5 are critical for the homeostatic survival of T cells and for metabolic reprogramming. If there is too little activation of intracellular C3 and C5, there's a deficient Th1 response, leading to recurrent infections. Too much intracellular C3 and/or C5 activation contributes to hyperactive Th1 responses such as those observed in rheumatoid arthritis and other autoimmune diseases. The hyperactive response can be normalized pharmacologically by inhibiting the intracellular complement activity.

Although initially discovered in T cells, these complosome-regulated pathways seem to operate in a broad range of cells. We are defining the functional roles and regulative mechanisms and assessing the biological relevance of the intracellular and autocrine complement. We hope to develop druggable targets in these pathways to treat autoimmune diseases. To achieve this goal, we are focusing on the complosome composition in different cells, the functions of the complosome, and how it is regulated.

In our research, we use immune and tissue cells—from healthy donors, patients with complement deficiencies, patients with T-cell-driven autoimmune disease, and patients with deviations in novel complosome-regulated pathways—to do gene and microRNA arrays, epigenetic-landscape evaluation, and proteomic and metabolomic assessments. This approach will be combined with appropriate mouse models to define the biological significance of proteins and pathways and to develop preclinical animal models for future pharmacological targeting.

Understanding the functions of the complement system will deliver new knowledge about cell biology in health and disease.

JOSEPH MARCOTRIGIANO, PH.D., NIAID

Senior Investigator and Chief of Structural Virology Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases

Education: Rutgers, The State University of New Jersey, New Brunswick, N.J. (B.A. in chemistry); The Rockefeller University, New York (Ph.D. in molecular biophysics)

Training: Postdoctoral fellow and research associate, Center for the Study of Hepatitis C, The Rockefeller University

Before coming to NIH: Associate professor with tenure, Department of Chemistry and Chemical Biology, Center for Advanced Biotechnology and Medicine, Rutgers University

Came to NIH: In January 2017

Selected professional activities: Faculty Scholar, Howard Hughes Medical Institute

Outside interests: CrossFit; cooking

Website: https://www.niaid.nih.gov/research/joseph-marcotrigiano-phd

Research interests: My laboratory is investigating how positive-sense RNA viruses enter human host cells, replicate, and evade the immune response. In particular, we are interested in how the hepatitis C virus (HCV) enters cells and evades the immune response; exploring the mechanisms of viral polyprotein processing; and examining how the innate immune system distinguishes self from viral RNAs. Our long-term goal is to develop an effective HCV vaccine, novel antiviral drugs, and immunomodulators of retinoic-acid-inducible gene I for use as broad-based antiviral agents.

About two percent of the world's population is infected with HCV (approximately 150 million people), and an estimated 3 to 4 million more individuals become newly infected each year. Without treatment, hepatitis C may lead to cirrhosis, liver failure, and liver cancer. There are several FDA-approved direct-acting antivirals for HCV, some of which are prohibitively expensive, but there is no vaccine against the virus.

HCV is an enveloped virus with an outer shell composed of many copies of two glycoproteins, E1 and E2. My laboratory developed a cost-, labor-, and time-efficient method for the large-scale production of recombinant glycoproteins in mammalian cell lines. Using this production system, we found that HCV E2 does not share any similarity with other viral glycoproteins, including those from closely related viruses, suggesting that HCV may use a novel entry mechanism.

Numerous viruses, many of which severely impact human health around the globe (such as human immunodeficiency virus, Zika virus, dengue virus, West Nile virus, chikungunya virus, and severe acute respiratory syndrome coronavirus), use a gene-expression mechanism wherein one gene encodes a single polyprotein that is post-translationally cleaved into individual proteins.

To fully understand polyprotein processing in each step of the viral lifecycle, we examined changes in viral-protein properties before and after polyprotein processing. We have determined the structure of the precleavage form of a portion of the alphavirus replication machinery. Our findings, which have provided new insights into viral polyprotein processing and pathogenesis, may be applicable to other important human viruses that undergo polyprotein processing.

In our research that examines the innate immune system, we are trying to understand the mechanism of self versus non-self recognition and immune-signaling actions of certain receptors that detect the presence of viral RNA in infected cells. So far, we have determined the structure of the RNA-binding domains of one of the cytoplasmic proteins.

ZENAIDE (ZENA) QUEZADO, M.D., CC

Senior Investigator and Chief of Pediatric Anesthesia and Critical Care, Department of Perioperative Medicine, Clinical Center

Education: Universidade Federal do Ceará, Fortaleza, Ceará, Brazil (M.D.)

Training: Residency, Department of Medicine, Albert Einstein Medical Center, Temple University (Philadelphia); Fogarty Clinical Fellow, Critical Care Medicine Department, NIH Clinical Center; residency and cardiac anesthesia fellowship, Department of Anesthesia and Critical Care, Harvard's Massachusetts General Hospital (Boston); clinical fellow, Shriners Burn Hospital (Boston)

Before coming to NIH: Anesthesiologist, Children's National Health System (Washington, D.C.); professor of anesthesiology, Critical Care Medicine and Pediatrics, George Washington University (Washington, D.C.); director, Pain Neurobiology Laboratory and Animal Neurobehavioral Core, Center for Neuroscience Research, Children's Research Institute (Washington, D.C.)

Came to NIH: In 1990 for training (1990–1994); in 2000 as anesthesiologist at NIH Clinical Center; later became chief of the Department of Anesthesia and tenure-track investigator (2005–2010); returned in January 2017 as a senior investigator

Selected professional activities: Associate senior examiner, American Board of Anesthesiology; elected member, Association of University Anesthesiologists, Society for Pediatric Research

Outside interests: Collecting art; traveling around the world to learn about other cultures

Research interests: As a pediatric anesthesiologist, I take care of children before, during, and after surgery. During this perioperative period, one of my major concerns is treating pain. Inspired by my clinical work, I also do basic research—using mouse

CONTINUED ON PAGE 18

Recently Tenured

CONTINUED FROM PAGE 17

models—to understand the neurobiology of pain and nociception, develop and evaluate therapeutic agents for treating pain, and develop methods for objectively measuring it.

In my lab, we use mouse models of sickle-cell disease (SCD) and models of autism-like behavior. People with SCD suffer acute and chronic pain that is often inadequately treated. The SCD mice also have high susceptibility to pain. Conversely, some children with autism-spectrum disorders seem to have either a low tolerance for or a low response to pain, as do mice with autism-like behaviors.

In our search for therapeutic agents to treat pain, we have found that the FDA-approved sedative dexmedetomidine, when used in the perioperative period, can significantly decrease the need for opioids. In children undergoing tonsillectomies, my team found that those who were given dexmedetomidine before surgery had a longer opioid-free interval post-surgery than children who were not given the sedative beforehand. These findings were reproduced by others and have changed the way we treat children's pain during the perioperative period.

A major challenge in my work is the lack of ways to objectively measure pain. Clinicians can ask adults to rank their pain on a scale of 1 to 10, with 10 being the worst. But babies, very young children, or children with developmental disabilities may not be able to verbally express how much they hurt. Thus, it's difficult to gauge how much pain a child is in and figure out how to treat it. And it's unclear whether children with autism feel less or more pain compared with other people or whether they are just unable to communicate how they feel.

In an effort to develop objective measures for pain, we collaborated with NIH's Center for Information Technology to adapt a peripheral neuropathy-diagnostic technique for use as a noninjurious, neurospecific nociceptive behavior assay that elicits and detects pain-avoiding behavior in mice. With this paradigm, we can study the effects of age, sex, and neurologic diseases on pain and monitor the efficacy of pain treatment. We are also developing mobile applications to continue to monitor pain intensity and medication compliance while patients are at home.

This fall, I will be heading up a new pediatric observation unit, which will provide additional support for patient safety in pediatric research. The unit will include four beds where children who require closer observation will have cardiovascular and respiratory monitoring.

JOSHUA N. SAMPSON, PH.D., NCI-DCEG

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

Education: Pomona College, Claremont, Calif. (B.A. in chemistry and mathematics); Stanford University, Stanford, Calif. (M.S. in biophysical chemistry); University of Washington, Seattle (M.S. and Ph.D. in biostatistics)

Training: Postdoctoral fellow, Department of Biostatistics, Yale University (New Haven, Conn.)

Came to NIH: In 2009 as a principal investigator in NCI-DCEG's Biostatistics Branch

Selected professional activities: Associate editor, *Annals of Applied Statistics*; statistical editor, *Journal of the National Cancer Institute*

Outside interests: Running; kayaking; reading

Website: https://irp.nih.gov/pi/joshua-sampson

Research interests: I am fascinated by the genetic causes of cancer. At NCI-DCEG, I have been fortunate to have collaborated on several complex and exciting genome-wide association studies (GWAS). As a statistician, I have been developing more-efficient designs for studies and more-powerful methods for analyzing data. I have developed a new framework for identifying groups of rare variants associated with cancer, a new analysis for identifying causal variants in GWAS in related individuals, and an approach for identifying associations within only a subset of individuals. The latter approach was recently applied to a GWAS in an attempt to identify genes associated with the risk of secondary neoplasms among childhood-cancer survivors. I have also tried to describe and quantify the heritability of a range of cancers and show that for any given cancer, the majority of heritability is likely explained by a unique set of underlying genetic loci.

In addition, I am curious about understanding how known risk factors increase the risk of cancer. Towards this aim, I am working with a talented postdoctoral fellow, **Andriy Derkach**, to identify metabolites that may be mediators between risk factors, such as body mass index and diet, and cancer risk.

Over the past two years, I have been part of a team of NCI researchers that is evaluating the efficacy of a single dose of the human papillomavirus vaccine (typically the vaccine is given in three doses over a six-month period). **Mitchell Gail** and I are developing an innovative statistical approach—that accounts for such complexities as a low infection rate, a lack of a placebo arm, and missing data—for analyzing the study results.

Finally, I have had the opportunity to work on a variety of other epidemiologic studies. I have explored many factors—such

as the microbiome, epigenetics, and physical activity—that are associated with health. To better understand how physical activity and its complement, sedentary time, are associated with risk of disease, I have developed methods to assess the measurement error of accelerometers, described novel patterns of activity, and evaluated techniques for handling compositional data.

ZHENGPING ZHUANG, M.D., PH.D., NCI-CCR

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

Education: Shanghai Second Medical University, Shanghai, China (M.D.); Molecular Biology and Pharmacology, Department of Pharmacology, Wayne State University, Detroit (Ph.D. in Molecular Biology and Pharmacology)

Training: Residency in general surgery, Rui Jin Hospital, Shanghai Second Medical University; postdoctoral fellow, Harvard Medical School (Boston); residency in transitional medicine, Henry Ford Hospital (Detroit); research associate, University of Michigan (Ann Arbor, Mich.); residency in anatomic pathology, Laboratory of Pathology, NCI

Came to NIH: In 1993 for training; in 1996 became attending staff pathologist and co-director of the Developmental Molecular Diagnostic Unit, Laboratory of Pathology, NCI; in 1999 became head of Molecular Pathogenesis Unit, NINDS; in December 2016, became senior investigator

Selected professional activities: Adjunct professor, Department of Neurology, Uniformed Services University of the Health Sciences School of Medicine (Bethesda, Md.)

Website: https://irp.nih.gov/pi/zhengping-zhuang

Research interests: My laboratory is gaining insights into the pathophysiology of central nervous system (CNS) and other tumors. We focus on inherited and somatic mutations in the cancer genome to demonstrate their critical roles in tumor formation and progression; we develop and apply cutting-edge techniques to identify novel genetic and functional changes in cancer cells; and through collaborations with clinicians and scientists, we translate our laboratory findings into experimental drug development and human clinical trials.

Using functional genomics studies, we identified and characterized cancer-causing gene mutations. For example, we were the first to discover Pacak-Zhuang syndrome, a multiorgan human disorder characterized by the development of multiple paragangliomas (neuroendocrine neoplasms that may develop at different body sites), somatostatinomas (rare neuroendocrine tumors that arise from the pancreas or gastrointestinal tract), and congenital polycythemia (a slow-growing blood cancer in which the bone marrow makes too many red blood cells). We worked closely with NIH intramural physicians and scientists to explore the genetic make-up of a group of patients with similar tumor manifestations and polycythemia.

In our biotechnological advancements and applications work, we addressed the problem of isolating tumor cells from the morphologic heterogeneous solid-tumor specimens. My group developed a tissue-microdissection technique and co-invented laser-capture microscopy (LCM) to facilitate the procurement of highly purified specific cell types from histological tissue samples. The technique, together with the invention of the LCM, substantially improved and facilitated tissue-based cancer research.

We were also the first to identify and clarify the nature of the neoplastic cell in CNS hemangioblastomas and several other tumors found in von Hippel–Lindau (VHL) disease, an inherited disorder characterized by the formation of tumors and fluid-filled sacs in many parts of the body. In separate CNS-tumor studies, we identified several new genes involved in tumorigenesis in primary glial neoplasm (especially gliomas), discovered novel stem-cell-like populations in brain tumors, and elucidated a potential role for dysfunctional beta-catenin signaling in the activation of astrocytes that facilitates the genesis of astrocytomas.

In our drug-development and clinical-translation work, we identified small-molecule compounds that can be used to treat some cancers. We collaborated with a biotechnology firm to develop the drug LB100, an inhibitor of protein phosphatase 2A, which holds promise as a novel means of overcoming treatment-resistant cancer and was recently approved by the FDA for clinical trials. In phase 1 trials, LB100 was associated with the stabilization of several cancer types without dose-limiting toxicity (https://clinicaltrials.gov/ct2/show/NCT018376670). ●

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FROM THE OFFICE OF NIH HISTORY

Angel of Independence

BY MICHELE LYONS, OFFICE OF NIH HISTORY

Medallions and coins are both beautiful artwork and symbols of the achievements and people we value. The silver Mexican Medallion Libertad coin pictured here symbolizes an agreement between the Mexico National Council on Science and Technology and the United States National Institutes of Health. In 2006, the silver-dollar-size coin was given to then–NIH Director **Elias Zerhouni** to commemorate a joint program for training students from both countries in clinical research; allowing midcareer scientists to work in Mexico or in the United States short-term; bringing Mexican postdocs to NIH for short-term assignments; and identifying areas for joint research. This coin depicts the Angel of Independence soaring over the volcanos Popocatépetl and Iztaccíhautl (front side) and Mexico's coat of arms surrounded by historical versions (reverse side). ●

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