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Portraits Reflect the Rich Diversity of NIH's Workforce

BY VICTORIA TONG, OD

Walk down the hallway to the NIH Library in Building 10, and you'll come across a set of eye-catching stylized portraits splashed with red, blue, orange, and gold. Featured is a cultural mosaic of individuals who stand in contrast to the "white walls" or "dude walls" common to many academic and research establishments that are adorned by paintings and photographs of mostly white men. The vibrant display is part of the NIH UNITE initiative's "Power of an Inclusive Workplace Recognition Project," which was created to highlight a wide range of NIH employees. It has received glowing words of appreciation from NIH staff members for including people who look like them on those walls.

The UNITE initiative was established in 2021 to identify and address structural racism within the NIH-supported and greater scientific community. With representation from across NIH, UNITE strives to create an equitable and civil culture within the biomedical research enterprise, increase inclusivity and diversity in science, and reduce barriers to racial equity in the entire biomedical research workforce.

A surge of racially motivated violence in 2020 and health inequities highlighted by the COVID-19 pandemic further illuminated racial injustice in the United States. So, in the summer of 2020, NIH staff began discussions among themselves and with NIH leadership about how to improve equity and

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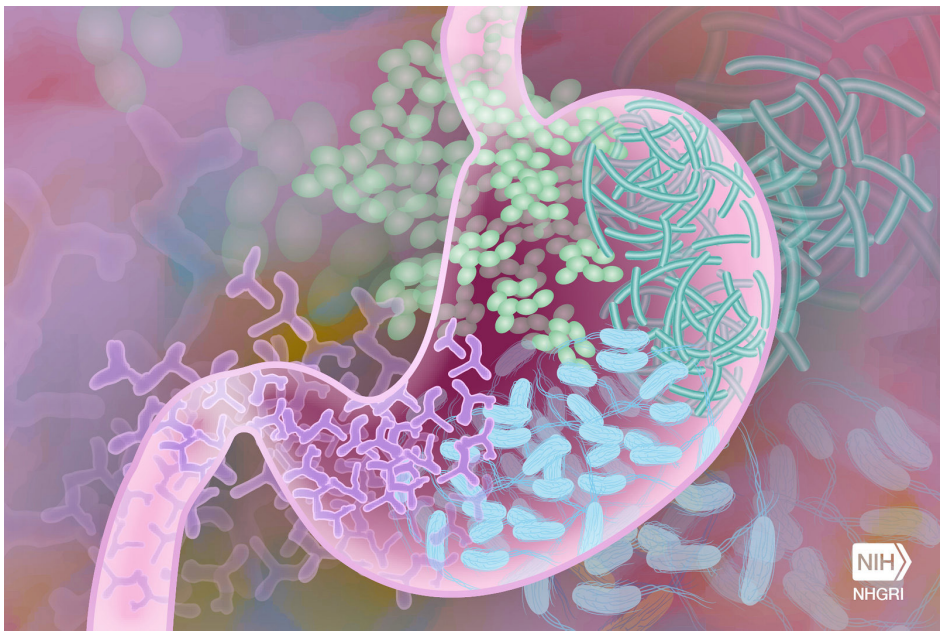
Bugs, the Brain, and Behavior

The Gut Microbiome's Role in Addiction

BY MICHAEL TABASKO, OD



CREDIT: NHGRI

The microbial communities that live in and on our bodies play a role in health and disease. NIH scientists have recently found that an imbalance in the healthy versus unhealthy microbes in our gut may play a role in neuropsychiatric conditions such as alcohol-use disorder (AUD) and other addictive behaviors.

We've all had that gut feeling, a prescient awareness telling us that something is amiss—or conversely that something is perfectly right indeed. But could our gut also influence us in other ways, such as how we engage in addictive behaviors? The concept of this bidirectional communication system, called the gut-brain axis, has been well established. Hardwiring our brainstem to our intestines is the vagus nerve. Hormones and other molecules produced in the gastrointestinal tract broker communication between the brain and gut via neuroendocrine pathways.

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Alignment of Methods with Hoped-for Outcomes

BY NINA F. SCHOR, M.D., PH.D., DDIR

Hard as it is to believe, the new year has arrived! True, the scientific community has long been comfortable with nuance and asymptotic approaches to "Truth" with a capital "T." How one interprets results of an experiment depends on how the experiment was done. Whether or not the experimental condition is different from the control condition depends on what controls were used and whether the controls fit the question being asked. It is no surprise, then, that as a biomedical scientist, I see many of the issues with which we are faced in the NIH Intramural Research Program (IRP) as nuanced as well. But with 2023 upon us and so many extraordinary human and philosophical resources around us, we must seize the opportunity to bring these "shining stars" into alignment to make our world brighter and clearer for all people.

For example, our IRP is a home for dozens of mentors and trainees. But we have not yet given full and consistent recognition to the wonderful process of teaching and learning from one another. What can we do to shine light on the full circle that has trainees maturing into mentors and mentors learning from their trainees?

The late Dr. Robert Joynt, a neurologist and once the Dean of the University of Rochester School of Medicine and Dentistry, is famous for having said, "You can't always be right; but you can always be kind." This aphorism is not bad guidance for us as laboratory and clinic mentors. There is a difference between being demanding or tough and being condescending or discouraging. We must constantly work to make it clear that the logic, the science, the experimental approach may be in question; but the value of the human being who is being mentored is not. This is not being "soft"; this is being an educator, a mentor.

We must also work to make it clear to our trainees, our faculty, and our staff that rudeness, hateful commentary, and embarrassing remarks made within earshot of others are never tolerable, whatever the impact factors of the speaker's latest publications. We have enormous intellectual freedom at the NIH. But this does not give us license to intimidate people who come here to work with us. Our objective is to train and nurture the next generation of biomedical scientists. We must demand excellence and rigor, but we must not alienate those we hope to recruit to our ranks and enchant with the wonders of science.

Another example is the richness of choice and scientific options right on our campuses. One of my passions, when I am not doing science or building biomedical programs, is making music. Among the instruments with which I do this is an electric keyboard that has many settings that allow me to make the keyboard sound like a trumpet or a violin or a steel drum or even a woodwind quintet. I have often said that there is a setting for every song and a song for every setting. For "Cabaret," the jazz trumpet works best; for "Sunrise, Sunset," it's the string orchestra. But play a song with a mismatched setting and it's either a joke or a disaster. Choosing experimental subjects for a study is a little bit like that, too, but the stakes are much higher.

For any study, we first need to ask whether the question is worth asking and answering. What will we do or do differently when we know the answer? Then we need to ask what the best subjects or systems are with which to answer the question. Animals should not be used for a study best done with induced-pluripotent stem cells or organoids. Mice should not be used for a study best done with Drosophila or people. Then, critically, we must determine the minimum number of subjects needed to arrive expediently and efficiently at a rigorous answer.

All NIH-funded studies that involve animal or human subjects must provide these calculations and justifications to the appropriate regulatory committees. Animal and human subjects must be housed and treated in a way that best ensures their health and comfort; this is important not only for the subjects but also for the integrity and rigor of the science and the believability of the results.

This approach represents an alignment of compassion, science, and cost effectiveness. Our ongoing taskforce efforts to identify and validate alternatives to the use of animals must also define the circumstances under which each kind of experimental system is the best for rigorously and expediently answering the question at hand. And our annual ceremonies of gratitude and tribute to those human families and animal subjects who do participate in our studies underscore the light they shine on the darkest of basic and clinical challenges we face.

Finally, in many institutions around the country, faculty on the tenure track have a very specifically codified set of benchmarks they must achieve and

document to be ready to be proposed for tenure. This usually happens at the associate or full professor level. By contrast, for those in the research track (the rough equivalent of NIH's staff scientists and clinicians) or on the administrative staff, there are often no specific benchmarks of advancement or success. Many remain at the same level with the same skill set, responsibilities, and accountabilities throughout their careers.

It makes me very proud, indeed, to realize that NIH has already taken steps to ensure that everyone—not only tenure-track investigators, but staff scientists, clinicians, and administrative staff, too—has the opportunity to advance, grow, learn, and bring their skills to bear on a new and higher level. For the vitality, diversity, creativity, and retention of our workforce, we must continue to make strides in this area. Not for one group or the other, but for everyone whose mission-critical work and passion make the NIH IRP everything it is and can be in the future.

In this new year of challenges and triumphs, moments of despair and many months of hope, may we all enable the alignment and appreciation of all our shining stars, each with their unique contributions to continuing to illuminate our world and its people. ●

Nina F. Schor began her official tenure as DDIR on November 6, 2022, after having served in an acting capacity since August. She was previously the Deputy Director of the National Institute of Neurological Disorders and Stroke.

Workshops and Trainings for NIH PIs, Staff Scientists, and Staff Clinicians

Once upon a time, the Office of Intramural Research (OIR) offered a two-day "New PI" course for new tenure-track investigators. The course taught them how to lead and manage a research group and how to work with and mentor trainees. With the help of OIR's Office of Intramural Training and Education (OITE), that two-day course evolved into a yearlong series of workshops and seminars for the new PIs. Eventually the courses were open to senior PIs, too. And soon after, a similar curriculum was offered to Staff Scientists and Staff Clinicians. This year, OIR is offering one curriculum that's open to all NIH faculty—all PIs, Staff Scientists, and Staff Clinicians.

Highlights of the trainings offered

Introduction to Mentoring Trainees: For all supervisors in the Intramural Research Program; covers general information on mentoring trainees (postbacs, graduate students, and postdocs). The course will provide an overview of resources available for supervisors and discuss best practices for dealing with issues in your research group.

Raising a Resilient Scientist Series: Five units, covering communication, resilience, inclusivity, conflict, feedback, and trainee wellbeing, will help you to support your biomedical trainees. Each unit will explore ways to manage common challenges in research groups by means of a webinar and facilitated small groups designed to build a community improving training at the NIH. You are encouraged to attend the entire series, but each unit may be attended as a stand-alone.

Tools for Managing Trainees Series: This series' six webinars will help you increase your skills in interviewing; setting expectations; understanding the needs of postbacs, graduate students, and postdocs; writing letters of recommendation; and preparing your trainees to leave.

Research Career Management for Faculty: These sessions will help you navigate your career at NIH.

Coaching and Case-Study Drop-in Groups:

OITE Wellness Advisors will facilitate stand-alone drop-in groups as part of the "Raising a Resilient Scientist" series. It's recommended that you attend the workshops first, but even if you can't, you are invited to come to a drop-in group. Additionally, executive coaches are available for PIs, Staff Scientists, and Staff Clinicians. Contact **Sharon Milgram** to discuss personal coaching.

- **NIH PIs:** Discuss the stresses and challenges of being a PI, mentoring trainees, and running a research group. Participants will have an opportunity to focus on their own wellness and resilience needs, discuss their experiences and concerns, hear from other PIs, and share strategies for addressing stress.
- **NIH Staff Scientists and Clinicians:** Discuss the stresses of being a Staff Scientist or Staff Clinician, including having to juggle such diverse responsibilities as doing one's own work, mentoring trainees, supporting the work of the research group, and meeting the expectations of the PI. Participants will have an opportunity to focus on their own wellness and resilience needs, discuss their experiences and concerns, hear from other Staff Scientists/Clinicians, and share strategies for addressing stress. ●

For more information, a list of sessions, and to register visit https://www.training.nih.gov/for_staff/trainingsupport/workshops_trainings.

From the Fellows Committee

A Culture of Integrity: Ethical Expectations for NIH Trainees

BY LARISA GEARHART-SERNA, NCI

"A CULTURE OF POSITIVE ETHICAL behavior helps build public trust," said Deputy Ethics Counselor **Eric Hale** in the National Cancer Institute's Ethics Office. "Maintaining public trust is critical to the mission of the NIH."

Positive ethical behavior means conducting research responsibly and ethically (with honesty, objectivity, and integrity) as well as complying with other government ethics policies that have to do with outside activities and accepting awards. So, let's take a moment to review what you as a trainee need to know. (Read the online version of this article for links to the *Sourcebook* and other resources mentioned in this article.)

Ethical conduct policies

NIH's research ethics policies and guidelines set standards for how research should be conducted including the sharing of genomic and human data, collaborations between extramural and intramural scientists, sharing resources, storing and tracking human biospecimens, reporting of clinical research results, mentoring and training, and investigating allegations of research misconduct. There are even policies addressing controversial topics such as dual-use research (work that is intended to be beneficial, but if misapplied, could cause harm) and the use of human fetal tissue and human stem cells.

One component of conducting research responsibly is to report to the appropriate channels if you see something that may be problematic in the intramural program. If you witness or suspect research misconduct (fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results), you can contact the Agency Intramural Research Integrity Officer (AIRIO) in the Office of the Director, or you can choose to report anonymously. If you are uncertain whether research misconduct has occurred, you can contact **Lori Conlan** in the Office of Intramural Training and Education (OITE) for advice, or the NIH Office of the Ombudsman for a confidential conversation. Importantly, "trainees remain in full control of whether, when, or how they will proceed, if at all," said NIH Ombudsman **Victor Voloshin**, Director of the Center for Cooperative Resolution.

Outside activities and awards

In addition to being expected to conduct research ethically, you need to be aware of other government ethics policies that regulate what outside activities you can participate in and what awards you are allowed to accept. The guidelines differ depending on whether you are a non-full-time-equivalent (non-FTE) trainee or an FTE trainee. Non-FTE trainees include summer interns, graduate students, postbacs, postdocs, and visiting fellows (foreign nationals). FTE trainees include research fellows and clinical fellows.

Although some guidelines differ depending on the type of trainee you are, everyone is are expected to abide by the HHS Standards of Conduct and all applicable federal policies, confirmed **Nancy O'Hanlon**, Supervisory Ethics Specialist at the NCI Ethics Office.

Bioethics

To learn more about bioethics in general, check the "Bioethics" section in the *Sourcebook* and with the NIH Department of Bioethics, which provides research, training, and a Bioethics Consult Service, and offers courses, ethics grand rounds, and colloquia. Bioethics "is a field that examines the often-vexing questions about right and wrong that inevitably arise in the conduct of medical research and clinical care," said **Christine Grady**, Chief of the NIH Department of Bioethics.

Training in ethics

Worried that you might not be able to keep track of everything you need to know? Never fear, NIH provides virtual training courses and offers annual refreshers, too. Check the *Sourcebook's* "Ethical Conduct" section for "Responsible Conduct of Research Training" (RCR), which covers how to avoid research misconduct and questionable research practices as well as how to foster an ethical scientific environment. NIH intramural trainees are required to take at least eight hours of RCR instruction—some within three weeks of arrival at NIH—and programs are tailored according to the type of trainee you are.

In addition, OITE provides a virtual mandatory training to help you understand the more general type of government ethics policies and your responsibilities as a trainee.

Final thoughts

Use this article's resources to guide your great work here at the NIH, adherent to all applicable research, government employment, and bioethics policies. ●

Larisa Gearhart-Serna, a Postdoctoral Fellow in the National Cancer Institute's Technology Transfer Center, is a member of The NIH Catalyst *Editorial Board.*

To get a complete list of resources and links, read the online version of this article at https://irp.nih.gov/catalyst/31/1/the-training-page.

New Director of NCATS: Joni L. Rutter, Ph.D

ADAPTED FROM NIH NEWS RELEASE AND NCATS DIRECTOR'S CORNER

Joni L. Rutter—who went from being Deputy Director of NIH's National Center for Advancing Translational Sciences (NCATS) in 2019, to Acting NCATS Director in 2021, to being named the official Director in November 2022—is excited to be leading NCATS into a future where more treatments will be delivered to all people more quickly.

"Our programs are nimble and can pivot quickly to address public health emergencies," she wrote in the online NCATS Director's Corner on November 8, two days after she began her new role. "We are creative in how we leverage our resources to address high-level needs across all diseases. And because the needs far exceed the scope of any one organization, we employ team science to share ideas, knowledge, and expertise."

Rutter is overseeing a diverse portfolio of research activities focused on improving the translational process of turning scientific discoveries into health interventions. The portfolio includes the Clinical and Translational Science Awards (CTSA) Program, which is one of NIH's largest supported programs and has played an important role in the agency's COVID-19 response. In addition, she is directing innovative research programs to advance diagnoses and treatments, including gene therapies, for some of the more than 10,000 known rare diseases. She will also lead labs at NIH that drive team science with both private and public partners to create and test innovative methods for improving, and speeding up, the drug-development process.

As the NCATS Acting Director, Rutter created and expanded strong networks across public and private sectors and has championed approaches for leveraging real-world data and artificial intelligence and machine learning to rapidly address public health questions. In the area of rare-disease research, she led an initiative that used data from health care systems to calculate approximate costs for the millions of people with rare diseases. This and related initiatives prompted recommendations, such as enhancing the collection of rare-disease patient data, to reduce the economic and medical burdens facing this community. She also created a multidisciplinary team that developed the National COVID Cohort Collaborative, a partnership among organizations to provide a national database of electronic health records. It is now one of the largest collections of secure and deidentified clinical data in the United States for COVID-19 research.

Rutter's career at NIH began more than 20 years ago. After earning a Ph.D. in pharmacology and toxicology from Dartmouth Medical School (Hanover, New Hampshire) in 1999, she joined the National Cancer Institute as a postdoctoral fellow and studied gene-environment interactions in breast, ovarian, and melanoma cancers. From 2003 through 2016, she held various positions in the National Institute on Drug Abuse (NIDA) including as Director of the Division of Neuroscience and Behavior, where she oversaw and developed research portfolios in basic and clinical neuroscience. She also coordinated the NIDA Genetics Consortium and biospecimen repository.

In 2016, she established and became the Director of Scientific Programs for NIH's *All of Us* Research Program, which aims to advance precision medicine by building a diverse database that can inform thousands of studies on a variety of health conditions. The program is focused on ensuring that the one million United States participants who enroll represent all communities and backgrounds. She spearheaded efforts to ensure that the program focused on diversity and inclusion from the outset so that the participant cohort places emphasis on groups that are underrepresented in biomedical research (*PLos One* **15:**e0234962, 2020).

CREDIT: NCATS

Joni L. Rutter was named NCATS Director in November 2022.

Rutter has continued efforts to reduce health disparities through translational science approaches and to enhance diversity, equity, inclusion, and accessibility among NCATS staff and the broader translational science workforce.

Rutter sees the NCATS community as strong and resilient. "That's important because we face incredible health challenges," she said. "We need team science and innovative approaches that can bring more treatments to people. Working across our collective biomedical ecosystem is critical for doing just that." ●

Portraits

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CREDIT: JEFFREY EVERETT, MEDICAL ARTS

CREDIT: JEFFREY EVERETT, MEDICAL ARTS

Two of the portraits on display at the NIH Clinical Center: (Top) **Sadhana Jackson**, M.D., Distinguished Scholar Tenure-Track Investigator, NIAID and NCI; (Bottom) **Joel Vega-Rodrigues**, Ph.D., Stadtman Tenure-Track Investigator, NIAID.

inclusion in the workplace. Rising out of these conversations was what eventually became the Recognition Project, spearheaded by tenure-track investigator **Sadhana Jackson**. Jackson is a pediatric neuro-oncologist at the National Institute of Neurological Disorders and Stroke and the National Cancer Institute. As an African American pediatric neuro-oncologist, Jackson works in a highly specialized field comprising few experts and even fewer people of color.

"The lack of representation on the walls and on the sculptures and busts throughout [the medical field] in essence motivates me to enhance inclusion and diversity at the NIH and in my medical field," said Jackson.

Driven by her own academic experiences, as well as hearing those of her NIH colleagues from underrepresented groups who did not feel a sense of belonging or inclusion, Jackson spoke up about diversifying the portraits displayed around campus in an effort to better reflect NIH's current workforce. NIH leadership, including former Director **Francis Collins** and then-Deputy-Director **Lawrence Tabak**, agreed and the Recognition Project was on its way to becoming a reality.

UNITE comprises five committees, and Jackson co-chairs the T committee, which focuses on transparency and communicating the findings of the other four committees. Once the Recognition Project was approved, the T committee began brainstorming a list of NIHers to feature in the portraits and reviewed notable quotes to be included alongside the displays.

After choosing which staff members and quotes to highlight, the T committee began collaborating with NIH's Medical Arts Branch to design the artwork. Staff initially submitted their photos to be used in the visuals. But the artistic team proposed that creating illustrated representations of each individual would act as a unifying factor, allowing everyone to be seen as an equal part of the NIH community. **Jeffrey Everett**, senior designer at the Medical Arts Branch, hand-drew each portrait and crafted the color schemes and dynamic patterns, which were inspired by a variety of cultural influences. During the UNITE committee meetings, Jackson shared progress of the portraits that Everett had created.

"Because his artwork was so beautiful, and because our NIH staff were so beautiful, everybody got jazzed up about it," Jackson said.

From the creation of the first portrait to the official unveiling of the complete art installation in April 2022, the process took a little less than a year. Currently, the portraits are located in the Clinical Center (Building 10, along the hallway outside the NIH Library and in the B1 Cafeteria), Building 31, and Building 1.

The "Power of an Inclusive Workplace Recognition Project" has received an outpouring of support. Jackson has received direct emails thanking her for leading the project as well as messages from the people in the portraits who wanted to share that their boss or co-worker was grateful and honored for being featured.

The existing portrait installations are just the beginning for the Recognition Project. Jackson and the T committee have discussed expanding the project to include outdoor artwork, such as banners and murals, throughout campus, as well as include contributors to the NIH. These future installations would highlight NIH staff involved with varied on-campus occupations, including deliveries, security, ground maintenance, food preparation and management, fire fighters, and police officers; essentially front-line staff who wouldn't necessarily see the current new portraiture inside the buildings. Medical Arts has already come up with designs that could be displayed on loading docks, the Gateway Center, and light-pole banners, and there are still plenty of other available spaces around the main campus and other NIH campuses that will become home to future installations. ●

Victoria Tong was a Pathways Editorial Intern in summer 2022 at The NIH Catalyst. *She is a freshman at the University of California at Los Angeles and expects to major in chemistry.*

Read more at https://irp.nih.gov/catalyst/31/1/portraits-reflect-the-rich-diversity-of-nihs-workforce.

Toxic Protein and Aging Combine Forces to Drive Brain Disease

NIA Study Suggests New Therapeutic Targets for Pair of Age-Related Illnesses

BY BRANDON LEVY, OD

Aging wears down all parts of our bodies, from our bones to our brains. It's no surprise, then, that it's the main risk factor for neurological illnesses like Parkinson's disease and dementia. However, the precise reason why has long remained a mystery. New research from the National Institute on Aging (NIA) suggests that the aged brain is a fertile ground for the spread of a harmful protein associated with several neurological diseases, and that the toxic protein itself ages immune cells in the brain (*Mol Neurodegener* **17:**60, 2022).

Just as research on Alzheimer's disease has focused primarily on two proteins called amyloid-beta and tau, scientists have honed in on a protein called alpha-synuclein as the probable main villain responsible for Parkinson's disease, in which the death of certain neurons in the brain causes cognitive and movement problems. Like amyloid-beta and tau in Alzheimer's disease, alpha-synuclein builds up in the brains of patients with Parkinson's disease and a form of dementia called Lewy body dementia (LBD).

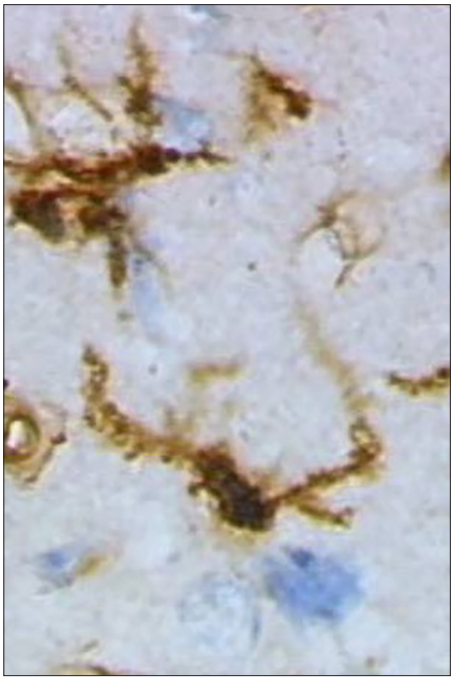
NIA Senior Investigator **Eliezer Masliah** has spent his career studying alpha-synuclein and its role in neurological illnesses. However, until he came to NIA, his experiments tended not to take into account the influence of aging on those diseases.

"I spent 30 years in academia doing this work and only occasionally thought about aging," said Masliah, the new study's co-senior author along with NIA Senior Investigator **Ranjan Sen**. "We were studying all these models of these diseases and testing all these drugs and we were using mostly middle-aged animals. Really, it wasn't until I came to NIA and started to hear so much about aging from my colleagues and heard about all the new mechanisms people were discovering behind aging that I became more interested in it."

With this new perspective in mind, Masliah's lab teamed up with Sen's group in order to determine how aging interacts with alpha-synuclein in the brains of mice. To do so, the researchers injected alpha-synuclein protofibrils into the brains of two sets of mice: one group that was only three to four months old and another that was 18 to 19 months old. These protofibrils can induce similar consequences in mice to those seen in humans with Parkinson's or LBD because they cause alpha-synuclein to build up in, and spread through, the animals' brains.

In fact, the study found, the alpha-synuclein spread much more in the brains of the older mice than in those of the younger animals. What's more, the older mice that received alpha-synuclein injections showed less of a fear response to a sound that they had previously been taught to associate with a mild foot shock, suggesting their memories were impaired. In the younger mice, on the other hand, the alpha-synuclein injections had much less of an effect on their response to the fear-inducing sound. Interestingly, while the NIA scientists observed alpha-synuclein's effects on cognition in both male and female mice, the protein only appeared to decrease motor coordination in male mice.

"There has been a lot of interest at NIA about understanding sex differences in neurodegenerative disorders," Masliah said. "We know in Lewy body dementia that women are affected differently than men, and also Alzheimer's disease tends to be more common in women than in men. There may be a difference in how sex hormones affect the disease or some other factor that we don't understand, but that's why it's important when designing these sorts of experiments to include both sexes."



An NIA study suggested that a protein called alpha-synuclein drives aging and makes microglia in younger mice act more like those in older ones. Shown: Microglia stained with a brown chemical and viewed under a microscope.

The alpha-synuclein injections also appeared to influence the number and behavior of immune cells in the animals' brains. Mice that received them had more immune cells called T cells and microglia in their brains one month later compared to untreated mice, and these cells were more active as well. Furthermore, these effects were amplified in the older mice compared to the younger mice.

When the researchers examined the activity of genes in those microglia, they found that the alpha-synuclein injections altered the activity of numerous genes related to inflammation. Many of those

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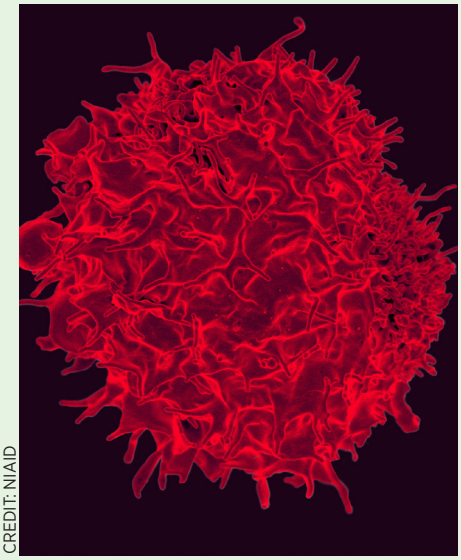
Intramural Research Briefs



CREDIT: NIAID

NIAID: A recent study by NIAID scientists and their collaborators has yielded a promising cancer vaccine that reduced colorectal tumor growth in mice. Shown: colorized scanning electron micrograph of a T lymphocyte.

NIAID: EXPERIMENTAL CANCER VACCINE SLOWS TUMOR GROWTH IN MICE

A recent study by NIAID scientists at the Vaccine Research Center and their collaborators at Vaccitech North America (Baltimore) has yielded a promising cancer vaccine that reduced colorectal tumor growth in mice. The treatment works much like a normal vaccine by priming the immune system to target an antigen—in this case a tumor-derived protein. While most vaccines promote antibody production, this vaccine, named SNAPvax, instead prepares cytotoxic killer T cells to recognize and attack tumors. The vaccine was administered intravenously.

The investigators also discovered that the intravenous delivery of the vaccine circumvents the tumor immunosuppression common in local tumor environments. This was due to the vaccine's adjuvant (an additive used to stimulate the immune system to react to the antigen) by increasing the production of type I interferons (IFN-I) in the blood and tumor, which are important immune-system-signaling molecules. The production of IFN-I reversed tumor-induced immunosuppression. By effectively removing the brakes induced by the body's immune response to the tumor, the killer T cells faced fewer obstacles to mounting their attack. Vaccitech North America plans to develop the platform as a treatment for human papillomavirus cancers in 2023. (NIH authors: F. Baharom, R.A. Ramirez-Valdez, M. Dillon, D. Hermans, S. Fussell, K.K.S. Tobin, A.S. Ishizuka, and R.A. Seder, *Cell* **185:**4317-4332.e15, 2022)

[BY JONATHAN CHU, NIAID]

NIA, NIAID, NCI: LIVE TRACKING OF IMMUNE CELL SIGNALING

For the first time, scientists were able to study real-time behaviors of nuclear factor-kappa B (NF-kappa-B), a protein involved in regulating immune and inflammatory responses in inflammatory cells. An NIA-led team of researchers developed mouse strains that allow the monitoring of this important protein's activity.

This study examined RelA and c-Rel, two of the five NF-kappa-B family proteins. The team found differences in how cells communicated with each other depending on whether the cells were primary cells, taken directly from tissue, or immortalized cells, grown in a lab. The data also showed as the mice aged, c-Rel had a more prominent role for inflammatory responses in microglia, which are brain immune cells implicated in neuroinflammatory diseases, such as Alzheimer's. In addition, isolates of various tissues established that RelA and c-Rel amounts decrease at certain stages of maturity for immune cells, such as T lymphocytes and myeloid cells. The authors hope using these mice will advance research in aging, inflammatory diseases, and immunity. (NIH authors: S.M.T. Rahman, M. Aqdas, E.W. Martin, F. Tomassoni-Ardori, P. Songkiatisak, K.-S. Oh, S. Uderhardt, Q.C. Claybourne, R.A. McDevitt, R.N. Germain, L. Tessarollo, and M.H. Sung, *Cell Rep* **41:**111682, 2022)

[BY ROBIN ARNETTE, NIA]

NIEHS: NEW TOOLS REVEAL HOW CADMIUM EXPOSURE AFFECTS HEART DEVELOPMENT

NIEHS researchers developed three cell models to better understand the link between low doses of the metal cadmium (Cd) and cardiovascular disease. Cd, which is derived from refining and manufacturing sources, has been associated with congenital heart defects.

The investigators first studied how Cd exposure can affect formation of the mesoderm—one of the three germ layers in animal embryos—by using a three-dimensional model made of embryonic stem cells (ESCs). A two-dimensional cell model was then used to determine how Cd affects cardiac differentiation: Levels of NKX2, a protein involved in heart development, were measured. The scientists used an ESC line containing a green fluorescent protein attached to the *NKX2* gene to measure differentiation to cardiomyocytes. Finally, they used another 3D model to simulate the beating heart and investigate how Cd affects normal heart movement and function.

The team found that exposure to low doses of Cd can reduce cardiomyocyte differentiation by suppressing a critical pathway in cell-fate determination, reduce amounts of *NKX2* and other cardiac-specific genes, and inhibit proper heart function. This study gives insight into the mechanisms of Cd-induced heart abnormalities and provides a new tool for studying other environmental exposures and their disease associations. (NIH authors: X. Wu, Y. Chen, A. Luz, G. Hu, and E.J. Tokar, *Environ Health Perspect* **130:**117002-1 to 117002-11, 2022)

[BY LARISA GEARHART-SERNA, NCI]

NHGRI, NIMH: BRIDGING THE GAP BETWEEN GENETICS AND ADHD

By demonstrating differential gene expression in regions of the brain associated with attention-deficit hyperactivity disorder (ADHD), scientists at NHGRI and NIMH have made a significant step toward connecting the

dots between the disorder's symptoms and genetics.

While there are known genetic risk factors as well as brain regions and activity that are associated with ADHD, a direct connection between them has been lacking.

Researchers compared RNA-sequencing data from the postmortem brain tissue of individuals with or without ADHD and examined gene expression in two brain regions implicated in ADHD: the caudate and the anterior cingulate cortex (ACC). In the ACC, the team identified significant upregulation in the expression of 14 genes in brain tissue with ADHD compared with control brain tissue. For example, they saw differences in gene expression for the neurotransmitter glutamate, which signals between brain cells and is important for attention and learning.

The authors note that the findings show ADHD shares similarities with other conditions, such as autism, and may reflect differences in how the brain functions. (NIH authors: G. Sudre, D.E. Gildea, G.G. Shastri, W. Sharp, B. Jung, Q. Xu, P.K. Auluck, L. Elnitski, A.D. Baxevanis, S. Marenco and P. Shaw, *Mol Psychiatry* 2022; DOI:10.1038/s41380-022-01844-9)

[BY CHARLESICE GRABLE-HAWKINS, OD]

NINDS: MOUSE STUDY EXPLORES HOW BRAIN ACTIVITY IS FINE-TUNED

When our brains aren't being flooded with new information, inhibitory synapses dampen neural activity—an essential step in consolidating information and forming memories during sleep. NINDS scientists revealed a new daily pattern in inhibitory synapses related to the sleep-wake cycle.

The researchers recorded electrical signals in the mouse hippocampus, a part of the brain that supports memory formation, to examine inhibitory synapse activity during sleep and wakefulness. During wakefulness, steady inhibitory activity increased, while fast inhibitory activity decreased. In addition, awake mice also showed a higher enhancement of the activity-dependent inhibitory response, hinting that inhibitory synapses might be strengthened more by wakefulness than sleep.

Further experiments showed that synaptic changes in awake mice resulted from an increased number of gamma-aminobutyric acid type A (GABAA) receptors. GABA is an inhibitory neurotransmitter that suppresses neural activity. Blocking GABAA receptors reduced synaptic changes, suggesting that the accumulation of these receptors during wakefulness may contribute to greater inhibitory synaptic plasticity, a critical factor in learning and memory.

The investigators examined two inhibitory interneurons, parvalbumin or somatostatin, and found that parvalbumin, but not somatostatin, contributed to more GABAA receptors and stronger connections in awake mice.

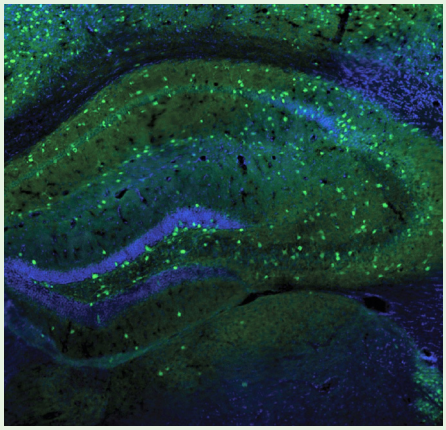
The new findings could help researchers understand the human sleep-wake cycle and memory, as well as abnormal brain rhythms in neurological disorders, such as epilepsy. (NIH authors: K. Wu, W. Han, and W. Lu, *PLoS Biol* **20**:e3001812, 2022)

[BY KIMBERLY MORGAN]

NCI, NIAID: SOME DRUGS MAY INCREASE SUSCEPTIBILITY TO SARS-COV-2 INFECTION

A research team led by NCI scientists **Guoli (Scarlett) Shi** and **Alex Compton** has defined a new mechanism by which a class of FDA-approved drugs known as mTOR inhibitors causes immunosuppression and could make people more susceptible to infection by respiratory viruses such as SARS-CoV-2 and influenza A. Those drugs include rapamycin and its derivatives (rapalogs) and are used to treat people with cancer and autoimmune conditions.

Traditionally, mTOR inhibitors are thought to cause immunosuppression by inhibiting the body's infection-fighting T cells. But the scientists discovered that rapamycin also degrades antiviral membrane proteins inside of a cell, disarming the cell's intrinsic defenses against pathogen invasion.



CREDIT: W. LU LAB, NINDS

NINDS: NINDS scientists revealed a new daily pattern in inhibitory synapses related to the sleep-wake cycle. Shown: Interneurons (green) in a mouse hippocampus, which play a subtle but powerful role in balancing neural activity during the sleep-wake cycle.

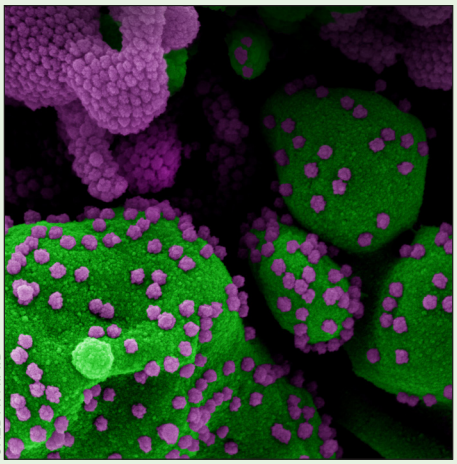
Using mouse and hamster models of infection, the investigators found that exposure to rapalogs enhanced SARS-CoV-2 titers in lungs and exacerbated COVID-19 severity compared with control animals. Further experiments on primary human respiratory cells showed that rapalogs made those cells more susceptible to SARS-CoV-2 infection, at least in part by disabling intrinsic immunity and facilitating virus entry.

The team also identified a less potent rapalog—ridaforolimus—that had no significant effect on susceptibility to viral infection or disease severity. "We can use this variant of rapamycin as a template for the development of next-generation mTOR inhibitors that inhibit cancer cell proliferation without limiting a person's defenses against virus infection," Compton said. (NIH authors: G. Shi, A.I. Chiramel, T. Li, K.K. Lai, S. Majdoul, T. Dempsey, P.A. Beare, J.W. Yewdell, S.M. Best, and A.A. Compton, *J Clin Invest* **132**:e160766, 2022; DOI:10.1172/JCI160766)

[BY SHIVALEE DUDUSKAR, NCI]

Read longer versions of these briefs, including photos, at https://irp.nih.gov/catalyst/31/1/research-briefs.

COVID-19 Timeline at NIH (November–December 2022)



CREDIT: NIAID

Colorized scanning electron micrograph of an apoptotic cell (green) heavily infected with SARS-COV-2 virus particles (purple), isolated from a patient sample. Image from NIAID Integrated Research Facility in Fort Detrick, Maryland.

November 1: An NIH-funded study finds that blood pressures rose during the pandemic (*Hypertension* **79:**2733–2742, 2022).

November 10: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update and warns of a triple threat to public health with influenza, respiratory syncytial virus, and COVID-19 circulating this winter. He reports that NIH will not be pursuing the COVID-19 vaccination requirement for health care workers but urges staff to remain up to date with vaccinations. Tabak reminds staff of NIH guidance on dependent care during duty hours and bringing children onto NIH locations and encourages employees to talk to their supervisors about workplace flexibilities to balance work and family responsibilities.

November 18: The CDC updates its COVID-19 community levels, moving Phoenix, Arizona, from low to medium. All other NIH locations remain at their current levels.

November 20: NIH scientists speak to National Public Radio about the declining efficacy of monoclonal antibodies against new SARS CoV-2 variants. "Monoclonals had their day, like the Model T or the biplane," said NIAID's **Carl Dieffenbach**, Director of the Division of AIDS and lead of NIH's Antiviral Program for Pandemics. "Now it's time to move on."

November 21: NIAID awards more than $12 million to three institutions for the development of antiviral therapies to treat diseases caused by viruses with pandemic potential.

November 22: NIH launches the MakeMyTestCount.org website, developed through NIH's Rapid Acceleration of Diagnostics Tech program, which allows users to anonymously report the results of any brand of at-home COVID-19 test.

December 1: The *New England Journal of Medicine* publishes a perspective by NIAID Director **Anthony Fauci** reflecting on the perpetual challenge of infectious diseases. (*N Engl J Med* **387:**2009-2011, 2022).

December 2: The CDC updates its COVID-19 community levels. Framingham, Massachusetts, moves from low to medium and Detroit, Michigan, moves from medium to low. All other NIH locations remain at their current levels.

December 2: The CDC releases a report that associates the drug Paxlovid (nirmatrelvir plus ritonavir) with decreased hospitalization rates among adults with COVID-19. A second report releases data showing that the bivalent mRNA vaccines provided additional protection against symptomatic SARS-CoV-2 infection.

December 8: The FDA amends the emergency use authorizations of the bivalent Moderna and Pfizer-BioNTech COVID-19 vaccines to include children down to 6 months of age.

December 9: The CDC updates its COVID-19 community levels. Phoenix, Arizona, moves from medium to high. Detroit, Michigan, and Rocky Mountain Laboratories in Hamilton, Montana, move from low to medium.

December 9: **Lawrence Tabak** (Performing the Duties of the NIH Director) emails staff with a coronavirus update, noting that new COVID-19 cases and hospitalizations are increasing nationally. He brings attention to the FDA's announcement this week authorizing vaccines for children as young as 6 months, as well as CDC data released on December 2 showing the effectiveness of the antiviral Paxlovid and mRNA bivalent boosters.

December 15: The *Journal of Clinical Investigation* publishes a paper reporting that NIH scientists found that some cancer and autoimmunity drugs may increase susceptibility to infection by respiratory viruses such as SARS-CoV-2 and influenza A (*J Clin Invest* **132:**e160766, 2022).

December 15-16: The FDA and NIH COVID-19 Scientific Interest Group host a virtual COVID-19 research workshop. Scientists from both agencies deliver talks covering recent findings in COVID-19 virology, immunology, therapeutics, and more.

December 16: In an NIH videocast, NIAID Director **Anthony Fauci** reflects on his 54-year career at NIH, including having advised seven United States presidents, and his commitment to following the science through outbreaks of infectious diseases, from HIV to Ebola to COVID-19. Videocast (NIH only) at: https://videocast.nih.gov/watch=48728.

December 16: The CDC updates its COVID-19 community levels. Baltimore, Maryland (Bayview Research Center), moves from low to medium community level and Phoenix, Arizona, moves from high to medium. All other NIH locations remain at their current levels.

December 19: NIBIB's RADx Tech program makes available an early version of a best-practices document that provides recommendations for making at-home COVID-19 diagnostic kits accessible to all users.

December 23: The CDC updates its COVID-19 community levels. Montgomery County, Maryland, moves from low to medium and Rocky Mountain Laboratories in Hamilton, Montana, moves from medium to low.

December 30: All NIH locations are at medium in CDC's COVID-19 community level classification. ●

Read a more detailed version of this timeline, complete with links, at https://irp.nih.gov/catalyst/31/1/covid-19-timeline-at-nih-november-december-2022.

Harnessing Exposome Data to Predict Disease

NIEHS Identifies Environmental Exposures Associated with Diabetes

BY MARLA BROADFOOT, NIEHS

Efforts led by researchers at the National Institute of Environmental Health Sciences (NIEHS) have shown how knowledge of the exposome, or the totality of our environmental exposures, can be harnessed to transform research on human health and disease. Now, the publication of a high-impact, clinically relevant paper from a decades-long study of environmental exposures demonstrates that a framework known as precision environmental health is coming of age.

Creating the evidence base

The Personalized Environment and Genes Study (PEGS) has collected health, family history, environmental exposures, and lifestyle data on more than 20,000 North Carolinians since its inception 20 years ago. The PEGS team has compiled genetics data on a subset of that cohort by sequencing the whole genomes of 4,700 participants.

In a study published in November in the journal *Diabetes Care*, NIEHS researchers examined how this data can be tapped to predict a person's risk of developing type 2 diabetes (T2D). Using statistical methods and machine learning, they identified 76 environmental exposures associated with the disease (*Diabetes Care* DOI:10.2337/dc22-0295, 2022).

"We were able to recapitulate known risk factors, as well as identify previously unknown associations with asbestos and coal dust exposure," said lead author **Alison Motsinger-Reif**, Chief of the NIEHS Biostatistics and Computational Biology Branch.

The team combined 13 of these environmental exposures to create a predictive value known as a polyexposure score. They compared the predictive performance of this score with a polygenic risk score based on genomic variants associated with diabetes and an overall clinical score built using established risk factors such as body mass index and prediabetes.

To their surprise, the researchers found that the scores based on environmental exposures provided a much stronger indicator of T2D odds than those based on genetics.

"Our findings provide a good demonstration of precision environmental health in one disease," said Motsinger-Reif. Her team can expand this appoach to other diseases such as hypertension, stroke, and other cardiovascular diseases.

The study is expanding in other ways. It is moving beyond self-reported environmental exposures to more granular and reliable measures such as incorporating geospatial data, epigenetic data, and health records data from partner institutions — the University of North Carolina and Duke University.

"We are now better positioned to advance the scientific framework we call precision environmental health," said **Rick Woychik**, Director of NIEHS and of the National Toxicology Program.

Precision environmental health combines environmental exposure research with genetic and epigenetic analysis to gain a more complete picture of a person's disease risk. Precision environmental health is also informed by exposomics, and both are key focus areas for NIEHS that will be featured in the institute's next strategic plan.

Catalyzing the conversation

The NIEHS efforts regarding the advancement of exposomics has included promoting the concept through meetings, workshops, and webinars, as well as supporting its implementation through technology development, infrastructure support, and funding individual studies, said **Yuxia Cui**, Health Scientist Administrator in the NIEHS Exposure, Response, and Technology Branch.

CREDIT: NIEHS

Exposomics and precision environmental health are crosscutting research areas that involve not only NIEHS but also other institutes across NIH.

She co-organized a series of virtual workshops that used innovative open-space technology, a meeting format that allowed each workshop to be open, self-directed, and completely collaborative. More than 400 individuals from around the globe participated.

Data collected from the series helped formulate an operational model for conducting experiments in exposomics. Participants agreed to establish guidelines for best practices and enable coordination among various exposome efforts. The meeting reports will help define next steps for operationalizing exposomics. A lot of work remains to be done, however.

Cui and others at NIEHS are developing an operational model that will help investigators understand how to collect exposomic data that can be shared across the biomedical research community. ●

Marla Broadfoot is a writer and editor at the NIEHS Office of Communications and Public Liaison. In a former life, she was a postdoctoral fellow in clinical molecular genetics at NHGRI.

Bugs

CONTINUED FROM PAGE 1

CREDIT: NIDA

Lorenzo Leggio's lab is studying the gut microbiome and neuroendocrine pathways to better understand mechanisms underlying addiction and to develop new treatments.

Then there's the bugs. Our microbiome—teeming communities of diverse microbes that live on and within us—plays an integral role in human physiology from the proper functioning of the immune system to the digestive system. Acting through the gut-brain axis, an imbalance in healthy versus unhealthy gut flora, a condition known as dysbiosis, has been linked to disorders such as anxiety, depression, and obesity. Now researchers are asking a different question: Could dysbiosis be a part of the puzzle in neuropsychiatric conditions such as alcohol-use disorder (AUD) and other addictive behaviors? Recent research suggests it might.

Binge drinking is one risk factor for developing AUD. For men that means consuming five or more alcoholic drinks on an occasion (in about two hours); for women, it's four or more. Binge drinking represents a massive public health problem in the United States and is associated with automobile injuries, gun violence, and domestic violence, and can lead to serious diseases. Of great concern is that the earlier an individual starts binge drinking, the higher the risk of developing AUD.

There are only three approved medications and a small number of effective behavioral interventions to treat AUD, and so it is critical to shed light on how it develops and to find new diagnostic tools and therapeutic targets.

Identifying addiction pathways

Seeking to understand mechanisms underlying addiction and to develop new treatments is physician-scientist and Senior Investigator **Lorenzo Leggio**, who heads the Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN) Section, a joint National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism (NIAAA) translational and clinical laboratory. CPN conducted pioneering work demonstrating in rat models and humans that ghrelin, commonly known as the hunger hormone, influences addictive behaviors such as alcohol craving and excessive consumption. Moreover, they found that when rats were given alcohol at a binge level for many weeks their gut microbiome tipped into the dysbiotic, leading to a decrease in microbial diversity compared with controls (*J Neuroendocrinol* DOI:10.1111/jne.12663, 2018).

Might those findings be relevant to people? Leggio's group next collaborated with Elise Weerts at Johns Hopkins Bayview Medical Center (Baltimore) and Claire Fraser at the University of Maryland Institute for Genome Sciences (Baltimore). Weerts established a baboon model of binge drinking that has been proven to be effective at screening for new medications that could potentially be used in clinical trials. Using this model, the research team studied how the baboon's microbiome and metabolome—consisting of bioproducts such as proteins and peptides generated from cells—changed in response to chronic alcohol drinking.

Three groups of male olive baboons (*Papio anubis*) were studied: The control group drank Tang to match the calories consumed by the alcohol-binge-drinking groups. A second group had been binge drinking for approximately two years and the third had been drinking heavily for about 10 years. Surprisingly, a marked difference was discovered only in the microbiome and metabolome of the 10-year drinking group. Populations of beneficial gut bacteria in the Lachnospiraceae and Prevotellaceae families declined, whereas the opportunistic pathogen in the Streptococcus genus increased. The long-term-drinking baboons also showed an increase in markers of oxidative stress and certain microbe metabolites that were not present in the control or two-year drinking groups (*Transl Psychiatry* **11:**609, 2021).

Leggio found the results intriguing. "Our findings tentatively suggest that

CREDIT: NIAAA

Lorenzo Leggio's lab is analyzing data from a completed outpatient clinical study that included a craving (cue-reactivity) procedure in a bar built in a laboratory. Laboratory-based bars have been used to study medication effects, cue reactivity, and alcohol-use expectancies in social and dependent drinkers.

alcohol doesn't just change the microbiome and metabolome in a transient way," he said. "You need chronic, prolonged, binge drinking in order to lead to a sustained change."

A causal link between the microbiome and brain has yet to been shown, but it's important to demonstrate that alcohol alters the microbiome because accurate biomarkers to make neuropsychiatric diagnoses are lacking. If microbial changes are a consequence of chronic binge drinking, then those changes could be a way to objectively identify people with unhealthy alcohol use.

Currently, the CPN lab is analyzing data from a recent NIAAA outpatient clinical trial conducted at the NIH Clinical Center (CC) that compared healthy control subjects to individuals with AUD. That study promises to test associations between alcohol use in humans and changes in the microbiome and metabolome, as well as how those factors interact to influence behavior and physiology.

Future research at CPN looks to investigate whether an unhealthy gut could precede the development of AUD or play a role in maintaining it. "If that were true," said Leggio, "then you could pharmacologically manipulate the gut microbiome as a way to treat AUD." He pointed to preliminary evidence in a human study from Belgium showing that dysbiosis in the gut correlated with increased alcohol craving (*Proc Natl Acad Sci USA* **111:**E4485-E4493, 2014). Craving is a critical predictor of recurrence in substance-use disorders.

Experimental treatments

So what might new therapeutic approaches look like for AUD? Using a procedure called fecal microbiota transplant (FMT), a small NIH-funded study at Virginia Commonwealth University (VCU) in Richmond, Virginia, transplanted stool into 20 volunteers with severe AUD and liver cirrhosis. Half of the participants received a placebo implant and the other half received bacteria from a healthy person's stool. Compared with the control group, FMT recipients showed an increase in beneficial gut bacteria and had higher concentrations of short-chain fatty acids (SCFAs)—an important microbial byproduct that helps maintain intestinal lining integrity. Excessive intestinal permeability is thought to leak toxins into the body and has been associated with several inflammatory and mental health conditions and AUD. Nine of the participants treated with FMT experienced a short-term reduction in craving and drank less, compared with only three in the placebo group (*Hepatol* DOI:10.1002/hep.31496, 2020).

CREDIT: NIH CLINICAL CENTER

Jennifer Barb (pictured) and Chief **Gwenyth Wallen** in the Clinical Center's Translational Biobehavioral and Health Disparities Branch collaborated on a clinical study with scientists in the National Institute on Alcohol Abuse and Alcoholism. They found that the gut microbiomes became more diverse and healthier in people with alcohol-use disorder who had recently abstained from drinking alcohol.

In a follow-up study, the VCU team demonstrated that the behavioral changes observed after FMT could be transmitted through microbial transfer: Mice colonized with post-fecal-transplant stool (from the human participants of the first study) reduced their acceptance of, intake of, and preference for alcohol compared with pre-fecal-transplant colonized mice and control mice who received a sterile transplant (*Nat Comm* **13:**6198, 2022).

Leggio noted the vast diversity of human microbiota varies depending on factors such as age, sex, race, and co-morbidities. Thus, manipulating the gut microbiome, even if proved effective in future large studies, might not work out for every patient. Other researchers have proposed a related treatment option of increasing dietary fiber intake, which has been linked with better mental health by boosting SCFA production.

NIH-funded scientists are also exploring how FMT might be used to treat alcohol-related liver disease (ALD), in which the microbiome may play a role in the effects of alcohol on the liver. In parallel with rising unhealthy alcohol use in the United States and worldwide, ALD rates have also been increasing, with the largest surge seen in young people and women. Without effective interventions for AUD, the mortality rate for ALD is expected to double by 2040.

Searching for a brain-bug connection

The benefits of abstaining from alcohol or reducing the consumption of it are well known and may extend to our gut health, too. Researchers in the Clinical Center's Translational Biobehavioral and Health Disparities Branch (TBHD)—including Bioinformatics Scientist **Jennifer Barb** and Principal Investigator and Chief **Gwenyth Wallen**—collaborated with NIAAA

CONTINUED ON PAGE 14

Bugs

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CREDIT: JENNIFER BARB, CC

Katherine Maki, in the Clinical Center's Translational Biobehavioral and Health Disparities Branch, is part of a team that is analyzing functional-MRI data from patients with alcohol-use disorder to determine if activity in certain brain regions correlate with changes in the gut microbiome.

scientists in a clinical study with 22 newly abstinent inpatients with AUD. The group found that the patients' gut microbiomes began to recover over the course of four weeks, becoming more diverse and healthier (*Gut Microbes* **11:**1608–1631, 2020).

Since that study, improved genomic-sequencing technology has associated specific genera of gut microbes, such as Morganella, with mental-health disorders such as depression and anxiety, which are common in patients with AUD. TBHD Assistant Clinical Investigator **Katherine Maki** and Barb are collaborating with **Reza Momenan** (Director of NIAAA's Clinical Neuroimaging Research Core) on a retrospective secondary analysis of the data from the abstinence trial. They are incorporating genomic sequencing of the gut microbiome samples with structural-magnetic-resonance-imaging scans to determine whether activity in certain regions of the brain related to stress might correlate with the presence of suspected pathological microbes and with symptoms such as sleep disturbance, anxiety, depression, alcohol withdrawal, and craving.

A holistic approach

People with substance-use disorders often have several medical issues that may also be linked to addictive behavior. In many cases, people with AUD have severe oral-health problems, such as periodontitis, and are sent for a dental workup by National Institute of Dental and Craniofacial Research (NIDCR) clinicians when they come into the CC (*Open Forum Infect Dis* **6**:S895–S896, 2019). To better treat the whole person, TBHD is designing a new protocol with an interdisciplinary team of investigators from NIDCR and NIAAA to study the oral microbiome and general oral-health practices in those patients.

Barb noted that this holistic approach is a missing component in research, and important to understand given the mouth's close proximity to the brain. For example, bacteria in the mouth from a highly infected tooth could have implications on the brain through byproducts produced in the bloodstream.

"There could be a bidirectional relationship with oral health, the brain, AUD, and poor oral hygiene because you are under the influence [of alcohol]," she said.

Opposite of the gut, less microbial diversity in the mouth is thought to be healthier. Previously, TBHD found that the oral microbiome in patients who abstained from alcohol did indeed become healthier and assessments of oral health improved during the course of inpatient treatment. Furthermore, oral microbial changes were associated with the type of alcohol that the patient consumed, with overall diversity being lowest among wine drinkers (*J Oral Microbiol* **14:**2004790, 2022).

TBHD scientists are not only treating the immediate causes of AUD, but also educating those patients on the importance of sleep and proper nutrition, both of which have "a major influence on the gut microbiome," said Barb. "We want to think about the whole person and help patients to not only stop drinking, but [also] think about all the components of health when they leave."

The study of our bugs' role in behavior is still in its infancy. And what we uncover may turn out to be a more universal picture of the pathways that integrate our resident microbial activity with our own physiology.

"From an evolutionary standpoint the body cares less about distribution, organizational charts, and chain-of-command," said Leggio. "It's a democratic system. All organs, components, and residents in our body are important and have a voice!"

To learn more

Other NIH scientists are studying the microbiome, too, including Distinguished Investigator **Yasmine Belkaid** at the National Institute of Allergy and Infectious Disease, and Senior Investigator **Julie Segre** at the National Human Genome Research Institute, who spearheaded NIH's Human Microbiome Project. Researchers such as Leggio and Senior Investigator **Andrew Holmes** (NIAAA) have also collaborated with renowned gut-brain axis expert John Cryan at University College Cork (Cork, Ireland). To watch Cryan's lecture at NIH on the gut-brain-axis go to https://videocast.nih.gov/watch=17162. And to hear a lecture by Claire Fraser about the microbiome and genomics hosted by former NIH Director **Francis Collins**, go to https://videocast.nih.gov/watch=40165. ●

Michael Tabasko is the Science Writer-Editor for The NIH Catalyst.

Toxic Protein

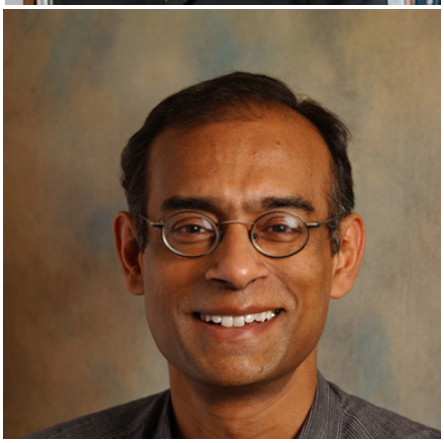
CONTINUED FROM PAGE 7

genes also behaved differently in older mice compared to younger mice even when the animals did not receive alpha-synuclein injections, suggesting that alpha-synuclein makes microglia in younger mice act more like those in older mice. In addition, when the researchers conducted an analysis to determine how those genes are regulated, they found that some of the genes are influenced by a chemical called colony stimulating factor 2 (CSF2), which is secreted by T cells and certain other immune cells. That finding bolsters those of other research that has only recently begun to link CSF2 to neurological illnesses.

"I think the fact that we found a link to CSF2 suggests that all these excess T cells that are getting into the brain might be secreting more CSF2, and this CSF2 is detected by microglia," Masliah explained. "The microglia become activated, and then we see dysregulation in all these other inflammatory pathways. That's very important because it suggests that targeting either CSF2 or its receptor in microglia might prevent the acceleration of aging in microglia that appears to be triggered by alpha-synuclein."

Now that the study has given Masliah's and Sen's teams a broad view of how alpha-synuclein and aging affect the brains of mice, the group plans to study the effects of those factors in mice that lack specific types of immune cells in their brains, such as T cells or microglia. They are also curious to investigate how alpha-synuclein and aging affect the brains of mice with immune cells that either can't produce or can't respond to CSF2. Such experiments will build on the findings of the recent study to produce a more detailed picture of the ways both aging and alpha-synuclein wreak havoc on the brain, information that is critical for creating new treatments.

"Our findings suggest that pro-inflammatory pathways that are triggered by aging could also be triggered in a similar way by accumulation of alpha-synuclein," said Masliah. "They are running in parallel and also probably feeding into each other. I think we can develop therapeutic strategies for diseases like Parkinson's and Lewy body dementia by looking at these age-related inflammatory pathways." ●



Based on their study, NIA scientists **Eliezer Masliah** (top) and **Ranjan Sen** (bottom) proposed that aging-related inflammation influences outcomes of pathological spreading of alpha-synuclein and suggest that targeting neuro-immune responses might be important in developing treatments for Parkinson's disease and Lewy body dementia.

Brandon Levy is a Health Communications Specialist for NIH's Intramural Research Program.

This article is adapted from the December 20, 2022, post in the *I Am Intramural Blog*: https://irp.nih.gov/blog/post/2022/12/toxic-protein-and-aging-combine-forces-to-drive-brain-disease.

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
FNIH: Foundation for the NIH
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

Recently Tenured


URSULA BUCHHOLZ , NIAID


NICHOLAS GUYDOSH, NIDDK


SENTHIL MUTHUSWAMY, NCI-CCR


TONYA WHITE, NIMH


SABRINA WONG, NINR

URSULA BUCHHOLZ, D.V.M, PH.D., NIAID

Senior Investigator and Chief, RNA Viruses Section, Laboratory of Infectious Diseases (LID), National Institute of Allergy and Infectious Diseases

Education: Free University Berlin, Berlin (D.V.M.; Ph.D. in virology)

Training: Research fellow, Free University Berlin; postdoctoral fellow, Institute of Clinical Virology, Federal Research Institute for Animal Health (Tübingen, Germany)

Before coming to NIH: Principal Investigator with tenure, Institute of Molecular Biology, Federal Research Institute for Animal Health (Insel Riems, Germany)

Came to NIH: In 2002 as a Staff Scientist, Respiratory Viruses Section, LID, NIAID

Outside interests: Enjoys outdoor activities with family and friends—hiking, biking, sailing; enjoys music, especially her beginner cello lessons

Website: https://www.niaid.nih.gov/research/ursula-buchholz-phd

Research interests: My laboratory studies the molecular virology, pathogenesis, and immune response of human respiratory pathogens, including respiratory syncytial virus (RSV), human parainfluenza viruses (HPIVs), and human metapneumovirus. We are using insights from our basic virology studies to develop effective mucosal vaccines against respiratory viruses.

The pneumovirus RSV is the most important cause of severe acute lower respiratory illness in infants and children worldwide and is a leading cause of infant hospitalizations. There are no licensed vaccines. We recently advanced two promising live-attenuated vaccines into pediatric clinical studies and found that a single intranasal dose was safe and induced an immune response in RSV-seronegative children, warranting further evaluation *(J Infect Dis* **221:**534-543, 2020; *J Infect Dis* **222:**82-91, 2022). These lead candidates are advancing to later-stage clinical trials.

We are also using paramyxoviruses and pneumoviruses as vaccine vectors to express protective antigens of RSV or other emerging pathogens. In 2020, we expanded our program to include the development of vector-vaccine candidates for intranasal immunization against SARS-CoV-2, the virus that causes COVID-19. In a recent study, we generated a live-attenuated parainfluenza-virus-vectored vaccine candidate expressing the SARS-CoV-2 prefusion-stabilized spike protein (B/HPIV3/S-6P) and evaluated its immunogenicity and protective efficacy in rhesus macaques (*Macaca mulatta)*. We found that a single intranasal immunization with B/HPIV3/S-6P vaccine candidate was highly immunogenic and protected macaques against SARS-CoV-2 (*Cell* **185:**4811-4825, 2022). Our data support the further development of this vaccine candidate for potential use as a stand-alone vaccine and/or in a prime or boost combination with injectable SARS-CoV-2 vaccines for infants and young children. The B/HPIV3/S-6P vaccine candidate will be evaluated in a phase 1 study.

NICHOLAS GUYDOSH, PH.D., NIDDK

Senior Investigator and Chief, Section on mRNA Regulation and Translation, Laboratory of Biochemistry and Genetics, National Institute of Diabetes and Digestive and Kidney Diseases

Education: Harvard University, Cambridge, Massachusetts (A.B. in chemistry); University of Cambridge, Cambridge, England (M.Phil. in chemistry); Stanford University, Stanford, California (Ph.D. in biophysics)

Training: Postdoctoral Fellow, Department of Molecular Biology and Genetics, Johns Hopkins University School of Medicine (Baltimore)

Came to NIH: In 2016 as a Stadtman Investigator and Acting Chief of his current section

Outside interests: Reading; being outdoors; exploring the Washington, D.C., area with his daughter

Website: https://irp.nih.gov/pi/nicholas-guydosh

Research interests: I lead a research group that is seeking to learn how cells change the expression of genes by controlling how ribosomes translate messenger RNAs (mRNAs) during protein synthesis. We're interested in the mechanisms that underlie the basic steps of translation as well as how these processes are regulated to maintain cellular health. We have made several key advances that have relied on enhancements to the ribosome-profiling methodology: We use a high-throughput footprinting approach to map the positions of ribosomes along mRNAs.

One area we are studying is ribosome recycling, the process by which ribosomal subunits are separated from each other and from mRNA after the completion of protein synthesis and are made ready to be reused in the next round of translation. Scientists did not know how recycling worked or if it was promoted by particular proteins. We recently discovered that recycling occurs in stages and each subunit of the ribosome is removed separately by specific proteins (*Nat Commun* **12:**2976, 2021). Because these proteins are encoded by oncogenes and can be mutated in people with autism, our finding suggests ribosome recycling is an important process to consider for understanding cancer, autism, and potentially other neurological diseases.

We are also interested in the consequences of cases where translating ribosomes bump into each other. It turns out that these ribosome collisions occur more often when cells experience stress, such as starvation. We discovered that ribosome collisions activate a key signaling pathway—the integrated stress response—that helps the cell cope with stress and plays broad roles in neurological diseases, cancer, and viral infections. (*Mol Cell* **79**:588-602.e6, 2020).

SENTHIL MUTHUSWAMY, PH.D., NCI-CCR

Senior Investigator and Chief, Laboratory of Cancer Biology and Genetics, Center for Cancer Research, National Cancer Institute

Education: Tamil Nadu Agricultural University, Coimbatore, India (B.Sc. in agricultural sciences and M.Sc. in genetics); McMaster University, Hamilton, Ontario, Canada (M.Sc. in biology; Ph.D. in biology)

Training: Postdoctoral Fellow, ARIAD Pharmaceuticals (Cambridge, Massachusetts); Postdoctoral Fellow in cell biology, Harvard Medical School (Boston)

Before coming to NIH: Harvard Medical School: Director of the Cell Biology Program and of Translational Research, Beth Israel Deaconess Medical Center; associate professor, Department of Medicine and Pathology, Beth Israel Deaconess Medical Center; and investigator, Harvard Ludwig Cancer Center

Came to NIH: In 2022

Outside interests: Gardening; taking photographs; hiking; playing badminton

Website: https://irp.nih.gov/pi/senthil-muthuswamy

Research interests: During my postdoctoral fellowship, I was among the first to use three-dimensional cell cultures (organoids) to bridge the gap between growing cells as flat monolayers and in vivo to study oncogenesis (*Nat Cell Biol* **3**:785-792, 2001). In my laboratory, we continue to generate patient-tumor-derived organoid cultures (*Nat Med* **21:**1364-1371, 2015) and use them for investigating drug response, biomarkers (*JCI Insight* **5:**e135544, 2020), metastatic progression (*Nat Cell Biol* **15:**189-200; 2013), and personalized cancer treatments (*Clin Cancer Res* **28:**708-718, 2022).

More recently, we developed a tumor organoid-immune cell co-culture platform in which peripheral-blood-derived T cells undergo a dramatic clonal expansion (1,000- to 100,000-fold). These organoid-primed cytotoxic T (opT) cells express tumor-targeting T-cell receptors (TCRs) and are useful for cell-therapy applications (*J Immunother Cancer* **9:**e003213, 2021). Expansion of T cells in response to antigens naturally expressed on the surface of tumor organoids defines opT culture as a unique, empirical platform to identify tumor-selective cytotoxic cells for use in immune-therapy applications and to identify a new class of TCRs and tumor antigens.

The three-dimensional culture of epithelial cells is exquisitely suited for studying apical-basal polarization and its role in cancer biology. Although we were the first to show that polarity proteins function as tumor suppressors in mammals (*Cell* **135:**865-878, 2008; *Nat Cell Biol* **8:**1235-1245, 2006), our recent studies have challenged this notion. We find that cell polarity proteins function as positive regulators by altering cell metabolism and the trafficking of cell-surface proteins to provide growth and survival advantage to cancer cells (*Nature* **569:**275-279, 2019). Consistent with our findings, many cell-polarity proteins are overexpressed or amplified in cancer (*Biochim Biophys Acta Rev Cancer* **1869:**103-116, 2018). This highlights a new opportunity for using tumor organoids and immune-cell co-culture platforms to investigate how cell-polarity proteins regulate changes in cellular metabolome, cell-surface proteome, and cell signaling to promote metastatic-cancer progression and treatment resistance.

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Recently Tenured

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TONYA WHITE, M.D., PH.D., NIMH

Senior Investigator and Chief, Section on Social and Cognitive Developmental Neuroscience, National Institute of Mental Health

Education: University of Utah, Salt Lake City (B.S. in electrical engineering); University of Illinois at Champaign/Urbana (M.S. in electrical engineering); University of Illinois College of Medicine, Chicago (M.D.); University of Minnesota, Minneapolis and Saint Paul, Minnesota (coursework toward Ph.D. in biomedical engineering); Erasmus University Rotterdam, Rotterdam, Netherlands (Ph.D. in developmental neuroscience)

Training: Combined residency in pediatrics, in psychiatry, and in child and adolescent psychiatry, University of Utah; postdoctoral research fellowship, University of Iowa Hospitals and Clinics (Iowa City, Iowa)

Before coming to NIH: Professor of Pediatric Population Neuroimaging in the Departments of Child and Adolescent Psychiatry and of Radiology and Nuclear Medicine, Erasmus University Rotterdam

Came to NIH: In July 2022

Outside interests: Cross-country, telemark and Alpine skiing; cyclng; paddling; hiking; spending time wih family and friends doing outdoor activities, or over food and drink; listening to books on tape; and writing

Website: https://www.nimh.nih.gov/research/research-conducted-at-nimh/principal-investigators/tonya-jo-hanson-white-md-phd

Research interests: Children or adolescents with the same psychiatric diagnosis can have varying degrees of core and comorbid symptoms. Even identical twins differ in specific characteristics. My long-term goals are to better understand individual differences—including the interplay among genes, environment, and random processes—in youth with mental-health disorders. Even twins who are concordant for a specific disorder, such as autism, may have considerable differences in symptoms. Thus, a better understanding of factors that can influence symptoms can shed light onto the underlying mechanisms of mental-health problems. My recent work has pointed to both prenatal and early life as critical periods to foster optimal brain development and to reduce the risk for children developing a psychiatric disorder.

It is interesting that the core symptoms of specific disorders, albeit differences in severity, have classic patterns that cluster together and allow for identification. Thus, one of my other goals is to apply machine-learning and pattern-recognition algorithms to be able to extract the brain-based patterns associated with the spectrum of symptoms. I also have a long-standing interest in developing primary prevention strategies for young children to (hopefully) help curb the onset of neurodevelopmental disorders.

My group recently conducted several population-based neuroimaging studies to investigate the bidirectional, longitudinal relationship between behavioral traits, including autistic traits, and brain morphology in children. Whereas we found that the interplay between autistic traits and structural brain measures are relatively stable across childhood, children with depression, anxiety, aggression, and attention problems show greater brain changes over time. Timing matters. We demonstrated that higher levels of autistic traits are associated with lower gyrification (the development of fissures and folds on the brain's surface) between 6 and 15 years of age. Overall, our findings point toward alterations in specific brain regions that are involved in social cognition (*Mol Autism* **13:**31, 2022; *Am J Psychiatry* **175:**54-62, 2018; and a paper, in press, in the *Journal of the American Academy of Child and Adolescent Psychiatry*).

SABRINA WONG, PH.D., R.N., NINR

Senior Investigator and Scientific Director, National Institute of Nursing Research

Education: University of British Columbia, Vancouver, British Columbia, Canada (B.S.N.); University of California at San Francisco (M.S. and Ph.D. in nursing)

Training: Postdoctoral Fellow at the Institute for Health Policy Studies, University of California at San Francisco

Before coming to NIH: Associate Director, Research School of Nursing, and Professor of Nursing, University of British Columbia

Came to NIH: In September 2022

Outside interests: Running marathons and ultramarathons; hiking; enjoys other outdoor activities

Website: https://www.ninr.nih.gov/aboutninr/sabrina-wong

Research interests: I have a long-standing interest in the organization and delivery of primary health care services and how to reduce inequities in health and health care. I have combined my expertise in psychometric measurement, use of mixed methods, patient-oriented research, and use of large data such as administrative and electronic medical record data (*Healthc Policy* **17:**19–23, 2021). I have led ongoing work to develop primary health care science, including the development of federating primary-care electronic medical records into Canada's largest data repository of its kind, the Canadian Primary Care Sentinel Surveillance Network.

I was pleased to be recognized as one of Canada's leading experts in primary health care research: I was nominated principal investigator of a community-based primary health care innovation team grant; asked to provide consultations internationally; and invited to contribute an editorial in the *British Medical Journal* (*BMJ* **346:**f3777, 2013).

I help identify issues where primary care can intervene. One important matter is the inappropriate prescribing of antibiotics for treating respiratory tract infections (RTIs)—25% to 68% of prescriptions for RTIs are potentially avoidable (*Can Commun Dis Rep* **48:**157-163, 2022). Finding ways to provide useful information from electronic medical record data to inform quality improvement interventions in primary care can, for example, raise awareness about inappropriate antibiotic prescribing practices and could be vital to advancing antimicrobial stewardship.

I am also exploring how team-based primary care (in which two or more health professionals work collaboratively to provide comprehensive, continuous, and coordinated care) contributes to high-performing health care services. In a recent study, we determined that primary-care teams are most effective when they are small (fewer than 11 professionals), they communicate informally with one another, and they share the practice's mission, values, and objectives. Larger teams that rely primarily on electronic medical records to coordinate care were less effective (*J Interprof Care* **26:**1-10, 2022).

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2023 Demystifying Medicine Schedule

BRIDGING EXCITING DEVELOPMENTS IN BIOLOGY AND ENGINEERING WITH MEDICINE

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- **January–May 2023**
- **Watch via https://videocast.nih.gov**

The Demystifying Medicine Series includes presentations on pathology, diagnosis, and therapy in the context of major disease problems and current research. This series is designed to help bridge the gap between advances in biology and their application to major human diseases. Each session includes clinical and basic science components presented by NIH staff and invitees. All students, trainees, fellows, and staff are welcome to participate.

For more information about signing up for email notifications as well as course materials, and speaker profiles, go to https://demystifyingmedicine.od.nih.gov.

Jan. 10: Anthony Fauci, MD (former NIAID Director), *COVID and Beyond*

Jan. 17: Andrea Lisco, MD, PhD (NIAID) and John Schiller, PhD (NCI), *Human Papilloma Virus Vaccination and the Prevention of Cancer*

Jan. 24: Nihal Altan-Bonnet, PhD (NHLBI) and Natalie Porat-Shliom, PhD (NCI), *Salivary Secretion of Epidemic Viruses*

Jan. 31: Douglas Melton, PhD (Harvard University), Diabetes Mellitus: Great Progress; Courtney Duckworth, MD (Harvard University–Boston Children's Hospital), *Diabetes: The Marathon of Life*

Feb. 7: Yanick Crow, MD, PhD (University of Edinburgh) and Raphaela Goldbach-Mansky, MD (NIAID), *The Interferonopathies: Interferon Running Amok*

Feb. 14: William Robinson, MD, PhD (Stanford University) and Judith James, MD, PhD (Oklahoma Medical Research Foundation), *The Role of Epstein-Barr Virus and Molecular Mimicry in Autoimmune Disease*

Feb. 21: John O'Shea, MD (NIAMS) and Angela Christiano, PhD (Columbia University), *The Use of JAK Inhibitors in Autoimmune Disease*

Feb. 28: Adam Phillippy, PhD (NHGRI) and Cyndi Tifft, MD, PhD (NHGRI), *The Human Genome at 20*

March 7: Philip Castle, PhD, MPH (NCI) and Robert Nussbaum, MD (Invitae) *Tests for Early Cancer: Facts vs. Opinions, Can We Detect Early Cancer?*

March 14: Saul Villeda, PhD (University of California, San Francisco) and Luigi Ferrucci, MD, PhD (NIA), *Neurodegeneration and Aging: Are they Preventable or Reversible*?

March 21: Andrew Knoll, PhD (Harvard University), *It's a Bacterial World*

March 28: Nicola Fox, PhD (NASA)and Freddy Escorcia, MD, PhD (NCI), *Solar Winds and Magic Bullets: Making Our Way in a World of Radiation*

April 4: Nelson Spruston, PhD (Janelia HHMI) and Marcus Raichle, MD (Washington University-St. Louis), *How is the Brain Organized and How Does it Work?*

April 11: Roland Griffiths, PhD (Johns Hopkins) and David Olson, PhD (University of California, Davis), *Psychobiology: Mushrooms.....Others*

April 18: Aaron Cypess, MD, PhD (NIDDK) and Kevin Hall, PhD (NIDDK), *Fat: Biology and Staying Thin*

April 25: Charles Rotimi, PhD (NHGRI) and Clement Adebamowo, BM, ChB, ScD, FWACS, FACS (University of Maryland), Out of Africa: *Genomic and Environmental Determinants of Global Health*

May 2: Kandace Tanner, PhD (NCI) and other speaker to be named, *Cancer: Metastasis and Drivers*

May 9: John Coffin, PhD (Tufts and NCI) and Paolo Lousso, MD, PhD (NIAID), *mRNA: Will it Deliver us from Illness?*

May 16: Speaker to be named.

NIH Families Had to Fight for Their Right to Vote

Case Worked Its Way Up to the Supreme Court

BY KATE NAGY, NIA

When 20-year-old Edward Tabor tried to register to vote at the Montgomery County, Maryland, Board of Elections office in February 1968, he saw his application, and his parents' voter cards, destroyed in front of him. The subsequent protest by the Tabor family and their neighbors eventually reached all the way to the United States Supreme Court. At stake—for certain NIH staff and for others across the country—was nothing less than the exercise of the Constitutional right to vote.

The issue was that Tabor and his parents who both worked in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—**Herbert Tabor** (1943-2020) and **Celia Tabor** (1952-2005)—lived on the NIH campus in one of the 15 brick houses located in the northeast corner. In 1963 the Maryland Court of Appeals had ruled, in a case outside NIH, that individuals living on federal government property didn't meet Maryland residency requirements for voting. The application of the ruling to NIH in 1968 by the Board of Elections effectively disenfranchised not only the Tabors and their neighbors but also other NIH scientists and employees who lived in the apartment building Building 20 (since demolished) on campus.

CREDIT: EDWARD TABOR

Edward Tabor on the NIH grounds in 1969. When he tried to register to vote at the Montgomery County, Maryland, Board of Elections office in February 1968, he saw his application—and his parents' voter cards—destroyed in front of him.

Shortly after Ed Tabor's abortive attempt to register, his parents and other campus residents received notices from the Board of Elections that they had been removed from the voter rolls. Apartment resident **Tillye Cornman** (see sidebar) sought legal representation for the NIH residents and obtained pro bono representation by Montgomery County Democratic Chairman and political activist Richard Schifter. Schifter quickly obtained an injunction allowing previously registered campus residents to vote in the 1968 presidential election.

"That basically allowed everyone to vote that year except me," said Ed Tabor, now a retired physician-scientist in the National Cancer Institute (1988-1995) living in Bethesda. Another campus resident had also been barred from registering shortly after Tabor's interaction with the Board of Elections but left NIH shortly thereafter. A second court order permitted Tabor to vote in a 1969 special election.

The Federal District Court restored voting rights to the NIH plaintiffs, but the Maryland Attorney General appealed that decision to the United States Supreme Court. Twelve individual plaintiffs, including Ed Tabor, were represented.

CREDIT: EDWARD TABOR

Celia and **Herbert Tabor** standing next to their family house on the northeast corner of the NIH grounds in 1967. In 1963 the Maryland Court of Appeals had ruled, in a case outside NIH, that individuals living on federal government property didn't meet Maryland residency requirements for voting.

Assistant Attorney General Robert Sweeney, arguing for the state, expressed sympathy for the residents but stated, "In a government of laws and not of men…this question should not and cannot be decided out of sympathy for the Appellee's position." Schifter, meanwhile, argued that denying NIH residents the right to vote violated the Constitution's equal protection clause.

The Supreme Court justices agreed, with one referring to the state's arguments as "much ado about nothing," and in a unanimous decision handed down in June 1970 [*Evans v. Cornman*, 398 U.S.419(1970)] permanently restored the residents' voting rights. Ed Tabor was able to register and vote in the 1970 midterms and 1972 presidential election—although by that time he was away at medical school at Columbia University (New York) and voted absentee.

It's unclear why the Board of Elections suddenly started to enforce the 1963 law disenfranchising residents of federal enclaves five years after the Appeals Court decision. According to Ed Tabor, attorney Schifter had a theory. "He told me that more United States government employees were Democrats than Republicans at that time," said Tabor. "And [Schifter believed that] the actions of the voter registration office seemed to be calculated to decrease the number of registered Democrats."

Tabor remembers that the elections workers immediately recognized his fairly obscure address as being on the NIH campus. "Clearly they were waiting for someone from NIH to attempt to register," he said. Notably, Schifter did not assert this theory in his oral argument before the Supreme Court, and the number of previously registered Democrats involved in the lawsuit only slightly exceeded the number of previously registered Republicans (6 versus 4).

Since 1970, Evans v. Cornman has been cited in several other Supreme Court cases involving voting rights, including an unsuccessful case supporting Washington, D.C., statehood. And it made a big impression on Ed Tabor. "I was very serious about voting in every election for many years after that," he said. ●

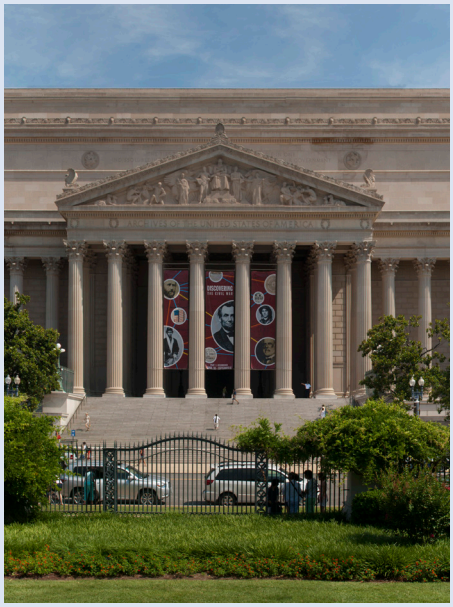
Kate Nagy is Deputy Director of the National Institute on Aging Office of Planning, Analysis, and Evaluation, where she coordinates strategic planning and reporting efforts. Prior to NIA, she spent nine years in strategic planning, evaluation, and scientific communications at the National Cancer Institute.

Tillye Cornman, M.D.: A Remarkable Life

BY KATE NAGY, NIA

Tillye Cornman, who spearheaded the legal effort to restore voting rights to NIH campus residents, was born in New Orleans in 1916, the oldest of eight children. A graduate of Louisiana State University's medical school (New Orleans), Cornman was practicing neurology and psychiatry when she was shot outside her office by a patient undergoing treatment for mental illness. She used a wheelchair for the rest of her life due to the resulting spinal cord injury.

Her rehabilitation sparked a lifelong interest in the field, and after retraining as a physiatrist, she became head of the NIH Clinical Center Rehabilitation Medicine Department in 1954. Colleagues remember her as an unwavering advocate for her patients and a dedicated member of the staff. In 1955, she told the *NIH Record* that "The concept of rehabilitation is really teamwork" and was quick to acknowledge the contributions of other members of her team.



CREDIT: DAVID SAMUEL

In the 1960s, **Tillye Cornman's** complaint to then-United States Attorney General Robert Kennedy resulted in the construction of a ramp outside the National Archives building so it was wheelchair-accessible (photo taken in 2010).

CREDIT: OFFICE OF NIH HISTORY AND STETTEN MUSEUM

Tillye Cornman at the NIH Clinal Center in 1961. Cornman served as head of the NIH Clinical Center Rehabilitation Medicine Department and spearheaded the legal effort to restore voting rights to NIH campus residents

She retired in 1988 but served as a consultant for the Clinical Center after that. For most of her career, she lived in a first-floor flat in the apartment building on the NIH campus, where she raised her daughter as a single mother while working full time.

Family and colleagues remember Cornman as a powerful advocate not only for her patients but also for the causes she championed. For example, her complaint to then-United States Attorney General Robert Kennedy resulted in the construction of a ramp outside the National Archives building after she was unable to traverse the front stairs in her wheelchair.

Cornman died in Gaithersburg, Maryland, aged 82, in 1999. She was survived by a daughter, two grandchildren, a great-grandchild, and hundreds of patients whose lives she touched during her four decades of service. ●

Died in 2021 (not listed last year)

Barbara V. Allen (died October 2, 2021, at 82) was a researcher at the National Cancer Institute and the National Institute of Dental and Craniofacial Research, where she studied pain.

Margaret (Margo) Campbell Heun Bradford (died December 30, 2021, at 75) was Operations Manager at the NIH Children's Inn and the founding Operations Manager at the NIH Safra Family Lodge.

George J. Galasso (died November 5, 2021, at 89) was a pioneer in antiviral research whose efforts led to the successful treatment of many viral infectious diseases and cancer. He retired in 1996 as the Associate Director of Extramural Programs and later that year became the first leader of the Foundation for the NIH.

Edmund A. Gehan (died September 28, 2021, at age 92) spent his career as a biostatistician at the National Cancer Institute and elsewhere.

James E. Hamner III (died June 6, 2021, at 88), studied oral cancer at the National Institute of Dental Research and the National Cancer Institute.

S. Peter Nissley (died in March 2021, at 84), was a pioneer in the field of insulin-like growth factors. He spent most of his career in the National Cancer Institute and retired in 2005.

Samuel H. Wilson Jr. (died April 23, 2021, at 82) was a protein biochemist in the National Cancer Institute and later the Deputy Director (later Acting Director) of the National Institute of Environmental Health Sciences (NIEHS). Through his leadership, NIEHS developed initiatives to create more precise measurements of human exposures to harmful pollutants.

Died in 2022

Bernard W. Agranoff (died October 21, 2022, at 96) joined the National Institute of Neurological Disorders and Stroke in 1952, where he studied the role of lipids in cell signaling within the nervous system. He is one of the founding editors of the classic textbook *Basic Neurochemistry*, now in its 50th year.

Israel L. Burch (died July 19, 2022, at 49) was a 20-year veteran of NIH Fire and Rescue Services and was Acting Fire Chief of the NIH Fire Department.

Maurice B. Burg (died April 24, 2022, at age 91) was a Scientist Emeritus in the National Heart, Lung, and Blood Institute (NHLBI). As Chief of NHLBI's Laboratory of Kidney and Electrolyte Metabolism, his work in defining the kidney-transport mechanism became the foundation for an understanding of kidney function that underlies much of contemporary nephrology.

C. Thomas "Tom" Caskey (died January 13, 2022, at 83) is renowned for his characterization of the *HPRT* gene and identification of its mutations in patients with Lesch-Nyhan syndrome, and for his discovery of a novel genetic mechanism for human disease including fragile X syndrome and myotonic dystrophy.

Homer D. Chalifoux (died September 8, 2022, at 88), a biomedical engineer at NIH, developed an improved dialysis machine.

Lois J. Dienes (died September 18, 2022, at 81) worked as a nurse at NIH.

Paul Farmer (died February 21, 2022, in Rwanda, at 62) was a global health leader, physician, medical anthropologist, Harvard professor, author, and longtime friend of NIH. He spent decades expanding health care access and providing medical care to the world's poorest, underserved populations.

Mary C. Fraser (died March 5, 2022, at 70), a Clinical Research Nurse Specialist in the National Cancer Institute's Division of Cancer Epidemiology and Genetics (NCI-DCEG), pioneered the central role of nurses in long-term studies of families at increased risk of cancers and was a nationally acknowledged expert in the long-term effects of cancer therapy.

Norma Lee Funger (died July 4, 2022, at 90) was a philanthropist and a board member of the Children's Inn at NIH.

John Jacob Gart (died January 24, 2022, at 90) retired in 1991, as Chief of Mathematical Statistics and Applied Mathematics Section in the National Cancer Institute.

Harriett Greenwald (died November 9, 2022, at 87) was the Executive Director of the NIH Alumni Association and Editor of its newsletter. She worked diligently at preserving NIH history and coauthored a history of the National Institute of Allergy and Infectious Diseases. Her husband, **Peter Greenwald**, was the Director of the National Cancer Institute's Division of Cancer Prevention and Control.

Dianne Kay (died November 3, 2022, at 84) and her husband oversaw the construction of the NIH Children's Inn.

David R. Kominz (died November 4, 2022, at 98), who studied muscle and protein biochemistry, began his career as a medical researcher at NIH and as an officer in the U.S. Public Health Service. By the time he retired in the early 1970s, he had become Section Chief of Bioenergetics in the Laboratory of Biophysical Chemistry within the National Institute of Arthritis and Metabolic Diseases.

Carl Levanthal (died February 22, 2022, at 88) was a neuropathologist who began his career at NIH in 1964 and retired in 1996 as a Division Director in the National Institute of Neurological Disorders and Stroke.

Sanford "Sandy" Markey (died February 6, 2022, at 79), a mass spectroscopist, founded the Laboratory of Neurotoxicology in the National Institute of Mental Health in 1996, and served as its Chief until his retirement in 2013. His group first identified a compound that was a cause of chronic Parkinsonism.

Susan F. Meikle (died August 1, 2022, at 62) worked for various hospitals in Colorado, New Mexico, and Arizona before joining the Centers for Disease Control and NIH, rising from epidemiologist and medical officer to senior scientist and then to Program Director at the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development.

Doris M. Merritt (died April 12, 2022, at 98) was the first Acting Director of NIH's National Center for Nursing Research in 1986.

Barbara F. Mishkin (died January 7, 2022, at 85), a lawyer, began her career as a bioethicist helping the National Institute for Child Health and Human Development prepare proposed regulations to protect children as research subjects. She became the pre-eminent voice in

the protection of human subjects in biomedical research and institutional review boards in the United States. Her husband was National Institute of Mental Health cognitive neuroscientist **Mortimer Mishkin**, who died in October 2021.

Mark Mueller (died November 19, 2022, at 55) worked in scientific planning for the Division of AIDS Research in the National Institute of Allergy and Infectious Diseases (NIAID). He was also a Health Specialist at the NIH Vaccine Research Center and a member of the NIAID Pandemic Preparedness Task Force.

James E. Nagel (died September 29, 2022, at 78), a pediatrician, started working as a scientist for NIH in 1979 and spent 30 years there.

Neal Nathanson (died August 11, 2022, at 94), a pioneering researcher on polio and HIV/AIDS, was the Director of NIH's Office of AIDS Research 1998-2000.

David Michael Neville (died January 14, 2022, at 87) was a pioneer in immunotoxin research and spent 48 years at the National Institute of Mental Health. After he retired in 2008, he co-founded Angimmune (Rockville, Maryland).

Ward Odenwald (died March 3, 2022, at 71), a PI in the National Institute of Neurological Disorders and Stroke (NINDS), came to NIH in 1978, and later became Chief of the NINDS Neural Cell-Fate Determinants Section. His lab developed comparative genomics tools to aid in the analysis of gene regulatory DNA and the evolution of viruses, including Zika and Ebola.

Roger O'Neill (died May 8, 2022, at 50) was a Postdoctoral Fellow at NIH and went on to work for biotech companies, including Applied Biosystems where he helped develop the reagent used by both NIH and Celera in their race to sequence the human genome.

Joost J. "Joe" Oppenheim (died May 14, 2022, at 87) was a pioneer in the field of immune-cell regulation and response and one of the first to acknowledge the importance of intercellular cytokine signals in the regulation of immune defenses against infections and tumors. He started his career at NIH in 1962 in the post-graduate program and trained as a Clinical Associate at the National Cancer Institute (NCI). In 1966, he started his lab at the National Institute of Dental Research. He served as the Medical Director of the United States Public Health Service from 1975 to 1983, then moved to the NCI in 1983 and served as the Chief of the Laboratory of Immunoregulation until 2015.

Marianne K. Oskarsson (died November 7, 2022, at 86) spent 25 years at the National Cancer Institute. Her work included the discovery of genes that play a major role in leukemia and other cancers.

Beverly Ann Peterkofsky (died June 13, 2022, at 90), a biochemist who spent 40 years at NIH, was a trailblazer as a female lead scientist having to overcome many obstacles of bias and prejudice in order to advance her career to the level of Section Chief. She was also a violinist, playing with the NIH Orchestra and various string quartets. Her husband, **Alan Peterkofsky**, is a Scientist Emeritus in the National Heart, Lung, and Blood Institute.

John E. Porter (died June 3, 2022, at 87), a former member of the U.S. House of Representatives (1980-2001), was a long-time champion of biomedical research and played a key role in doubling the NIH budget. The Porter Neuroscience Research Center, which opened in 2014—on the NIH Bethesda, Maryland, campus—is named for him.

E. Arthur "Art" Robertson (died September 9, 2022, at 78) was a pathologist who worked at NIH for 10 years in the 1970s.

Paul Shinn (died November 17, 2022, at 46) was a foundational member of the National Center for Advancing Translational Sciences and its Division of Preclinical Innovation. He pioneered methods to automate the screening of drug combinations.

Earle Silber (died June 21, 2022, at 97) was a neuropsychiatrist who, in addition to having a private practice, held teaching and research positions at the National Institute of Mental Health and elsewhere.

Lucius E. Sinks (died June 3, 2022, at 91) pioneered an aggressive treatment of cancer in children that dramatically increased their chances of survival. (He was Chief of Pediatrics at Roswell Park Memorial Institute in Buffalo, New York, at the time—in the 1960s.) He came to the National Cancer Institute in 1984, where he served as a Branch Chief until 1990 when he left to become Cancer Center Director at Middlesex Hospital (Middletown, Connecticut).

Michael Sporn (died September 29, 2022, age 89) had a 35-year career at the National Cancer Institute (NCI) that started in 1960. As Chief of the Lung Cancer Branch, his lab made groundbreaking discoveries that established the field of retinoids. Later, as Chief of NCI's Laboratory of Chemoprevention, his lab was credited with novel insights into how tumor cells communicate with each other and for the breakthrough discovery of transforming growth factor-beta. In 1995, he left NCI to become a Professor of Pharmacology and Medicine at Dartmouth Medical School (Hanover, New Hampshire), where he pioneered the design and development of synthetic triterpenoid drugs for the treatment of cancer and other chronic diseases. In 2018, at the age of 85, he founded Triterpenoid Therapeutics, Inc. (Braintree, Massachusetts), which is working to commercially develop his final discoveries.

Ji Ming Wang (died December 24, 2022, at 72), a Senior Investigator in the National Cancer Institute, joined NIH in 1990 and studied the role of chemoattractant receptors in infection, inflammation, immune responses, and cancer progression for over 30 years.

Robert P. Wersto (died November 16, 2022, at 68), a research scientist who held a Ph.D. in biochemistry and biophysics, worked in the National Cancer Institute, the National Heart, Blood, and Lung Institute, and in the National Institute on Aging, from which he retired five years ago as the Director of the Core Flow Cytometry Lab. ●

Read more obituaries and longer versions of these online at https://irp.nih.gov/catalyst/31/1/obituaries-2022.

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PHOTOGRAPHIC MOMENT

Bringing Home the Gold

COURTESY OF NAOMI HUANG, NCI

When she's not in the lab, National Cancer Institute (NCI) Staff Scientist **Naomi Huang** (second from left) is sliding heavy polished granite stones across a sheet of ice in a sport called curling. Huang, who's from Taiwan, has only been playing for two years with a local curling club that includes other NIHers, but she's good enough to be on the Chinese Taipei women's curling team. The team recently won a gold medal at the 2022 Pan Continental Curling Championship, held in Calgary, Canada. Read more online at https://irp.nih.gov/catalyst/31/1/photographic-moment. ●

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