THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

NATIONAL INSTITUTES OF HEALTH • OFFICE OF THE DIRECTOR | VOLUME 31 ISSUE 4 • JULY–AUGUST 2023

Conference Probes Essence of Aging, Frailty, and Disease

BY *NIH CATALYST* STAFF

A gray-bearded Marshall Allen, leader of the legendary jazz ensemble called Sun Ra Arkestra, jaunted onto the stage at The Birchmere in Alexandria, Virginia recently, looking like a kid in his 70s. He then proceeded to wail on the alto sax for 90 minutes—focused and inventive, rising with ease, turning and pointing to his band of a dozen-plus musicians, always in command.

Remarkable is the fact that Allen is not in his 70s. He is 99.

What is the secret of Allen's longevity? The occupation of jazzman tends not to produce many nonagenarians. Toots Thielemans had a good run to 94, albeit on a less-strenuous instrument, the chromatic harmonica. Swing jazz drummer Viola Smith died in 2020 just shy of her 108th birthday. But examples of others are fewer than notes on a toy xylophone.

Perhaps Marshall Allen is a so-called super-ager? A super-ager is someone who ages more slowly than most people and thus is less affected by frailty and chronic disease compared to others in their 80s or 90s.

Just a few weeks after Allen's local concert, scientists gathered for the fourth NIH Geroscience Summit, April 24–26, at the Natcher Conference Center on the NIH Bethesda campus. A discussion of super-agers, like Allen, was one of the many topics on the agenda.

The summit built on previous gatherings held in 2013, 2016, and 2019. A decade

CONTINUED ON PAGE 4

Hail to the Helix

National DNA Day Celebrates Genomics Coming of Age

BY MICHAEL TABASKO, OD

CREDIT: NHGRI

DNA Day 2023 featured thought-provoking discussions about the present state of genomic research and even dared to entertain with a spirited competition between former NHGRI and NIH Director Francis Collins and current NHGRI Director Eric Green, to determine who is the G.O.A.T. (Greatest of All Time) NHGRI director.

Like the elegant double helix itself, DNA Day 2023 at NIH wove together intersecting threads. "Threads of discovery from basic science and threads of necessity that spring from human disease," said **Lawrence Brody**, Director, Division of Genomics and Society at the National Human Genome Research Institute (NHGRI), to kick off the 20th Anniversary Symposium at Lipsett Auditorium. National DNA Day was designated by Congress and is recognized annually on April 25 to commemorate the successful completion of the Human Genome Project (HGP) in

CONTINUED ON PAGE 14

CONTENTS

E PLURIBUS UNUM, BUT ONLY IF WE MAKE IT SO

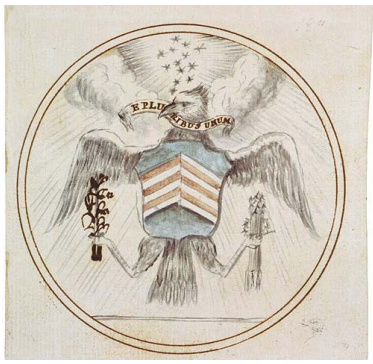
BY NINA F. SCHOR, DDIR

Did you ever notice how good Mother Nature is at taking a motif from one setting and repurposing it in another? It seems that, if "lock and key" is good enough for an enzyme and its substrate, then why should it not work for an antibody and its hapten? Or a receptor and its ligand? Similarly, the process of amplification—activate one molecule, which in turn activates two molecules, each of which, in turn, activates two molecules making four, and so on through the geometric series—works for glycogen synthesis, the clotting cascade, complement activation, and more. Methylation regulates protein activity one way or another, on DNA by regulating transcription frequency; on histones, by regulating which transcription factor binds to DNA; on oncoproteins, by regulating protein half-life.

The point is that learning or inventing or discovering something in one environment may allow its application to a totally different environment with breakthrough results. Mother Nature cross-pollinates across components of her systems. This creates both efficiencies and synergies that result in whole, complex organisms that comprise a tractable, finite number of nucleic, amino, and fatty acids, and sugars. It's like the way, with just red, yellow, blue, black, and white, we can make any color at all.

But none of this would happen if single environments or compounds or colors isolated themselves in silos. Synergy comes from mixing, from juxtaposition of disparate elements in unanticipated ways.

In an analogous fashion, our intellectually, socially, and demographically diverse NIH workforce can only achieve its maximal potential through dialogue across fields, technologies, model systems, and approaches. It is a historical and political fact that we are divided into institutes, centers, and offices by topical organ system, age, or disease process. But the best science happens and the best medicine results at the interfaces.



CREDIT: NATIONAL ARCHIVES

The 1782 design for the Great Seal of the U.S.

I have always characterized my career as life at the interfaces. Were I to have the chance to do it over again, I would do at least this part exactly the same way. The science is exciting, unexpected, novel, revealing, and, yes, fun when you venture out past your comfort zone and juxtapose ideas and approaches that never sat side by side before. As Miss Frizzle used to say on *The Magic School Bus*, "Take chances! Make mistakes! Get messy!" And by all means, cast your net widely across the magnificently broad landscape of the NIH.

Summer is here and our campuses are perfect for taking walks from one building to another. I recommend getting out to meet the many. ●

***E Pluribus Unum*, a motto of the United States, means "Out of many, one." *E Pluribus Unum* has appeared on the Great Seal of the United States since 1782.**

Inaugural Victoria A. Harden Lecture

The Art of Telling NIH History, Story by Story

BY SATABDI NANDI, NIA

Life may be like a box of chocolates. But the story of NIH history? That's more like a marble cake, according to **Victoria Harden**, founding Director of the Office of NIH History and Stetten Museum (ONHM).

"One can cut through it in many different ways to tell in detail specific parts of the story" of this one delicious cake with its many swirls, Harden said.

Harden delivered, fittingly enough, the inaugural Victoria A. Harden Lecture in NIH History, one of four planned quarterly lectures in the new ONHM History and Context seminar series. Harden retired from NIH in 2006.

ONHM's current Director, **Kim Pelis**, hopes the series will find its own place in NIH history. "[Harden's] talk was a tour de force, setting the stage for future NIH history lectures, and more, with wisdom, depth, and wide-ranging brilliance," said Pelis. In the lecture, Harden covered the broad arc of NIH's history and gave a glimpse into the many activities undertaken by ONHM over the years.

Blending history and medicine

Harden's father's side of the family fought in World War II, and she grew up intrigued by their stories and life experiences. A high school teacher's stories about influential women sparked an early interest in history. Harden would go on to earn her doctorate in American history at Emory University (Atlanta) in 1983. The following year, she joined the National Institute of Allergy and Infectious Diseases (NIAID).

While at NIH, she authored several books including *Rocky Mountain Spotted*

Fever: History of a Twentieth-Century Disease and, after she retired, *AIDS at 30: A History*.

To celebrate NIH's centennial year in 1987, **DeWitt Stetten, Jr.**, who at that time served as Senior Scientific Advisor to former NIH Director **James Wyngaarden**, founded the NIH Museum of Medical Research—later named in his honor—to preserve the instruments used for research at NIH. Harden was appointed Director, NIH Historian and Curator to implement the development of the Stetten Museum and the Office of NIH History.

Harden continues to serve the office as a special volunteer and considers herself a lifelong champion for NIH history. She conveyed the importance of connecting scientific and social milestones to weave a story on how they influence biomedical research trajectories. For example, after the death of actor Rock Hudson in 1985 from an HIV-related illness, the Reagan administration freed up money for HIV research, much of which was conducted at NIH.

Harden's advice to young people looking to make history? "When the door opens, one has to have trained well enough to walk through that door and seize the opportunity," she said.

CREDIT: THE OFFICE OF NIH HISTORY AND STETTEN MUSEUM

Anthony Fauci, NIAID, and **Victoria Harden**, ONHM, at the 1993 AIDS and the Public Debate Conference.

CREDIT: THE OFFICE OF NIH HISTORY AND STETTEN MUSEUM

Harden spoke at the opening of the second iteration of the exhibit about Nobel laureate Marshall Nirenberg in 2002.

Timely archival of history

"It is of key importance that NIH history continues to be written, as historians of the future will begin with evidence that we leave behind," said Harden.

She urges current leadership to ensure that oral histories are recorded, particularly for those investigators who are recognized in their fields, and that all scientists and administrators are educated in the need to document their work. In addition, focused history projects may be undertaken by professionally trained historians, NIH physicians, scientists, or administrators.

Harden encourages everyone to contact ONHM before they retire for advice about archiving photographs and documents and about donating instruments. "Seventy-five years from now an unidentified photograph is worthless unless it is cataloged," she said, "so it is important to capture identifying information before it is lost."

It is difficult to predict what will be historically significant tomorrow. Harden simply advises casting a broad net. Those materials will inform the stories that the American people—who ultimately fund NIH research—will value over time. ●

Satabdi Nandi, a postdoctoral fellow in the National Institute on Aging's Laboratory of Molecular Biology and Immunology, is investigating the generation of antibody diversity in mouse B cells. Outside of work, she enjoys visiting museums to learn about the past, diverse cultures, and the motivation behind artists' creations.

ONHM's History and Context seminar series will highlight historical topics of interest to the NIH community. Events will range from traditional lectures to conversations between those telling, and those making, history—with additional formats to be explored. The Harden Lecture will be delivered by a scholar of note who will speak on a topic that spotlights NIH's rich history. To watch the May 4 VideoCast of Harden's lecture, visit https://videocast.nih.gov/watch=49384.

since that first summit, scientists are narrowing in on some startling revelations about the nature of aging.

The ageless pursuit of understanding aging

The Buddha, Siddhartha Gautama, described aging as one of the three universal characteristics of existence and taught the importance of developing an understanding of impermanence and cultivating a mindset of acceptance. Aristotle observed that aging seemed to be influenced by lifestyle and family heredity and not solely determined by the passage of time.

Geroscience furthers our exploration of the concept and realities of aging, a science with philosophical undertones.

"There is no consensus definition of geroscience, but it can be understood as the search for ways to translate knowledge of molecular and cellular mechanisms of aging into ways to improve health at older ages," said **Ronald Kohanski**, Director of the Division of Aging Biology (DAB) at the National Institute on Aging (NIA) and organizer of the summit.

"Geroscience was founded upon an observation that age is the major risk factor for many diseases and the general decline of function over time," Kohanski told the *Catalyst*. "Age as the passage of time is not modifiable, [however] we know from basic research in the biology of aging that many aging traits may be reversed or accelerated, clearly indicating that *aging* is modifiable."

The term *geroscience* was popularized by **Felipe Sierra**, a past director of DAB who retired in 2020. Sierra has described geroscience as distinct from basic aging research in several ways. Whereas biology of aging research typically focuses on understanding the molecular and cellular mechanisms underlying the aging process—changes in gene expression and metabolism, for example—geroscience is a more interdisciplinary field that aims to apply insights from basic and behavioral research to delay the onset of age-related disease and to improve human healthspan and lifespan.

Strategies involve identifying new targets for drug development, exploring the potential of lifestyle interventions such as exercise and diet, or investigating the role of stem cells in aging and disease. As such, geroscience has a more translational focus than basic research in its quest for practical interventions to improve human health.

Sierra and Kohanski created the trans-NIH Geroscience Interest Group (GSIG) in 2012 as a platform to explore this integrative concept. In little over a decade, geroscience has become a mature, international field of research, as evidenced in part by the changing of the name of the journal *Age; Journal of the American Aging Association* to *GeroScience* in 2014.

Some notable advances in geroscience research at and funded by NIA include:

- Identification of aging biomarkers such as epigenetic changes, gene-expression patterns, and changes in the microbiome
- Development of senolytic therapies such as drugs targeting cells that secrete inflammatory factors and accumulate
- Revelation of the role of inflammation
- Advancements in genetic engineering to study the effects of specific genetic mutations on age-related diseases
- Identification of interventions that can extend lifespan in animal models, including caloric restriction

The first geroscience summit helped produce the geroscience hypothesis that slowing the rate of aging will improve health at older ages by delaying the onset of disease and reducing severity when diseases arise.

This fourth summit was "both retrospective and prospective," Kohanski said, in addressing how to leverage new technologies in a clinical setting while pushing the basic science to the next level.

Is prolonged aging extending suffering?

The fourth geroscience summit theme was "Geroscience for the Next Generation," a nod to younger investigators taking more interest in aging research. Divided nearly evenly over nine sessions and three seven-hour days—all archived at videocast.nih.gov—the summit brought together dozens of scientific presenters from diverse backgrounds, including several from the NIH intramural research program.

The first session, not addressed in previous summits, was on health disparities. Speakers included two NIH institute directors: **Eliseo J. Pérez-Stable**, Director of the National Institute of Minority Health and Health Disparities (NIMHD), and **Shannon Zenk**, Director of the National Institute of Nursing Research (NINR).

The session explored what may be obvious, that health disparities affect health negatively. Less understood, however, is the effect of disparities on the aging process and how these disparities affect an individual's health over their life course.

As seen in the broader field of geroscience, the data can seem contradictory.

- Some in marginalized minority populations with poor access to health care living remarkably long, healthy lives—clues that their longevity might lie in high levels of physical activity or the emerging scientific explication of resilience
- Certain non-industrialized Indigenous populations living traditional lifestyles, largely free of chronic disease of aging
- Younger populations with diseases such as cancer or HIV in which aging appears accelerated, likely as a result of chronic inflammation, among other causes

In the second session, Sofiya Milman, Associate Professor in the Department of Medicine at Albert Einstein College of Medicine (New York), set the tone with a slide that revealed that the true burden of aging is many years of declining health. The

onset of chronic disease, on average, extends from approximately age 50 to age 85.

Milman said she and her colleagues are focused on a target to delay the onset of poorer health to a five-year range around age 80 and compress that 30-year span to just five years. A more ambitious goal is to delay the onset of chronic disease until age 90, population wide.

"This is a very realistic, biologically plausible concept," Milman said, "because we do have people among us—people who live very long lives, centenarians and supercentenarians—who don't only live to age 100 and beyond but also maintain their health almost the entirety of their lives."

> "Many aging traits may be reversed or accelerated, clearly indicating that aging is modifiable."
>
> – RONALD KOHANSKI, NIA

Milman presented data revealing how most centenarians, compared with people with average lifespans, delay the onset of morbidity by up to 30 years. How?

Research points to strong genetic factors: poorly defined "longevity genes," many related to hormonal pathways. One biological pathway involves signaling via growth hormone and insulin-like growth factor-I, Milman said. Diminished signaling via this pathway appears to delay aging, resulting in longer healthspan in both animal models and humans.

To better understand the protective genetic variants that promote healthy aging, Milman and colleagues launched the SuperAgers Family Study in 2022 with the goal of recruiting 10,000 people aged 95 or older with no significant cognitive impairment, like jazzman Marshall Allen.

Luigi Ferrucci, NIA Scientific Director, explained the global increase in life expectancy over the last 180 years: from age 45 to about age 85. But with that came an increase in the years with disability.

"The problem is that this incredible success in [prolonging life expectancy] comes with taxes," Ferrucci said. That tax includes extending illness and disability during that longer lifetime.

One problem appears to be that disease begets disease. Males over age 70 with a single chronic disease have a 20% chance of developing a second disease. If they have two diseases, they have a 23% chance of developing a third. If they have three diseases, they have a 31% chance of developing a fourth. And if they have four diseases, they have a 51% chance of developing a fifth.

This is multimorbidity, which is the co-occurrence of two or more chronic conditions so common among the elderly, and geriatric syndromes, a catch-all category crudely summed up in the expression "it sure does suck getting old."

Geriatrics traditionally treats diseases as they develop. But geroscience may lead to an era of proactive geriatric medicine, Ferrucci said. "Imagine you can affect the process that leads to disease instead of treating the disease," Ferrucci told the *Catalyst*. "That would be a complete revolution in health care. You can make the best healthcare in the world, but if you are only mitigating the disease that is already there, you only expand the period that people live with this disease; you never expand the period of life that is characterized by [good] health and the enjoyment of life. Geroscience is the promise that this will be possible."

Mathematics of aging

Summit speakers also explored the mathematics of aging: methods for measuring good health and modeling declining health. The progress in development of biomarkers was presented by **Nathan Basisty**, an NIH Distinguished Scholar in the NIA Translational Geroproteomics Unit.

Stratification biomarkers hold great promise in this regard, Basisty said, directing the audience to the work of Stephen Kritchevsky, a professor of gerontology and geriatric medicine at Wake Forest University School of Medicine (Winston-Salem, North Carolina).

Stratification biomarkers can include a variety of measures—epigenetic marks, telomere length, circulating proteins, and metabolites—that change with age and can be used to estimate biological age. Such biomarkers can help target interventions to those who are most likely to benefit.

NIH Intramural's Role

"Intramural research at NIH plays a critical role in advancing geroscience," Kohanski said, naming just a few contributions to date:

- Senior Investigator **Rafael de Cabo**, Translational Gerontology Branch, develops methods and interventions that support healthy aging and prevent or delay the onset of functional decline and age-related disease
- The Baltimore Longitudinal Study of Aging (BLSA) examines heterogeneity in human health and function with age
- The IRP-led Study of Longitudinal Aging in Mice serves as a comparative animal model counterpart to the BLSA

Summit organizers noted that there is no universally accepted meaning among clinicians for the concept of geroscience. This hinders the creation of clinical trials and thus the direct clinical applications of geroscience. As such, we have yet to capitalize on geroscience as a clinically helpful tool for predicting health outcomes, preventing disease, enhancing resilience, and treating geriatric syndromes. ●

All three days of the summit are archived individually at https://videocast.nih.gov. The third day's recording, at https://videocast.nih.gov/watch=49460, concludes with a nice overview of the entire summit—in case you are worried about aging too much while watching the entire event.

With an Eye to the Future

Kapil Bharti is NEI's New Scientific Director

BY DEVIKA BOSE, NEI

CREDIT: DUSTIN HAYES, NEI

Kapil Bharti is NEI's new Scientific Director

KAPIL BHARTI WAS NAMED Scientific Director of the National Eye Institute (NEI) in May. Bharti will support the NEI mission to eliminate vision loss and improve quality of life through vision research.

"Dr. Bharti is a world-class translational vision scientist, a thoughtful planner who understands interdisciplinary work, and an outstanding leader," NEI Director **Michael F. Chiang** told the *Catalyst*. "I am very excited about the energy and ideas he will bring to NEI and about the collaborative opportunities with other institutes at NIH and beyond."

Bharti is best known for his research on degenerative eye diseases using induced pluripotent stem (iPS) cells. His lab continues to refine that technology and identify potential therapies for vision loss through collaborative work with the National Center for Advancing Translational Sciences.

Vision researchers have been among the first to embrace advanced technologies such as single-cell genomics, data science, and artificial intelligence to bring cell and gene therapies to patients. As scientific director, Bharti plans to continue that trend and use those and other cutting-edge techniques in new ways. "It is exciting for me to combine all these technologies to further both basic and translational vision science," he said. And as a seasoned mentor, he has an eye toward the next generation. "[We need to] train our fellows not only to become dedicated scientists but also to become modern-era leaders that work on equity and diversity," he said.

Bharti's journey at NIH started in 2004 as a Postdoctoral Fellow in **Heinz Arnheiter's** lab in the National Institute of Neurological Disorders and Stroke. Arnheiter suggested books by evolutionary biologist Richard Dawkins and nurtured Bharti's interests through lab projects, such as studying the roles of transcription factors MITF and PAX6 in eye development. Those two transcription factors regulate genes critical to the formation of a tissue called the retinal pigment epithelium (RPE) that supports the photosensitive part of the retina.

Bharti has since authored over 50 peer-reviewed papers and 30 reviews and book chapters. His work was among the first to reveal the importance of cooperative actions of transcription factors in pigment biology and eye development (*PLoS Genet* **8**:e1002757, 2012; *PLoS Genet* **10**:e1004360, 2014); show the role of primary cilium in cell maturation (*Cell Rep* **22**:189-205, 2018); describe a path for an autologous iPS cell-based therapy (*Sci Trans Med* **11**:eaat5580 2019); and use artificial intelligence-based cellular image analysis as a release criteria in cell therapy (*J Clin Invest* **130**:1010-1023, 2020).

Bharti was named NEI's first Earl Stadtman Investigator in 2012. That year he started the Ocular and Stem Cell Translational Research Section, part of the Ophthalmic Genetics and Visual Function Branch (OGVFB).

His lab uses RPE cells as an in vitro disease model for studying conditions such as age-related macular degeneration (AMD), late-onset retinal degeneration, and Stargardt disease. Patient RPE is generated by using iPS cells, which are created by collecting and then reprogramming a patient's own blood or fibroblast cells.

According to OGVFB Chief **Brian Brooks**, Bharti has a reputation for innovation. For example, previous NEI Scientific Director **Sheldon Miller** designed a project in collaboration with Bharti to transplant an RPE patch created from an AMD patient's stem cells to cure blindness. Because a major caveat of transplanting tissues and organs into humans is rejection, the scientists generated the AMD patient's own stem cells in the lab. Bharti led a team that carried out preclinical studies for the RPE patch transplant, ultimately obtaining FDA approval for the procedure. In August 2022, an AMD patient at the NIH Clinical Center became the first person in the United States to successfully undergo an iPSC-RPE transplant.

Bharti's early interest in biology was instilled by his mother, who was a science teacher. He earned a master's degree in biotechnology at the Maharaja Sayajirao Rao University of Baroda (Vadodara, Gujarat, India) and his doctorate in molecular cell biology from Johann Wolfgang Goethe University (Frankfurt, Germany) in 2003. He credits his diverse educational background as foundational for his success in translational and collaborative research. Outside of work, he enjoys jogging or sitting down to a good spy and political suspense show. And after hours, you might find him hanging out with lab colleagues at their regular haunts in downtown Bethesda. ●

Devika Bose is a molecular and stem-cell Research Associate in Bharti's lab in the Ocular and Stem Cell Translational Research Section and uses stem-cell-derived RPE cells to study different retinal degenerative diseases. Outside of work, she enjoys traveling, cooking, hiking, binge watching programs on Amazon Prime, and reading.

Bioengineering to Advance by Collaboration and Inclusion

Manu Platt and the Trans-NIH BETA Center

BY STEPHEN ANDREWS, NCI

CREDIT: ALLISON CARTER, GEORGIA INSTITUTE OF TECHNOLOGY

Manu Platt is director of the trans-NIH Biomedical Engineering Technology Acceleration (BETA) Center.

"I AIM TO BE THE SCIENCE connector," said **Manu Platt** of his role as director of the newly created trans-NIH Biomedical Engineering Technology Acceleration (BETA) Center. Established by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) in January, the BETA Center will serve as a hub for expert teams of technology developers at the NIH intramural program and beyond to work together to rapidly address pressing health needs.

NIBIB chose wisely with its recruitment of Platt, who joined NIH in February (*Read more about Platt's education and professional background at* https://irp.nih.gov/catalyst/31/3/colleagues-recently-tenured). With a passion for collaboration in an interdisciplinary environment, Platt can leverage his broad experience in tissue regeneration, cardiovascular bioengineering, and HIV and AIDS outreach to foster scientific innovation that cultivates systemic improvements in health care technology across the globe.

"Science is a people business," said Platt, who also serves as NIBIB's Associate Director for Scientific Diversity, Equity, and Inclusion. Indeed, his research has long been motivated by adopting an inclusive mindset.

"Bioengineering is primarily about communication and brainstorming exciting ideas with others, the opportunity to bring fresh ideas and fresh faces to the table when solving problems," he said. "Let's bring that [mindset] to the NIH."

The goal of the BETA Center is to develop cutting-edge, broadly applicable technologies that enable scientists to answer medicine's big questions. One unit is perfecting more powerful and precise microscopes; another unit is a microfabrication laboratory, led by BETA Center Deputy Director **Nicole Morgan**, where scientists can design devices to the precise specifications required for their experiments. Platt's own lab is involved in understanding how strokes occur in children with sickle-cell disease using computational fluid dynamics, imaging, and biological methods. They hope the BETA Center's modeling capabilities and collaborations with NIH clinicians might lead to more predictive diagnosis and treatment options.

Other areas of emphasis will include wearable biosensors, engineered and synthetic biology, nanomaterials and biomaterials, artificial intelligence, computation, and informatics.

Bioengineering and medicine are inherently interdisciplinary, Platt said, which is why a fundamental objective of the BETA Center is to expand upon diversity, equity, inclusion, and accessibility to maximize the flow of creative ideas. Platt aims to apply such experiences as BETA Center Director. One strategy he will use is listening sessions structured to provide an equal playing field in a lab or office and allow everyone on the team to provide input and feedback.

Ready to get a project off the ground with BETA? Platt invites interested researchers to email him or Morgan directly to start.

An online portal and website for engineers seeking to collaborate and access BETA Center services is in the works. "In the near future, an interested investigator will have a discussion with a dedicated group of BETA Center expert scientists and engineers to learn the needs and directions of that researcher and guide them toward resources they know about and perhaps other techniques that they did not know about, but could be incredibly useful for their research goals," said Platt.

He adds that potential scientists should expect to discuss their research goals, find practical solutions to their questions, and be trained on new equipment, software, and techniques. "We are working on building relationships that lower the administrative hurdles to accessing new resources that may be housed within other institutes. The goal here is to lower the bar to trying new things and novel technologies."

Platt is optimistic for the future. "Science can bring people together," he said, adding that valuing other's ideas and giving them a platform to share can be a catalyst for simultaneously improving both the diversity and the power of research conducted at NIH.

"We need to make sure that engineers know that there is a community here." ●

Stephen Andrews, a postbaccalaureate research fellow in the National Cancer Institute, is studying molecular genetics and tumor modeling related to neuroendocrine tumors of the small intestine and pancreas. Outside of the laboratory, he enjoys running, cycling, cooking, and visiting art galleries.

To learn more about collaborating with and accessing BETA Center services, email Manu Platt (manu.platt@nih.gov) or Nicole Morgan (morgann@mail.nih.gov).

Measuring Metabolism at the Speed of Light

Irene Georgakoudi's WALS Lecture on Label-Free, High-Res Imaging

BY ANNELIESE NORRIS, NCI

CREDIT: TUFTS UNIVERSITY

Irene Georgakoudi is pushing the envelope with a new, advanced imaging technique that has the potential to detect cancer earlier, assess disease progression, and inform better treatments.

Bioengineers build tools, always pushing the envelope on what is possible. They make technology better, faster, or easier to use. A new, advanced imaging technique can—quite literally—shine light on the potential to detect cancer earlier, assess disease progression, and inform better treatments.

On May 24, Irene Georgakoudi, Professor of Biomedical Engineering at Tufts University (Boston, Massachusetts) delivered a Wednesday Afternoon Lecture Series (WALS) talk, "Label-Free Monitoring of Metabolic Function with Micron-Scale Resolution: From Mitochondria to Humans," describing such advances.

Celebrating the spirit of collaboration that runs deep in the bioengineering community, Georgakoudi's visit to NIH was part of a two day mini-symposium that included poster presentations and lectures organized by the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

"Her analysis techniques go way beyond the traditional approaches," said NIBIB Director **Bruce Tromberg** in his welcome to Georgakoudi, who is also director of the Advanced Microscopic Imaging Center at Tufts. "In fact, she is the first in our field to generate unique mitochondrial information content from subwavelength structures; it's a kind of functional super-resolution."

Metabolic function as a measure of health and disease

Understanding and measuring how cells metabolize energy gives key information on the health of our busy mitochondria, which play an essential role in aging and the development of diseases such as cancer, aging, osteoarthritis, and neurodegenerative and cardiovascular diseases. However, current established methods to assess metabolic function such as radiographic, exogenous label, or mass-spectroscopy-based approaches can be invasive, often require contrast agents, or lack resolution.

"One of the challenges we're particularly interested in addressing regarding [measuring] metabolic function is that metabolic changes are highly dynamic, some occurring in the context of milliseconds," said Georgakoudi. "Others we would like to be able to monitor over weeks, days, and years." Another challenge has been detecting different metabolic states often present in cells right next to each other.

To address such challenges, the Georgakoudi lab pioneered the use of label-free, non-linear two-photon optical microscopy. This powerful imaging technique relies on lasers that emit short pulses of long-wavelength, low-energy photons that penetrate into living tissue while minimizing tissue damage. When two of these photons are absorbed at the same time by NADH and FAD, they cause fluorescence. NADH and FAD are two naturally present co-enzymes associated with an array of metabolic pathways and mitochondrial status. The resulting 3D micron-scale-resolution images are then analyzed for insights into the metabolic condition of the sample tissue.

Broad application for label-free, non-linear optical imaging

"We hope to change the paradigm of cervical precancer detection," said Georgakoudi of a promising use for the optical imaging technology. Her team identified significant differences in mitochondrial organization and metabolic function between healthy cervical tissue and pre-cancerous lesions. She envisions a future where a two-photon microendoscope might be used in the clinic instead of biopsies to quickly and accurately diagnose precancerous lesions, which could then be treated on the spot.

Her new imaging approach has also revealed distinct mitochondrial organization in the living cells of patients with vitiligo, an autoimmune condition resulting in patches of skin-pigment loss.

Further analysis has found that those lesions secrete inflammatory factors which may drive disease persistence. Because the optical imaging technique is non-destructive, Georgakoudi's team is able to monitor how each patient responded to a skin grafting procedure over the course of several weeks.

Optical metabolic imaging may also give clues into life-extending pathways and lead to treatments for age-related diseases. Using the nematode *Caenorhabditis elegans* as a model, Georgakoudi and colleagues have demonstrated that worms deprived of a riboflavin transporter had better metabolic health and significantly longer

lifespan, compared to controls.

Joint health can be assessed, too. In a mouse model for osteoarthritis, the optical imaging method detected very early metabolic remodeling changes in injured joint cartilage, before the onset of pain. The findings demonstrate how a better understanding of disease progression might improve how and when treatment is delivered.

As bioengineers do, Georgakoudi is poised to continue innovating, pushing the envelope of technology. "Our label-free two-photon optical metabolic imaging approaches reveal some very unique insights about metabolic function in living specimens and especially in humans" she said, but added, "We still have a way to go if we want to improve the way we diagnose and treat disease." ●

Anneliese Norris, a postdoctoral fellow at the National Cancer Institute, is studying how signal interactions coordinate limb development. In her spare time, she enjoys reading and building with LEGO.

A VideoCast of Irene Georgakoudi's lecture is available at https://videocast.nih.gov/watch=46083 (NIH only).

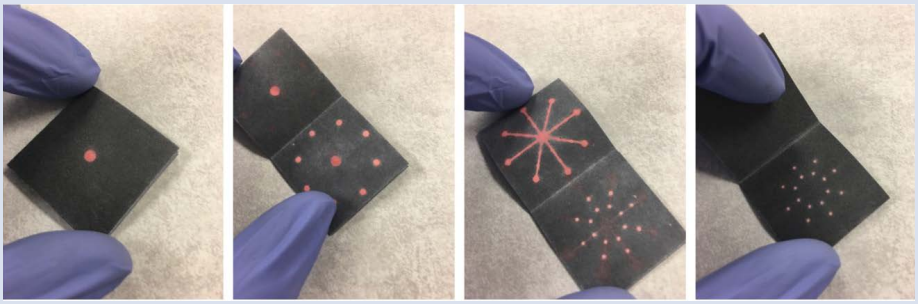
Bioengineers Collaborate, Innovate, Across NIH

BY MICHAEL TABASKO, OD

Wearable sensors, rapid diagnostics, biomaterials that speed up healing and deliver cancer vaccines, and more: On the day before Georgakoudi's WALS lecture, a gathering of bioengineering experts assembled for what was billed as a "conclave" to "highlight novel biomedical imaging and engineering technology that they develop, and use, in their work," according to Steven Zullo, a program officer with the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Zullo and fellow NIBIB Program Officer Afrouz Anderson organized the event, which also showcased poster presentations on the FAES Terrace. Here's a glimpse of the creativity applied to real world problems.

Creating lifesaving diagnostics: Diarrhea is a leading cause of childhood mortality in developing countries, but a low-cost diagnostic tool called the Paper Origami Multiplex Sensor has the potential to change that. **Lichen Xiang**, a research fellow at the National Institute of Nursing Research, developed the rapid, point-of-care test that detects eight common gastrointestinal pathogens in stool with over 98% accuracy and sensitivity.

Many more snapshots of bioengineering innovations are available to read online at https://irp.nih.gov/catalyst/31/4. The talks given by NIH intramural investigators are archived at https://videocast.nih.gov/watch=49750.



CREDIT: LICHEN XIANG, NINR

Shown is the paper origami multiplex sensor developed by Lichen Xiang which detects eight common gastrointestinal pathogens in stool for making rapid and accurate diagnoses in developing countries.

NIH Research Festival Coming Into Focus

The first "celebration of intramural science" since 2019

Save the Date
September 18–22, 2023

LECTURES, POSTERS, INFORMATION TABLES, VENDOR EXHIBITS

Special events:
9/21 – NAS Mini-Symposium
9/22 – Philip Chen Technology Transfer Lecture

Watch the evolving agenda at
https://researchfestival.nih.gov

NIDCR Celebrates 75 Years of "Scientific Strides"

BY MICHAEL SOMES, NIDCR

CREDIT: NIDCR

Harold Slavkin, former NIDCR director, at a brainstorming session to create the NIDCR mission, which today reads: "Our mission is to advance fundamental knowledge about dental, oral, and craniofacial (DOC) health and disease and translate these findings into prevention, early detection, and treatment strategies that improve overall health for all individuals and communities across the lifespan to promote oral health for all."

During the Second World War, rampant tooth decay disqualified nearly 20 percent of military recruits from service. To address this issue, President Truman signed legislation on June 24, 1948, to create what would eventually become the National Institute of Dental and Craniofacial Research (NIDCR). Today, NIDCR is celebrating its 75th anniversary by highlighting past accomplishments and presenting a vision for the future.

No fewer than three former NIDCR directors—**Harold Slavkin**, **Lawrence Tabak**, and **Martha Somerman**—as well as NIDCR's current director, **Rena D'Souza**, took the stage to trumpet NIDCR history in March at the annual conference of the American Association for Dental, Oral, and Craniofacial Research in Portland, Oregon. This well-attended, two-hour symposium was titled "Scientific Strides of the NIDCR: 75 Years and Beyond."

Slavkin, while director, invited groups of then-National Institute of Dental Research (NIDR) employees, about 10 at a time, to join him for discussions to promote greater collaboration. One topic of frequent discussion was how to better capture the breadth of NIDCR's research portfolio. Ultimately, these efforts culminated in persuading Congress to add "Craniofacial" to NIDR's name, leading to its present initials and reflecting the institute's broadened research mission.

Tabak emphasized the key role collaboration across the institute played in moving NIDCR forward. He specifically highlighted the role NIDCR played in Medicaid's policy to reimburse pediatricians for preventative care.

Somerman further expanded connections across disciplines and increased NIDCR's clinical research efforts. Each set the stage for D'Souza, who has since built upon Somerman's progress to address the "fuzzy middle" of preclinical research that occurs between basic science efforts and clinical trials. D'Souza emphasized the need to stay nimble and flexible, while always centering the patient. As with the other directors, her efforts to keep expanding NIDCR's network of collaborators and new researchers is ongoing.

"Seventy-five years ago, Harry Truman was scratching his head" at the epidemic of dental decay affecting Americans, D'Souza reminded the audience. "He felt the need to create a national institute that would look at the biology of this condition. We stay true to that mission today."

Continued advancement

NIDCR's intramural research advancements that have shaped dentistry and oral medicine were discussed and celebrated at the symposium. The research projects, ranging from molecular-level basic science studies to translational work and clinical treatments, were presented by six NIDCR intramural investigators.

- **Marian Young**, Deputy Scientific Director, Senior Investigator, Molecular Biology of Bones and Teeth Section
- **Pamela Robey**, Senior Investigator, Skeletal Biology Section
- **John Chiorini**, Associate Scientific Director, Scientific Resources; Chief, Adeno-virus Associated Biology Section
- **Niki Moutsopoulos**, Associate Scientific Director, Tenure Track/Assistant Clinical Investigator Faculty Development and Investigator, Oral Immunity and Infection Section
- **Ashok Kulkarni**, Senior Investigator and Chief, Functional Genomics Section; Director, NIDCR Gene Transfer Core
- **Janice Lee**, Clinical Director and Chief, Craniofacial Anomalies and Regeneration Section

Young kicked off the section by presenting her work on how bones form. That knowledge might reveal ways to use tissue engineering and regenerative medicine to ameliorate specific musculoskeletal diseases.

"You have to figure out how things work before you can figure out how to fix them," Young said. (*See sidebar to learn more about Young's work.*)

Robey highlighted the role played by specialized bone-marrow fibroblastic cells in building and dismantling bone. Fibroblasts secrete proteins that help construct and maintain the structural framework of tissues. Robey is interested in the role these cells play in replacing and regrowing tissues that have been lost to disease or injury.

Much of Robey's work involves developing animal models to study bone and cartilage defects and characterizing the various cell types that might function as tools for regenerating human tissue.

Gene therapy represents another area that has advanced during NIDCR's 75 years of research. Chiorini is exploring ways to repair the salivary gland after being damaged by cancer-treatment radiation. Development of this therapy began almost 40 years ago. Over the past 20 years, NIDCR researchers have addressed critical steps in the process such as how to introduce new genes to the salivary gland, which genes to introduce, and which animal models are best to test the techniques.

The Gene Transfer Core at NIDCR has produced transgenic and knockout animal models for use in preclinical research across NIDCR's extramural and intramural programs, Kulkarni added.

CREDIT: NIDCR

CREDIT: NIDCR

NIDCR Director **Rena D'Souza** (left) moderates a panel of NIDCR intramural researchers (from left to right) **Pamela Robey**, **Marian Young**, **Janice Lee**, **Ashok Kulkarni**, **John Chiorini**, and **Niki Moutsopoulos**.

NIDCR's research has stretched to the broader fields of microbiology and immunology, according to Moutsopoulos. She and colleagues aim to leverage their focus on rare diseases to better understand the basic biology of human oral diseases, including common forms of periodontitis.

Lee highlighted two recent, pandemic-era clinical studies, which included the identification of SARS-CoV-2 in the oral cavity, and a treatment study for fibrous dysplasia, a rare disease in which bone is replaced with fibrous scar tissue. Lee also highlighted how NIDCR's seven clinical investigators and the team of nurses, physicians, and support staff in the Clinical Center form a strong network and build successful collaborations.

Still much to do

D'Souza shared an ambitious vision for the next 25 years. She hopes NIDCR research will help to achieve the following:

- Make salivary screening a regular part of oral health
- Contribute to a 50% reduction in the prevalence of dental cavities
- Identify the connections between periodontal disease and systemic conditions
- Prevent head and neck cancers

We will report back on our progress in these areas and more in 25 years—when NIDCR turns 100. ●

Michael Somes is a writer and editor with NIDCR's Office of Communications and Health Education. When he's not writing, he can be found on Minnesota's bike trails or ski hills, depending on the season.

Looking Back on 42 Years with NIH

Young reflects on science and mentorship.

Michael Somes: What was it like working at NIDCR when you first joined?

Marian Young: I came from a small operation at the University of Connecticut, so when I got to NIH the labs really seemed like mega labs.

Somes: Any advice you could share on your mentoring approach?

Young: Everyone you mentor is different. They have different career goals and interests, so you need to be flexible and tailor your approach to fit their needs.

Somes: What advice would you give to colleagues just starting their research careers at NIH?

Young: Find a niche for yourself, something that is unique to you. With NIH you are really only limited by your ideas, your focus, and your discipline. Enjoy the ride.

Read the full interview in the online version of this article at https://irp.nih.gov/catalyst/31/4.

CREDIT: BILL BRANSON

The NIH Catalyst featured Young's mentorship of an aspiring dentist in the May-June 2014 issue.

Nurturing Diversity in STEM

Lessons Learned from Studying the Microbiota

BY TAYLOR FARLEY, NIAID

CREDIT: TAYLOR FARLEY

A HEALTHY MICROBIOME IS A diverse microbiome, not unlike the workplace.

The origin of research on microbiota, microorganisms found in a specified environment, dates back to the late 1600s with Dutch scientist Antoine van Leeuwenhoek's revolutionary development of the microscope, which he used to observe "animalcules," now known as bacteria, from his own oral and fecal microbiota.

The definition of the microbiota has since been expanded to include all organisms living within and upon the body, including bacteria, viruses, fungi, and protozoa.

Most of these microorganisms are indispensable for nutrient acquisition. They provide resilience from infection and are key educators of the host immune system. Recent reports have linked the microbiota to driving host responses to immunization, cancer therapies, and development of allergic and inflammatory diseases. Put simply, humanity would not be able to thrive without our microbial companions.

An observable pattern emerges throughout these studies: highly diverse microbiota typically indicates a healthy host system. Conversely, in disordered states there is often an establishment of a dominant microbe, or class of microbes, that might provoke disease.

The prevailing theory is that diversity of our gut microbial ecosystem equates to health and links to host resilience, adaptation, and evolution. Thus, many therapeutic advancements targeting the microbiota focus on establishing or supporting a variety of bacteria for the betterment of the host.

Diversity in STEM and the problem of attrition

But these evolving scientific concepts cheering on diversity must not remain solely under the microscope. We need diversity, equity, inclusion, and accessibility (DEIA) throughout our workplace as well.

Science, Technology, Engineering, and Math (STEM) are the pillars of innovation and discovery. The fruits of these fields impact us all, from the medicine that cures our ailments, to the technology we use daily. To combat biases in these innovations, it is vital that the individuals designing protocols, performing studies, and developing novel technologies reflect the diverse populations that their products and discoveries will affect.

Further, research from the business sector parallels what we see when studying the microbiota—diversity within the workforce breeds resilience and improves innovation. In fact, mathematical frameworks to model teams of problem solvers conclude that identity-diverse groups outperform more homogenous groups due to greater functional diversity and ability to source solutions from multiple angles.

Attrition within STEM is highest in women, underrepresented minorities, first generation students, and those from low socioeconomic backgrounds. NIH workforce surveys have highlighted challenges in maintaining diversity, particularly in positions of senior leadership. Given these results, it then begs the question of how we can better establish and support growth of these vital members of our NIH community.

Best practices

In 2021, the National Science and Technology Council, released "Best Practices for Diversity and Inclusion in STEM Education and Research: A Guide By and For Federal Agencies." These guidelines identify barriers to DEIA in STEM, including discriminatory policies, hostile workplace climate, compensation disparities and cost of education, lack of support and mentorship, fear of stereotyping or bias, and inaccessibility for individuals with disabilities. Reflecting upon these barriers, the council suggests four areas for advancing DEIA within STEM.

STEM Pathways: Investigate why individuals enter and exit STEM careers and create pathways to success. For example, the National Institute of General Medical Sciences grants Science Education Partnership Awards to support educational activities that encourage the engagement of individuals from diverse backgrounds within the biomedical sciences.

Access and Recruitment: Develop initiatives that combat barriers to entry and improve outreach to minority-serving institutions.

Retention: Foster nutrients that are required to retain and encourage the growth of diverse community members. The NIH recently released "The Fiscal Years 2023-2027 NIH-Wide Strategic Plan for DEIA" which outlines key

DEIA measures for both intramural and extramural NIH-funded labs.

Achievement and Advancement: Increase access and opportunity, motivation, and morale for achievement with DEIA in mind. For example, the NIH Distinguished Scholars Program recruits investigators who have a commitment to building diversity within the biomedical research workforce.

DEIA belongs in STEM *and* in our microbiota

Allow me to take the microbiota analogy one step further. There are two commercially available strategies to promote a healthy gut ecosystem: probiotic and prebiotic therapies. Probiotic treatments seed a few well-defined "good" bacteria into the gut, and prebiotics are compounds that specifically encourage the growth of favorable bacteria. Supplements containing both are termed synbiotics. It is likely that synbiotics will soon become commonplace.

From synbiotic to synergistic, diversity is the future of microbiota research and STEM at-large, and DEIA *is* the future of NIH. Similarly, it is not sufficient to bring 'biotics or underrepresented individuals into milieus that are not built to support and sustain them. If we want to foster longstanding diversity within our STEM ecosystem, we must study the factors necessary to nurture these vital members of our community and apply solutions for the health and betterment of us all.

Diversity is our strength—both in our guts and at the precipice of discovery. ●

Taylor Farley is a doctoral candidate at the University of Oxford studying innate-like immune responses to the microbiota in the gut during homeostasis and inflammation. When not in the NIAID lab, she enjoys playing guitar, rock climbing, and cheering on The Roommates during their Sunday LGBTQ+ Stonewall Kickball season.

"Give Me My Flowers"

New NIH EDI Director's Speaker Series kicked off May 10

BY *NIH CATALYST* STAFF

EDI Director **Kevin Williams** gifted **Yvonne Thompson Maddox** a painting as a thank you gift. "This gift from us to you is representative of us trying to give you your flowers while you're still here to enjoy them," Williams said to Maddox, reminiscing about the song he often sung in church titled "Give Me My Flowers."

The first NIH Office of Equity, Diversity, and Inclusion (EDI) Director's Speaker Series event was hosted May 10 featuring a fireside chat between EDI Director **Kevin Williams** and longtime NIHer, **Yvonne Thompson Maddox**.

Maddox, now retired, worked her way up through the ranks from health administrator to former Acting Deputy Director of NIH, as well as Deputy Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. She also served as Acting Director of the National Institute on Minority Health and Health Disparities.

Maddox was Senior Strategic Advisor for the NIH Path to Excellence and Innovation Initiative, an effort aimed at equipping Historically Black Colleges and Universities (HBCUs) with tools and resources needed to successfully compete for NIH funding opportunities. She also was a big supporter of the NIH Medical Research Scholars Program.

"In policy and practice, a commitment to DEIA is everyone's responsibility," she said, as she reflected on her time at NIH. Her fondest memories rested upon all the mentees and mentors she met along the way—in particular, she highlighted the advocacy and support of NIH's first woman director, **Ruth Lillian Kirschstein**.

Williams said scientific progress relies on diversity. "Science is an inherently collaborative and interdisciplinary field and scientific breakthroughs often come from a combination of different perspectives, skills, and backgrounds," he said.

"A lack of diversity in the workforce can hinder scientific progress by limiting the range of perspectives and ideas that are brought to the table. Diverse teams perform better than homogeneous ones both in terms of scientific outcomes and team dynamics. By promoting EDI in science, we can demonstrate our commitment to fairness, transparency, and social responsibility, which can help build public trust in science." ●

The EDI Director's Speaker Series aims to promote cultural awareness and provide learning opportunities for the NIH community through this new series. For more information visit https://www.edi.nih.gov/.

Hail to the Helix

CONTINUED FROM PAGE 1

National DNA Day was designated by Congress and recognized annually on April 25 to commemorate the successful completion of the Human Genome Project in 2003 and the discovery of DNA's double helix in 1953.

2003 and the discovery of DNA's double helix in 1953. The day celebrated those intersecting milestones and featured thought-provoking discussions about the present state of genomic research—even daring to entertain with a spirited competition between former NHGRI and NIH Director **Francis Collins** and current NHGRI Director **Eric Green** to determine who is the G.O.A.T. (Greatest of All Time) NHGRI director.

The April 25 VideoCast is available at https://www.genome.gov/event-calendar/NHGRI-National-DNA-Day-20th-Anniversary-Symposium.

Genomics research across NIH

The March–April 2003 issue of the Catalyst highlighted Green's vision for genetics research as the newly minted NHGRI Scientific Director. He predicted that the coming era would be defined by "figuring out what are the best ways to use the fruits of the HGP for doing research into human genetic diseases." The ensuing years have both enhanced our understanding of who we are and provided fresh challenges. Now as NHGRI Director, Green moderated a panel discussion at DNA Day about how the HGP and NHGRI have influenced research across NIH.

Human development

At the start of life, genetic testing has the potential to diagnose a myriad of disorders. However, gaps still remain in our knowledge of gene expression during human development; it is imperative to understand developmental gene expression in the placenta, in the fetus, in the young infant, and throughout childhood, according to **Diana Bianchi**, Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Bianchi spoke about the importance of trans-NIH collaborations, such as the Developmental Genotype-Tissue Expression project.

Partnerships have long existed between NICHD and NHGRI. A collaboration between Green's lab and NICHD two decades ago identified a gene responsible for a common form of inherited deafness. At that time, Green was dreaming about "what's going to be one of the largest zebrafish facilities in the world," he said to the *Catalyst* (March–April 2003, page 6). Zebrafish (*Danio rerio)* have since become an important model organism to study human genetic diseases. In 2012, a state-of-the-art zebrafish core was built, and NIH-wide research has since uncovered the genetic underpinnings of several human health conditions including cholesterol metabolism and human growth anomalies.

Fueled by tech

On the heels of the HGP's completion, NHGRI was eager to tackle hard problems. "How do you grapple with massive data sets, study thousands of genes all at once, and mine this information efficiently to find genes that are implicated in human disease?" asked Green (March–April 2003, page 6). Technology, it turns out, was the answer.

Josh Denny, Chief Executive Officer of the *All of Us* Research Program, touched on the staggering leaps in technology that have fueled the genomics boom—advances in cloud computing, data storage, and access to electronic health records have been transformative. Moreover, sequencing costs

CREDIT: NHGRI

NCATS Director **Joni Rutter** holds up original copies of *Nature* and *Science* from February 2001 highlighting the publication of a working draft of the human genome, as NICHD Director **Diana Bianchi** (right), coparticipant in a panel discussion, listens.

CREDIT: NHGRI

NHGRI Acting Deputy Director **Vence Bonham, Jr.**, asked Columbia University's Sandra Soo-Jin Lee, and Genevieve Wojcik of Johns Hopkins, how genomic research can be strengthened by more accurately describing people and the things that have an impact on their health.

have fallen from "billions to hundreds," said Denny. Still, access to all those data pose new questions, such as how to take complex data and make it useful and transparent to health care providers.

Not just genes

National Heart, Lung, and Blood Institute Director **Gary Gibbons** studies racial health disparities in cardiovascular disease. Before coming to NIH in 2012, he was one of the first extramural investigators to receive funding to study changes in the epigenome in cardiovascular biology.

"Why do African Americans have a higher risk of hypertension?" Gibbons once asked his Harvard Medical School professor. That professor urged him to explore the genetic component, even if other factors were at play. Gibbons did just that, and he reflected on how partnerships with NHGRI have been instrumental in understanding the molecular basis of hypertension and hypercholesterolemia, and how it now informs precision medicine programs. He has a deep appreciation of how other factors—the proteome, microbiome, and exposome—interact with gene expression. Gibbons established a new protocol called GENE-FORECAST, which is the Genomics, Environmental Factors and the Social Determinants of Cardiovascular Disease in African-Americans Study.

From A-T-C-G to the clinic

National Center for Advancing Translational Sciences (NCATS) Director **Joni Rutter** remarked on the exciting evolution of gene therapy, particularly to treat rare conditions caused by gene mutation. NCATS was born from the HGP; it was founded in 2011 to usher basic science findings through the translational-science pipeline. Notably, the Early Translation Branch, formerly known as the NCATS Chemical Genomics Center and originally the NIH Chemical Genomics Center, was created in 2008 to translate the HGP into biology and disease insights leading to new therapeutics.

Rewind to 20 years ago, and then-new NHGRI Clinical Director **William Gahl** was interested in rare diseases "beyond just knowing what the gene is, [but] being able to develop therapies" (March–April 2003, page 4). Gahl created the Undiagnosed Diseases Program in 2008 (September–October 2010, page 1), which grew into a worldwide model one decade later (May–June 2021, page 14).

Rethinking population descriptors

Researchers and scientists who use genetic and genomic data should rethink and justify how and why they use race, ethnicity, and ancestry labels in their work, according to a new National Academies of Sciences, Engineering, and Medicine report.

In a separate DNA Day session, researchers who contributed to that report discussed how we can strengthen genomic research by more accurately describing people and the things that have an impact on their health. "Identify categories that really address the questions you're asking," said Columbia University's (New York) Sandra Soo-Jin Lee. Lee urged investigators to resist typological thinking and assume groups are discrete categories. Genevieve Wojcik of Johns Hopkins Bloomberg School of Public Health (Baltimore) cautioned that descriptors in population genetics often lie along lines of race. "If you're using race as a surrogate for environment, maybe you should be measuring the environment," she said.

To conclude the day's events—but not before the audience voted him G.O.A.T. in a nail-biting tiebreaker—Francis Collins delivered the 2023 Louise M. Slaughter National DNA Day Lecture. And of course, he was accompanied by his guitar. ●

***The NIH Catalyst* is commemorating 30 years of publishing with a series of updates to past coverage. In this issue, we highlight the evolution of genomic research at NIH.**

CREDIT: NHGRI

To conclude the day's events, **Francis Collins** , the G.O.A.T., delivered the 2023 Louise M. Slaughter National DNA Day Lecture. And of course, he was accompanied by his guitar.

Remember when?

It goes without saying that the *Catalyst* has covered a lot of news about Collins, but what was fun to find were our first year's coverage when Collins first joined NIH. Check out the following articles in previous issues for a glimpse at how his journey to becoming the G.O.A.T. began.

Collins Begins Post as New Genome Project Head (March–April 1993)

BY SEEMA KUMAR, MANAGING EDITOR

NCHGR's Intramural Genetics Hub Gets Rolling (November–December 1993)

BY CELIA HOOPER, SCIENTIFIC EDITOR

Francis Collins, new NIH Director: *"I am one of you," says Collins to the NIH intramural community.* (August–September 2009)

BY LAURA STEPHENSON CARTER, EDITOR-IN-CHIEF

Francis Collins, M.D., Ph.D., G.O.A.T.

Intramural Research Briefs

CREDIT: MARIAN YOUNG, NIDCR

NIDCR: Disrupting a sugar-laden protein called biglycan impaired bone growth and fracture healing in mice. Shown: Skeletal stem cells from healthy mice formed clusters of cartilage-producing cells that were later replaced by bone.

NIDCR: SCIENTISTS FIND PROTEIN ESSENTIAL TO BONE REPAIR IN MICE

A sugar-laden protein called biglycan appears central to bone integrity, strength, and proper fracture healing, according to an NIDCR-led study. The findings may help scientists understand why some fractures heal poorly and could provide insights into diseases marked by bone loss, such as osteoporosis.

To understand the role of biglycan in bone growth and healing, the scientists bred mice that lacked the protein. Compared with their healthy counterparts, mice born without biglycan had thinner, hollower, and weaker leg bones—signs resembling osteoporosis in humans. The lack of biglycan also disrupted the normal sequence of fracture repair. In biglycan-deficient mice, fewer skeletal stem cells migrated to the fracture site to form a mass, or callus, that protects the fracture as it heals. Although the calluses eventually turned into new bone, the structure was irregular, indicating that the lack of biglycan can undermine bone healing.

A closer look at the mice's skeletal stem cells hinted at a possible reason. During the normal healing process, skeletal stem cells first become cartilage-producing cells, which are later replaced by bone-forming cells. But stem cells isolated from biglycan-deficient mice and grown in the lab developed straight into bone, skipping the formation of cartilage, which normally serves as a template for new bone growth.

These findings suggest that biglycan's role in bone healing may relate to its influence on skeletal stem cells. With more research, the study could inform strategies to better heal fractures and treat bone disorders. (NIH authors: R. Shainer, V. Kram, T.M. Kilts, L. Li, A.D. Doyle, D. Martin, and M.F. Young, *Front Physiol* **14**, 2023)

[BY TIFFANY CHEN, NIDCR]

NIDA: ASSOCIATION BETWEEN CANNABIS AND SCHIZOPHRENIA IN YOUNG MALES

Researchers at NIDA and at the Copenhagen University Hospital of Denmark (member hospitals located in various cities) have found that young men with cannabis-use disorder (CUD) are at increased risk of developing schizophrenia.

In this study, the authors analyzed data from almost 7 million individuals in nationwide Danish health records over the course of 50 years. Researchers estimated the number of schizophrenia cases that could be linked to CUD at a population level.

Males with CUD in the 16–20 age group were more than twice as likely to develop schizophrenia compared with females. Similar results were shown in the 21–25 year age group. However, no differences were observed between the sexes for those aged over 25.

The authors estimated that 15% of schizophrenia cases among males aged 16–49 could have been avoided by preventing CUD in 2021. For young men aged 21–30, the number of preventable cases may be as high as 30%. In contrast, only 4% of schizophrenia cases in females aged 16–49 might have been prevented.

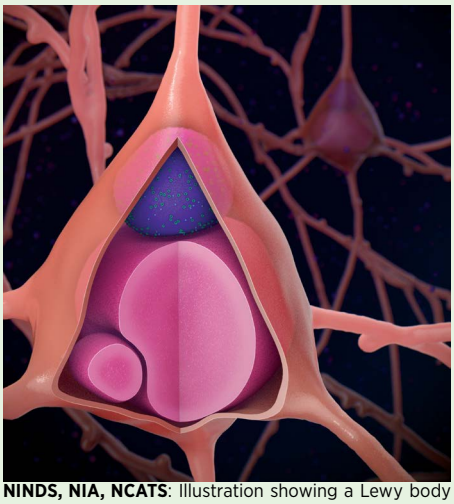
These findings highlight the importance of early detection and treatment of CUD, particularly in young males. "As access to potent cannabis products continues to expand, it is crucial that we also expand prevention, screening, and treatment for people who may experience mental illnesses associated with cannabis use," said NIDA Director and study coauthor **Nora Volkow.** (NIH authors: W. Compton, E. Einstein, N.D. Volkow, and B. Han, *Psychol Med* 2023)

[BY ANNELIESE NORRIS, NCI]

NINDS, NIA, NCATS: LARGE GENETIC CHANGES CONTRIBUTE TO DEMENTIA RISK

A study conducted by a trans-NIH group of investigators and their collaborators discovered several genetic risk factors for Lewy body dementia (LBD), frontotemporal dementia (FTD), and ALS-associated dementias. Non-Alzheimer's dementias may account for up to 30% of all dementias in older adults.

The scientists analyzed thousands of DNA samples using computer algorithms and machine learning to identify structural variations (SVs). SVs are large regions of genomic variation that can represent hundreds, or even thousands, of nucleotides at once. In the FTD and ALS group, the researchers



CREDIT: SONJA SCHOLZ, NINDS

NINDS, NIA, NCATS: Illustration showing a Lewy body (purple) within a neuron, the characteristic pathological feature of Lewy body dementia.

identified known SVs in the *C9orf72* and *MAPT* genes, which demonstrated that the algorithms were properly working. In the LBD group, a previously unknown variant in the *TPCN1* gene was discovered that is also associated with Alzheimer's disease. The research team has made the analysis code and raw data available to all researchers to study their genes of interest.

Other rare pathogenic SVs likely associated with non-Alzheimer's dementias were also revealed. "With each discovery, we shed light

on the mechanisms behind neuronal cell death or dysfunction, paving the way for precision medicine to combat these debilitating and fatal disorders," said NIA Senior Investigator **Bryan Traynor**. (NIH authors: K. Kaivola, R. Chia, J. Ding, M. Rasheed, K. Billingsley, R. Dewan, A. Stark, A. Ray, S. Solaiman, P.A. Jerez, L. Malik, L. Ferrucci, S.M. Resnick, T. Tanaka, J. Raphael Gibbs, B.J. Traynor, and S.W. Scholz, *Cell Genomics* **3**:100316, 2023)

[BY STEPHEN ANDREWS, NCI]

NHGRI, NLM: NEW HUMAN PANGENOME REFERENCE CAPTURES GENOMIC DIVERSITY

NIH researchers and a team led by the NHGRI-funded international Human Pangenome Reference Consortium released a new draft human pangenome, incorporating sequences from 47 genetically distinct individuals from around the world.

Hailed as the "Book of Life," the human reference genome released more than 20 years ago has been foundational in the field of human genetics. It originally consisted of genetic fragments from a small pool of individuals, and most of the sequence originated from one donor. Although refined through the decades, that reference does not reflect the vast genetic complexity of the human species, potentially biasing and introducing inequities in genomic analyses.

Most diversity within our species is driven by small genomic deviations. Those range from larger structural variants (SVs) to smaller single-nucleotide polymorphisms (SNPs), and insertions and deletions (indels). The updated pangenome more accurately identifies SNPs and indels that have important implications in the discovery and diagnosis of rare genetic disorders.

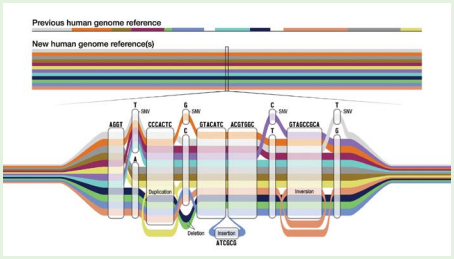
Further, SVs, which have remained largely unexplored because of the limitations of using a single reference genome, are more easily identified, broadening the horizons of future genome-wide association studies which detect genetic markers of disease.

Future work will expand this resource to include full-genome analyses of at least 350 individuals within a diverse global cohort, ultimately bringing more equitable health information to people around the world. (NIH authors: A.L. Felsenfeld, V.A. Schneider, B.I. Schultz, M.W. Smith, H.J. Sofia, F. Thibaud-Nissen, S. Koren, A. McCartney, S. Nurk, M. Rautiainen, A. Rhie, B. Walenz, and A.M. Phillippy, *Nature* **617**:312-324, 2023)

[BY TAYLOR FARLEY, NIAID]

NCCIH, NIA, NINDS, NIDCD, NHGRI: NIH SCIENTISTS CREATE MUSIC-BASED INTERVENTION TOOLKIT

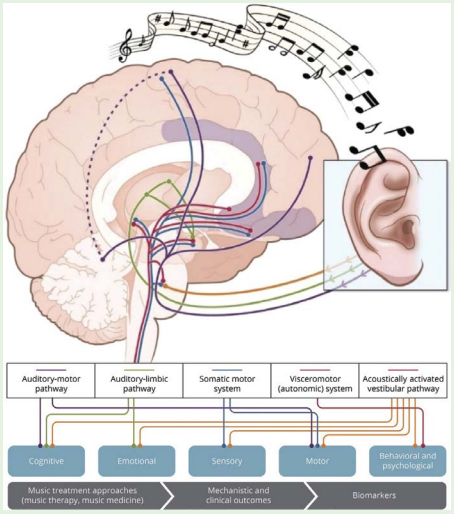
For neurologic disorders, such as stroke and traumatic brain injury, music-based interventions (MBIs) have shown tantalizing potential to improve quality of life by helping to manage symptoms, slow disease progression, and facilitate rehabilitation. Patients may prefer this approach because it can be affordable, accessible, and noninvasive. Yet, precisely how MBIs should be applied to therapy has not been established; the evidence has been anecdotal, limited to small-scale clinical trials or not designed within a scientific framework.



CREDIT: DARRYL LEJA, NHGRI

NHGRI, NLM: The new pangenome reference is a collection of different genomes from which to compare an individual genome sequence. Like a map of the subway system, the pangenome graph has many possible routes for a sequence to take, represented by the different colors.

Enter the NIH MBI Toolkit, a resource created by representatives from the Trans-NIH Music and Health Working Group, the Renée Fleming Foundation, the Foundation for the NIH, and other experts and collaborators. The toolkit is intended to guide future research on music and human health and to provide



CREDIT: ADAPTED WITH PERMISSION FROM *NAT REV NEUROSCI* 15:170-180, 2014

NCCIH, NIA, NINDS, NIDCD, NHGRI: Illustration showing the pathways underlying the neural and physiologic responses to music.

standards and tools for investigators seeking NIH funding for MBI studies.

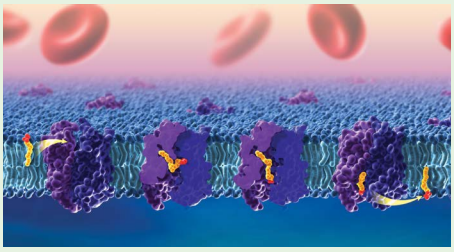
The NIH MBI Toolkit provides guiding principles and implementation strategies to design high-quality experiments and drive reproducible results: essential elements to investigate, consistent descriptive terminology to differentiate among different types of MBIs, and relevant biomarkers to assess treatment response. The toolkit also highlights proven assessment methods that allow collection of rigorous behavioral measurements such as alertness, language, memory, and motivation.

Although the authors focused on brain disorders of aging, they envision that the MBI Toolkit might also be modified for use in other diseases across the lifespan. (NIH authors: E. Edwards, C. St. Hillaire-Clarke, D.W. Frankowski, R. Finkelstein, T. Cheever, W.G. Chen, L. Onken, A. Poremba, R. Riddle, D. Schloesser, C.E. Burgdorf, N. Wells, and F.S. Collins, *Neurology* **100**:868-878, 2023)

[BY SEPPIDEH SAMI, CC]

NICHD: ZEBRAFISH MODEL REVEALS HOW BRAIN ACQUIRES OMEGA-3 FATTY ACIDS

Omega-3 fatty acids are vital to the development of the brain, where they act as a primary structural component of cell membranes. Sourced solely through our diet, omega-3 fatty acids must cross the blood-



CREDIT: ETHAN TYLER, NIH MEDICAL ARTS

NICHD: Docosahexaenoic acid (DHA) is an essential omega-3 fatty acid that is important for a healthy nervous system. This model shows how DHA and other omega-3 fatty acids cross the blood-brain barrier through the lipid transporter Mfsd2a.

brain barrier by interacting with selective transporters called flippases.

One of the most abundant of those is Mfsd2a, and mutations in this protein have been linked to neurological conditions such as dyspraxia, dyslexia, and microcephaly. Using a zebrafish model (*Danio rerio*), NICHD researchers and their colleagues are among the first to show precisely how Mfsd2a delivers omega-3 fatty acids to the brain.

By using single-particle cryoelectron microscopy, the investigators took snapshots of the Mfsd2a protein as it flipped the omega-3 fatty acid in the form of DHA-LPC across a cell membrane. The resulting images and subsequent 3D structural determination of Mfsd2a revealed the most detailed molecular analysis of Mfsd2a to date and identified three pockets within the protein used to maneuver fatty acids, in contrast to a previously proposed linear tunnel model.

The findings shed light on the mechanisms of other similar fatty acid transporters and could help inform how drugs are delivered across the blood-brain barrier. (NIH authors: L.T.F. Lai, and D. Matthies, *Nat Commun* 14:2571, 2023) ●

[BY JONATHAN CHU, NIAID]

NEWS FROM AND ABOUT THE SCIENTIFIC INTEREST GROUPS

NEW SIG: Cannabinoid Science and Medicine Interest Group

HIGHLIGHTING THE UNIQUE AREAS of research related to cannabis and cannabinoid science is the new Cannabinoid Science and Medicine Interest Group (CSMIG), which fosters engagement and communication among a diverse community of researchers in basic, clinical, and regulatory sciences. CSMIG will cover topics such as recent publications, emerging trends, innovative technologies, and opportunities for collaboration. The focus will be on sharing knowledge and exploring safer approaches to improve human health through the study of cannabinoid therapeutics.

This scientific interest group (SIG) serves as a platform for initiating constructive discussions and gathering feedback on research ideas and findings. It will provide mentoring opportunities for trainees, with the objective of establishing a network of scientists committed to advancing translational sciences in the field of cannabinoids. Discussions and meetings will be conducted through Zoom, hybrid, or in-person research seminars. Seminar speakers will include both intramural and extramural scientists in the field, who will present their work. NIH employees, researchers, and professionals from other extramural organizations are encouraged to join the CSMIG if they can contribute to the NIH mission and benefit from the group's discussions and activities.

For more information, go to https://oir.nih.gov/sigs/cannabinoid-science-medicine-interest-group or contact **Malliga Iyer**, (National Institute on Alcohol Abuse and Alcoholism) at malliga.iyer@nih.gov.

Join the CSMIG LISTSERV and receive notices of meetings, visit https://list.nih.gov/cgi-bin/wa.exe?SUBED1=CSMIG&A=1

A Sampling of SIGs

- 3D Printing and Modeling
- Antibody
- Bioethics
- Bioinformatics
- Biomedical Engineering
- Breastfeeding and Human Lactation
- Cancer Metabolism
- Chemistry
- Cell Cycle
- Chromatin and Chromosomes
- Chronobiology and Sleep
- Consciousness Research
- COVID-19
- Cytokine
- Deep Learning in Biomedical Imaging
- Dietary Supplement
- DNA Repair
- Drosophila
- Gene Therapy
- Genetic Counseling
- Global Health
- GlycoBiology
- Health Disparities
- Hispanic Health Research
- Immunology
- Inflammatory Disease
- Lambda Lunch
- Natural Products
- Nurse Practitioner/Physician Associate
- PAIN
- Pancreatic Cancer
- Patent Law & Technology Transfer
- Pediatric Clinical Research
- Religion, Spirituality, and Health
- Science of Science Communication
- Stem Cell
- Virology
- Virtual and Augmented Reality
- Zebrafish Frog

See full list at https://oir.nih.gov/sigs

From the Fellows Committee

Building Professional Development Core Competencies While at NIH

BY LARISA GEARHART-SERNA, NCI

NIH TRAINEES HAVE ACCESS TO A plethora of professional development programming through the NIH Office of Training and Education (OITE). While it may be a daunting task to sift through the offerings—which include workshops, VideoCasts, training modules, articles, and resource pages—OITE staff do not recommend that you try to attend or consume everything. Rather, first determine which offerings will benefit you most and help build your core competencies.

Core competencies are a blend of skills and experience future employers or educational institutions will seek, according to OITE. Core competencies provide an excellent roadmap for career and professional development.

Six OITE core competencies are recommended. NIH offers the following programming under each.

1. Career exploration

OITE's most prominent offerings include the OITE Careers Blog and the NIH Career Symposium. OITE also has several prepared guides, including the "Guide to Resumes and CVs," "Guide to Cover Letters," "Preparing for Your Professional School Interview," and "Writing Successful Applications for Biomedical Research Training Programs." The VideoCast "Interviewing Basics" can be helpful when you start to interview for positions. Additionally, OITE hosts a Job Search Series with available slides that touches on multiple topics within the job-search timeframe. They suggest attending career development activities in your professional societies and undergoing informational interviews with those in your prospective career fields. Make an appointment with a career counselor if you would like to discuss these topics in depth or have other questions or career development needs.

2. Communication skills

Good communication is key to any profession. OITE provides programming in writing, speaking, grant writing, and other professional communication skills. For example, read "Guidelines for Writing Professional E-mail." In addition, VideoCasts are available on "Improving Spoken English," "Written Communication Skills," "Communicating Science: Tools for Scientists and Engineers," and more.

3. Teaching and mentoring

Teaching and mentoring other lab members and trainees are part of the job at NIH. VideoCast resources may help hone your skills in this arena. Resources include:

- Mentoring Training Seminar: Summer Interns Are Coming—Are You Ready?
- Tips for Mentoring a Summer Intern and Leading a Journal Club

When mentoring, consider sharing information about building core competencies and directing your mentees to the OITE trainee resources page.

4. Leadership and management

Leadership ability is a quality many employers look for in an applicant. Read OITE's resource for personal management via self-advocacy, called "Putting Your Best Foot Forward: Self Advocacy for Scientists," and look for special workshops offered throughout the year on the topics of leadership and management.

5. Mandatory trainings

Mandatory trainings at NIH focuses on responsible conduct of research and includes trainings for postbacs and graduate students, postdocs, and "Your Rights and Responsibilities as a Trainee." For more information on this topic, see the *Catalyst* Training Page article entitled "A Culture of Integrity: Ethical Expectations for NIH Trainees." That article includes a section on all required research trainings as an NIH trainee.

6. Wellness

Above all, wellness should be on your priority list while at NIH. The OITE offers several health and wellness resources. Part of wellness may be belonging to a professional community beyond your own lab by connecting with like-minded individuals such as the affinity groups listed in the article "You Are Not Alone! Resources for Finding an NIH Community." Other wellness events and resources are available, such as the NIH Wellness Toolkits, and a variety of fitness classes are offered through the NIH Fitness Center.

The Fellows Committee encourages you to take advantage of these and other offerings from OITE and from the training office at your IC. Find upcoming events on the OITE upcoming events page, or explore OITE VideoCasts of prior workshops or educational OITE YouTube videos. These professional development resources can help build vital core competencies while at NIH and pave the way for future career success. ●

Larisa Gearhart-Serna is a former postdoctoral fellow at the National Cancer Institute's Technology Transfer Center and was a member of The NIH Catalyst *Editorial Board. She now works in business development and marketing for life sciences investigators at Stanford University.*

A complete list of resources and links are available in the online version of this article at https://irp.nih.gov/catalyst/31/4/the-training-page.

Three Years Trending: Curating COVID-19 Article Lists

Learn more about a process that may be useful for other topics, too.

BY CHRIS BELTER, NICHD

CREDIT: CHRIS BELTER

THREE YEARS AGO, I STARTED SENDING lists of research articles about COVID-19 that were trending on social media to the NIH COVID19RESEARCH listserv. In this article, I reflect on how that started, how it has gone, and where it might be going.

The idea for these lists came in early 2020. As a librarian at the time, I was focused on helping colleagues keep up with the emerging research on COVID-19. By early April, I was generating daily lists of all new COVID-19 articles for colleagues to manually screen for importance. The lists started at around 500 articles per day but grew to over 1,000 per day within just two weeks. No one could keep up at that pace, so I started looking for ways of filtering the lists to highlight articles that were likely to be important for our HHS colleagues.

Altmetric attention scores seemed to be a promising way to do that. Altmetric scores measure online activity associated with articles, such as how often they are posted about in social media, saved to reference management software, or mentioned in news stories. I was investigating altmetrics for other purposes and noticed that articles about COVID-19 had especially high scores, so I started using altmetric scores to filter my COVID-19 lists. By late April 2020, I had developed this method.

Each day, I used altmetric.com to obtain the 50 articles with the highest altmetric attention scores over the previous two days and then filtered the list to only retain articles about COVID-19. The resulting "trending articles" list became the list I sent, and still send, to the COVID19RESEARCH listserv.

The method worked because most of the articles with the highest altmetric scores each day were about COVID-19. From May 2020 through December 2021, around 30 of the top 50 articles each day were about COVID-19, and some days it was over 40.

But starting in early 2022, the number of COVID-19 articles in the top 50 began to decline and has continued to decline since. This is partly because the total number of new COVID-19 articles is declining, but it is mostly because the articles that are published do not attract as much attention as they used to. People are moving on.

The articles included in these lists tended to be on topics that affect people's lives. Vaccines, treatments, transmission, new variants, and long COVID all attracted significant attention. Most of the major discoveries on COVID-19 made the lists.

Of course, altmetric attention is not always positive. Many of the articles with the highest scores were also the most controversial. Topics such as the origin of COVID-19, masking, lockdowns, hydroxychloroquine, and ivermectin appeared often in these lists, and many top articles were later retracted. It seemed important, however, to keep these articles in the lists to ensure readers knew what was being discussed.

Despite these drawbacks, the lists have inspired readers to ask about trending article lists on other topics. Such lists can be generated in the same way as the COVID-19 list by changing certain parameters.

CREDIT: ALTMETRIC.COM

Altmetric's "donut" is a visual representation of sources of attention from across the world wide web.

For example, I have developed lists of articles on topics of interest to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) that were in the top 500 for attention score over the prior week and lists of articles supported by NICHD in the top 500 over the prior month.

To generate these lists, I pull the top 500 articles for the designated timeframe and apply the relevant topic filter to the resulting list. Expanding the number of top articles retrieved is especially important because few topics have articles in the top 50 in any timeframe.

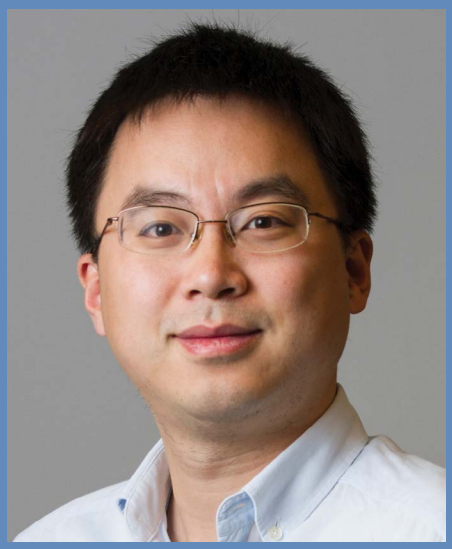
More detailed instructions and sample code for generating such lists are available in my trending articles GitHub repository, available at https://github.com/christopherBelter/trendingArticles.

The trending COVID-19 lists will end at some point. As pandemic response measures wind down and as altmetric attention shifts to other topics, the need for and method of generating these lists are both declining. Until then, I will keep sending the lists and engaging with the NIH COVID-19 Scientific Interest Group. ●

Chris Belter is the lead analyst and evaluator for the NICHD Division of Extramural Research, where he analyzes NICHD's research portfolios to inform strategic decisions and coordinates analytical activities across the Division. Prior to joining NICHD, he was a bibliometrics informationist at the NIH Library. In his spare time, he enjoys hiking, travel, and cooking Italian food.

Recently Tenured

ASTRID HAASE, NIDDK



BIN ZHU, NCI

ASTRID HAASE, M.D., PH.D., NIDDK

Senior Investigator, RNA Biology Section, Laboratory of Cell and Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Education: University of Vienna, Austria (M.D.), University of Basel, Switzerland (*Ph.D. in Biochemistry*)
Training: Postdoctoral Fellow at the Cold Spring Harbor Laboratory (CSHL) in Cold Spring Harbor, New York (2007—2015); graduate student at Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, Switzerland (2002—2007); undergraduate researcher at the Institute for Molecular Pathology (IMP)in Vienna, Austria (2000—2002)
Came to NIH: In 2015 as a Stadtman Tenure-Track Investigator at NIDDK.
Outside interests: I enjoy spending time with my family, another RNA enthusiast and a creative 6-year-old princess. We love road trips, music, and cooking together.
Website: https://irp.nih.gov/pi/astrid-haase

Research interests: Retroviruses and transposons pose a threat to genome stability. In the ongoing arms race with these mobile genetic elements, host genomes suffer insults, accumulate scars, and in rare instances adopt transposon sequences for their own use. But above all, they establish control. RNA-guided immunity, the CRISPR/Cas method, and RNA interference pathways restrict mobile genetic elements to protect genome integrity.

We study PIWI-interacting RNA (piRNA) that controls transposon activity in animal germ cells to ensure the survival of species. Self-nonself discrimination is at the very core of successful defense and relies on complementary base pairing in RNA-guided immunity. How the millions of piRNA sequences faithfully discriminate self from nonself and adapt to novel genomic invaders remain key outstanding questions in genome biology. Our previous studies revealed mechanisms of piRNA biogenesis (*Nat Commun* **10**(1):8282019; *iScience* **25**(6):104427, 2022) and function (*Genome Res* **31**(11):2058-2068, 2021; *Proc Natl Acad Sci U S A* **116**(23):11111-11112, 2019), and developed novel methods for future research (*Nucleic Acids Res* **50**(15):e90, 2022).

PiRNAs are largely confined to germ cells, but the initial epigenetic restriction they impose is maintained in adult somatic cells. However, age and disease weaken epigenetic maintenance, and unleashed transposons trigger toxicity and drive mutagenesis. Understanding how transposons are controlled has fundamental implications for age-related diseases, cancer biology, and autoimmune disorders, all of which are associated with progressive loss of transposon control. My team strives to elucidate conserved mechanisms of piRNA-guided transposon restriction with the overarching goal to understand how genomes resolve conflict, establish control, and achieve cooption of resident transposons.

BIN ZHU, PH.D., NCI

Senior Investigator, Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI-DCEG)

Education: University of Michigan, Ann Arbor, Michigan (*Ph.D. in biostatistics*)
Training: Postdoctoral associate in the Department of Statistical Science, Center for Human Genetics, Duke University (Durham, North Carolina)
Came to NIH: In 2012 as a tenure-track investigator in the Biostatistics Branch, NCI-DCEG
Outside interests: Reading; hiking; strength training
Website: https://irp.nih.gov/pi/bin-zhu

Research interests: I lead a research team that integrates statistics and genomics to understand the etiology of mutational signatures and reveal tumor heterogeneity. Our research involves developing statistical methods and tools as well as conducting scientific investigations to extract mutational signatures and identify their etiologies across different study designs and platforms.

CONTINUED ON PAGE 22

We also aim to reveal inter- and intratumor heterogeneity, with implications for translation and clinical practice.

Recognizing the importance of understanding the relationship between germline variants and tumor somatic mutations, we were the first to identify an inverse association between common germline risk variants and somatic mutation burden in breast cancer (*Br J Cancer* **115**(6):752-760, 2016). We co-led a pan-cancer, genome-wide association analysis of common germline variants and mutational signatures and identified an APOBEC deletion polymorphism associated with mutational signatures attributed to APOBEC deaminases (*Nature* **578**(7793):82-93, 2020). Although the etiology of the APOBEC signature has been well studied, identifying the underlying causes for many other signatures remains challenging. Therefore, we proposed a semiparametric kernel independence test (SKIT) to improve the power to infer the etiology of new mutational signatures (*J Am Stat Assoc* **116**(536):1648-1661, 2021).

We are also interested in understanding inter- and intratumor heterogeneity to improve cancer diagnosis and treatment. For example, our study on gallbladder cancer (GBC) revealed the existence of intertumor heterogeneity in the GBC tumor microenvironment, suggesting that GBC tumors with immunoreactive microenvironments could be potentially treated by immunotherapy (*J Hepatol* **74**(5):1132-1144, 2021). In addition, we investigated intratumor heterogeneity and subclones of papillary renal-cell carcinoma (pRCC) and found that pRCC generally has much less intratumor heterogeneity in driver-gene mutation and copy-number alteration than clear-cell renal-cell carcinoma. This discovery suggests that one biopsy is likely sufficient for diagnosis and molecular analyses of pRCC (*Nat Commun* **11**(1):3096, 2020). ●

COVID-19 Timeline at NIH (May–June 2023)

May 1: The NIH Clinical Center announces that it will discontinue at-will testing for COVID-19 after June 1. The program began on May 19, 2020, and processed nearly 300,000 tests.

May 2: The NIH Office of Research Services asks that outdated COVID–19 posters or signs be removed from NIH properties. This includes removing masking signs, distancing posters, elevator markers, and bathroom guidance from every building except for Building 10.

May 5: The World Health Organization determines that COVID-19 is now an established and ongoing health issue that no longer constitutes a public health emergency of international concern.

May 5: An NIH study identifies differences in the immune cell profiles and autonomic dysfunction in people with long COVID neurological symptoms. The findings offer insight into biological mechanisms and point to possible treatments. (*Neurol Neuroimmunol NeuroInflammation* **10**:e200097, 2023)

May 9: The NIH Office of Research Services announces that Eurest Dining Service's Eatify food program will end on May 22. The pandemic-era service allowed for online food ordering and pickup at campus dining locations. This summer will also see a return of the Building 45 cafeteria service and the omelet station in Building 31.

May 11: The Biden Administration allows the COVID–19 Public Health Emergency Declaration to expire, which had been in effect since January 31, 2020.

May 11: The CDC announces that they are replacing COVID-19 community levels with COVID-19 hospital admission levels to guide prevention decisions.

May 11: A large-scale, multicohort collaborative study supported by NIH finds that preexisting obstructive sleep apnea was associated with increased risks for long COVID (*Sleep* 2023).

May 15: Approvals are no longer needed for large meetings on NIH property of 50 or more people regardless of COVID-19 community level.

May 15: The NIH Clinical Center (CC) announces that it will soon transition to a policy requiring staff to wear masks when near patients but making masking voluntary when they are no longer in proximity to patients. The CC further announces plans for an evaluation of what additional entry and exit points might be able to reopen.

May 22: The NIH Clinical Center reduces staffing at mask-distribution stations. Staff will be located in the north and south lobbies to facilitate the mask-dispensing process on weekdays during peak times only. Self-serve mask dispensers are available at both lobbies and in Multi-Level Parking 9. Parking Lot 3 will continue to have a person distributing masks around the clock.

May 25: A large study coordinated through the NIH's Researching COVID to Enhance Recovery initiative identifies long COVID's most common symptoms, potential subgroups, and initial symptom-based scoring system, with the aim of improving future diagnostics and treatment (*JAMA* **329**:1934–1946, 2023).

June 3: President Joseph Biden signs a bill to raise the United States debt ceiling, which "claws back" some COVID-19 relief funds, including some made available to the National Institute of Allergy and Infectious Diseases.

June 5: The NIH Clinical Center announces masks are required in patient-care areas only.

June 26: Several NIH Clinical Center (CC) entry and exit points reopen to allow for easier access into the CC's masking-optional non-patient care areas, beyond the north and south lobbies. Some doors will remain closed or on badge reader access only for security purposes. ●

In early 2020, beginning with a Jan. 23 entry titled "NIH officials discuss novel coronavirus that recently emerged in China," former Catalyst *Editor-In-Chief Laura Stephenson Carter began the COVID-19 timeline to record what was going on at NIH during the pandemic. After three and a half years, this issue concludes the COVID-19 Timeline at NIH. Most entry points of the famed NIH Building 10 have reopened, and we will take that as our cue to exit.*

A Ground-moving Groundbreaking

Progress made on new SRLM wing

BY *NIH CATALYST* STAFF

CREDIT: CHIA-CHI CHARLIE CHANG

Pictured from left to right are Alfred Johnson, Hugh Auchincloss, Nina Schor, Dan Wheeland, James Gilman, HHS Deputy Secretary Andrea Palm, Lawrence Tabak, Tara Schwetz, Courtney Aklin, Debara Tucci, Griffin Rodgers, and Gary Gibbons..

Groundbreakings. You know the deal: People in fake hardhats with their gold-colored shovels carefully placed 10 percent into a pile of dirt shipped in and neatly boxed for the momentous occasion. Very scripted. Very boring.

But ah, not so with the groundbreaking for the Clinical Center's planned Surgery, Radiology, and Laboratory Medicine (SRLM) Wing on May 16, located on the northwest side of the storied Building 10, scheduled for completion in 2028.

If we had a nickel for every person who has noted how remarkable this groundbreaking was…well, maybe that adds up to only 65 cents. Still, 13 people independently and without prompting randomly stating how much they enjoyed the groundbreaking is extraordinary.

The NIH Catalyst team recommends our readers watch an archive of the 42-minute event on NIH VideoCast via https://videocast.nih.gov/watch=49625 (NIH only). Each talk was lively and spot on. One for the NIH history archives, for sure. Speakers in order of appearance included:

- Lawrence Tabak, Acting NIH Director
- Andrea Palm, U.S. Deputy Secretary of Health and Human Services
- Alfred Johnson, Deputy Director for Management, NIH
- Daniel Wheeland, Director, Office of Research Facilities, NIH
- Nina Schor, Deputy Director for Intramural Research, NIH
- James Gilman, Chief Executive Officer, NIH Clinical Center
- Steven Rosenberg, Chief, Surgery Branch, National Cancer Institute, NIH

CREDIT: CHIA-CHI CHARLIE CHANG

Alfred Johnson provided one of the many lively remarks at the May 16 groundbreaking celebration for the new Clinical Center's Surgery, Radiology, and Laboratory Medicine (SRLM) Wing.

If you agree with our assessment, please send us a nickel. We will apply it to a future Wednesday Afternoon Lecture Series (WALS) coffee reception. ●

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

U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
National Institutes of Health
Building 1, Room 160
MSC 0140
Bethesda, Maryland 20892

FIRST-CLASS MAIL
POSTAGE & FEES PAID
DHHS/NIH
Permit No. G-802
Publication No. 23-6250

Official Business
Penalty for Private Use $300

Printed on at least 20% recycled content paper and can be recycled as office white paper.

CATALYTIC REACTIONS?

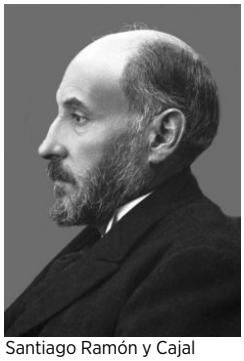
If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; or mail: *The NIH Catalyst*, Building 1, Room 160.

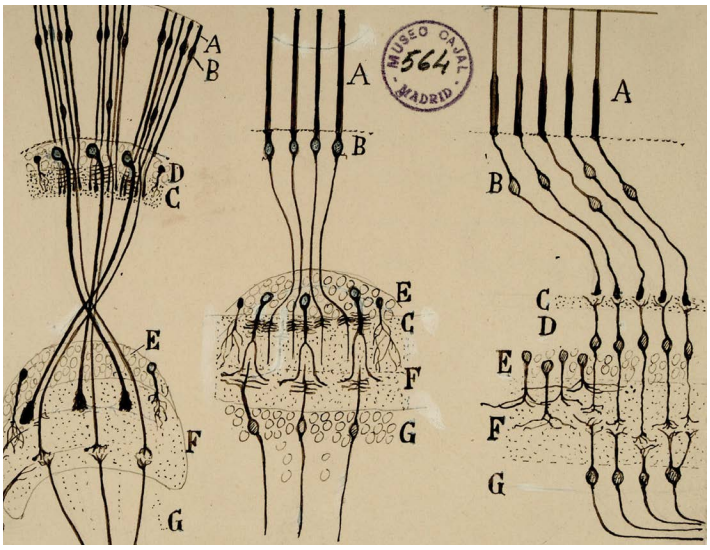
Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

LONGER ARTICLES AND MORE PHOTOS ONLINE AT
https://irp.nih.gov/catalyst/31/4.

PHOTOGRAPHIC MOMENT

Cajal Drawings on Display at NIH


Santiago Ramón y Cajal



CREDIT: CAJAL INSTITUTE, SPANISH NATIONAL RESEARCH COUNCIL

The seventh round of original "Cajal" drawings have arrived to the Porter Neuroscience Center, Building 35. At the turn of the 20th century, Santiago Ramón y Cajal, a Spanish physician and scientist, was the first to describe the structure of the nervous system with exquisite precision. Shown in his schematics of insect (left), cephalopod (middle), and vertebrate (right) retinas, highlighting their similarities. All of these retinas are composed of photoreceptors (A), which are activated by light and transmit signals through synapses of intermediary cell types (B, C, F) onwards toward deeper brain processing (G). Be sure to stop by and see the full exhibit on the first floor of Building 35. ●

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

Address correspondence to:
Building 1, Room 160, NIH
1 Center Drive
Bethesda, MD 20892
Ph: 301-402-1449
e-mail: catalyst@nih.gov

The NIH Catalyst online:

https://irp.nih.gov/catalyst

PUBLISHER
NINA F. SCHOR
Deputy Director for Intramural Research, OD

EDITORS
JANICE LEE
Clinical Director, NIDCR
Deputy Director for Intramural Clinical Research
RICHARD S. CHADWICK
Scientist Emeritus, NIDCD
CHRISTOPHER WANJEK
Director of Communications, OIR

ACTING MANAGING EDITOR
JENNIFER HARKER

SENIOR SCIENCE WRITER-EDITOR
MICHAEL TABASKO

COPY EDITOR
SHAUNA ROBERTS

CONTRIBUTING WRITERS
Stephen Andrews, Chris Belter, Devika Bose, Taylor Farley, Susan Giuliani, Jennifer Harker, Satabdi Nandi, Anneliese Norris, Nina Schor, Larisa Gearhart-Serna, and Michael Somes

RESEARCH BRIEFS
Stephen Andrews, Tiffany Chen, Jonathan Chu, Taylor Farley, Anneliese Norris, and Seppideh Sami

PHOTOGRAPHERS/ILLUSTRATORS
Bill Branson, Allison Carter, Chia-Chi Charlie Chang, Dustin Hayes, Darryl Leja, Ethan Tyler, Lichen Xiang, Marian Young