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A Rare Day Brings Fierce Focus to Rare Diseases

Rare Disease Day Highlights Tenacity of Love, Science

BY JENNIFER HARKER, *THE NIH CATALYST*

Leap year brings us an extra day every four years for the celestial and the earthly to sync. Rare days such as these also bring focus to rare diseases, which at NIH offers patients, family members, and the intramural and extramural scientific communities a day to showcase outcomes that reach far beyond synchronicity.

For example, few things are more moving than watching the progression of a child go from deep suffering to laughing and sledding in the Michigan snow. Not many families facing rare diseases have such heartwarming outcomes, but NIH's commitment to battling the long diagnostic and treatment odyssey is making great strides toward ensuring more kids are laughing and playing in the snow by the time the next leap year rolls around.

Hundreds gathered on Feb. 29 at the Natcher Conference Center on the NIH Bethesda campus to speak of medical advances, network, and show their support for the rare disease community.

Dominique Pichard, director of the NCATS Division of Rare Diseases Research Innovation, shared a story about her daughter's lengthy journey to diagnosis of Rett syndrome. As a mother and physician, she vowed to improve this process for others.

"I don't want a single person affected by rare disease to have to have that long of a diagnostic and treatment odyssey," she told the audience.

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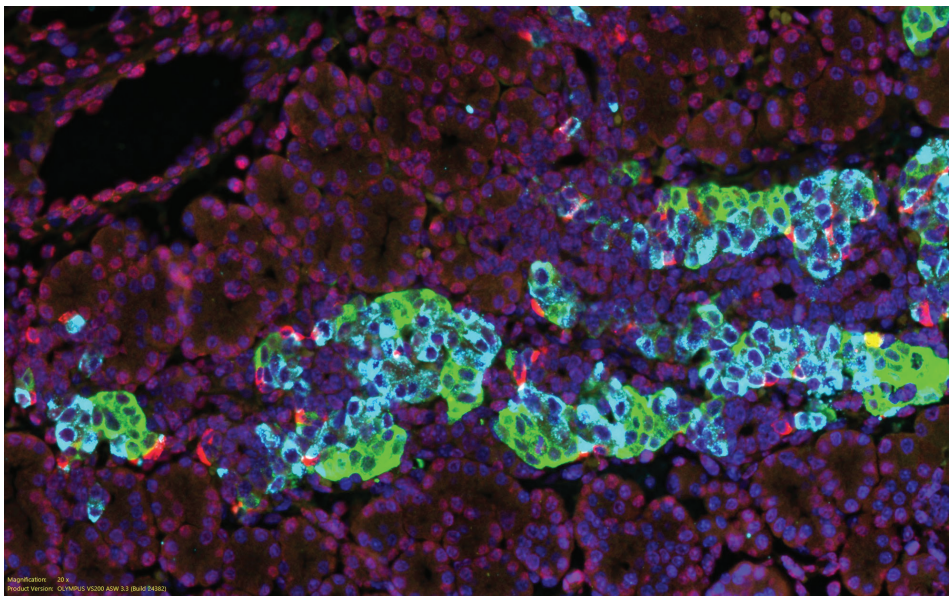
The Perplexing Pancreas

Multidisciplinary Research Tackles an Increasingly Common Pancreatic Disorder

BY MICHAEL TABASKO, *THE NIH CATALYST*



CREDIT: JI-HYEON LEE, NIDDK

Shown here are cells in an embryonic mouse pancreas and three principal endocrine hormones: beta cells making insulin (sky blue), alpha cells making glucagon (green), and delta cells making somatostatin (red) with the fluorescent stain DAPI shown in blue identifying nuclei.

Each year, upward of 275,000 hospital stays for acute pancreatitis occur in the United States, costing 2.6 billion dollars in health care spending, according to 2018 estimates (PMID: 30315778). Experts believe that the increase is, at least in part, explained by the obesity epidemic and the increased prevalence of metabolic disease.

Why such a connection? Some of the most common causes of acute pancreatitis include gallstones and high concentrations of triglycerides, both of which are associated with metabolic syndrome. Yet alcohol use is the second leading cause following gallstones

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Faculty Recruitment in the Gray Zone

Striking the Right Balance Between Transparency and Discretion

BY NINA F. SCHOR, DDIR

Every year, the NIH recruits new faculty at every level. Many tenure-track faculty come to us through our Stadtman and Lasker Scholars searches. Others are recruited through IC-run searches, a process that also nets new staff scientists and staff clinicians and fills administrative leadership positions throughout our community.

When it comes to senior leadership-level searches, however, some NIH faculty perceive a sense of secrecy, and that sense leads to suspicion of inequity and unfairness. But we tread a very thin line between the need for discretion and the desire for transparency.

You can imagine the situation: If the names of candidates are released too early in the process, the word of their candidacies could get back to their institutions and colleagues before they have had a chance to convey that information. Worse, those who do not progress in the search process may become known as having been "rejected" by the search committee.

Meanwhile, as the search committee is waiting for the 30 days of ad posting and other required processes to be completed, for everyone to review the applications, and for virtual interviews to be completed, the members of the IC's IRP faculty are thinking nothing is happening.

Clearly, before finalists are chosen in any leadership search, the names of applicants, interviewees, and those serving as reference sources cannot and should not be released beyond the search committee. If such information gets out, we will quickly cease getting applications for leadership positions. But it is important to give the faculty, staff, and trainees in the IC for which the search is being conducted periodic updates on the progress of the process of the search to provide a sense of the momentum of the process.

Either the search committee chair—or, if the IC director thinks it unwise to release the name of the search committee chair, the IC director—should periodically speak at an IC IRP faculty meeting to indicate where in the search process the search committee is and give a general idea of the vigor of the outreach process and responsiveness of applicants to that process.

Statements such as, "The search committee has reached out to both academia and industry, and to professional organizations and schools, that reach potential applicants across the demographic and scientific spectra," or "Beginning early next month, the search committee will be conducting virtual interviews of its first round of qualified applicants. This group is quite diverse in many ways," can go a long way toward assuring everyone that there is movement in filling the position and that attention is being given to maximizing the likelihood there is a diverse applicant pool.

> We tread a very thin line between the need for discretion and the desire for transparency.

I hope you can appreciate the complexity and sensitivity of the next steps for leadership-level searches. Here's the gist, replete with potential pitfalls.

Once the first round of interviews is completed, those who are potential finalists should be told of their status and informed that the process of reference checking will subsequently begin, giving them a chance to let those likely to be referees hear from them, rather than hearing it for the first time from us.

From this list will be derived the "short list" of finalists. Finalists for leadership positions should best be told that they will be asked to give a talk that includes both a summary of their own work and career, and their early-stage vision for the enterprise they might lead.

I usually say to finalists, "This part of the talk should be aimed at giving us an idea of your priorities and how you think and engage with people. We realize you may not yet know the whole landscape or the rules of government; if you are chosen for the position, you will not be held to the letter of what you present. Just tell us what, if we made you the leader today, you would think would be important to do in your first year and by your fifth year."

The invitees to the talk should, at a minimum, include everyone in the IC's IRP and allow for both in-person and virtual attendance. Finalists should optimally be onsite for this talk, as their visit should include meetings with PIs, administrative and scientific staff, tenure track and non-tenure track faculty, trainees, and, of course, the selecting official. This should be a mixture of individual and group meetings, as appropriate to the situation and position.

Optimally, feedback should be solicited anonymously from each person in the IC's

IRP and everyone that met (in person or virtually) with each of the finalists.

Everyone polled should be asked whether they attended the talk and/or participated in an individual or group meeting with the finalist. The selecting official, upon reviewing all the data available, must then make a choice of to whom to make the first offer of the position. This information cannot be disclosed to anyone else at this point.

Imagine what it would be like to have the "first choice" person turn down the offer and then have all the PIs in the IC know that the person ultimately chosen was the second or third choice of the selecting official.

The process of negotiation, Ethics Office vetting, salary setting, and identification of appropriate space takes weeks and sometimes months. All during this time, it may appear to the members of the IC that nothing is happening.

Again, just imagine being the lead candidate, provisionally accepting the position, having your acceptance announced, and then having the Ethics Office decide, for example, that your spouse's current employment or investments preclude your federal employment.

Confidentiality must be maintained, and the substance of the negotiation and the identity of the finalist with whom the negotiation is taking place must not be revealed to the public.

As with any complex process that includes the need for confidentiality, ethical conduct, and human interaction, there are guardrails around the process of leadership recruitment.

There is much that can be done to balance those imperatives with ensuring that those inside NIH have a sense that something important is moving apace and the best interests of science, people, and the NIH are prominent parts of the equation. ●

Symposium Marks 20th Anniversary

Graduate Student Research Symposium

The Graduate Partnerships Program in the Office of Intramural Training and Education (OITE) showcased research conducted at NIH by graduate students for the 20th year. This year's symposium, held Feb. 15, boasted 123 posters and featured 34 students competing in the elevator pitch competition. Congratulations to all the winners and presenters. ●

MARLEEN VAN DEN NESTE

A keynote roundtable discussion on scientific leadership featured Deputy Director for Intramural Research **Nina Schor** (middle) and NIH Principal Deputy Director **Lawrence Tabak** (right), moderated by OITE Director **Sharon Milgram** (left).

MARLEEN VAN DEN NESTE

The NIH Graduate Student Research Symposium was held Feb. 15 at the Natcher Conference Center in Bethesda, Maryland. This year marked the 20th anniversary of the event.

OITE, ULRIKE KLENKE

Elevator Pitch Competition winner **Ivan Alcantara** presented "State-Dependent Prioritization of Feeding and Parenting Behaviors." **Michael Krashes**, NIDDK, serves as Alcantara's mentor.

RESEARCH AWARD WINNERS

BIOCHEMISTRY | CELL AND MOLECULAR BIOLOGY

Alexandra Hollo (NHLBI, University of Pécs)

Kyle Schwab (NEI, Temple University)

BIOINFORMATICS | BIOSTATISTICS | EPIDEMIOLOGY

Brad Olinger (NIA, Johns Hopkins University)

Theressa Ewa (NCI, University of Cambridge)

CARCINOGENESIS | TUMOR BIOLOGY

Yonit A. Addissie (NCI, University of Maryland)

PHARMACOLOGY | CLINICAL AND TRANSLATIONAL SCIENCE | STRUCTURAL BIOLOGY

Jose F. Delgado (CC, University of Maryland)

IMMUNOLOGY, VIROLOGY, AND MICROBIOLOGY

Timothy Johnston (NIAID, University of Pennsylvania)

NEUROSCIENCE, BEHAVIORAL SCIENCES, AND PSYCHOLOGY

Aaron Limoges (NIMH, Columbia University)

Angela Y. Fan (NIMH, Monash University)

Yizhen Z. Zhang (NIDCR, Brown University)

NEW PROPOSAL

Jackson White (NICHD, University of Oxford)

Yasmin Padovan-Hernandez (NIDA, Johns Hopkins University)

ELEVATOR PITCH COMPETITION WINNERS

Ivan Alcantara (NIDDK, Brown University)

Shakira Rodriguez Gonzalez (NIDDK and Johns Hopkins University)

Drashty Mody (NIDCR, Indiana University)

Health Care Is Not Designed for Those Who Need It Most

Matthew Weed Delivers Powerful Talk on Making Health Care Accessible to All

BY JOHN CARLO J. COMBISTA, NIMH

CREDIT: MATTHEW WEED

More than half of all U.S. adults have at least one chronic health condition and 1-in-4 adults has a disability, according to the Centers for Disease Control and Prevention. Disability and health care go hand in hand, and yet health care remains far behind the curve in making care and health-related information accessible.

Matthew Weed, a health care accessibility consultant with a doctorate in genetics, spoke about bridging this gap at NIH. Weed is uniquely qualified to speak on the topic. His presentation, "Optimizing Outcomes for Patients with Chronic Illnesses and Disabilities," was based on his personal struggles managing a chronic health condition (type 1 diabetes) and a disability (total blindness) while weaving in his contributions to helping NIH improve accessibility efforts.

Two main points that Weed touched upon during his talk focused on ensuring advancements and accommodations actually work as intended:

- *Translating technological advancements into real-world use to ensure accessibility*: Learning to use devices at home and alone can quickly get complicated, he noted, as he demonstrated blood glucose checks as a patient with visual impairment.
- *Building infrastructure accessibility*: Weed shared ways to make or keep NIH's clinics and laboratories accessible to people with disabilities—from parking, elevators, and building passageways, to ramps, doors, and carpets. For example, he pointed out that most ramps are not actually accessible or safe and that all elevators should have sound prompts, such as one ding for up and two for down.

Accessible health information is imperative

Weed's work with NIH started in 1994 as a summer research trainee at NIEHS (Durham, North Carolina). While there, he toured with facilities management to help them ensure laboratory areas and outdoor sidewalks remained hazard-free and physically accessible. He later served as a science-trained beta tester on accessible PubMed from 1999 to 2010, and more recently, he worked to improve the accessibility of the NIH Library website for blind visitors.

Communication and community engagement make health care accessible to everyone, according to Weed. He pointed out that NIH ICs can enhance the accessibility of health information products such as brochures and reports. Weed emphasized that many of these materials are not easy to read on screen readers, a common tool used by people who are blind or visually impaired.

"The more difficult we make science and health information to navigate, the harder it will be to communicate with a lot of people out there," Weed said. "Also, if we don't think about how we communicate science, then scientists and health care professionals are always going to be behind in the battle to legitimize what we do."

Real people, real world

Weed encouraged scientists and health care professionals alike to engage in the community outside of hospitals and laboratories to understand the needs of patients because health care happens everywhere. "Most science happens in the lab, but most of the effects of science happen in the real world."

He advised NIH ICs and CCs create an advisory council inviting people with chronic illnesses and various disabilities to serve as representatives and be involved in the decision-making processes regarding accessibility. He also advocated more inclusion of people with disabilities in clinical trials.

The NIH does this to some degree, Weed said, but there is always room for improvement. "This is really important to be conscious of because we know that these people are least likely to appear in appropriate numbers in clinical trials. We may be misspending a lot of money on trials because we are not matching them to the people who need them the most," he said.

Changing attitudes

Growing up in Colorado Springs, Colorado, in the 1970s, he experienced firsthand the struggles of managing his diabetes, particularly when complicated by his total blindness. During the lecture, he demonstrated how still today common diabetes management is anything but accessible with unreadable medicine labels

and the confusion caused by the shapes of medicine vials, insulin pens, and inhalable insulins—all with different dosages to be taken at various times and days.

Health care, put simply, is not designed for people with disabilities or language barriers, he said.

"The choices health professionals make, and the attitudes they carry, can have huge, huge impacts on patient outcomes and compliance," Weed said. "Please do not add to our challenges by asking patients to overcome your negative attitudes as well as their health concerns. Rather, please help reduce the barriers we face by keeping open minds and seeing your patients as people, not health conditions."

In spite of Weed's blindness and lifelong battle with type 1 diabetes, he has managed to achieve more than most healthy and sighted individuals. In fact, he has earned five degrees from three Ivy League universities, including that doctorate in genetics. Obtaining these degrees was no easy feat considering the struggles he faced in addressing the accommodations he needed to succeed in his studies.

During his talk, he shared the abysmal percentage of medical students with physical and sensory disabilities who matriculated (0.56%) or graduated (0.42%) between 2001 and 2010 (PMID: 22450188).

Today, he dedicates time to "helping good people do great things" through mentorship and consultancy. He now uses those experiences he faced and overcame to mentor students of diverse backgrounds and health conditions by helping them apply to their dream undergraduate and graduate programs as well as helping them succeed throughout their studies.

John Carlo Jadormeo Combista is a predoctoral fellow in the NIMH Oligodendroglial Interactions Group under the supervision of Tobias Merson. He is interested in how the brain develops and functions by exploring how patterns of myelination within specific neural circuits emerge. Outside of academia and writing, he is passionate about singing and volunteers to work with vulnerable populations.

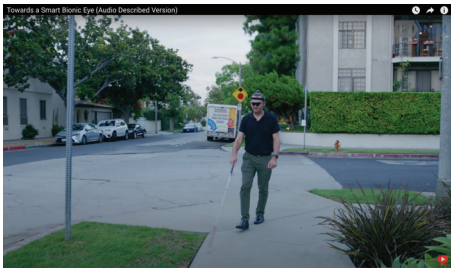
NLM Bionic Eye Video Describes Scenes for Visually Impaired Using AI

NLM IS MAKING HEALTH INFORMATION ACCESSIBLE IN MEANINGFUL WAYS

Vision loss effects an estimated 18 million Americans, 710,000 of whom experience total blindness, according to the International Agency for the Prevention of Blindness 2020 Vision Atlas report.

As Matthew Weed advocates, communicators can take action to make health communication more accessible for people who are visually impaired. A video created by the National Library of Medicine (NLM) communication team used an artificial intelligence program called Audible Sight to enhance a video they developed about a retinal and brain implant called the Bionic Eye.

The video features an NIH Director's New Innovator Award-winning project that brings together artificial intelligence, virtual reality, visual prostheses, and retinal and brain implants. The Bionic Eye is an assistive technology device that can help individuals who are blind to better navigate their surroundings.



The Bionic Eye video project offered the perfect opportunity to try out the new AI technology. The proprietary AI program swiftly generates audio descriptions for video scenes. What would take a human days to complete, the program can complete in minutes.

See, and hear, for yourself. The audio-enhanced video is available on YouTube at the following link: https://youtu.be/vlpG_WRLfw0?si=mjydNJLiwVvaxmUd. ●

Rare Disease Day

CONTINUED FROM PAGE 1

According to NCATS Director **Joni Rutter**, it takes an average of six years for accurate diagnosis of a rare disease. She shared the many ways in which NIH is advancing the research to speed such processes.

"We have uncovered common genetic threads that can lead to universal therapies, from gene editing and gene therapy approaches to antisense oligonucleotides," Rutter said. "We can also be thinking about how we can design new clinical trials or basket trials that test one therapy on many different rare diseases. So, in this way, we are not just chasing treatments, we are leapfrogging toward cures."

NIH CC CEO **James Gilman** also restated the CC's commitment to rare diseases. "The clinical center does more rare disease research than any place else on the planet," he said. "Still, of the 7,000 identified rare and neglected diseases for which we know the molecular cause, only about 500 have approved treatments. NIH is collaborating with multiple partners to speed up the development of effective treatments and the clinical center is proud to play an important role in those efforts."

The Bespoke Gene Therapy Consortium, which is co-led by NCATS, is one such example that involves a multi-IC collaboration and partnership with the Foundation for the NIH, the U.S. Food and Drug Administration (FDA), and multiple private organizations that work together to speed development of novel cell and gene therapies.

Rare Disease Day at NIH is an annual daylong hybrid event hosted jointly by NCATS and the CC. This year's event featured intramural and extramural scientific efforts, cross-agency partnerships, panel discussions with experts, rare diseases stories by patients living with a rare disease or their family members, in-person exhibits and scientific posters, and an art exhibition. ●

View photos from the 2024 Rare Disease Day at NIH at irp.nih.gov/catalyst.

Intramural Research Briefs

NINDS, NHLBI, NIDDK, CHI, NIMH, NIDCR, NIDA, NIA, NIEHS, NINR, NIAID, NCCIH, NIAMS, NCI: NIH SCIENTISTS OFFER NEW CLUES INTO CAUSES OF POST-INFECTIOUS ME/CFS

A team of multidisciplinary researchers across NIH has discovered how feelings of fatigue are processed in the brains of people with post-infectious myalgic encephalomyelitis/chronic fatigue syndrome (PI-ME/CFS).

The study took a comprehensive look at ME/CFS that developed after a viral or bacterial infection using state-of-the-art techniques to examine 17 people with PI-ME/CFS who had been sick for up to five years. They compared that cohort's results to a cohort of 21 healthy controls. Results from functional magnetic resonance imaging (fMRI) brain scans showed that people with ME/CFS had lower activity in a brain region called the temporal-parietal junction, which may cause fatigue by disrupting the way the brain decides how to exert effort.

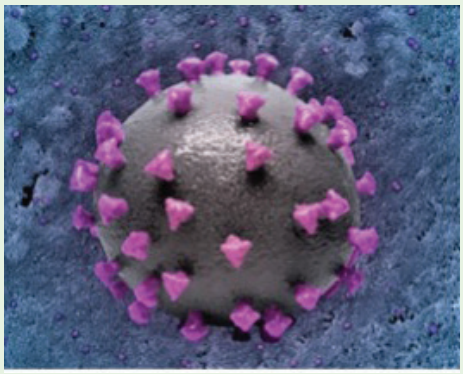
The researchers analyzed spinal fluid collected from participants and found abnormally low concentrations of catecholamines and other molecules that help regulate the nervous system in people with ME/CFS compared with healthy controls. Reduced concentrations of certain catecholamines were associated with worse motor performance, effort-related behaviors, and cognitive symptoms.

These findings, for the first time, suggest a link between specific abnormalities or imbalances in the brain and ME/CFS. "We think that the immune activation is affecting the brain in various ways, causing biochemical changes and downstream effects like motor, autonomic, and cardiorespiratory dysfunction," said **Avindra Nath**, clinical director at NINDS and senior author of the study.

Brian Walitt, associate research physician at NINDS and first author of the study, said they may have identified a physiological focal point for fatigue in this population. "Rather than physical exhaustion or a lack of motivation, fatigue may arise from a mismatch between what someone thinks they can achieve and what their bodies perform," he added. (NIH authors: B. Walitt, M. Hallett, S. Jacobson, Y. Enose-Akahata, P. Bedard, B. Calco, A. Gavin, D.S. Goldstein, S.G. Horovitz, K.R. Johnson, A. Jones Govan, K.M. Knutson, N. Malik, P.M. McGurrin, G. Norato, T. Popa, L.B. Reoma, F. Safavi, B. Smith, B.J. Stussman, C. Vizioli, A. Nath, K. Singh, S. Hassanzadeh, M. Levin, M.N. Sack, S.R. LaMunion, K. Chen, R.J. Brychta, A.B. Courville, R. Apps, J. Chen, F. Cheung, A. Mukherjee, B.A. Sellers, J.J. Barb, L.M.K. Chin, M.S. Deming, B. Drinkard, S. Solin, S.A. Turner, S.B. Yang, A. Williams Buckley, S. Sinclair, J. Snow, P.D. Burbelo, L.R. Feng, L. Ferrucci, R. Moaddel, S.A. Gabel, G.A. Mueller, J.D. Kreskow, L.N. Saligan, J.J. Lyons, F. Safavi, N. Madian, B.J. Stussman, A.L. Mammen, S. Muñoz-Braceras, K. Pak, I. Pinal-Fernandez, J.A. McCulloch, and G. Trinchieri. https://doi.org/10.1038/s41467-024-45107-3.)

[REPRODUCED FROM A FEB. 21 NIH PRESS RELEASE WRITTEN BY NINA LICHTENBERG, NINDS]

NCI, NIAID: UNIQUE FEATURES OF OMICRON SPIKE PROTEIN ENHANCE INFECTIVITY, IMMUNE EVASION



CREDIT: NIAID

NCI, NIAID: 3D print of a SARS-CoV-2 virus particle with spike proteins shown in purple.

Researchers at NCI and NIAID recently discovered that the Omicron spike protein, which mediates viral entry into host cells, can bind to cells of the nasal passage more effectively than previous variants, including Delta, and aid in Omicron's improved ability to infect hosts. By creating 3D cultures of nasal epithelial cells to recapitulate conditions in the upper airway, the investigators compared several strains of SARS-CoV-2, including ancestral strains, Delta, and multiple subvariants of Omicron.

They discovered a divergence in the pathways that Delta and Omicron variants used for cellular entry facilitated by their unique spike proteins.

This distinctive pathway bestowed resistance to antiviral factors typically produced by host cells during infection by Omicron, highlighting a potential mechanism for immune evasion and enhanced spread.

This research adds to the understanding of the mechanisms involved in SARS-CoV-2 infection for different strain lineages, particularly the highly abundant Omicron variant, and could help guide the design of future vaccines and antiviral treatments. (NIH authors: G. Shi, T. Li, K.K. Lai, R.F. Johnson, J.W. Yewdell, and A.A. Compton, PMID: 38291024)

[BY TAYLOR FARLEY, NIAID]

NIMH: COGNITIVE BEHAVIORAL THERAPY ALTERS BRAIN ACTIVITY IN CHILDREN WITH ANXIETY

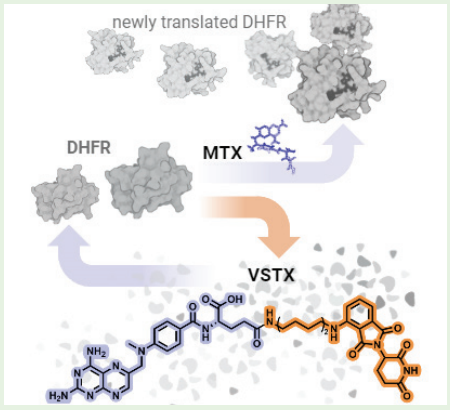
NIMH researchers discovered that cognitive behavioral therapy (CBT) normalized some areas of brain hyperactivation in children with anxiety, providing clues as to which brain regions may be associated with therapeutic responses. Pediatric anxiety disorders are common and can persist into adulthood, when they can become chronic and more difficult to treat. CBT, which helps correct dysfunctional thought processes and behaviors, is the standard treatment for pediatric anxiety.

To investigate CBT's effectiveness in children, researchers used fMRI to compare brain activity in non-anxious children with brain activity in anxious children who received 12 weeks of CBT. Before CBT, anxious children's brains showed hyperactivation in many regions, including areas in frontal and parietal lobes and the amygdala that help regulate cognition and emotion. CBT improved brain function in numerous overactive areas. Heightened

activity persisted in others, including the amygdala, suggesting that reducing activity in those areas may require extended CBT or more targeted treatments.

Researchers also compared the children with anxiety who received CBT with a different group of untreated children at temperamental risk of developing anxiety disorders. Comparisons between those groups showed that the anxiety-associated brain activity in the at-risk group remained stable over time, demonstrating how the observed changes in the brains of children who received CBT were likely related to treatment and not the passage of time. (NIH authors: S.P. Haller, H.L. Grassie, E.L. Jones, A. Mallidi, E. Berman, K.M. Lewis, K. Kircanski, and M.A. Brotman, PMID: 38263879)

[BY KIM MORGAN, NINR]



CREDIT: JAMES INGLESE, NCATS

NCATS, NCI: While the presence of methotrexate leads to greater concentrations of DHFR, versortrexate (VSTX) leads to the breakdown of DHFR.

NCATS, NCI: RETOOLED METHOTREXATE MAY POINT TO NEW THERAPIES FOR CANCER, AUTOIMMUNE DISORDERS

A reengineered version of the drug methotrexate, designed by a research team led by NCATS, could lead to new tools to develop more treatments for cancer, autoimmune disorders, and rare diseases.

"This research provides scientists new tools to unravel the enigmatic properties of methotrexate and similar compounds," James Inglese said in a press release. Inglese directs the NCATS Assay Development and Screening Technology laboratory and is corresponding author on the study.

Methotrexate is a mainstay in the treatment of blood cancers and rheumatoid arthritis. The drug blocks a protein, dihydrofolate reductase (DHFR), that plays a key role in helping cells multiply.

A translational science research team from NCATS, NCI, and the University of Oklahoma (Oklahoma City) created and investigated compounds called PROteolysis TArgeting Chimeras (PROTACs) that incorporate methotrexate. PROTACs hijack the cell's natural waste disposal machinery to destroy a protein—in this case, DHFR. One of the new PROTACs, called versortrexate, broke down DHFR in several cancer cell lines while appearing to be less toxic than methotrexate.

Versortrexate's very specific activity opens a range of possibilities for development. The PROTAC could be used as a chemical tool to better understand DHFR activity, and it also could reveal how similar antifolate drugs work. Combining versortrexate with a companion drug that inhibits another protein in a key biochemical pathway might prove effective at creating new antiproliferative indications.

"Molecules like methotrexate can be scaffolds for the next generation of therapeutics or chemical probes," Inglese explained. (NIH authors: S. Rana, P. Dranchak, J.L. Dahlin, L. Lamy, W. Li, E. Oliphant, J.H. Shrimp, R. Tharakan, D.O. Holland, K.M. Wilson, S.K. Durum, D. Tao, and J. Inglese, PMID: 37875111)

[BY TERRY RUDD, NCATS]

NIAID: ANTIBODY-BASED HIV VACCINE PROVIDES PROTECTIVE IMMUNITY

The next generation of vaccine development for human immunodeficiency virus (HIV) is being pursued at NIAID's Vaccine Research Center (VRC). In a recent study, VRC researchers found that a novel class of vaccines delivering three different types of antibodies were each independently able to prevent and neutralize simian immunodeficiency virus (SIV), which infects non-human primates.

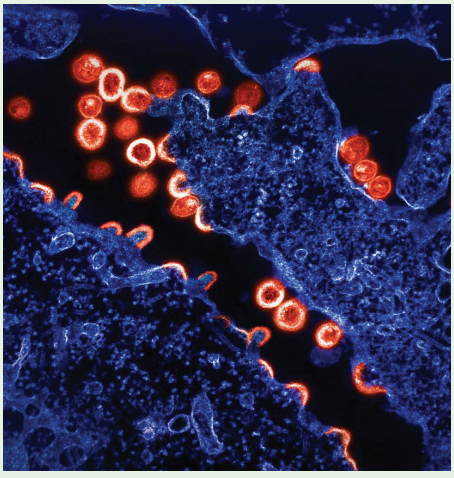
The three antibodies—one derived from a person with HIV and the two others from previously vaccinated rhesus macaques (Macaca mulatta)—targeted HIV's fusion peptide, a molecular structure that allows the virus to dock with and infect a cell. Rhesus macaques are monkeys with immune systems similar to those of humans. Animals in each of four groups received either the human-derived antibody at a high or low dose, or one of the two macaque antibodies. Five days later, the animals were challenged with a strain of SIV. All three antibodies provided statistically significant protection from SIV with the degree of protection being dose dependent.

Furthermore, breakthrough infections were seen in some of the initially protected animals in the macaque antibody groups after they underwent a SIV rechallenge a month later. When the investigators sequenced viral RNA from these reinfected animals, they found that the virus may have remained sensitive to neutralization by the infused antibody. This result suggests that the concentrations of the infused antibody in these infected animals had dropped to levels that were unable to prevent infection.

"Optimizing dosing [strategies] and broadening the neutralizing responses against HIV-1 to target its fusion peptitde would be a useful strategy for HIV vaccines," said lead author Amarendra Pegu, who is head of antibody research at the VRC's Virology Core.

The findings could inform the design of a human vaccine. (NIH authors: A. Pegu, S.E. Lovelace, M.E. DeMouth, M.D. Cully, K. Wang, S.D. Schmidt, M. Choe, C. Liu, X. Chen, E. Viox, A. Rowshan, J.D. Taft, B. Zhang, K. Xu, H. Duan, L. Ou, J. Todd, R. Kong, N.A. Doris-Rose, P.D. Kwong, R.A. Koup, and J.R. Mascola, PMID: 38232141) ●

[BY DIANNE LEE]



CREDIT: NIAID

NIAID: Transmission electron micrograph of HIV-1 virus particles (red) budding and replicating from a segment of a chronically infected H9 cell (blue).

NHLBI Pilots Internal Generative AI Tooling

BY MEAGAN MARKS, NIAAA

Generative artificial intelligence (AI) tools based on large language models (LLMs) such as OpenAI's ChatGPT, Google's Gemini, or Microsoft's Copilot have received both cheers and jeers for their ability to lighten workloads and increase efficiency in the workplace. But accompanying this new wave of generic public-access tooling comes an undercurrent of trustworthiness concerns and ethical considerations.

These concerns arise because the data entered into these public LLMs are not fully controlled, and caution should be exercised when assessing its output. For these reasons, the NIH Office of the Chief Information Officer recommends no sensitive information be shared with the public models. NIH employees have expressed their desire for this type of tooling and technology for their day-to-day work, however, so a team at NHLBI created an internal version in which the tooling can be utilized while sensitive information is protected.

Called **NHLBI Chat**, this internal-only LLM chatbot tool developed for NHLBI staff emulates the functionality of public models while being customizable for NHLBI users.

"This technology can accelerate how the NIH operates if employees know how to best use it in a safe manner," said **Nick Asendorf**, scientific information officer at the NHLBI Office of Scientific Information. Asendorf collaborated on the tool with colleagues **Anthony Fletcher** and **Robyn Wyrick**.

According to Asendorf, NHLBI Chat is a "front-end wrapper" that leverages models available in Microsoft's OpenAI Service. The available models are not trained on NIH, NHLBI, or medically specific data, yet the data entered and received by NHLBI employees is kept within NHLBI's data center. The additional internal functional layer allows employees to enter sensitive research-related information without the data exposure and breaching issues that would come with using the public models.

Using NHLBI Chat can increase work efficiency by taking over tedious work-related tasks, thus giving NHLBI employees more time to focus on research projects, patient care, or administrative or business tasks. For example, you can ask NHLBI Chat to summarize a paper, proofread a grant, draft an email, or write a line of code.

"I wouldn't treat patients with it, but there are definitely good uses for this software," said Fletcher, adding that the program can be especially helpful for fellows who are non-native English speakers because it can help with grammar and word choice on important documents.

The creators of NHLBI Chat are hopeful that all NIH employees will have access to this kind of internal tooling soon.

ARTIFICIAL INTELLIGENCE SYMPOSIUM
Friday, May 17, Masur Auditorium

Share your AI-related research at the upcoming NIH AI Symposium, sponsored by NHLBI, in partnership with FAES. Abstract submissions for poster presentation or a short talk of 12–15 minutes are encouraged. Online abstract submission and event registration is available at https://forms.microsoft.com/g/4WpdBXcEu6.

Important dates:
March 15: Abstract submission deadline
April 5: Notifications
May 3: Event registration deadline

For now, the chatbot is in its pilot phase and has only been released to a testing group at NHLBI. There are still restrictions on patient-related information and other sensitive data that must be worked through, and technical use and cybersecurity training will be necessary, too.

"It once took technological knowledge, infrastructure, and authorization to get to use email the way we do now," Wyrick explained. "We are at that same point with large language models and other AI interactive tools."

Fletcher agreed, adding, "This system does hallucinate, so you can ask it a question and it could just flat out lie to you. Like a Google search, you need to have the best judgment about what you are being told."

The next step is to create a concrete strategy on how this type of technology can be enabled at other ICs across NIH.

"We need a unified approach that is rooted in security, but also in scientific discovery and experimentation," said Asendorf, adding "we also need to get this type of technology into the hands of everyone so that they can learn best-use cases, pitfalls, and how to integrate this tooling into their daily workflows."

The trio developed an NHLBI Chat Training Video (NIH-only) and recommend that interested individuals review the NIH Guidelines to Public Tooling Use webpage (all links are available in the online version of this article at irp.nih.gov/catalyst.) ●

Meagan Marks is a postbaccalaureate fellow in David Lovinger's Laboratory for Integrative Neuroscience at NIAAA, where she studies motivation and reward. In her spare time, she enjoys exercising, playing the guitar, and exploring the D.C. area.

A Public Health Approach to Reducing Firearm Violence

An Intriguing WALS Talk Points to a Way Forward

BY ANNELIESE NORRIS, NCI

CREDIT: HARVARD UNIVERSITY

David Hemenway

The United States has, by far, the highest firearm-related violence rates among high-income countries. For example, American children aged 5-14 are 27 times more likely to be victims of firearm violence compared to children in other high-income countries. In 2021, 134 people died in the United States per day from firearm violence—more so from firearm suicides than firearm homicides.

"This is a big public health problem," said David Hemenway, professor of health policy at Harvard University (Boston), during a Wednesday Afternoon Lecture Series (WALS) talk in January. Fortunately, this is a problem that can be addressed using sound public health approaches.

Hemenway highlighted the successful harm reduction public health campaign for motor vehicle safety as an example of what can be achieved. Fatalities per mile driven have fallen by 90% due to manufacturing safer cars and other efforts to create safer driving environments. Drivers are little different today than in the 1950s, he noted, but the driving environment has made driving safer.

Rumble strips on the sides of highway lanes, reduction of trees lining roads, and the structural, functional, and technological safety modifications automakers have made to create safer vehicles over the years were all examples he offered. "It is hard to change people's behavior; it is much easier and more cost-effective to make their environments safer," he explained.

Everyone is part of the solution

Because the United States has more households with firearms than any other country, a public health approach that gets everyone involved in working toward harm reduction is key.

Applying that same approach to firearms as we did years ago to driving begins with placing less blame and sharing responsibility. A harm-reduction approach involving everyone as part of the solution would include gun manufacturers, gun dealers, gun owners, and gun safety trainers. It also includes those you would not necessarily think of, such as barbers and hairdressers, universities, and even banks—all different sectors of society can help solve the problem.

Safe environments save lives

Hemenway made it clear he is not trying to ban firearms, but he does want to make them safer. For example, modifications can be adopted to reduce firearm accidents by manufacturing personalized firearms—much like a cell phone that can recognize an owner's fingerprint. Other priorities include training firearm owners on measures to reduce the high suicide rates among them and their families.

One success story Hemenway credits to a Harvard colleague of his, Cathy Barber, who is the founding director of Means Matter, who along with Clark Aposhian, chair of the Utah Shooting Sports Council, helped develop a public service announcement (available on YouTube as "Cathy Barber: The 'Perfect' PSA").

Working together, public health and firearm experts created a suicide prevention module, "11 Commandments of Gun Safety," which is similar to the campaign "Friends Don't Let Friends Drive Drunk." The module offers advice such as when an emotional crisis is cause for concern, firearm owners might consider temporary off-site storage of their firearms. "Finding allies among gun owners, it turns out, is not that hard," said Hemenway.

Moving forward, Hemenway will explore lead poisoning among children of firearm owners. Bullets have lead in them, and after a shot is fired, the lead residue can remain on clothing, and children may eventually eat or inhale the particles. This is an underexplored area of research, and Hemenway is excited to learn more.

An underfunded epidemic

A roadblock for the public health approach to firearm violence harm reduction has been the historic lack of federal funding for research. Hemenway, whose research is funded primarily by foundations, highlighted that firearm research has been grossly underfunded in the United States.

There has been movement on this front, however. A White House initiative established the first Office of Gun Violence Prevention in 2023. NIH established the Firearms Research area of categorical spending in 2020 as part of the Research, Condition, and Disease Categorization system. Each year, OBSSR coordinates the annual $12.5 million appropriations from Congress to conduct research on firearm injury and mortality prevention. ●

Anneliese Norris, a scientist at NCI, is working on HIV dynamics and replication. In her spare time, she enjoys reading and building with LEGO®.

Meet 18 New Stadtman Investigators

BY *THE NIH CATALYST* STAFF

Neurodevelopmental cell regulation, environmental and occupational exposures, and precision therapies are just a few examples of the exciting new research explored by the latest cohort of scientists selected for the Earl Stadtman Tenure-Track Investigators Program.

The Stadtman program, which began in 2009, is named for renowned biochemist, senior investigator, and mentor Earl Stadtman (1919–2008), who devoted his 57-year NIH career to identifying the mechanisms of cellular energy expenditure and metabolism.

The program crosses all areas of biomedical research, designed to attract a diverse group of talented early-career scientists who might not typically apply to NIH via general searches conducted by individual institutes and centers (ICs).

Here, the *NIH Catalyst* introduces the 18 Stadtman investigators who were part of the 2020 recruitment cycle and joined various NIH ICs between 2021 and 2022.

MICHAEL AREGGER, PH.D.
NCI-CCR
Functional Genomics Section, Molecular Targets Program

Research: Applies functional genomics approaches to study genetic dependencies in renal cell carcinomas and examines how cancer cells rewire gene expression and metabolism to adapt to changing environmental conditions. (2021)

A. ROUF BANDAY, PH.D.
NCI-CCR
Genitourinary Malignancies Branch

Research: Explores the genomic alterations that govern the development of bladder cancer and confer resistance to therapies. (2022)

DAN BENJAMINI, PH.D.
NIA
Multiscale Imaging and Integrative Biophysics Unit

Research: Investigates the relationship between microstructure, chemical composition, and function in the aging brain, with a focus on neurodegeneration and neuroinflammation, by extending the functions and use of magnetic-resonance imaging. (2021)

CORNELIS BLAUWENDRAAT, PH.D.
NIA
Integrative Neurogenomics Unit

Research: Dissects the genetic architecture of Parkinson's disease and other neurodegenerative diseases using a variety of genomic methods and techniques. (2021)

LISA BOXER, PH.D.
NCI-CCR
Laboratory of Genome Integrity

Research: Explores the role of chromatin regulation in neural development and how mutations in chromatin regulators lead to neurodevelopmental disorders and cancer. (2022)

LI CHEUNG, PH.D.
NCI-DCEG
Biostatistics Branch

Research: Develops novel statistical approaches to characterize the etiology and natural history of cancer and collaborates with epidemiologists and clinicians to translate those statistical insights into novel precision prevention strategies. (2021)

PATRICK DOLAN, PH.D.
NIAID
Quantitative Virology and Evolution Unit

Research: Studies the evolution and host-virus interactions of positive-sense RNA viruses, such as Picornaviridae and Flaviviridae, using experimental and computational tools. (2021)

AKINTUNDE EMIOLA, PH.D.
NIDCR
Microbial Therapeutics Unit

Research: Explores the microbiome to predict disease and outcomes, develops ways to modulate the microbiome to improve human health, and is specifically interested in developing antimicrobial prodrugs and phage therapy strategies to inhibit detrimental oral pathogens while preserving beneficial commensals. (2021)

ASHLEY ELIZABETH FRAKES, PH.D., NIDDK
Glial Biology Section, Genetics and Biochemistry Branch

Research: Aims to understand how glial cells, the non-neuronal cells in the brain,

regulate aging and disease to identify the required components of this response, which may produce novel therapeutic targets to prevent or delay age-onset disease. (2021)

CARLOS GUARDIA, PH.D.
NIEHS
Placental Cell Biology Group; Reproductive and Developmental Biology Laboratory

Research: Applies basic science mechanisms to understand the effect of environmental stressors on human pregnancy, with a particular focus on placenta development, structure-and-function processes, and in vitro placenta modeling. (2021)

MASARU KANEKIYO, D.V.M., PH.D., NIAID
Molecular Immunoengineering Section; Vaccine Research Center

Research: Explores the vaccine-host interface to define immunological principles that inform the design of effective vaccines against challenging targets such as influenza virus. (2022)

ALEXANDER KEIL, PH.D.
NCI-DCEG
Occupational and Environmental Epidemiology Branch

Research: Applies statistical and theoretical methods to estimate human health effects of exposure mixtures from occupational and environmental exposures across the life course. (2022)

MIKHAIL KOLMOGOROV, PH.D., NCI-CCR
Cancer Data Science Laboratory

Research: Develops algorithms, mathematical models, and tools using computational genomics to address fundamental questions about living systems through the analysis of large-scale sequencing data. (2022)

GABRIEL STARRETT, PH.D.
NCI-CCR
Laboratory of Cellular Oncology

Research: Explores how tumor viruses, including polyomaviruses and papillomaviruses, contribute to the development of cancer using sequencing, bioinformatics, and classic wet bench molecular biology. (2021)

KOSUKE TAMURA, PH.D.
NIMHD
Socio-Spatial Determinants of Health Laboratory

Research: Investigates how neighborhood physical and social environments affect cardiovascular disease risk among minority groups using geospatial methodologies, such as geographic information systems and global positioning systems. (2021)

For more information on the Stadtman program, how to apply, and links to stories about other Stadtman investigators, go to https://irp.nih.gov/careers/trans-nih-scientific-recruitments/stadtman-tenure-track-investigators.

LEANDRO VENDRUSCOLO, PH.D., PHARM.D., NIDA
Stress and Addiction Neuroscience Unit

Research: Studies the neurobiology that underlies drug- and stress-related behaviors; and develops new models of drug addiction and investigates the neurobiology of enhanced drug taking and drug seeking based on the concept that these maladaptive behaviors involve neurotransmitter imbalance in brain regions that are involved in reward, stress, and executive function. (2022)

MARK WAGNER, PH.D.
NINDS
Neocortex-Cerebellum Circuitry Unit

Research: Observes the interaction between the two major brain centers of learning, the neocortex and the cerebellum, to characterize their connectivity and model the system dynamics to extract the basic neural computations that support our ability for general learning. (2021)

QUAN WANG, PH.D.
NIDDK
Section of Nanoscale Single-Molecule Dynamics, Laboratory of Chemical Physics

Research: Explores and develops new and improved methods that expand the capability of single-molecule fluorescence spectroscopy in solution to gain biophysical insights by directly monitoring processes. (2021) ●

The Perplexing Pancreas

CONTINUED FROM PAGE 1

and is responsible for 25% of acute pancreatitis cases.

The powerful pancreas is a large gland behind the stomach that secretes the endocrine hormones glucagon, somatostatin, and insulin and produces enzymes that help digest food. Pancreatitis occurs when these enzymes, which can be activated by a variety of causes, damage the pancreas and lead to inflammation. Pancreatitis can be acute or chronic, and either form is serious. It can lead to complications such as nutrient malabsorption, diabetes, damage to other organs, and death.

There is no known common mechanism underlying pancreatitis, and its triggers run the gamut from trauma, surgery, certain medications, genetic predisposition, and even a scorpion sting.

Investigators from across NIH's Intramural Research Program are using multifaceted approaches that both directly and tangentially explain the strikingly different pathways that lead to pancreatitis and ultimately inform better prevention and management. Perhaps most importantly, those scientists' diverse work illustrates how interdisciplinary science can yield a wealth of new discoveries.

Searching for genes

"You have to be a good detective in pancreatitis. The treatments are very different," said **Robert Shamburek** at NHLBI's Cardiovascular Branch. Shamburek studies rare genetic causes of lipid disorders such as hypertriglyceridemia, which often results in pancreatitis.

Most of the rare genetic cases involve young children who develop pancreatitis and must be put on a nearly no-fat diet. His protocol makes use of the Clinical Center's Genomics Opportunity (CCGO) program, which enables researchers to do whole exome sequencing of patients and sometimes their entire families. This program enabled him to identify two genetic mutations that were associated with hypertriglyceridemia. Shamburek found that if both parents are carriers of one of those genetic mutations—an extremely rare occurrence—then their child will more than likely develop the condition.

Furthermore, by leveraging CCGO data, his team discovered that when one parent carries a mutation, if that parent becomes obese, uses alcohol, or develops diabetes, then they have about a 1-in-250 chance of developing a lipid disorder and eventually pancreatitis themselves. Shamburek hopes that identifying these rare genetic variants could inform new precision medicine prevention approaches and therapeutics.

Taming triglycerides

Lasker Scholar **Rebecca Brown** in NIDDK's Section on Translational Diabetes and Metabolic Syndromes, Diabetes, Endocrinology, and Obesity Branch is an endocrinologist doing translational research. She studies patients with lipodystrophy, a rare disorder in which the body does not have adequate fat depots to store energy, leading to severe insulin resistance and elevated circulating triglycerides.

According to Brown, upward of 20% of these patients develop acute or chronic pancreatitis. Some of those patients are deficient in the hormone leptin, which helps regulate appetite, and she treats them—often successfully—with recombinant leptin (metreleptin) (PMID: 29644599).

Despite the treatment, some patients still have persistent high triglycerides and pancreatitis. In collaboration with Shamburek, Brown published the results of a small clinical trial using volanesorsen to activate lipoprotein lipase, an enzyme that breaks down fats in the bloodstream, and showed that the drug substantially lowered triglycerides (PMID: 36195542). The mechanisms behind volanesorsen might also help other metabolic conditions.

"We're looking at a technique to quantify uptake of fat from the bloodstream into the fat cell in patients with lipodystrophy and healthy controls," said Brown. If successful, tracking precisely where fats are being stored could then be used in clinical trials testing drugs in common forms of obesity and diabetes.

NHLBI's **Alan Remaley**, senior investigator in the Lipoprotein Metabolism Laboratory, is a pathologist who does basic science that is informing how we might treat pancreatitis in the future. Remaley's team studies peptides that activate lipoprotein lipase. A recent paper showed how those peptides substantially helped clear triglycerides in the muscle and fat of mice (PMID: 37547254).

The discovery could lead to a new treatment for the common adult forms of acute pancreatitis due to acute elevations of triglycerides. Clinical trials are likely a few years out.

Inflammation and autoimmunity

Inflammation and autoimmunity are yet another path to pancreatitis. **Warren Strober** at NIAID's Mucosal Immunity Section studies mucosal inflammation and immune response in gastrointestinal disorders, including pancreatitis.

He published a paper in 2016 on the immunopathogenesis of pancreatitis that established mechanisms demonstrating that pancreatitis is a unique form of inflammation and one that could be potentially treated with newer, more targeted therapies (PMID: 27848953). Further work by the Strober lab proposed that blocking a specific immune pathway in the autoimmune form of pancreatitis could be a successful treatment approach (PMID: 30401468).

Shmuel Muallem, senior investigator in NIDCR's Epithelial Signaling and Transport Section, is also working the autoimmunity angle and testing new treatments. His team studies the

mechanisms that govern how electrolytes such as calcium and bicarbonate are ferried across cellular membranes and what role those pathways play in autoimmune pancreatitis and Sjögren syndrome. In the pancreas, ductal cells secrete bicarbonate to neutralize acidic contents in the digestive tract, and those ducts can be damaged during disease. Ongoing research at Muallem's lab is exploring how drugs currently approved to treat cystic fibrosis might be repurposed to correct dysfunctional fluid secretion in mouse models of Sjögren syndrome and pancreatitis (PMID: 28634110).

Alcohol use disorder

"Every patient with pancreatitis should be assessed for AUD," or alcohol use disorder, said **Nancy Diazgranados**, intramural deputy clinical director at NIAAA. That's because alcohol use is the leading cause of chronic pancreatitis and second only to gallstones in acute cases. Alcohol and its metabolites can damage pancreatic tissue, and Diazgranados advises that education on how less alcohol is better should be a part of the intervention for every patient with pancreatitis.

Diazgranados conducts deep phenotyping of patients with AUD at the CC, where they undergo detox and receive counseling and multiple therapies. Researchers there collect data on behaviors, conduct neuropsychological tests and questionnaires, and do imaging and genetic testing alongside a control group without AUD. She sees three or four patients each year in her protocols who also have pancreatitis.

Treatment for pancreatitis with AUD overlaps with that for other types, that is, to temporarily stop eating, manage pain, hydrate, and then slowly resume a fat-free diet. "If it's not treated properly, it can be fatal," said Diazgranados, adding that for the patient with AUD, medications, psychological interventions, and support groups are important for recovery, too.

She refers health care professionals to an NIAAA Core Resource on Alcohol "Medical Complications: Common Alcohol-Related Concerns," which includes a chapter on pancreatitis and AUD to help guide clinical decision-making.

Fat and neurological control

At NIDDK, Senior Investigator **Sushil Rane** in the Integrative Cellular Metabolism Section of the Diabetes, Endocrinology, and Obesity Branch, is known for his work on pancreatic islet development and studying how insulin-producing beta cells maintain glucose homeostasis in the body. But in recent years, his lab has taken an interest in pancreatic pathophysiology and is investigating how fat arises in the pancreas.

According to Rane, it is an understudied topic that could mechanistically inform the understanding of disease areas such as pancreatic cancer, diabetes, and pancreatitis and of how we treat each because fat cells produce inflammatory cytokines and hormones that disrupt exocrine and endocrine functions.

"There is potential for fat to be made in the pancreas, but its [genetic] design suppresses that. So, is there something like inflammation or a genetic mutation that triggers this genesis of fat?" asked Rane. "Or is metabolism or another process driving fat deposition there?" His team currently has studies in the pipeline to address these questions.

Teasing out the nuanced neuroscience of pancreatic function is another fresh focus in the Rane lab. A recent study demonstrated a connection between the hypothalamus and beta cells (PMID: 35108515), and ongoing work is exploring how the vagus nerve might also control endocrine hormones. "We're figuring out how the pancreas talks to the overall machinery in the brain and vice versa," said Rane. ●

Editor's note: The scientific discoveries happening every day at the NIH result in breakthroughs that improve human health. Across our ICs, health topics such as pancreatitis are researched in a variety of ways. The NIH Catalyst *hopes to reveal these multifaceted approaches to health research with a series of articles like this one. We hope these articles will pave a catalytic path to increased collaboration. If there is a health-related focus we can cover to highlight your lab's research, please let us know by emailing us at catalyst@nih.gov.*

CREDIT: NIDDK

Rebecca Brown

CREDIT: SUSHIL RANE

Sushil Rane

CREDIT: NIAAA

Nancy Diazgranados

The Promise of Public–Private Partnerships

NIH Hosts First-ever Industry Day

BY SEPPIDEH SAMI, CC

CREDIT: NIAID

The new year kicked off with a renewed commitment to ensuring that research conducted at NIH translates to real-world advancements for human health. NIH Director **Monica Bertagnolli** spoke about the promise of successful collaboration between NIH scientists and private industry at NIH's inaugural Industry Day, held Jan. 18.

"When we think about delivering on NIH's mission, we know that includes making sure that insights and discoveries that emerge from our research get out into the world and improve people's lives," she said, adding, "NIH does not bring new products and services to market—the agency and nation rely on productive industry partnerships to achieve this."

Industry Day was a virtual conference that boasted 1,200 registrants, 50% of which were non-NIH, including about 30% from industry. Organizers **Bibi Bielekova**, chief of NIAID's Neuroimmunological Diseases Section; **Amy Klion**, chief of NIAID's Human Eosinophil Section; and **Mukul Ranjan**, senior advisor for Innovation and Technology Transfer at NIAID, said the event aimed to help junior scientists better understand the benefits and challenges of government–industry collaboration. At the heart of the conference were panels of scientific leaders from NIH, academia, and industry who showcased how synergistic partnerships are tackling problems at the forefront of biomedical research.

New gene therapies

Case in point: Last year, the FDA approved the first-ever gene therapy for sickle cell disease (SCD), the result of a successful NIH-industry collaboration between **John Tisdale**, chief of NHLBI's Cellular and Molecular Therapeutics laboratory, and Bluebird Bio's Melissa Bonner, who is now chief scientific officer of Nvelop Therapeutics (PMID: 35773052). Hemoglobin disorders such as SCD can be fatal and are among the most common inherited genetic diseases in the world. SCD is defined by sickle-shaped red blood cells that restrict circulation and can cause anemia, pain, and organ damage. SCD can potentially be cured with a bone marrow stem cell transplant from a healthy donor, but the procedure carries significant risk. By using a viral vector to reprogram a patient's own stem cells to generate healthy red blood cells, the therapy eliminates the need for a matching donor and thus the risk of graft rejection.

Tisdale and Bonner shared their complex journey in bringing the treatment to market. One challenge was determining the amount of stem cells that needed to be treated to correct SCD. Another involved exhaustive genetic analyses to ensure the new genetic instructions were only reaching their intended target. Only a successful industry partnership could help overcome these challenges. Of course, none of these studies could come to fruition without the patients who voluntarily participate in clinical trials. "They're really our partners in bringing these transformative therapies to bear," Tisdale said.

Novel vaccines

Human papillomavirus (HPV) infections can cause cervical and other types of cancers, which **John Schiller**, deputy chief at NCI's Laboratory of Cellular Oncology, has studied for years. Schiller spoke at Industry Day about the importance of being proactive about reaching out to industry with the discoveries made in the lab.

For example, pharmaceutical companies used Schiller's group's discoveries to develop and bring to market the first commercial vaccines for HPV using human papillomavirus-like particles (VLPs) (PMID: 22961341). VLPs have unique properties that also enable them to selectively bind to cancer cells and can be configured to deliver antitumor compounds.

That unique ability caught the attention of Elisabet De Los Pinos at Aura Biosciences, who collaborated with Schiller to show how modified VLPs were effective and durable in treating a type of eye cancer (PMID: 29242243). The drug has moved into clinical trials, and with more research, De Los Pinos sees the potential to treat a wide range of cancers.

Better biomarkers

What if a simple blood draw could provide early detection of organ transplant rejection? That's the idea behind analyzing cell-free DNA (cfDNA), a technique being pioneered by NHLBI Lasker Scholar **Sean Agbor-Enoh**. When cells are damaged, cfDNA is released into the blood and retains signatures that enable scientists to trace it back to its origin. Using cfDNA as a biomarker has shown promise in detecting

lung and heart transplant rejection months before symptom onset.

Agbor-Enoh teamed with four hospitals to study the use of cfDNA instead of an invasive biopsy to monitor rejection in lung transplant patients. He credits the NHLBI Office of Technology Transfer for working seamlessly with industry partners to get the new protocol published within 18 months (PMID: 35063338), and noted that the monitoring protocol has since been adopted by multiple centers across the United States and Canada.

A balanced ecosystem

Although much of Industry Day focused on productive partnerships, several speakers touted ways to improve public-private partnerships. Actionable steps included adhering to widely accepted data standards and ensuring clear goals are communicated from the outset.

"None of us works in isolation," said Industry Day speaker Gary Nabel, founding director of NIAID's Vaccine Research Center and, later, MODEX Therapeutics.

Organizers plan to make NIH Industry Day an annual tradition. "This was a fantastic and informative experience for the first year. I look forward to attending next year," wrote one attendee in a post-event anonymous survey. ●

CATALYTIC EVENTS

A smattering of catalytic events happening around the NIH in March and April.

MARCH

3/12 Demystifying Medicine: Cognitive Loss, Dementia, and Neurodegenerative Disorders. Rebecca Gottesman and Sonja Scholz (NINDS). 4–6 p.m., VideoCast: https://videocast.nih.gov/watch=54045.

3/13 Scientific Workforce Diversity Seminar Series: How Does Diversity Impact Innovation in Team Science? 10:30 a.m., on Zoom: https://nih.zoomgov.com/webinar/register/2717056879150/WN_ZbP6RiG_Q6qdh6uVEVHC2w#/registration.

3/14 NIH Laboratory Managers Working Group Webinar Series: NIH FreeStuff Website Demonstration noon–1 p.m. Virtual: email LMWG@nih.gov for link.

3/19 WALS: The Promises and Perils of AI in Biomedical Research and Health Care Delivery. Vint Cerf, Google. 1:30 p.m., VideoCast: https://videocast.nih.gov/watch=54305.

3/26 Demystifying Medicine: Behavioral Genetics, Man Meets Dog. Elaine Ostrander and Philip Shaw (NHGRI) 4–6 p.m., VideoCast: https://videocast.nih.gov/watch=54037.

3/28 NIH Laboratory Managers Working Group Webinar Series: Government Scientific Source, Qiagen and Agilent. noon–1 p.m. Virtual: email LMWG@nih.gov for link.

APRIL

4/3 *NIH Catalyst* Interest Meeting. 11:30 a.m., Building 10, in the FAES Student-Faculty Academic Center, classroom 1.

4/3 NIH Director's Lecture: Dynamic Interplay of Circadian Rhythms and Sleep on Health, Phyllis C. Zee. 2 p.m., VideoCast: https://videocast.nih.gov/watch=52619.

4/11 Minority Health 5K Walk/Run/Roll. 11:30 a.m. to 1 p.m., NIH Bethesda Campus. Register online: https://forms.office.com/g/7ygV0ANUDs.

NATIONAL MINORITY HEALTH MONTH

4/15 NIH Director's Lecture: The Future of CRISPR: What's Ahead for Genome Editing, Jennifer A. Doudna. 1 p.m., Masur Auditorium or VideoCast: https://videocast.nih.gov/watch=52420.

4/25 30th Annual NIH Take Your Child to Work Day and Earth Day. 9 a.m. to 4 p.m. Preregistration opens March 12. For more information: https://takeyourchildtowork.nih.gov.

4/29 Women Scientists Advisors hosts the 2024 Women Scholar Symposium featuring feature three FARE awardees: Chaido Stathopoulou, NCI; Jennifer Ish, NIEHS; Jennifer Zink, NCI. 2–4 p.m. Zoom link: https://nih.zoomgov.com/j/1609806867?pwd=T1JNVTE4WUdVbXBMQXBTZWxTRFBZQT09.

COMING SOON

The Demystifying Medicine Series will host Holden Thorpe, editor-in-chief of the *Science* family of journals, and Vardit Ravitsky with the Hastings Center, on May 7, 4–6 p.m., in Lipsett Auditorium, to discuss "Artificial Intelligence in Scientific Publishing." Also available on VideoCast at https://videocast.nih.gov/watch=54049.

NIH ABBREVIATIONS

CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
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
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health

Lasker Clinical Scholars Are Coming for Cancer

Intramural Research Program Supports Cutting-Edge Cancer Research

BY BRANDON LEVY, *I AM INTRAMURAL BLOG*

The cumulative years of experience among NIH researchers is truly astounding, with some scientists having spent half a century or more studying various forms of disease. As incredibly valuable as their hard-earned wisdom is to finding new treatments, any scientific field also benefits tremendously from a constant influx of young talent. That's where the Lasker Clinical Research Scholars Program, a partnership with the Lasker Foundation, comes in.

The Lasker program identifies promising early-career physician-scientists in a wide variety of fields and provides them with funding and resources to start their own independent lab at NIH.

Purely by coincidence, the latest Lasker Scholars happen to all specialize in the study and treatment of cancer. Read on to learn more about the new ideas and bounding enthusiasm these scholars are bringing to NIH's fight against this perplexing disease.

Investigating immunotherapies for cancer in kids

Age may be the most important risk factor for developing cancer, as someone over the age of 60 is more than 40 times as likely to be diagnosed with the illness as someone below the age of 20. This makes it a particularly cruel twist of fate when cancer strikes a child, reinforcing **Rosa Nguyen**'s commitment to focus her career on combating cancers in children.

Nguyen studies a form of cancer called neuroblastoma. Her first personal experience with neuroblastoma occurred during her first year of clinical fellowship, when she treated a young boy with a commonly used immunotherapy designed to entice his immune system to attack his cancer.

"Once the infusion started, the little boy screamed at the top of his lungs due to pain, which is a common side effect of this treatment," Nguyen recalled. "I left the room mortified. I understood that we wanted to combat his cancer by any means possible, but it came at a significant cost."

As Nguyen learned more about neuroblastoma, she discovered that grueling immunotherapy regimens like the one she administered to that boy do not help 40% of patients. She resolved to develop more effective immunotherapies that would not cause such severe side effects.

"Countless clinical experiences since have shown me the dire need for better immunotherapies not only to treat neuroblastoma, but also other pediatric solid tumors," she said.

Since joining NIH, Nguyen has made significant strides toward that goal, alongside diverse teams of colleagues from across the NIH. She helped develop a new immunotherapy for neuroblastoma that uses CAR T cells, which are genetically manipulated immune cells that scientists have given the ability to recognize and attack a patient's tumor.

Now, running her own lab as a Lasker Scholar, Nguyen hopes to refine this treatment and help guide it through clinical trials at NIH so that it can one day make its way into cancer clinics around the world.

Seeking lymphoma's weak spots

For **Samuel Ng**, joining the NIH as a Lasker Scholar meant his career had come full circle since a summer internship at NIH during his junior year of college. That internship was what cemented his goal to make science and medicine a permanent part of his life.

"I had this nebulous idea that I wanted to be a physician, and I did all the pre-med courses, but it wasn't until that experience at NIH that I had a template for what being a physician-scientist could be."

The immune cells that Ng studied at NIH that summer, called T cells, would become a common thread throughout his research career. Nowadays, Ng's lab studies what goes wrong in T cells to cause them to become cancerous.

The specific class of cancers he studies, collectively known as T-cell non-Hodgkin lymphomas, has proven more difficult to treat than non-Hodgkin lymphomas caused by problems with B cells.

To help research T-cell lymphomas catch up to its B-cell cousin, Ng has been developing cell models of one type of T-cell non-Hodgkin's lymphoma—specifically, angioimmunoblastic T-cell lymphoma (AITL), which is one of the most common subtypes of the illness.

"When I started my postdoc, there weren't very many cell lines for T-cell lymphomas, and particularly for AITL, none existed," he explained. "We are using these cell lines to identify genetic vulnerabilities that could be exploited therapeutically."

"There's been so much development on the B-cell side that I knew if I wanted to move the needle, T-cell lymphoma was a place where my work would really make a difference," he added.

Since Ng launched his lab at NIH, he said that he hopes his team can more quickly achieve life-saving breakthroughs for patients with T-cell lymphomas.

"That's ultimately whom we're doing all of this for, and I'm just very humbled to have the privilege to participate and try

Rosa Nguyen, M.D., Ph.D.
NCI-CCR

Samuel Ng, M.D., Ph.D.
NCI-CCR

Ramya Ramaswami, M.B.B.S.
NCI-CCR

Nitin Roper, M.D.
NCI-CCR

Payal Khincha, M.B.B.S.
NCI-DCEG

CREDIT: "I AM INTRAMURAL BLOG"

to help them this way."

Improving treatment for HIV patients with cancer

When HIV attacks the immune system, it makes the body more vulnerable to not only other infectious diseases, but also to cancer. Infectious agents, such as the Kaposi sarcoma-associated herpesvirus (KSHV), can even cause cancer themselves.

Ramya Ramaswami has spent the past four years studying not only the cancer caused by KSHV, known as Kaposi sarcoma, but also other ailments that sometimes come along with it.

"KSHV can lead to a panoply of conditions that can emerge at the same time as Kaposi sarcoma, making people very unwell," Ramaswami explained. "Kaposi sarcoma is very distinct on the skin and many other conditions caused by KSHV are often missed. This can be a problem because the treatments may be different depending on the nature of KSHV disorders."

Ramaswami hopes to provide physicians with better diagnostic tools "so that patients can receive timely and targeted treatment to improve their outcomes." And now that she has been selected as a Lasker Scholar, she plans to expand her research to exploring other virus-associated cancers, in addition to Kaposi sarcoma, that disproportionately affect people living with HIV.

"This population is often excluded from cancer clinical trials and is often unable to benefit from cancer care advancements," she noted. "I wanted to help drive change for this population."

That work requires Ramaswami to collaborate with experts in a range of fields, including fellow cancer physicians, virologists, and immunologists.

"My work is naturally collaborative," she said. "I love the interactions and the learning between scientists and clinicians from different disciplines."

Lung cancer's response to immunotherapy

As an avid skier and tennis player who commutes to and from work on his bike, **Nitin Roper** knows well the tremendous power of the lungs. Once he catches his breath each morning, he picks up where he left off in his mission to improve treatment for lung cancer.

Roper is focused specifically on small cell lung cancer, a type of tumor thought to arise from cells in the lungs known as neuroendocrine cells, which secrete hormones into the blood in response to signals from the body's nervous system.

Roper arrived at NIH in 2015 as a medical oncology fellow with "little background in the lab, having spent the last many years in clinical training," he recalled. "I expected to do clinical research, but I soon realized that the most significant discoveries that could be made in cancer occur in the lab, and NIH has outstanding laboratories and translational research opportunities."

Now with eight years in the lab under his belt, Roper is using the resources provided by the IRP and the Lasker Scholars Program to change the way doctors treat neuroendocrine lung cancers as well as neuroendocrine tumors that form in other parts of the body.

His lab's first step in that endeavor is identifying the molecular factors that predict how small cell lung cancer responds to immunotherapy. By doing so, his research may one day help make immunotherapies more effective and increase the ability to match patients to the right treatments.

"When immunotherapy became a major new treatment option for lung cancer, it was clear to me that this would be a critical area to work on," Roper said. "If any of these new treatment approaches developed in my lab improve patient lives, I would be satisfied that I picked the right career path."

Families with elevated cancer risk

Sometimes, careers are passed down through families just like genes. This was certainly the case for **Payal Khincha**, who was inspired to become a doctor by her father, who works as a surgeon in India.

It was only later in life, though, that Khincha fell in love with research. In 2012, she met **Sharon Savage**, an NCI senior investigator, who at the time was studying families with a much different inheritance than the one Khincha received from her father.

Due to certain inheritable gene mutations, some people tend to develop cancer at higher rates than the general population

CONTINUED ON PAGE 18

population, and at much earlier ages. Savage specializes in studying those families, and Khincha joined her research group.

Khincha would eventually take over as the lead researcher on one long-term study of Li-Fraumeni Syndrome (LFS), a condition caused by mutations in the TP53 gene that dramatically increases the risk of developing multiple types of cancer. The cellular systems that suppress cancer in individuals with LFS are so thoroughly disrupted that it is not uncommon for people with the condition to get their first cancer diagnosis before age 35.

By examining the biological reasons why people with LFS are so vulnerable to cancer and developing improved methods of monitoring them for tumors, Khincha hopes she can help stop cancer from affecting their lives so significantly.

"The impact of the research we do and the answers that we find are so important to the families who are affected by these disorders," Khincha said. "LFS is among the most severe cancer predisposition syndromes with extremely high lifetime cancer risks starting from infancy. The need for science is so high, and every discovery is critical to their outcomes."

Now as a Lasker Scholar, Khincha will continue to learn more about LFS as well as the life lessons she learns from her patients and their families. "I have learned about resilience, acceptance, grief, and the importance of a big-picture perspective on life," Khincha said. "I truly believe they have helped make me a better person, physician, and scientist." ●

Brandon Levy is a health communications specialist for the NIH Intramural Research Program.

This article was adapted from the "I Am Intramural Blog," available at https://irp.nih.gov/blog. To learn more about the Lasker Foundation visit https://laskerfoundation.org/education/lasker-clinical-research-scholars/.

Harvey Alter and the Discovery of Hepatitis C

New Exhibit Celebrates Work of NIH Nobel Laureate

The Office of NIH History and Stetten Museum hosted a ribbon-cutting ceremony Feb. 14 in celebration of the exhibit "Harvey Alter and the Discovery of Hepatitis C: Making Our Blood Supply Safe." The exhibit is located in the central corridor of the Warren Grant Magnuson Clinical Center, Building 10.

Alter was awarded the Nobel Prize for Physiology or Medicine in 2020, along with Michael Houghton and Charles Rice, for their discoveries that led to the identification of the hepatitis C virus.

The new exhibit is located near the FAES coffee shop, so you can grab a cup of coffee and enjoy Alter's humorous poem "I Never Had No Nobel Dreams," which he recited at the ribbon-cutting event.

Read more about Alter and the discovery of hepatitis C in "Milestones in the discovery of hepatitis C" (PMID: 36312838). ●

CREDIT: CHIA-CHI CHARLIE CHANG

A meeting of great minds: Anthony Fauci, Diane Dowling, Harvey Alter, James Gilman, Monica Bertagnolli, and Lawrence Tabak pose for a photo in front of the exhibit.

Lyuba Varticovski, Win Arias, and Anthony Fauci.

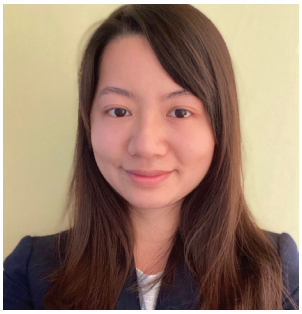
Making History: Devon Valera, James Gilman, Michele Lyons, Harvey Alter, Mark Riewestahl, and Kim Pelis.

Together again: Department of Transfusion Medicine colleagues pictured from left to right are Julie Juarez, Amanda Henning, Sarah Poag, Valeria De Giorgi, Harvey Alter, Susan Leitman, Kamile West-Mitchell, Sarah "Sally" Fowler, Maureen Miller, and David Stroncek.

From the Fellows Committee

Guiding Lights: Transformative Mentorship in the NIH Community

BY STACY LIANG, NIAID



CREDIT: STACY LIANG

Each of us plays multiple roles in our daily lives as both mentors and mentees. As a postdoctoral fellow in a laboratory, I am mentored by principal investigators and senior research colleagues. Simultaneously, I also mentor postbacs and new lab members. These mentorship experiences can be transformative and have long-term effects on our professional and personal lives, whether positive or negative.

A couple of fellows reached out to share successful mentorship stories. We thought it would be nice to share their stories as well as some mentoring resources that are available at NIH.

Binta Jalloh, a postdoctoral fellow at NCI, was an enthusiastic undergraduate student fascinated by science. During a college summer internship at the Woods Hole Marine Biology Laboratories, she met research scientists who inspired her to pursue a career in academic research. Among those heroes was Harold Gainer, NINDS scientist emeritus. Jalloh vividly remembers his telling her how talented she was and expressing his belief in her potential as a scientist. Since, Jalloh has held onto those encouraging words during the ups and downs of her research career. As a young refugee from Sierra Leone, born during the country's civil war, she shared that the transformative impact of Gainer's mentorship remains after his passing last November.

Samar Sayedyahossein, a clinical research scientist in the CC's Department of Laboratory Medicine, who has worked for several years with **David Sacks**, chief of Clinical Chemistry Service, offered a similar transformative story. Sayedyahossein has experienced profound growth, both personally and professionally, during her time at NIH. She credits Sacks' approach to data objectivity and scientific integrity, and noted one pivotal moment that occurred when facing a research challenge in which Sacks advised her to focus on strengths and make her way through limitations. Through that sage advice, Sayedyahossein not only conquered obstacles but also discovered her own resilience and adaptability.

Countless other stories unfold at NIH every day that are both positive and negative experiences. Mentorship is not unidirectional; it involves interactions between mentors and mentees. Jalloh and Sayedyahossein both believe a good mentor is someone who can recognize and nurture the strengths of a mentee, acknowledge them fairly, and guide them through the realities of imperfections and limitations.

Teaching and mentoring is one of the six core competencies of the Office of Intramural Training and Education (OITE). OITE offers guidelines on building relationships with mentors, covering topics such as understanding and establishing expectations, developing a mentor network, addressing issues, and integrating into research groups. OITE also provides a series of leadership and management training for those aspiring to be inspiring and supportive leaders in research and other fields, including cultivating talent from diverse backgrounds and promoting principles of diversity, equity, and inclusion.

Mentorship resources across NIH also include the Women of Color Research Network and the Women Scientists Advisors (WSA), which offer seminars and other networking opportunities. Subscribe to the WSA mailing list at women-fellows@list.nih.gov to learn more about upcoming events and opportunities.

Through shared experiences of guidance and support, these narratives illuminate the enduring legacy of mentorship, affirming its vital role in nurturing talent and driving progress within the NIH community. ●

Stacy Liang studies lipidomics during fungal infections as a NIAID Rocky Mountain Laboratories–Bethesda (Rocky-Beth) postdoctoral fellow.

JOIN US!

The NIH Catalyst is seeking volunteer photographers and writers to join our team.

If you are interested in science writing or photography, and would like to learn more about working with the *NIH Catalyst*, **please join us at 11:30 a.m., April 3**, at Building 10, in the FAES Student-Faculty Academic Center, classroom 1, for an informal, informational meeting. All are welcome!

Can Weight Loss Drugs Help the Addiction Crisis?

Repurposing Popular Diabetes, Weight Loss Drugs May Help Combat Alcohol Use Disorder

BY PETER MANZA, NIAAA

CREDIT: NIDA

Mehdi Farokhnia

CREDIT: NIDA

Lorenzo Leggio

The recent buzz around a class of weight loss medications known as glucagon-like peptide–1 (GLP–1) receptor agonists is undeniable. GLP-1 receptor agonists mimic the GLP-1 hormone—which is released primarily in the gut and makes you feel fuller on far less food.

The original purpose of these drugs was to aid glucose regulation, but the appeal of these drugs, which include semaglutide (the active ingredient in Ozempic, Wegovy, and Rybelsus), now extends beyond their ability to treat diabetes and help people shed pounds. Basic research, case reports, and patient anecdotes suggest that GLP-1 receptor agonists may also curb alcohol consumption.

Exciting, yes, but "we don't want to celebrate victory without the actual rigorous science," said **Lorenzo Leggio**, clinical director of NIDA and joint NIDA/NIAAA senior investigator in the NIDA Translational Addiction Medicine Branch.

Curbing cravings

Leggio and his colleagues, as well as other independent researchers, first recognized GLP-1 as a promising target for addiction nearly a decade ago.

For example, in a series of studies, the Leggio team observed that GLP-1 receptor agonism reduced alcohol consumption in mice, and that genetic variants affecting GLP-1 function influence a person's risk for alcohol use disorder (AUD) (PMID: 26080318). Support grew as other research teams found similar results. Research led by Leggio and **Mehdi Farokhnia**, staff scientist at the NIDA/NIAAA Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, explored the effects of semaglutide on excessive alcohol drinking in both mouse and rat models (PMID: 37192005).

> "We need a large menu of options to find the right fit for each patient."

Farokhnia and Leggio collaborated with NIDA/NIAAA Stadtman Investigator **Leandro Vendruscolo**, NIAAA Director **George Koob**, and researchers from Scripps Research Institute (La Jolla, Calif.) and University of Vienna (Austria) on that project. Later, another group of scientists in Oklahoma published case reports of people taking GLP-1 receptor agonists for weight loss who also had a significant improvement in their AUD symptoms (PMID: 38019594).

What makes GLP-1 receptor agonists so effective at reducing craving for food is probably what makes them also successful at lowering the urge to drink, according to Farokhnia. "There are a lot of [similarities] between alcohol craving and food-seeking behavior," Farokhnia explained, noting the common mechanisms between the two types of craving (PMID: 33536884). The GLP-1 system plays a crucial role not only in the experience of reward after eating or drinking, but also in moderating stress, "and both reward and stress are heavily involved in alcohol use," he added.

Preliminary evidence is promising. Leggio and Farokhnia emphasize, however, that it is premature to hail these medications as the next major advancement in addiction medicine. To date, only one randomized controlled trial—the gold standard for testing a medication's efficacy—of GLP-1 receptor agonists for AUD has been conducted. In that study, the primary endpoint was not met because exenatide, a GLP-1 receptor agonist, compared with placebo did not significantly reduce heavy drinking days in people with AUD (PMID: 36066977). Secondary analyses of that clinical trial suggested that people with comorbid obesity were successful in reducing alcohol consumption on exenatide compared with placebo, but leaner participants were not.

"This suggests that people with comorbid obesity and alcohol use disorder may benefit from these drugs," Leggio said, also speculating that exenatide may not be the best analogue for this purpose

and emphasizing that researchers are now very interested in semaglutide.

Are they safe?

Researchers also aim to understand the safety profile of GLP-1 receptor agonists in people with AUD, who often have comorbid health problems that could elevate their risk for side effects.

"These are pretty safe drugs overall," Farokhnia said, citing extensive evidence from GLP-1 trials for diabetes and obesity. "But they are not without risks. For example, though rare, there is a risk of pancreatitis because the pancreas also has GLP-1 receptors and people with AUD are already at higher risk of pancreatitis" (PMID: 37796527).

Scientists are also closely monitoring whether these drugs dampen motivation for rewards more broadly. If patients lose desire in other aspects of their lives beyond food and alcohol, it could increase their risk for developing mental health conditions such as anhedonia (the inability to feel pleasure), according to Farokhnia. Although more data are needed, a recent electronic medical records-based analysis is promising in showing no association between semaglutide prescriptions and risk of suicide (PMID: 38182782). These considerations prompted Leggio, Farokhnia, and other GLP-1 addiction researchers around the globe to publish a commentary urging physicians to not put the cart before the horse when it comes to prescribing GLP-1 receptor agonists to curb alcohol use (PMID: 38001271).

Currently, there are three FDA-approved medications for treating AUD, but they do not work for everyone. Compounding the issue, many people do not know about these options or have access to adequate care. Thus, the researchers conveyed enthusiasm for the potential of GLP-1 receptor agonists to aid in addiction treatment. "We know from clinical practice that we need a large menu of options to find the right fit for each patient," Leggio said. ●

Peter Manza, a research fellow at NIAAA, is studying how chronic drug use changes brain function and how the brain recovers after people enter treatment for substance use disorders.

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Watch Manza speak about his work in this recent segment of the NIH SciBites video series: https://irp.nih.gov/scibites/watching-the-brain-recover-from-opioid-use-disorder.

Food, Flora, and Function

Research Hints that Diet Choices May Affect Health by Modulating the Immune System

BY MICHAEL TABASKO, *THE NIH CATALYST*

CREDIT: NIAID

Yasmine Belkaid

If the saying "you are what you eat" holds true, the same might be said for our immune system, according to new research. Scientists from NIAID and NIDDK and their collaborators found that vegan and ketogenic diets remodeled the human microbiome and immune system, and each diet was found to have its own unique implications (PMID: 38291301). The results could open the door to a new era of research aimed at using dietary interventions as a way to modulate the body's immune response.

At NIDDK, **Kevin Hall**'s Integrative Physiology Section has a long-standing interest in understanding how the body and brain are affected by different kinds of diets. They conducted a clinical trial at the NIH CC in which 20 participants consumed either a high-fat, low-carbohydrate ketogenic diet, or a low-fat, high-carbohydrate vegan diet for two weeks, followed by the opposite diet for another two weeks, in random order.

As it turned out, diet changed the immune system significantly and rapidly, according to multi-omics analyses conducted by **Yasmine Belkaid**'s team at NIAID's Laboratory of Host Immunity and Microbiome.

"It was quite remarkable that such a short dietary intervention could remodel the immune system of all participants independently of their age, gender, BMI, ethnicity, or race," said Belkaid, who in January began a six-year term as president of the Institut Pasteur (Paris).

Diverging effects of diet

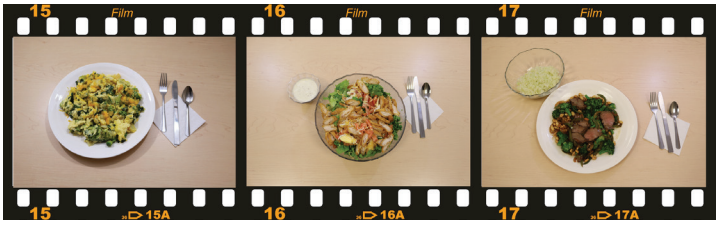
Cells of the adaptive immune system recognize specific antigens as a result of being exposed to outside elements such as a certain pathogen or vaccine. This exposure generates antibodies and orchestrates the immune system to respond in a very directed way that includes activation of T cells as well as enrichment of B cells, plasma cells, and natural killer cells. The ketogenic diet upregulated pathways linked to this adaptive immunity.

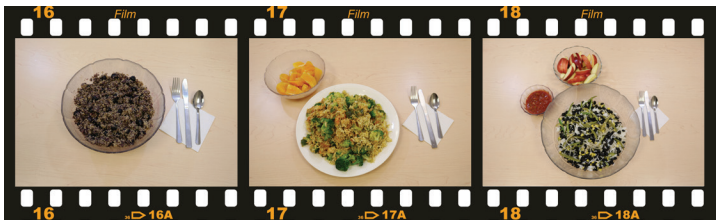
In contrast, the vegan diet activated pathways associated with innate immunity, the body's immediate first line of defense against any invading virus or pathogen. This includes quick-acting enzymes and defense cells in the skin and mucous membranes. The authors note, however, that they measured immune system changes—overall markers on which cells were being upregulated and which proteins were being expressed—and not function, as in someone's immune response to a vaccine.

Each diet differentially shifted the species of microbes colonizing the gut, an expected result based on prior studies (PMID: 24336217). For example, microbes that thrive on fiber proliferated on the vegan diet. Those types of microbes are known to release short chain fatty acids, a process thought to be beneficial in maintaining digestive health.

The ketogenic diet, which was relatively low in fiber, was associated with a strong downregulation of most microbial pathways, particularly those related to amino acid metabolism. However, that diet also upregulated the amino acid processes of the host.

The investigators think that the higher amount of protein consumed during the ketogenic diet might make those participants less reliant on microbe-derived amino acids. Although we know that the microbiome plays a role in regulating our immune system, exactly how it does that and





CREDIT: NIDDK

Keto Breakfast: Egg and Veggie Scramble (Egg, shredded cheddar/Monterey jack cheese, heavy cream, butter, onions, broccoli, spinach, salt)

Keto Lunch: Cobb salad (lettuce, shredded cheddar/Monterey jack cheese, tomatoes, bacon, chicken tenders, hardboiled egg, ranch dressing and salt)

Keto Dinner: Beef stir fry (beef roast, broccoli, green pepper, onion, soy sauce, canola oil, salt and peanuts) with cauliflower rice

Vegan Breakfast: Cinnamon, brown sugar and blueberry quinoa (quinoa, ground cinnamon, brown sugar, salt, blueberries)

Vegan Lunch: Tofu stir-fry (firm tofu, broccoli, sweet potato, nutritional yeast, green peppers and soy sauce) over basmati rice with a side of oranges

Vegan Dinner: Burrito bowl (basmati rice, black beans, salt, corn, green peppers, onions and lemon juice) with salsa and apple slices (lemon juice to prevent browning)

what differences in microbial communities mean are largely unexplored. "We are at early stages of understanding what the microbiome does, especially over long periods of time and how it interacts with the immune system in humans," said Hall.

In the future, precision nutrition interventions could be used to modulate the immune system and help manage chronic inflammatory disorders, according to Belkaid, but more controlled clinical studies are needed.

"Based on the large number of possible dietary interventions, the opportunity to harness nutrition has an enormous potential for human health," she said.

The metabolic effects of diet

The research builds off a 2021 clinical trial in which Hall's team sought to determine each diet's effect on the participants' voluntary energy intake (PMID: 33479499). Notably, both diets included foods that were minimally processed and provided a foundation of one kilogram of nonstarchy vegetables daily. The scientists found that participants on the vegan diet chose to consume nearly 700 calories fewer per day than when on the ketogenic diet.

Those unexpected results were at odds with the prevailing carbohydrate-insulin model of obesity, which posits that diets high in carbohydrates drive excess insulin production and increase energy storage in fat cells. In turn, that process would thereby deprive the rest of the body of energy, resulting in increased hunger and food intake.

The average American diet is high in ultraprocessed foods, which has been associated with increased energy consumption and weight gain (PMID: 31105044), so the shift to either whole food diet was beneficial.

"Both the vegan and ketogenic diets were quite healthy and both diets resulted in weight loss and metabolic improvements compared to baseline," said Hall.

Next steps

A new study supported by an NIH Bench-to-Bedside award from the Office of Dietary Supplements and led by **Aaron Hengist** in Hall's lab, in collaboration with **Michael Sack** at NHLBI and **Katherine Maki**'s group at the CC, will study immune and microbiota changes in people with diabetes and in people with obesity.

CREDIT: NIDDK

Kevin Hall

Participants will shift from a standard American diet to a ketogenic diet while taking a supplement called nicotinamide riboside, which boosts NAD+ concentrations inside cells. NAD+ is a coenzyme present in every cell that plays a critical role in regulating metabolism.

Previous studies have suggested a low-carbohydrate diet as a potential treatment for some people with diabetes and obesity (PMID: 29677013), and Hall hopes this new trial will explore how the supplement might augment the diet's effects. ●

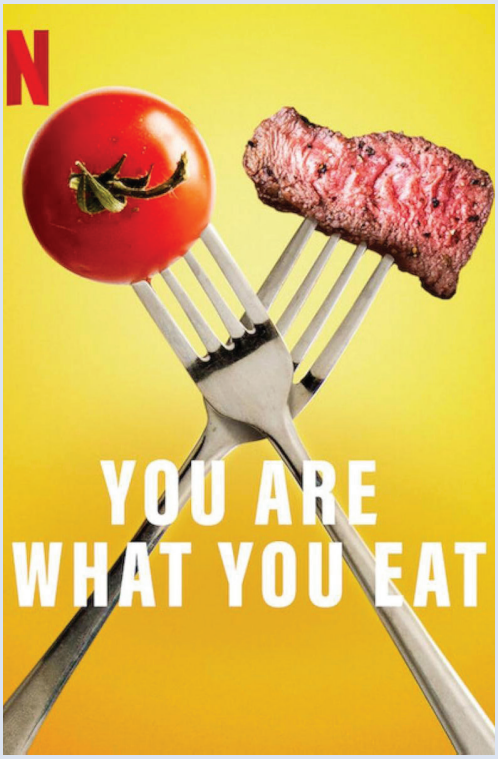
You Are What You Eat: A Twin Experiment

NETFLIX SERIES FEATURES NIH GRANTEE RESEARCH ON DIET AND HEALTH

Belkaid and Hall's findings come on the heels of a NHLBI-funded clinical trial that also discovered differing cardiometabolic effects of an omnivorous versus vegan diet in identical twins (PMID: 38032644) featured in the Netflix docuseries "You Are What You Eat: A Twin Experiment."

In that study, the vegan diet emerged as the most beneficial to human health, at least in the short term. By studying 22 sets of healthy identical twins, the researchers controlled for confounding factors such as age, sex, and genetics. One twin was randomly assigned to follow one diet, while the other twin followed the opposite diet. Participants were provided with meals for four weeks, after which they prepared their own meals, maintaining the assigned diet for the final four weeks.

Compared with twins on the omnivorous diet, the twins randomized to the vegan diet experienced significant decreases in low-density lipoprotein cholesterol concentration, fasting insulin concentration, and body weight. As in the NIH immune study, the authors note that both diets had healthy servings of vegetables and whole grains, and decreased sugars, and were likely an improvement over the participant's eating habits before study participation.



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PHOTOGRAPHIC MOMENT

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The 10th annual NIH–Bill & Melinda Gates Foundation (BMGF) Annual Leadership Workshop took place Jan. 29 at the John Edward Porter Neuroscience Research Center in Bethesda. Pictured left to right is NIH Director **Monica Bertagnolli**; Bill Gates; Trevor Mundel, president of BMGF Global Health; Chris Karp, director of BMGF Discovery and Translational Sciences; Food and Drug Administration Commissioner Robert M. Califf; NIAID Director **Jeanne Marrazzo**; and Anita Zaidi, president of the BMGF Gender Equality Division. ●

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