THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

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Research Festival to Celebrate NIH Past, Present, and Future

Three Days of Peace and Science

BY *THE NIH CATALYST* STAFF

Immerse yourself in a sea of intramural research at the 2024 NIH Research Festival on September 23–25 in and around Building 10 on the Bethesda campus.

Delve into NIH history, hear the latest biomedical breakthroughs, and glimpse fresh research directions from outstanding new investigators. From lectures to workshops to a bountiful spread of career- and science-supporting resources, attendees can expect a communal atmosphere to connect with colleagues old and new.

Here's a peek at what's happening. See the full agenda for times and locations at https://researchfestival.nih.gov.

Inspired by the past

Scientists of all career levels will be inspired by the NIH National Academy of Sciences (NAS) mini-symposium on September 24, at which three NIH PIs newly elected to NAS—**Thomas Kunkel** (NIEHS), **Kyung Kwon-Chung** (NIAID), and **Giorgio Trinchieri** (NCI)—will share insights about their scientific journeys, challenges, and breakthroughs that led to their distinguished accolade. (Part two of the NAS mini-symposium will be held on November 13 with NCI's **Steven Rosenberg** and **Sandra Wolin**.)

New to the festival is the Victoria A. Harden Lecture in NIH History on

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The Autoantibody Hunters

From PANDAS to Long COVID: Defining and Treating Infection-associated Conditions That Aren't So Black and White

BY MICHAEL TABASKO, *THE NIH CATALYST*

CREDIT: NIAID

Streptococcus pyogenes (group A strep), shown here as pink spheres, may trigger the immune system to create autoantibodies. Pictured is the normal immune response of a neutrophil (green) engulfing the bacterial invader.

The connection between infections and neuropsychiatric conditions can be unsettling, if not downright elusive. Consider a simple bout of strep throat, caused by *Streptococcus pyogenes* (group A strep), a nearly unavoidable hazard of growing up given the way the illness spreads like wildfire through school-aged kids.

Although the infection is usually treated successfully with antibiotics, it has been reported that some strep-infected children go on to abruptly develop neuropsychiatric symptoms that might include obsessive-compulsive disorder, motor or verbal tics, and other neurological abnormalities. The symptoms may eventually resolve, only to resurface with subsequent infections. Such is the clinical course of PANDAS, or pediatric autoimmune

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NIH Is Home to Life-long Learners

BY NINA F. SCHOR, DDIR

It is hard to believe that the fall season of 2024 is upon us. This, as it were, is the "Back to School" issue of the *NIH Catalyst*. Welcome back to all who took some well-deserved time during the summer months to relax and recharge, to enjoy the company of friends and family, and to connect with nature, the arts, personal hobbies, and whatever else makes you human and keeps you going!

This issue pays tribute, in part, to the discoverers and inventors of the past who have fueled some of the innovation that has improved our ability to understand and treat illness. As many of you know, I have spent my clinical life as a child neurologist and my research life as a pharmacologist. When I read through the content outline for this issue, I was reminded of how many medical challenges we face involve interactions of the immune system and endogenous or environmental triggers of it with the nervous system.

For example, many years after researchers at NIMH described the association of recent strep throat and a Tourette-like syndrome in children, neurologists are still debating whether a disorder called PANDAS and the related disorder PANS exist as discrete pathophysiological entities.

The possible connection is intriguing. However, confounders include observations that strep throat is so common in children, that association is not causality, that the vast majority of children with Tourette syndrome do not have recent strep infection, and that there is a well-established familial predisposition to Tourette syndrome across generations. What's going on here?

My own research has focused on the childhood cancer called neuroblastoma. Neuroblastoma affects the developing neural crest and consists of sympathetic nervous system cells that fail to fully mature, retaining their proliferative potential. Between 2% and 4% of children with neuroblastoma get a neurological syndrome called opsoclonus myoclonus, also known as dancing eyes–dancing feet syndrome. Opsoclonus myoclonus associated with neuroblastoma is further associated with developmental and behavioral regression and persists even after the neuroblastoma is cured.

> What better place than the NIH to unravel the next set of interdisciplinary mysteries?

This movement disorder is also associated with some adult cancers, albeit rarely. But in those cases, antibodies aimed at cancer antigens that cross-react with normal brain tissue in the cerebellum are often identified. Such is not the case with children with neuroblastoma and opsoclonus myoclonus. Yet immunomodulatory therapies do seem to decrease the severity of the syndrome and improve the outcome for these children.

When I was a graduate student at Rockefeller University (New York), I took a course called "Cellular Immunology," taught by Shu Man Fu (now professor emeritus at the University of Virginia) and Ralph Steinman (who died of pancreatic cancer in 2011). I remember thinking how phenomenological immunology was, with cells categorized based on what they did in a particular in vitro assay and antigens classified based on their association with cellular proliferation, differentiation, or senescence, respectively.

We have come a long way. There are mechanisms and genes and tools with which to understand such phenomena, of which we never could have dreamt when I was a student. But the story of the PANDAS and the PANS, and the challenge of opsoclonus myoclonus, tells us just how far we have yet to go.

With NIMH, NINDS, NIAID, NCI, and all our sister institutes in close proximity, what better place than the NIH to unravel the next set of interdisciplinary mysteries that link the immune system with the nervous system.

One of my roles as the DDIR is to provide opportunities for NIH scientists to collaborate and to be exposed to new ideas that can open new pathways of investigation. So, it is only fitting that this "Back to School" issue of the *Catalyst* also highlights the NIH Research Festival on September 23–25, a scientific immunotherapy symposium celebrating the career of Steven Rosenberg on September 26–27, and the 30th anniversary year of the Wednesday Afternoon Lecture Series (WALS), which runs from September through June—all rich fodder for insight and inspiration. I do hope you can take advantage of all that these opportunities have to offer. ●

Contemplating the Colorful NIH Canopy in Fall

How the Exquisite Trees on the Bethesda Campus Support the NIH Mission

BY SEPPIDEH SAMI, CC

CREDIT: ERIC BOCK

This medlar tree resides on Medlars Drive on the Bethesda campus. The tree was fruiting when this picture was taken in August.

Take a stroll on the NIH Bethesda campus and you will encounter a tapestry of trees, including two gorgeous Champion Trees, designated as the largest of their species in Montgomery County: One is an Allegheny chinkapin near Building 45, and the other is a black willow by the Stoney Creek Pond. Many new, smaller trees dot the campus, too, planted in remembrance of patient volunteers or NIHers who have died.

The 310-acre Bethesda campus is home to some 8,500 trees, more than 160 species, mostly native to the mid-Atlantic region, according to NIH landscape architect, **Connor Price**. Some are quite old; some have interesting biographies; and all join the human staff in supporting the NIH mission.

Consider NIH's two Trees of Hippocrates, said to be clones of the very tree that Hippocrates, the father of modern medicine, taught under on the island of Cos 2,500 years ago. In 1961, the Greek ambassador to the United States gifted a sapling from the Cos tree as a sign of friendship and source of inspiration.

CREDIT: NLM

The DNA barcode of the Tree of Hippocrates (*Platanus orientalis*).

That first tree thrived until the late 1980s, when fungal disease set in. NIH's landscape architect at that time, Lynn Mueller, worked to save the tree to little avail. He collaborated with the nonprofit Archangel Ancient Tree Archive to identify the genetic code of the historic tree and generate two more clones. One clone was planted outside NLM in 2014; the other stands at the Clinical Center's north entrance.

As sort of an inside joke, Mueller also planted fruiting medlar trees on Medlars Drive, the joke being that the road was named after the MEDLARS, the MEDical Literature Analysis and Retrieval System, the precursor to Medline.

Science supports the important influence of trees on the wellbeing of our planet and its inhabitants, helping to better manage human health (PMID: 32570770) and to buffer the impacts of a rapidly changing climate.

"There are many benefits to having trees nearby," said Price, citing "sequestering carbon from the atmosphere, reducing the amount of energy used for heating and cooling buildings, and providing a great food source as well as habitat for the wildlife."

Price oversees tree plantings, working closely with the design landscape architect team to weigh in on which species will thrive in specific areas. Sometimes, he allows exotic species without potential to be invasive, because they may be visually interesting, bear fruit for birds, or provide shelter for animals.

Price said he is building on the work of Brandon Hartz, landscape architect from 2016 to 2022, who had taken the reins from Mueller upon his retirement after 37 years of service during which he initiated the NIH reforestation program and installed numerous bluebird boxes. Hartz, among his many contributions, increased the tree plantings in the reforestation areas.

Every year, Price plants upward of 125 trees to keep up with the general loss due to severe weather events, disease, old age, or construction; more trees are planted to reach a forest conservation goal. In the forested areas, when safe, Price and his team will create a "snag" rather than remove a dying or a storm-damaged tree. They remove the tree top and branches but keep the trunk in place to serve as habitat for nesting birds and insects. The tree slowly decomposes, enriching the forest floor.

NIHers find the trees essential for work productivity. **Robert Scott**, a biologist in the NIMH Section on Neural Function, often takes walks among the trees after long bouts in the lab to reduce stress and improve his mood.

"While the work our lab does in understanding the mechanisms involved in the hormonal control of behavior is important to further the NIH mission, the human impact of our research often seems highly targeted and distant," said Scott, who, as a member of an NIMH employee advisory committee, arranged two Wellness Walks in the spring of 2024.

"The work that Connor and his team do is having an immediate impact on not just the health of the campus ecosystem, but, I believe, positive wide-ranging effects on the wellness of the very researchers whose goal it is to enhance health, lengthen life, and reduce illness and disability." ●

neuropsychiatric disorders associated with streptococcal infections. An unofficial diagnosis is sometimes made in the clinical setting but not without its skeptics (PMID: 30996598).

In 1998, NIMH's Susan Swedo and her colleagues were the first to establish clinical criteria defining PANDAS (PMID: 9464208). They proposed an autoimmune pathophysiology in which antibodies generated to fight the initial infection were cross-reacting with neural tissue in the basal ganglia, brain regions responsible for behavior and movement. This reaction is a well-studied mechanism known as molecular mimicry whereby microbial proteins that are structurally similar to host proteins result in autoantibodies that target host tissue.

Such molecular mimicry has been implicated in Sydenham chorea, a neurologic disorder associated with strep and rheumatic fever (PMID: 24184556), and in Nodding syndrome, in which a parasitic infection appears to give rise to autoantibodies that affect the brain (PMID: 28202777). So, PANDAS does seem to be consistent with other syndromes.

Some critics of the PANDAS hypothesis have pointed to a lack of reproduceable and robust studies validating the underlying mechanisms, diagnostic tests, and the efficacy of therapies, among other concerns. Recognizing these problems, Swedo, who retired from the NIH in 2019, proposed in 2012 the broader pediatric acute-onset neuropsychiatric syndrome, or PANS, which she and her colleagues said modifies the PANDAS criteria to eliminate etiologic factors (DOI: 10.4172/2161-0665.1000113).

The PANDAS-PANS issue is far from settled, but research into this broader connection between infection and neurological abnormalities continues at the NIH, specifically for a constellation of poorly understood infection-associated illnesses, such as long COVID, chronic Lyme disease, and myalgic encephalomyelitis-chronic fatigue syndrome (ME/CFS).

Maybe there's an underlying connection? Below is a snapshot of research investigating this topic, reflecting a new, multi-IC approach that involves a collaboration among NIAID, NINDS, and NIMH.

PANDAS revisited

New tools are at our disposal, and one emerging technology could unearth distinct autoimmune underpinnings of neuropsychiatric conditions. **Christopher Bartley**, chief of the Translational Immunopsychiatry Unit at NIMH, capitalizes on a new antibody profiling technique called phage display immunoprecipitation sequencing (PhIP-Seq), which identifies the targets of antibodies in biosamples, such as blood or cerebrospinal fluid, to uncover autoantibodies and give a detailed infection history not possible with conventional techniques.

Christopher Bartley, NIMH

PhIP-Seq uses modified bacteriophage programmed to display any known human or microbial protein in the form of short peptides that invite peptide-antibody interaction within a biosample. Bartley can use PhIP-Seq to precisely identify antibodies that indicate autoimmunity or a prior infection.

"Our library contains over 1.8 million peptides; half encode human proteins; the other half include proteins from over 4,000 microbes and viruses," said Bartley.

Bartley's team also adapted a technique called luciferase immunoprecipitation system, which was developed by NIDCR's **Peter Burbelo** in the early 2000s and measures how much antibody is present in a sample based on light emission, according to an NIDCR report. "It's incredibly sensitive," said Bartley, who is currently analyzing biosamples from Swedo's 2016 clinical trial that tested intravenous immunoglobulin (IVIG) as a treatment for PANDAS.

"We're really antibody hunting because the autoantibody [for PANDAS] hasn't been identified yet," he said. "We are using these platforms that allow us to determine the identity of the antibody targets, and then we can ask definitively if they only occur in PANDAS or if they occur more broadly. Secondarily, do they react with group A strep or other microbes?"

Bartley added that a diagnosis of PANDAS, for now, often is mischaracterized as seronegative autoimmune encephalitis (PMID: 37210100); it is not in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, which can complicate health insurance reimbursement.

In a separate hunting expedition, Bartley found autoantibodies in two teenage patients who had developed neuropsychiatric symptoms after COVID infection. That case report also validated a novel autoantibody against an intracellular protein implicated in a neurodevelopmental disorder and in schizophrenia (PMID: 34694339). And in an upcoming study using PhIP-Seq, Bartley and colleagues hope to demonstrate how some of the antibodies that bind to SARS-CoV-2 also bind to

CREDIT: CHIA-CHI CHARLIE CHANG

Adriana Marques, NIAID

human proteins, consistent with the concept of molecular mimicry.

Bartley also developed a PhIP-Seq analytic method that his colleagues used to identify an autoantibody profile in some people that was predictive for multiple sclerosis (MS) and showed that some of those patients have axonal damage years before symptom onset (PMID: 38641750). This result extends an established consensus that Epstein Barr virus (EBV) is necessary but not sufficient for developing MS, and it suggests that some people's immune systems may react—and cross-react—differently to EBV antigens compared with those who don't develop MS.

Down syndrome regression disorder (DSRD), too, might have an autoimmune component, said Bartley, who is a co-investigator on a related NIH-funded Bench-to-Bedside study with **GenaLynne Mooneyham** (NIMH), **Eliza Gordon-Lipkin** (NHGRI), Jonathan Santoro (Children's Hospital Los Angeles), and Aaron Besterman (Rady Children's Hospital, San Diego). In DSRD, children with DS lose functional status at a young age, and those patients seem to respond to immunotherapy, according to Bartley.

"We have an active research program looking for autoantibodies in those individuals and are admitting patients to the Clinical Center for phenotyping."

Post-treatment Lyme disease syndrome

Another compelling mystery is the long-term effects of Lyme disease, the leading vector-borne disease in the United States, caused by *Borrelia burgdorferi* bacteria and carried by ticks.

Most people who get Lyme disease will recover with antibiotic therapy, but a portion of patients will complain of fatigue, muscle and joint pain, sleep problems, and brain fog. This syndrome of nonspecific symptoms is called post-treatment Lyme disease syndrome (PTLDS).

In 2023, NIH awarded five projects to fund research aimed at better understanding the syndrome.

"Possible drivers of symptoms after Lyme disease [include] immune dysregulation, autoimmunity, antigen persistence or ongoing infection, preexisting and new conditions, and psychosocial influences. Our current work addresses all these areas," said **Adriana Marques**, chief of the Lyme Disease Studies Unit at NIAID's Laboratory of Clinical Immunology and Microbiology.

Marques' team is working on a clinical study that evaluates and follows patients with PTLDS. They are exploring different methods and markers to assess the cause of symptoms, which can help in the development of new treatment studies.

For example, they collaborate with investigators at Tufts University (Boston) to study antiphospholipid antibodies produced in response to *Borrelia burgdorferi* infection (PMID: 35289310).

The early data suggest that these antibodies showed up earlier after infection and were cleared more quickly, and more research is needed to determine whether these antibodies will help in early diagnosis of Lyme disease, in diagnosis of reinfection, or to track the response to therapy. Marques is also working with collaborators at Columbia University (New York), studying the antibody response at different stages of Lyme disease and PTLDS.

Long COVID and viral remains

Long COVID has been dominating the news. One theory on how long COVID perpetuates is that bits and pieces of the COVID virus—shards of RNA and proteins—remain in the body and continue to fuel a slow-burning immune response, contributing to inflammation and resulting in symptoms such as cognitive difficulties and fatigue.

"Are there differences in the types or amounts of viral remnants in long COVID participants compared to healthy volunteers?" asked **Brian Walitt**, a staff clinician in the Interoceptive Disorders Unit at NINDS and part of a multidisciplinary team running an ongoing long COVID clinical trial at the NIH Clinical Center.

"Data suggest there's residual material in people, but it's not clear how different it is in recovered versus not recovered individuals. Is there a difference in the host responsiveness to those remnants, and how do the viral remnants interact with the immune system?"

CREDIT: NINDS

Brian Walitt, NINDS

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NEI Launches New Funding Mechanism to "Innovate Together"

Intramural Grants Help Awardees Step Outside Comfort Zones, Gain Career-building Experience

BY KATHRYN DEMOTT, NEI

John Ball has long wanted to visualize the functional circuitry of individual cone photoreceptors. Now, thanks to artificial intelligence (AI) and a new NEI intramural grant program, Ball, a staff scientist in the Retinal Neurophysiology Section, will get his chance. In fact, seven projects funded by the "Innovate Together" program will enable NEI intramural postdoctoral fellows and staff scientists to explore new tools and techniques. The funding program also provides career-building experience in grant proposal writing and budget management, independent of involvement from primary investigators.

The seven grants awarded in this first round totaled $350,000. "AI, big data analysis, high-throughput screening, and other methods blossomed after most awardees finished graduate school," said NEI Scientific Director **Kapil Bharti**. This program encourages NEI intramural researchers "to get outside their comfort zone," he said.

With his grant, Ball will use cloud-based AI to segment and digitally reconstruct the structure of neurons within a very large 3D electron microscopy image. The data will come from a block of retina from the thirteen-lined ground squirrel (*Ictidomys tridecemlineatus*), a model for investigating cone-based eye diseases. "One of the challenges in neuroscience is that everything is so tightly packed together and interacting in complicated ways," said Ball. "It is difficult to tell what you are looking at. The 3D reconstruction of neuronal wiring from serial electron microscopy is a technique that has been around for decades, but automation and computers have increased the capability to explore these huge wiring diagrams to figure things out."

Gleysin Cabrera-Herrera, a postdoctoral fellow in the NEI Laboratory of Retinal Cell and Molecular Biology, specializes in the characterization of carbohydrates and proteins using mass spectrometry, but she wants to learn how to interpret genomics data. The grant supports her search for biomarkers of early age-related macular degeneration (AMD) by interpreting findings from AMD population genome-wide association studies and corresponding quantitative proteomics data.

For **Andrea Barabino**, a postdoc in the Ophthalmic Genetics and Visual Functions Branch, the NEI IRP grant will give him the chance to use novel approaches to study how two key retinal cells work together. The back of the eye is like a camera with sensors (photoreceptors) that capture light to make images and batteries (retinal pigment epithelial [RPE] cells) to provide energy. In eye diseases like AMD, these two cell types stop working well together, leading to vision loss. Barabino and **Ali Otadi**, a postbaccalaureate trainee in the same branch, proposed using stem cells, 3D printing, and unique proteins that act like glue to get the RPE and photoreceptors to stick together. "Bringing together RPE and photoreceptors in vitro in a more physiologically relevant system could help us understand how these cells interact in healthy and diseased eyes and could lead to new treatments," he added.

With her grant, **Ruchi Sharma**, a staff scientist, is forming a multidisciplinary team that will use AI and machine learning (ML) to find meaningful connections between disease-in-a-dish lab models and clinical research involving patients with AMD. "I have always loved the idea of a multidisciplinary team that brings together clinicians, big data scientists, and experts in AI and ML, and this funding opportunity has given me the chance to make that happen," said Sharma.

Joanne Li is stepping outside her comfort zone as a biomedical engineer and using the grant to collaborate with **Vineeta Das**, a postdoctoral researcher with expertise developing AI-based image analysis methods. Together, they plan to develop a system that combines high-resolution optical coherence tomography imaging and an AI-based analysis platform to detect the earliest sign of age-related diseases. "By having a system that images living human eyes at the cellular level and systematically analyzes and tracks changes over time, we hope to understand how the 'normal' path of aging deviates in diseases such as AMD," Li said.

"Scientists tend to stick with what they are good at," added Herrera. "The NEI IRP grant program challenges us to think outside our area of expertise and, more importantly, gives us funding to pursue those ideas." ●


BALL


BARABINO


DAS


CABRERA-HERRERA


LI


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SHARMA

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To answer these questions, Walitt and **Avindra Nath**, NINDS clinical director and senior investigator at the Section of Infections of the Nervous System, are launching a new study to analyze biopsies from tissue all over the body in living individuals. They intend to compare healthy participants after recovering from COVID with individuals with long COVID and look for remnants of SARS-CoV-2 RNA or proteins.

Data from the long COVID protocol have shown a dysregulation of antibody-producing B cells and infection-fighting T cells in some participants, and the investigators hope to determine whether some of that immune dysregulation might be due to the inability of some people to clear viral material.

Characterizing chronic fatigue

A condition that eerily shares some of the same symptoms experienced by those with long COVID, such as fatigue and cognitive difficulties, is myalgic encephalomyelitis-chronic fatigue syndrome (ME/CFS). A large multidisciplinary team at NIH was the first to link specific abnormalities or imbalances in the brain to the clinical symptoms of post-infectious ME/CFS. And the hunt is on for a cause.

Of note, the researchers used the same study design, common data elements, and comprehensive testing procedures as in the long COVID trial and found some overlap in the findings, including immune dysregulation. As with long COVID, the findings suggest that something in the periphery might be interfering with the immune system's taking full action.

"We looked at a subpopulation with ME/CFS that was triggered by an infection, mostly respiratory or [gastrointestinal] infections, and those patients likely have an immune system that is exhausted and unable to clear the antigen. The immune cells look very different in these individuals compared to those that clear the infection," said Nath, who was senior author on the study published earlier this year in *Nature Communications* (PMID: 38383456).

CREDIT: NINDS

Avindra Nath, NINDS

Immune-targeted therapies

Nath and Walitt now hope to launch a clinical trial to identify patients with long COVID and T-cell exhaustion and treat them with a PD-1 inhibitor, a checkpoint inhibitor drug sometimes used to treat cancer. According to Walitt, they hope to find out whether the treatment might help restore immune function and clear the viral material, perhaps having downstream effects on the central nervous system and other symptoms.

"It's the intervention most open to scientifically testing the clinical impact of the observed immune exhaustion that we have right now," he said.

Another trial underway is treating long COVID patients with IVIG, a nonspecific immunotherapy that delivers a concentrate of antibodies. "Some people have a dramatic response, and some people don't," said Walitt. "The idea is to understand who the responders are and who are not so that we can predict response and know who to give it to."

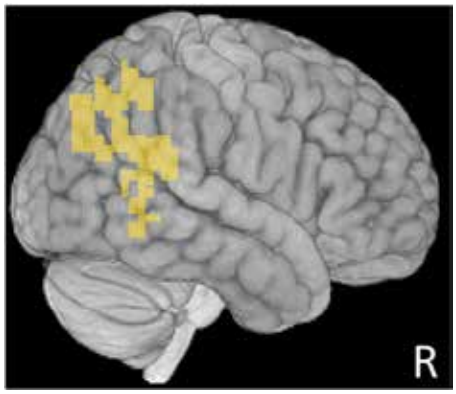
Aligning the research agenda

In 2023, the National Academies of Sciences, Engineering, and Medicine hosted a workshop titled "Toward a Common Research Agenda in Infection-Associated Chronic Illnesses."

The event was attended by several members of NIH leadership and focused on aligning research toward uncovering biological similarities between diseases that could perhaps lead to treatments that might work across multiple conditions.

According to Nath, the present time is a golden opportunity to study these diseases. "We've made certain breakthroughs, but there is a lot that remains unknown about a whole host of diseases that look very similar phenotypically but have different names," he said.

"If you find a treatment for one of them, then you might just find a treatment for all of them. There's room for specialists to really study them, apply their expertise, and make a real difference." ●



CREDIT: PATRICK BEDARD, NINDS

NIH researchers found persistent immune dysfunction in people with post-infectious ME/CFS, which the scientists hypothesize may have downstream effects by altering metabolites that affect brain function. Shown is a composite of functional magnetic-resonance images taken during a grip-strength test. The highlighted brain areas (bilateral temporoparietal junction, superior parietal lobule, right temporal gyrus) have decreased activity in patients with ME/CFS compared with those without the syndrome. Caption courtesy of NINDS.

Intramural Research Briefs

Read about Scientific Advances and Discoveries by NIH Intramural Scientists

NIDDK: NeEDL Finds Links in Genetic Haystack

Many inherited diseases, such as diabetes and Alzheimer's, may be caused by mutations interacting across multiple genes. With billions of possible mutations that could affect such interactions across the entire genome, however, finding these connections is like searching for the proverbial needle in a haystack. Now, a new tool developed by an international team that includes NIDDK researchers makes the search much easier. Called NeEDL, short for network-based epistasis detection via local search, this tool uses network medicine coupled with quantum computing to identify the most statistically relevant epistatic interactions (EIs) between point mutations called single nucleotide polymorphisms (SNPs).

EIs are a measure of the effect of an interacting group of genetic variations for which the whole effect could be much greater than the sum of its individual parts. Finding the EI between two SNPs is a common lab-based exercise, but finding the EI between five or more SNPs is too computationally daunting, requiring possibly millions of hours to compute on even the fastest supercomputer. To overcome this hurdle, the NeEDL team, led by **Markus Hoffmann**, a postdoc in the NIDDK lab of **Lothar Hennighausen**, first turned to a quantum computer at CERN in Switzerland and a support team at the University of Verona in Italy to develop the necessary algorithm upon which NeEDL is based. Quantum computers—rare, expensive to use, and still in the prototype stage—are nevertheless orders of magnitude faster than the fastest supercomputer.

With the algorithms computed, Hoffmann and his team created an EI search engine, of sorts—that is, NeEDL—that researchers can download and use on a fast computer (although, the super-er the better) to find clinically meaningful SNP connections. The free tool can analyze upward of 150,000 SNPs on a supercomputer, such as Biowulf at the NIH. Hoffmann, who created NeEDL as part of his doctoral thesis at the Technical University of Munich (Freising, Germany) and his postdoctoral fellowship at the NIH, said the tool is optimized for quantum computing and would be able to analyze tens of millions of SNPs rather quickly once these next-generation computers are fully developed. For now, NIDDK researchers hope to use the tool to identify possible SNP-based disease connections and then develop the animal models to test the NeEDL output. (NIH authors: M. Hoffmann, S.G. Lee, J. Jankowski, H.K. Lee, and L. Hennighausen, PMID: 39175109)

NIDCR, NHLBI, NCI: DRIVERS AND BIOMARKERS OF SYSTEMIC SCLEROSIS

Systemic sclerosis (SSc), also known as scleroderma, is an autoimmune condition that causes the skin and vital organs such as the lungs to become fibrotic and stiff due to atypical connective tissue growth. A research team led by **Wanjun Chen**, senior investigator in NIDCR's Mucosal Immunology Section, discovered a crucial interplay between microRNA-19b (miR-19b) and the cytokine interleukin-9 (IL-9) in the progression of SSc.

MicroRNAs are noncoding RNA molecules that are known to play a role in regulating gene expression in certain tissues and in immune cells. In a series of in vitro experiments, the investigators described a molecular pathway by which miR-19b was upregulated in SSc, driving production of IL-9, a cytokine secreted by helper T cell 9 (Th9) immune cells.

Using a mouse model of SSc, the investigators then showed that inhibiting miR-19b or IL-9 in mice with SSc reduced symptom severity, suggesting that high concentrations of miR-19b boosts the differentiation of Th9 cells, subsequently elevating IL-9 production and contributing to SSc pathogenesis. The scientists found similar mechanisms at play by analyzing gene expression in the cells of patients with SSc.

The findings could offer new therapeutic targets and serve as a biomarker for disease progression, and the authors note that more research is needed to understand the role of Th9-associated pathogenesis in other human diseases. (NIH authors: Y. Lim, S. Park, W. Jin, W.L. Ku, D. Zhang, J. Xu, L.C. Patiño, N. Liu, R. Kazmi, K. Zhao, Y.E. Zhang, and W. Chen, PMID: 39083380)

[BY HÉCTOR CANCEL-ASENCIO, NINDS]

NLM, NEI, CC: STUDY EXPOSES RISKS AND BENEFITS OF INTEGRATING AI INTO CLINICAL SETTINGS

CREDIT: NLM

NLM, NEI, CC: GPT-4V, an AI model, often made mistakes when describing the medical image and explaining its reasoning behind the diagnosis, even in cases where it made the correct final choice.

A multimodal artificial intelligence (AI) model known as Generative Pre-trained Transformer 4 with Vision (GPT-4V) can analyze both text and visual inputs. NIH researchers and their extramural colleagues found that this model can perform comparatively to human physicians in making a diagnosis based on medical images and associated clinical notes, but it exhibited flaws in its performance. According to the authors, the study builds on prior research that found that GPT-4V can accurately answer multiple-choice questions but did not thoroughly assess whether the model was using the correct underlying rationale.

The researchers tasked GPT-4V and physicians with answering 207 multiple-choice questions from the *New England Journal of Medicine* Image Challenge, an online quiz that presents medical images alongside a short description describing a patient's symptoms and then asks users to select the correct diagnosis. Investigators analyzed the model's proficiency in answering questions and its rationale within the three categories of image comprehension, medical knowledge recall, and step-by-step reasoning.

GPT-4V had a slightly higher overall accuracy in choosing the correct diagnosis (81.6%) compared to physicians (77.8%); however, the model had flawed rationale in 35.5% of the cases in which it nevertheless made the correct choice. Errors in the image comprehension category were particularly prominent. "Understanding the risks and limitations of this technology is essential to harnessing its potential in medicine," said **Zhiyong Lu**, senior investigator and corresponding author of the study, in a press release. (NIH authors: Q. Jin, R. Summers, M. Chiang, and Z. Lu, PMID: 39043988)

[BY MELANIE BARKSDALE, NIAID]

NCI: DNA FRAGMENTOMICS IDENTIFIES RISK OF PERIPHERAL NERVE SHEATH TUMORS

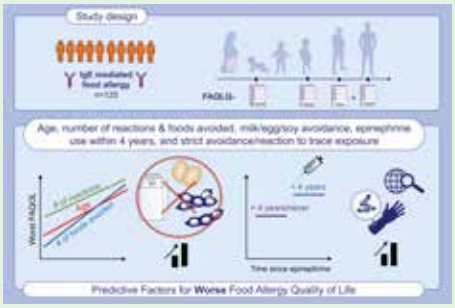
A team of pediatric oncology researchers from NCI and their university and hospital collaborators developed a noninvasive method for assessing tumor risk in patients with neurofibromatosis type 1 (NF1). NF1 is a genetic disorder caused by mutations in the gene for neurofibromin 1, which is essential for normal cell function. In the absence of this protein, peripheral nerve sheath tumors (PNSTs) can grow along nerves. These tumors can be malignant, classifying NF1 as a cancer predisposition syndrome.

The NCI-led team found that DNA fragmentomics—a novel technique for extracting biomarker information from blood-derived DNA fragments—is effective for early detection and risk assessment of PNSTs. The investigators extracted and sequenced cell-free DNA from blood samples of 101 patients with NF1 and 21 healthy control subjects. The resulting DNA fragments were then analyzed and used to successfully classify the tumors as benign, premalignant, or malignant.

The authors note that the findings could enhance early cancer detection and intervention, leading to better outcomes for individuals with NF1 at risk of developing malignant tumors. (NIH authors: R.T. Sundby, A. Pan, S.Z. Mahmood, O.H. Reid, B. Murray, S. Patel, A.N. Lucas, M. Fagan, A. Dufek, E. Dombi, A.M. Gross, B.C. Widemann, and J.F. Shern, PMID: 39093127)

[BY MEAGAN MARKS, NIAAA]

NIAID: FACTORS INFLUENCING QUALITY OF LIFE IN PATIENTS WITH FOOD ALLERGY VARY BY AGE



CREDIT: NIAID

NIAID: Researchers identified multiple factors that influence quality of life in people with food allergy, and they found the relative impact of those variables varied according to age.

Investigators at NIAID conducted a comprehensive study reviewing validated age-specific questionnaires to identify key predictors of quality of life of people with food allergies. Because food allergies, broadly speaking, has no cure, effective individualized treatments can only be developed and implemented if factors having the greatest influence on psychosocial wellbeing at different ages are well understood, according to **Pamela Frischmeyer-Guerrerio**, chief of NIAID's Laboratory of Allergic Diseases and senior author on the study, published in the journal *Allergy*.

Frischmeyer-Guerrerio's team analyzed questionnaire responses from 125 participants between the ages of 2 and 28 years with physician-diagnosed immunoglobulin E-mediated food allergies. Poor quality of life was associated with increasing age, stricter avoidance practices, and more severe reactions. Other predictors of quality of life included the timing and number of reactions and type and number of foods avoided, with allergies to milk, egg, soy, sesame, or wheat having a particularly negative impact. Moreover, the relative impact of those factors varied according to age. Upcoming work will examine parents' distress regarding their child's food allergies. "A better understanding of the factors affecting the parental burden of having a child with food allergy, and how these factors relate to those [variables] affecting the quality of life of the child, will be essential for clinicians to optimally support families with food allergy," Frischmeyer-Guerrerio told the *Catalyst*. (NIH authors: S.A. Kubala [now Children's Hospital of Philadelphia], F.D. Young, V. Callier, M.M. Rasooly [now University of Maryland Medical System], C. Dempsey, E. Brittain, and P.A. Frischmeyer-Guerrerio, PMID: 39096008)

[BY SEPPIDEH SAMI, CC]

NEI: NEW FACE-DETECTING NEURONS IDENTIFIED

The brain's ability to selectively recognize faces out of a field of visual information is thought to be processed within specialized populations of neurons known as "face patch" regions in the visual cortex. Deepening our understanding of this facial processing, researchers at NEI have identified a new, fast-acting face-detecting population of brain neurons. This newly identified circuit, located in the midbrain superior colliculus (SC), responds rapidly to faces and can detect faces in the periphery.

The research team recorded neuronal activity in rhesus macaques (*Macaca mulatta*) when images of face and non-face objects were shown in the monkey's peripheral visual field. They observed face-related responses in the SC that followed the presentation of visual cues by 40 milliseconds, significantly faster than face patch regions, and distinguished facial stimuli from other objects with nearly 80% accuracy. Further analysis revealed that SC neurons may receive their inputs from early visual processing regions in the cortex.

According to the authors, the findings suggest that neurons in the SC may serve as an early facial detection mechanism that steers visual focus to facial stimuli, in contrast to other face-selective regions that may serve to process facial information with greater detail. (NIH authors: G. Yu, L.N. Katz, C. Quaia, A. Messinger, and R.J. Krauzlis, PMID: 38959893) ●

[BY ASHLEY PRATT, NICHD]

CONTINUED FROM PAGE 1

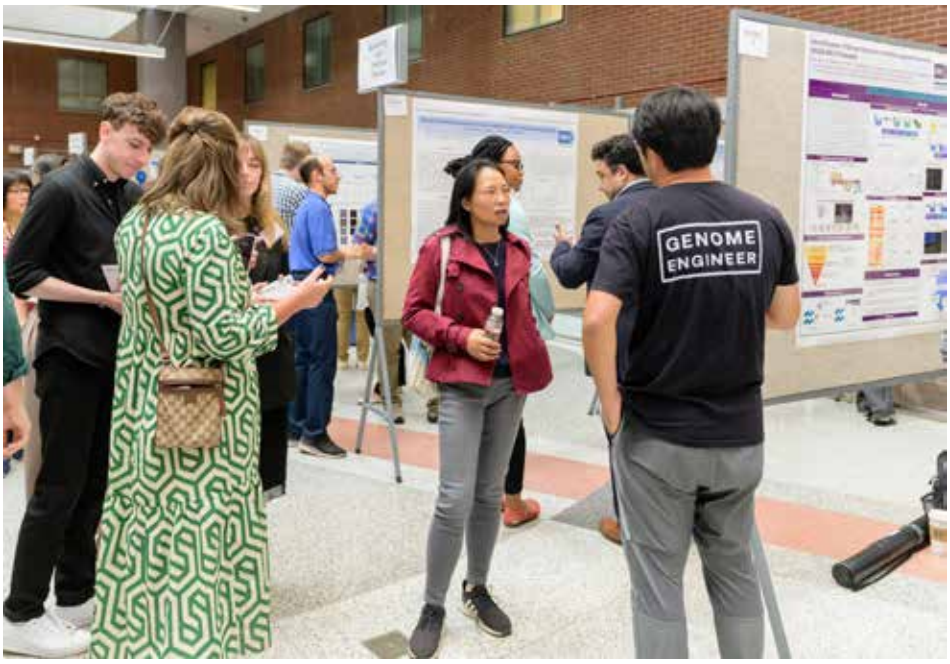
Wednesday, September 25, at which Christopher Phillips, professor of history at Carnegie Mellon University (Pittsburgh), will speak about the impact of early biostatisticians at the NIH. Did you know that clinicians had once ignored statistical concepts because they were interested in individuals, not averages, but that NIH showed how statistics were in fact essential to concepts such as causation and efficacy?

Bridging the past with the current will be the Philip S. Chen Jr., Ph.D., Distinguished Lecture on Innovation and Technology Transfer, also on Wednesday, September 25, presented by **Stephen Whitehead**, senior investigator and chief at NIAID's Arbovirus Vaccine Research Section. Whitehead will explain how the unique environment of the NIH Intramural Research Program has enabled him to develop, patent, and test a dengue vaccine—no trivial matter considering how the dengue virus has four distinct variations, or serotypes, and immunity to just one serotype is the greatest risk factor for more severe disease upon secondary infection with a different serotype.

CREDIT: NIAID

Stephen Whitehead will speak about his progress in creating a vaccine against dengue.

"Protection to all four serotypes is required, since partial protection is not only inadequate, it is also unsafe," Whitehead told the *Catalyst*. "Other dengue vaccines are recommended only for use in boosting or rounding out naturally acquired immunity. The NIH vaccine [now in clinical trials] is designed to elicit primary, complete immunity after a single dose."



CREDIT: MARLEEN VAN DEN NESTE, NIH

Research Festival attendees chat at a poster session in 2023. This year, over 400 posters will be presented in person at the FAES Terrace in Bldg. 10 on Monday, September 23, and virtually on Tuesday, September 24.

Equipped for the present

A microcosm of all that NIH provides will be on display at the NIH Resource Information Fair on Monday, September 23. Chat with representatives from the Collaborative Research Exchange, Center for Information Technology, Office of Technology Transfer, Child and Family Programs, and many more, all of whom will commandeer the Building 10 South Lobby.

Over at the NIH Library and in the FAES classrooms, join any of a dozen concurrent workshops. From behavioral (Stigma Scientific Interest Group), to occupational (Lab Managers Working Group and Division of International Services), to basic science (TGF Beta), there's surely a topic to pique your interest.

One such workshop is the Bioinformatics Community Fair at the NIH Library. Ask NCI's **Keith Hughitt** and **Amy Stonelake** anything on the topic of bioinformatics and data science and learn the basics of artificial intelligence (AI). Content is suitable for beginners to AI, bioinformatics, and data science.

Broader yet will be vendor exhibits and workshops on Tuesday and Wednesday, September 24–25. Learn about new tools and techniques from more than 150 vendors supporting biomedical endeavors. Additionally, the Green Labs Fair will take place on Thursday, September 26.

Eyes on the future

Sense the pulse of the tremendous diversity of intramural research by perusing one of five poster sessions, including four in-person sessions on Monday, September 23, comprising more than 400 posters, as well as a virtual poster session on Tuesday, September 24, for presenters from NIH satellite campuses.

CREDIT: MARLEEN VAN DEN NESTE, NIH

Research Festival-goers browse a table in the NIH Library at the NIH Resource Information Fair in 2023.

Concurrent with the posters, early- and mid-career principal investigators with a commitment to promoting diversity and inclusion in the biomedical research workforce will speak about their research at the NIH Distinguished Scholars Program (DSP) symposium on Monday, September 23.

Yukiko Asada, a tenure-track investigator in the CC Department of Bioethics, is a member of the 2023 DSP cohort and one such presenter.

"The DSP exemplifies the excellent NIH research environment that operates under the principles of intellectual curiosity, trust, freedom, and public good," Asada said about the program. Asada is PI of the FairLab What Makes a Good Life Study, which aims to draw insights from the public about the concept of social disadvantage through community dialogues, the subject of her lecture.

You do not want to miss the DSP science talks. **Julieta Lischinsky**, a Stadtman tenure-track investigator at NIEHS, will discuss the interplay between nature and nurture by investigating the developmental, cellular, and circuit mechanisms for the establishment of innate social behaviors in the limbic system across infancy and adulthood. **Tijana Ivanovic**, a tenure-track investigator at NIAID, will discuss her group's discovery of a viral adaptation strategy based on the variable shape of virus particles—a strategy used by many viral pathogens including some with pandemic potential. Also speaking is **Florencia Pratto**, a Stadtman tenure-track investigator at NIDDK. She will talk about how DNA replication influences the location and repair of DNA double-stranded breaks during mammalian meiosis.

CREDIT: NIH CC

Yukiko Asada will speak at the DSP Symposium about what makes for a good life, likely something to hear about!

Along with introducing the new 2024 scholars, the DSP also is welcoming senior faculty to serve as new mentors, namely **Alan Hinnebusch** (NICHD), **Stephanie London** (NIEHS), and **Pamela Schwartzberg** (NIAID), who will begin two-year terms working with scholar mentees.

Current mentors—**Susan Buchanan** (NIDDK), **Sharon Savage** (NCI), and **Paul Wade** (NIEHS)—are serving their last year with the DSP.

"The scientists I have gotten to know in my two cohorts are among the most talented people at the NIH and truly represent our future," said Buchanan. "The DSP brings in exceptionally qualified PIs in fascinating research areas."

Firmly rooted in the past, the first NIH Research Festival was held in 1986, then called NIH Research Day. Today, nearly four decades on, the event continues to represent the ever-advancing spirit of science and brings together the best that NIH offers. Will you be there? ●

2024 Research Festival

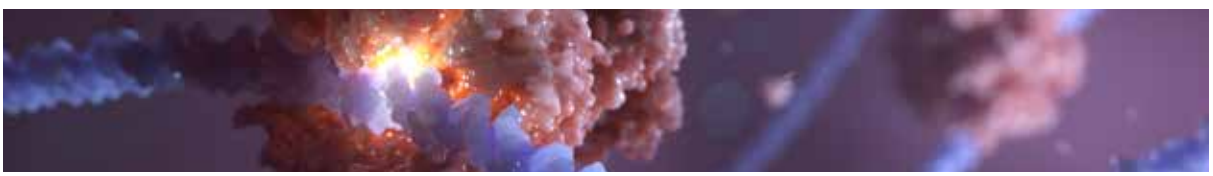
NIH's Annual Celebration of Intramural Research

Monday, Sept. 23: NIH Distinguished Scholars Program (DSP) Symposium; NIH Resource Services Fair; and Poster Sessions

Tuesday, Sept. 24: National Academy of Sciences mini symposium; VIRTUAL Poster Session; and vendor exhibits and workshops

Wednesday, Sept. 25: Philip S. Chen Jr., Ph.D., Distinguished Lecture on Innovation and Technology Transfer; Victoria A. Harden Lecture in NIH History; a special Wednesday Afternoon Lecture Series (WALS) presentation; and vendor exhibits and workshops

…and don't forget the Green Labs Fair on Thursday, Sept. 26.

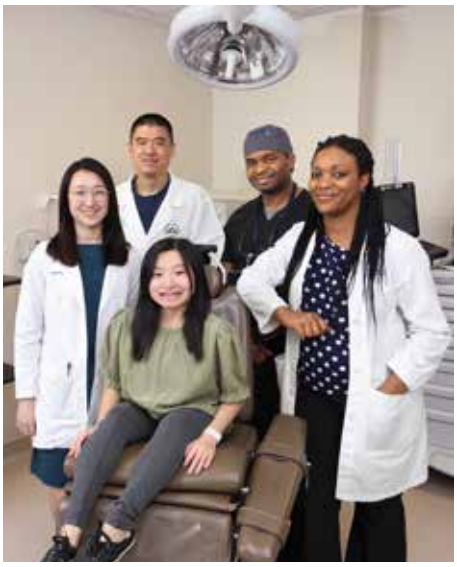


SEPTEMBER 23–25 * BETHESDA, MD * BLDG. 10

Clear Plastic Aligners Give Patients With Brittle Teeth New Smiles

Multicenter Clinical Trial Aims to Improve Oral Health for Those With a Rare Disorder

BY TIFFANY CHEN, NIDCR



CREDIT: NIDCR

Clinical trial participant MinFen Foreman (seated) posed with members of NIDCR's clinical team (from left to right), physician assistant Rachelle Chung, doctors Ling Ye and Ayodeji Awopegba, and research nurse Danielle Elangue, at a recent visit.

Although 18-year-old MinFen Lydia Foreman loves food—everything from dumplings and pho to fried chicken—she has to be extra careful with each bite.

"Sometimes little pieces of teeth can break off," said Foreman. "I can't really eat hard foods." Snacks like nuts, hard candies, and bowls of popcorn with half-popped kernels are off her menu.

Foreman was born with osteogenesis imperfecta (OI), a rare genetic disorder commonly known as brittle bone disease. It affects fewer than 20,000 people worldwide. Because OI disrupts collagen production, which is crucial for building strong bones and teeth, Foreman is smaller than most teenagers, and her bones break easily.

The condition not only undermines bone strength, but it can alter skull development and cause dentinogenesis imperfecta, a disorder marked by fragile and discolored teeth.

"Because of OI, these patients have an unusual teeth misalignment called posterior open bite, which means that their back teeth are not touching, while their front teeth are," said **Janice Lee**, NIH's deputy director for intramural clinical research and clinical director at NIDCR. "As you can imagine, this really limits their chewing capacity, and they may be swallowing food whole. It really is a quality-of-life issue for these individuals."

For the past year, Foreman has been part of an international multicenter clinical trial funded by NIH that is testing the effectiveness of FDA-approved clear plastic aligners to improve dental function in patients with OI. Lee leads the trial's NIH site.

Orthodontists usually treat misalignment of healthy teeth with braces and sometimes surgery in more severe cases. However, neither treatment is optimal for patients with OI, whose misalignments are complex and whose teeth are fragile.

"I had a patient with OI who chipped her upper front tooth eating a burrito," said **Ling Ye**, a volunteer orthodontist involved in the clinical trial. "Their teeth may appear normal, but they have weak structure. Conventional braces may not be a good option."

Surgeries to realign teeth by cutting the jawbones are also not an option. In part, this is because clinicians and researchers are unsure how the facial bones heal in patients with OI.

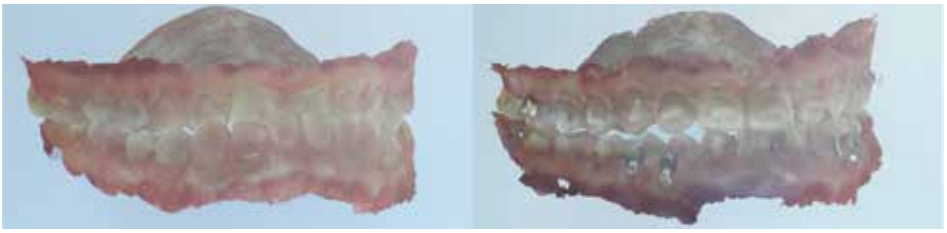
"It was clear that there is an enormous unmet need in the patient community, and there have been no clinical trials tackling this problem," said Brendan Lee, a pediatrician and geneticist at Baylor College of Medicine (Houston), who oversees the multicenter trial.

"Seeing how clear aligners are now in widespread use and relatively safe, our team wanted to test whether they could be a potential solution."

Twenty eight participants are currently enrolled in the clinical trial. Clinicians take 3D oral scans to customize the aligners to each patient's teeth and develop a two-year treatment plan. Over time, the clear aligners gently and evenly distribute pressure across the teeth to gradually reposition them.

CREDIT: NIDCR

The multisite clinical trial tests whether clear aligners can correct teeth misalignments in patients with brittle teeth due to osteogenesis imperfecta, also known as brittle bone disease.



CREDIT: NIDCR

Clinicians take 3D oral scans to track patients' progress. Scans of Foreman's teeth after one year of clear aligner therapy show improvement in her posterior open bite and underbite.

Patients usually wear a set of aligners for a week or two before moving on to the next set.

To evaluate dental function, the researchers follow up with patients in the clinic every two months. They assess treatment progress by comparing 3D oral scans over time and measuring chewing ability with a color-changing gum, which shifts from green to pink. The better a person chews, the pinker the gum becomes.

So far, the trial's clear aligners have shown promise as a gentler yet effective treatment for patients with OI. Patients have responded well to the treatment and have experienced few side effects.

Foreman's 3D scans show that the clear aligner is moving her teeth and improving her posterior open bite and underbite. According to the gum test, her chewing ability has improved.

"I have already noticed how different she feels about herself, her smile, and her teeth," said Dee Foreman, MinFen's mother. "It's about chewing, eating, and swallowing, but the changes in her face have also given her confidence in such a positive way."

Janice Lee, who is also an oral maxillofacial surgeon, noted that the therapy's aim is not one hundred percent perfection but is intended to offer an alternative to major surgeries that can be risky for patients.

CREDIT: NIDCR

The researchers evaluate Foreman's chewing ability with a color-changing gum that turns pinker the more chewing improves.

The team hopes the results can help guide orthodontic treatment for patients with OI and allow dental practitioners to feel confident in offering the therapy one day to patients.

Beyond benefiting the OI community, the clinical trial's results could further establish the safety of clear aligners and inform standards of care for the general population.

"Before the clear aligners, chewing meat was tough," said Foreman. "I had to chew for a long time, and it would get stuck in my teeth. Now, I can chew more easily, and I am excited to see my bite fixed and have a pretty smile."

The clinical trial is actively recruiting participants with OI aged between 12 and 40 years.

Visit the trial website at https://clinicalstudies.info.nih.gov/protocoldetails.aspx?id=000350-D&&query=1#summary for details. ●

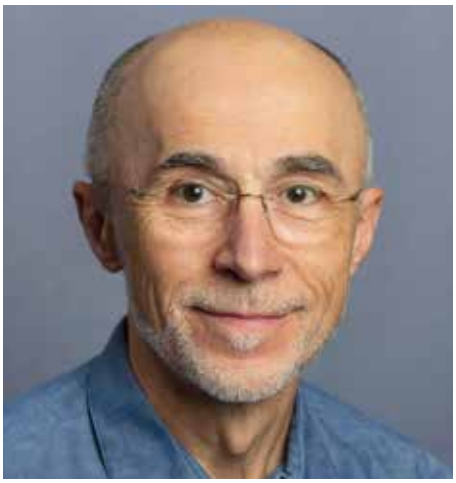
NIH ABBREVIATIONS

CARD: Center for Alzheimer's and Related Dementias
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
FNIH: Foundation for the NIH
FNLCR: Frederick National Laboratory for Cancer Research
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
NSTC: National Smell and Taste Center
OBSSR: Office of Behavioral and Social Sciences Research
OD: Office of the Director
ODP: Office of Disease Prevention
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health

NCCIH's New Clinical Director: Miroslav "Misha" Bačkonja, M.D.

Bačkonja Develops Clinical Models to Sense, Combat Pain

BY ANNELIESE NORRIS, NCI



CREDIT: NCCIH

NCCIH Clinical Director Miroslav "Misha" Bačkonja

Miroslav "Misha" Bačkonja has been named the new clinical director of the NCCIH Division of Intramural Research, where he helps to oversee the NIH Pain Research Center.

Bačkonja, an international leader in clinical and translational pain research and an expert on pain's underlying biological and neurobiological mechanisms, came to NIH in 2022 after serving as a professor in the Department of Anesthesiology and Pain Medicine at the University of Washington (Seattle). He also held leadership positions as professor of neurology at the University of Wisconsin (Madison) School of Medicine and Public Health and the University of Wisconsin Pain Treatment and Research Center.

"We are so fortunate to have Dr. Bačkonja take on the role of clinical director at NCCIH," said **David Shurtleff**, NCCIH's deputy director, acting scientific director, and acting director for the NIH Pain Research Center.

"He brings a wealth of enthusiasm, knowledge, expertise, and experience to our clinical pain research program."

Bačkonja grew up in what was formerly Yugoslavia and earned his medical degree from the University of Zagreb School of Medicine in Croatia. After he completed his studies, he was drawn to the United States and found himself at Creighton University (Omaha, Nebraska). Having initially started in family practice, Bačkonja recognized straight away that his passion was in neurology, and he discovered the challenges and his passion for pain management and research. After completing a residency and fellowship at the University of Wisconsin (Madison), Bačkonja stayed on as a faculty member.

Influenced by Jose Ochoa and Charles Cleeland while studying at the University of Wisconsin, Bačkonja became interested in human psychophysics and clinical pain research. He went on to receive a Mentored Clinical Scientist Research Career Development (K08) Award and spent five years working at the bench. From there, Bačkonja began conducting clinical research, which he enjoyed so much that "there was no going back," Bačkonja said.

Tailoring to individual patients

Bačkonja's work largely focuses on psychophysics using quantitative sensory testing, which is the systematic study of sensory capacities of the sensory nervous system by determining behavioral responses to physical changes in sensory stimuli (PMID: 23742795). For example, if a person has gall bladder pain, they often feel shoulder pain, which is due to sensory convergence mechanisms. By "studying those [sensations] systematically, we can quantify pain so we can understand it better," Bačkonja explained.

This quantitative sensory work dates back to the 18th century when German physiologist Moritz von Romberg (1795–1873) used bristles of horse hairs of varying thickness to study how people perceive sensation. Despite the longevity of psychophysics knowledge, pain treatment remains largely antiquated. This is something Bačkonja hopes we can remedy with modern biomedical approaches and tools.

Bačkonja is still learning the nuts and bolts of how the NIH works, and his vision as clinical director falls under the umbrella of translational pain research, from discovery to application in the clinic.

"There is no place like the NIH; it is really unprecedented, and I totally feel at home," said Bačkonja. One ongoing quantitative sensory testing clinical trial he leads is the Clinical and Scientific Assessment of Pain and Painful Disorders, in which participants are exposed to sensations that are unpleasant, neutral, and pleasant.

He brings a wealth of enthusiasm, knowledge, expertise, and experience to our clinical pain research program.

Another project Bačkonja is working on is a human experimental model with the goal of matching specific treatments to different pain mechanisms and hence reach a pain treatment tailored to each individual patient. This work further aims to establish models of deep phenotyping and development of biomarkers for pain, which will translate into comprehensive profiling of individual patients with pain.

For example, Bačkonja explained that when injecting 100 micrograms of capsaicin into the skin epidermis, a person will experience sensitivity, known as hyperalgesia, in that area for three hours, which gives researchers a window of three hours to study response to stimuli and therapeutic interventions.

According to Bačkonja, this experimental model offers neuroscientists the unique opportunity to study hyperalgesia, a phenomenon seen in patients with clinical pain but that can be induced temporarily without long-term sequela in healthy volunteers.

Teaching the next generation

Bačkonja has a passion for teaching and expanding the limited educational resources available in pain, both at the NIH and worldwide.

He both lectures at and is part of the brain trust of the Interactive Pain Lecture Series, which seeks to bridge the gap between clinical work and basic science. His hope for this series "is to make pain research more accessible to learners to open the door to study pain as a career," he said.

The spring 2024 series wrapped up in June and the next series, now being created by a national team of pain researchers, clinicians, and educators, will begin early in 2025.

From trials to trails

When he is not working, you might find Bačkonja strolling along the Bethesda Trolley Trail. As an amateur ornithologist, Bačkonja smiles when discussing the trail, where he often can be found looking up at the trees and identifying birds.

His favorite birds to spot there are the kingfisher, "because of its amazing flight pattern;" the northern flicker, "because its plumage;" and the gray catbird and northern mockingbird, "because of their song repertoire." ●

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https://irp.nih.gov/catalyst/32/5

Celebrating 50 Years of Cancer Immunotherapy Research

Symposium Marks Half Century of Steven Rosenberg's Research Discoveries, Mentorship

BY JOHN CARLO J. COMBISTA, NIMH

CREDIT: RHODA BAER, NCI

Rosenberg marks 50 years of scientific discoveries in cancer immunotherapy. Join the celebration at the September 26–27 symposium hosted in his honor: "Past, Present, and Future of Cellular Immunotherapy: Scientific Symposium Celebrating Steven A. Rosenberg's 50 Years at NCI."

It was 50 years ago, in 1974, when Steven Rosenberg came to NIH as Surgery Branch chief at NCI to spearhead the use of multimodality treatments in surgical oncology and a new field of cancer research: cellular immunotherapy.

Cellular immunotherapy can be traced back to when Rosenberg encountered two patients at Peter Bent Brigham Hospital in Boston during his surgical residency training whose metastatic cancers disappeared under unusual circumstances. He surmised that the remarkable regressions might have been due to the patients' own immune response.

Since, Rosenberg has become known as the father of cancer immunotherapy because under his leadership and mentorship, he and his teams of collaborators' decades of work have led to the use of immunotherapy for the treatment of cancer. In one such example earlier this year, the FDA approved lifileucel (Amtagvi) for the widespread use of tumor-infiltrating lymphocytes (TIL) for the treatment of melanoma.

To mark 50 years of immunotherapy at the NIH, NCI's Center of Excellence in Immunology will host a symposium on September 26 and 27 at Masur Auditorium, Building 10, on the Bethesda campus. Titled "Past, Present, and Future of Cellular Immunotherapy: Scientific Symposium Celebrating Steven A. Rosenberg's 50 Years at NCI," the event will comprise scientific presentations from experts in the field who will share their research with the aim of catalyzing the next 50 years of cellular immunotherapies.

"We are going to be talking about the major topics in modern immunology related to the role of the immune system in the response to cancer and the principles that guide the development of new cancer immunotherapies," said Rosenberg. "We have many of the world's experts in this field presenting their work concentrating on the use of cellular approaches to cancer therapy and presenting the best of new information that can help propel the field forward."

Joining Rosenberg as committee co-chair for the symposium is **Stephanie Goff**, senior research physician at the Surgery Branch. Goff is a surgical oncologist who was mentored by Rosenberg for four years between her surgical residency and her return to the Surgery Branch 10 years ago to continue her work there.

Want to learn more about those two patients whose metastatic cancer…disappeared? Register to attend "Past, Present, and Future of Cellular Immunotherapy: Scientific Symposium Celebrating Steven A. Rosenberg's 50 Years at NCI." Registration deadline is September 12.

"Dr. Rosenberg really wanted to focus on the science of what he has been able to accomplish," Goff said. "So we designed the symposium to have a session that will briefly focus on the initial studies, where we are now, and where we are looking to [for] the future to make cellular therapy better for patients with cancer. We have a phenomenal lineup of speakers, most of whom either trained in the Surgery Branch or collaborated with the Surgery Branch in very important ways. We are looking forward to the program."

Goff will be speaking in the first session about the origins of TIL and highlighting their 20-year effort to get that therapy across the finish line of FDA approval.

Other luminaries in the field to present include the 2018 Nobel Laureate in Physiology or Medicine James "Jim" Allison from MD Anderson Cancer Center (Houston), who developed a cancer therapy based on inhibition of negative immune regulation, and **James Kochenderfer**, a senior investigator at NCI who was instrumental in developing the first chimeric antigen receptor T cells to be used to treat lymphomas.

Symposium attendees also can look forward to poster sessions and dedicated time after each speaker to help facilitate further discussion.

"This is a great opportunity to celebrate what we do as medical scientists," said NCI Director **Kimryn Rathmell**. "The thrilling discoveries that took place over these last 50 years are nothing short of brilliant. Dr. Rosenberg, his team, and the patients who participated along the way all deserve the chance to be celebrated. It is a great opportunity to see what we can do

as dedicated scientific teams and preview what is possible in the future."

"I think the field of cancer, immunology, and immunotherapy has grown dramatically over the course of these many decades, and in my view, we're just getting started in learning how to apply immune principles to cancer treatment," said Rosenberg. "We need to work hard, know a lot, and collaborate to incorporate the best of all ideas in our research. I expect to see substantial progress in the future. I think that immunotherapy is one of the new areas that has the greatest potential for making progress in cancer treatment." ●

CREDIT: RYAN MORRIS, NATIONAL SCIENCE & TECHNOLOGY MEDALS FOUNDATION

Rosenberg has been awarded several accolades for his work over the years. One of them was the National Medal of Technology and Innovation in Medicine, the nation's highest honor for technological achievement, awarded by President Joseph Biden in a ceremony at the White House on October 24, 2023.

NIH NAS mini-symposium

Rosenberg, who was elected to the National Academy of Sciences in 2024, will provide an overview of his career in a lecture on Wednesday, November 13, as part of the annual NIH NAS mini-symposium. Each year the NIH hosts such lectures by those elected to the NAS. Rosenberg will be joined by NCI's Sandra Wolin, also newly elected.

***Note*: This is part two of the 2024 NAS mini-symposium. NIH scientists Thomas Kunkel (NIEHS), Kyung Kwon-Chung (NIAID), and Giorgio Trinchieri (NCI), will speak on September 24 at the NIH Research Festival.**

Social and Behavioral Sciences Research Resources Now Available

The NIH Behavioral and Social Sciences Research Coordinating Committee met on August 2 and discussed several social and behavioral sciences initiatives that reflect resources and news that NIHers can use.

Updated Clinical Trials Training

OBSSR released an updated electronic learning (eLearning) course for social and behavioral research conducted in the clinical setting. All NIH researchers who participate in clinical trials are expected to participate in this training and should retake the training every three years.

The Good Clinical Practice (GCP) for Social and Behavioral Research eLearning Course features updated information on regulatory changes and reporting requirements, a new module on community and stakeholder engagement, and the training now features enhanced accessibility for improved navigation.

A certificate of completion will be awarded after completing all 10 modules and knowledge tests. To access the course, or for more information, visit https://obssr.od.nih.gov/training/download-good-clinical-practice-social-and-behavioral-research-elearning-course.

White House Blueprint for Social and Behavioral Sciences

"Human behavior is a key component of every major national and global challenge we face," according to the executive summary of a new report titled "Blueprint for the Use of Social and Behavioral Science to Advance Evidence-based Policymaking."

The report was crafted by the Subcommittee on Social and Behavioral Sciences of the Committee on Science, which is part of the White House Office of Science and Technology Policy.

Several NIHers participated in this initiative, including **Jane Simoni** (OBSSR), **Bill Klein** (NCI), **Alyssa Harrell** (NCI), **Audie Atienza** (NCATS), **Paul Han** (NCI), and others.

Learn more about NIH's role in the planning and development of this effort and download the whole report at this link: https://obssr.od.nih.gov/news-and-events/news/director-voice/white-house-office-science-and-technology-policy-releases.

ODP Touts New Resource

In other news you can use, ODP announced an open-access supplemental journal issue, "Design and Analytic Methods to Evaluate Multilevel Interventions to Reduce Health Disparities," which was published by *Prevention Science* in July.

Learn more about the 12 featured papers highlighting best practices from methods to analyses at https://prevention.nih.gov/education-training/research-methods-multilevel-interventions-reduce-health-disparities.

Other resources mentioned at the August committee meeting included the following online resources: Methods: Mind the Gap Webinar Series, available at https://prevention.nih.gov/MindTheGap; and the NIH Research Methods Resources website, available at https://researchmethodsresources.nih.gov/ ●

Colleagues: Recently Tenured

Meet your recently tenured colleagues: **John Dekker** (NIAID), **Andre Larochelle** (NHLBI), **Jung-min Lee** (NCI), and **Sonja Scholz** (NINDS)

JOHN DEKKER, M.D., PH.D., NIAID

ANDRE LAROCHELLE, M.D., PH.D., NHLBI

JUNG-MIN LEE, M.D., NCI

SONJA SCHOLZ, M.D., PH.D., NINDS

JOHN DEKKER, NIAID

Senior Investigator, Laboratory of Clinical Immunology and Microbiology, NIAID

Education: Wesleyan University, Middletown, Connecticut (B.A. in molecular biology and biochemistry [biophysics track] and neuroscience, M.A. in neuroscience); Harvard Medical School, Boston (M.D.); Harvard University, Cambridge, Mass. (Ph.D.)

Training: Pathology residency, Massachusetts General Hospital, Boston; Fellowship in medical microbiology, Massachusetts General Hospital, Boston

Came to NIH: In 2013 as a medical officer and co-director of the Bacteriology, Parasitology, and Molecular Epidemiology Sections of the Microbiology Service, Department of Laboratory Medicine, NIH CC; in 2018 became a tenure-track investigator and Lasker Clinical Research Scholar, NIAID

Outside interests: Reading; eating; hiking

Website: https://www.niaid.nih.gov/research/john-p-dekker-md-phd

Research interests: Antimicrobial resistance (AMR) represents one of the most consequential problems in modern medicine, and its emergence and spread threaten to compromise central advances in the treatment of infectious diseases. Our research focuses on defining mechanisms mediating AMR in bacterial pathogens and understanding the remarkable adaptive changes these microbes undergo in response to the selective forces they encounter during host colonization and infection (PMID: 37832940). Through the study of clinical isolates, we attempt to understand the genomics, mechanisms, and physiology underlying these phenomena in the natural context of human host infection.

Recent and ongoing work in our lab: Understanding genome methylation and potential unappreciated involvement of phage-encoded methyltransferases in modulating antimicrobial resistance in the common gut microbe *Bacteroides fragilis* (PMID: 37429841); Characterizing how hypermutation due to selected mismatch-repair deficiencies may accelerate the evolution of AMR in acute infection in *Pseudomonas aeruginosa* (PMID: 31530672); Understanding the function and structure of the MexVW efflux pump and defining its role in mediating resistance to important cephalosporin-beta lactamase inhibitor combination antibiotics in *Pseudomonas aeruginosa* (PMID: 36399436); and Characterizing principles governing intrahost evolution in an emerging zoonotic pathogen, *Bordetella hinzii* (PMID: 34301946).

[COMPILED BY ARTHI RAMKUMAR, NIAID]

ANDRE LAROCHELLE, NHLBI

Senior Investigator, Laboratory of Regenerative Therapies for Inherited Blood Disorders, NHLBI

Education: University of Sherbrooke, Sherbrooke, Quebec, Canada (B.Sc. and M.Sc. in biochemistry); University of Toronto, Toronto (Ph.D. in molecular and medical genetics); McMaster University, Hamilton, Ontario, Canada (M.D.)

Training: Internal medicine resident, Mayo Clinic, Rochester, Minn; hematology-oncology fellow, NHLBI; postdoctoral fellow, NHLBI

Before coming to NIH: Resident in internal medicine, Mayo Clinic, Rochester

Came to NIH: In 2002 as a hematology-oncology fellow, NHLBI

Outside interests: Spirituality; artificial intelligence; fitness

Website: https://irp.nih.gov/pi/andre-larochelle

Research interests: My research program focuses on advancing regenerative medicine by targeting hematopoietic stem cells (HSCs) to develop novel therapies for inherited blood disorders. A primary focus is Fanconi anemia (FA), an inherited bone marrow failure syndrome caused by mutations in the FA-BRCA DNA repair pathway and hypersensitivity to inflammation. Our work focuses on the following three therapies:

1) Drug therapy: One of the key breakthroughs in my research is the identification of eltrombopag (EPAG) as a first targeted drug therapy for FA-associated bone marrow failure (NCT: 03206086). EPAG mimics thrombopoietin, a critical regulator of HSC survival, improving trilineage hematopoiesis by bypassing inflammatory blockades (PMID: 30803992) and activating DNA repair mechanisms (PMID: 30986494).

2) Gene therapy: We are pioneering ex vivo gene-based therapies for FA by using innovative methods based on CRISPR editing (PMID: 3309880; PMID: 33322084) and less toxic antibody-based conditioning regimens (PMID: 38464076). Additionally, we are exploring in vivo gene therapy using lipid nanoparticles for precise HSC delivery. These strategies aim to provide a one-time curative intervention for FA patients.

3) Cell therapy: For patients with depleted HSC reserves who may not respond to EPAG or are ineligible for gene therapy, we are exploring fundamental hematopoietic developmental processes to enable de novo generation of HSCs from human induced pluripotent stem cells (PMID: 31710911; PMID: 36672255; PMID: 37220178).

Future directions: Looking ahead, my research will continue to refine these therapies, focusing on enhancing in vivo gene- and cell-based interventions safety and efficacy. We aim to translate these discoveries into clinical applications, ultimately improving treatment outcomes for FA and other inherited blood disorders.

JUNG-MIN LEE, NCI

Senior Investigator, Head, Translational Oncology Section, Women's Malignancies Branch, NCI-CCR

Education: Yonsei University, Wonju College of Medicine, Seoul, South Korea (M.D.)

Training: Research fellowship in cell biology, Thomas Jefferson University, Philadelphia; residency in internal medicine, Albert Einstein College of Medicine, New York; research fellowship in functional imaging, Memorial Sloan-Kettering Cancer Center, New York; fellowship in medical oncology, NCI

Came to NIH: In 2008 as a medical oncology fellow in NCI; in 2011 as an assistant clinical investigator; Lasker Clinical Research Scholar, Women's Malignancies Branch, NCI

Outside interests: Travel; cooking; meditation

Website: https://irp.nih.gov/pi/jung-min-lee

Research interests: My research takes both bench-to-bedside and bedside-to-bench approaches. My lab studies mechanistic interactions of key molecules in DNA damage-response pathways using ovarian cancer preclinical models and produces in vitro and in vivo data to support next-generation clinical trials for relapsed ovarian cancer patients. We also develop the preclinical models to test the hypotheses that stem from my observations in the clinic. Our clinical trials incorporate the collection of patient tissue and blood samples to understand the biology and resistance to the drugs, and to develop the new hypothesis-driven clinical trials.

Our work demonstrated augmenting replication stress by modulating ATR-CHK1 signaling, one of the key DNA damage-response pathways, inducing DNA damage and cell death in relapsed ovarian cancer patients (PMID: 37343085). We also identified unique mechanisms of CHK1 inhibitor-resistance in ovarian cancer cell lines and patient tumor samples (PMID: 38555285), which provide novel insight for the development of next-generation clinical trials and translational studies. Ongoing work is focused on mechanical investigation of replication stress response and resistance to the drugs, and its biological relevance in ovarian cancer.

Future directions: My program is also investigating other gynecologic cancer models to investigate the new targeted agents as well as novel antibody drug conjugates.

SONJA SCHOLZ, NINDS

Senior Investigator, Neurodegenerative Diseases Research Section, Neurogenetics Branch, NINDS

Education: Medical University Innsbruck, Innsbruck, Austria (M.D.); University College London, London (Ph.D. in neurogenomics)

Training: Postdoctoral fellow in neurogenetics, NIA; neuroscience, Georgetown University, Washington, D.C.

Before coming to NIH: Internship and adult neurology residency, Johns Hopkins University Medical Center, Baltimore

Came to NIH: In 2015 as assistant clinical investigator, NINDS; Lasker Clinical Research Scholar

Outside interests: Reading; hiking with my husband; traveling; cats

Website: https://irp.nih.gov/pi/sonja-scholz

Research interests: I am a neurologist and neurogeneticist who specializes in movement and cognitive disorders. Neurogenetics has already revolutionized how we think about common neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease. In my laboratory, we extend powerful genomic techniques to other neurodegenerative diseases, such as Lewy body dementia (PMID: 33589841; PMID: 37388914), multiple system atrophy (PMID: 38701790), frontotemporal dementia (PMID: 33242422), progressive supranuclear palsy (PMID: 33341150), and corticobasal degeneration. The primary mission of my research program is to unravel molecular genetic mechanisms that cause or contribute to these devastating diseases. This knowledge highlights targets for drug development.

Future directions: We aim to incorporate molecular knowledge into our diagnostic, prognostic, and therapeutic approaches toward age-related neurological diseases. We will generate comprehensive genomic and multi-omic datasets in clinically deeply characterized patients. We hope to achieve actionable progress on making precision medicines a reality for patients suffering from complex neurodegenerative syndromes.

[COMPILED BY SEPPIDEH SAMI, CC]

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PHOTOGRAPHIC MOMENT

CREDIT: CHIA-CHI CHARLIE CHANG

New National Smell and Taste Center: NIDCD has established a new research entity, which originated from the NIH-wide intramural response to the COVID-19 pandemic. The new center, co-directed by Paule Joseph (NIAAA) and Joshua Levy (NIDCD), will focus on innovative research, comprehensive clinical care, and educational outreach to better understand both the normal and disordered chemical senses of taste and smell. The center's first symposium was held July 9. ●

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