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A Masterful and Multifaceted Molecule

TGF-beta Research Bridges Basic Science and Clinical Promise

BY MICHAEL TABASKO, *THE NIH CATALYST*

In the early 1980s, a discovery at the NIH revealed a protein that would forever change our understanding of cell signaling, development, and disease: Transforming growth factor beta (TGF-beta).

Initially investigated for its role in spurring cancer growth, TGF-beta has since emerged as a key player in a wide array of biological processes, from how cells develop to why some tumors are resistant to treatment. What began as a promising lead to fight cancer has since grown into a rich and diverse field of study, with NIH research continuing to lead the charge in unraveling the complexities of TGF-beta signaling and its role in human health.

TGF-beta origins

At the bench of the TGF-beta discovery were the late Anita Roberts and Mike Sporn, along with their NCI colleagues, who noted the protein's ability to confer oncogenic properties onto otherwise healthy cells.

The finding built on concepts already proposed at NCI that hormone-like growth factors could spark the development of unchecked malignancies (PMID: 7412807). Even earlier work uncovered the origins of oncogenes, or genes that could trigger cancer when activated (PMID: 176594).

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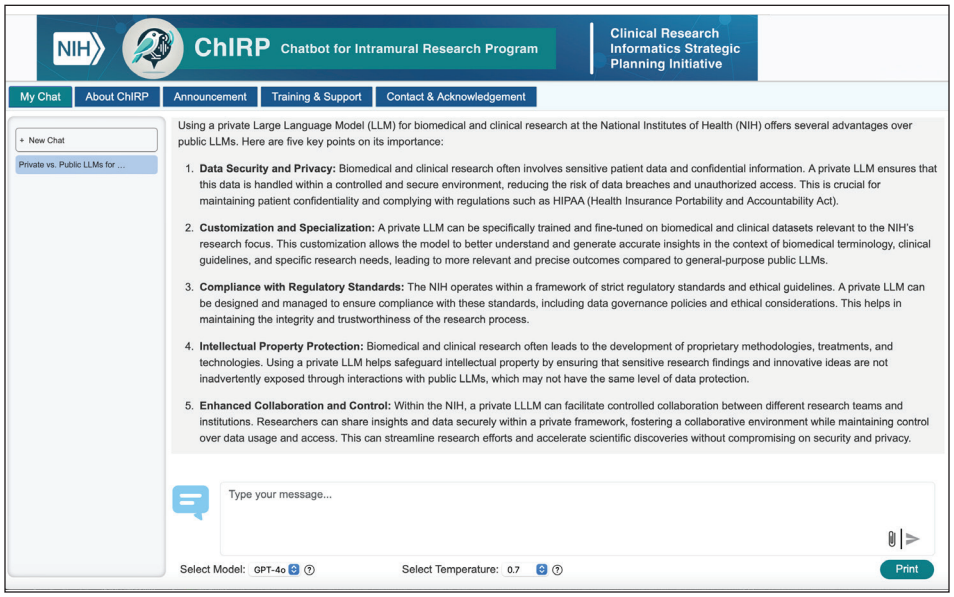
ChIRP: A ChatGPT Model for the NIH Intramural Community

BY ROBERT WAXMAN, CIT



ChIRP enables intramural scientists and clinicians to use ChatGPT without compromising external confidentiality or privacy. ChIRP is available via NIH VPN access at https://chirp.od.nih.gov.

Calling all humans: The NIH is piloting a generative AI service called ChIRP, short of Chatbox for the Intramural Research Program (IRP). Launched on January 7, this pilot program is powered by ChatGPT technology but caters solely to NIH staff and is confined to the NIH intranet.

The goal of the pilot is to perfect a ChatGPT service for NIH science and communication needs in the protective sphere of the NIH intranet to allow for the input of sensitive data, unpublished research results, and clinical research information. As such, CIT and its NIH partners who created the new platform need you to take ChIRP for a test drive—try it, push it, break it.

The pilot is open to all NIH staff. Those interested can register to participate in

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There Is No Challenge too Great for NIH

BY NINA F. SCHOR, DDIR

For the past several months, the word "challenge" keeps appearing everywhere. For many, it characterizes life at home or at work or in the grocery store. But from where does this word come, and what does it really mean? Doesn't everyone in science and medicine love a good challenge? Isn't that what drives many of us into careers in these fields?

According to the online etymology dictionary, Etymonline, the noun "challenge" was used in the early 14th century to mean "something one can be accused of; a fault; a blemish." It comes from the Latin verb *calumniari*, which means "to accuse falsely, misrepresent, slander." The accusatory connotation of the noun "challenge" is said to have begun to recede in the 15th century, but it was not until 1954 that it took on the sense of "a difficult task."

On the NIH campus and perhaps throughout the federal government, it seems both the old and the newer meanings of challenge have colored the perceptions of some. Indeed, the duration of service of some of our workforce has been challenged, and it has become challenging to remain calm and focused on why we are all here at NIH and what it is that the people of the United States and around the world depend on us to do and achieve. But this is, in fact, what we must do, and it is the very definition of leadership that demands that those privileged to hold such positions enable, empower, and facilitate the maintenance of calm and focus in our whole NIH workforce.

It is a tribute to our dedication to our singular focus on health and the science that underpins it that, after more than seven years on the Bethesda campus, I do not even know the partisan affiliation of a single one of my colleagues, and I daresay I have never shared with any of them my own such affiliation. It is simply immaterial. We are here to understand, improve, and restore the health of our nation's people and, through that endeavor, to do the same for people around the globe.

Within this column of the *NIH Catalyst*, those who read my words know that I have, in the past, been quite critical of our methods and our culture. I have tried to use both words and actions to move us, however asymptotically, towards a durable modus operandi that will ensure attainment of our vision of healthy people everywhere. But my eye and my goal have never swayed from that vision. It is too important and its targets are too precious to waste a single errant saccade!

I cannot do it alone, both because you may know a better or quicker path to the goal and because there is too much work to do for one person to do it. I am energized by my knowledge that I can count on all of you to remain steadfast and undistracted in the enterprise that brought us all to the venues in which NIH works day and night to bring health and understanding to all people and to enable all people to sustain this ideal long after we are gone.

NIH leadership is doing everything it can to enable its workforce to maintain that critical focus and the excellence of its work. Sometimes I think it is a shame that the outer walls of Building 1 are not transparent, as I suspect almost no one who is not within those walls has any idea how many hours, days, meetings, phone calls, and trips to various other government offices have gone into this effort. Please know that we see and appreciate all of you and remain excited about everything we know your science and medicine will make possible in the years ahead. ●

CREDIT: JENNIFER HARKER, *THE NIH CATALYST*

the ChIRP pilot at https://chirp.od.nih.gov.

ChIRP is many things

What is ChIRP? If you ask a commercial version of ChatGPT, you will learn that it is chromatin isolation by RNA purification. And that much is true. But we're talking about a homegrown ChIRP, one not yet known by ChatGPT.

NIH ChIRP is a secure, generative AI environment that uses large language model (LLM) technologies. LLMs are virtual AI systems trained on vast amounts of data to "understand" language. Once trained, they can generate natural, humanlike responses and complete actions such as analyzing and summarizing content, coding, designing, translating, and brainstorming ideas.

ChIRP currently uses the GPT-4o LLM developed by the OpenAI company and made available through the NIH STRIDES enterprise Azure cloud environment managed by CIT. ChIRP runs in an NIH environment, but no NIH internal information is integrated into the commercial models, and there is no data leakage outside of ChIRP or NIH.

This secure NIH environment allows staff to use sensitive data within ChIRP, like de-identified and anonymized clinical data, predecisional and draft policies, and nonpublic data, including scientific data and draft manuscripts. However, personally identifiable information is not permitted in ChIRP. Also, because the chatbot uses commercial models, it is not specifically trained or fine-tuned for NIH-specific or biomedical topics.

Overall, the pilot aims to create a secure environment for NIH staff to safely explore how generative AI technologies, such as LLMs and multimodal models (for example, those capable of processing images and other data types), can benefit NIH's biomedical research. Feedback from pilot participants will inform future AI efforts at NIH. ChIRP support is provided through the Clinical Research Informatics Strategic Planning Initiative (CRISPI), is funded by ODSS and OIR, and developed in collaboration with OD, CIT, NHLBI, and NIA.

Leaving the nest

The goal of the January launch event was to introduce ChIRP to the NIH community and help them understand what ChIRP is and to explain its potential uses, risks, and limitations. Event speakers also made sure attendees were aware of ethical concerns around using the tool such as the potential for amplifying biases, providing misinformation, exposing intellectual property, and plagiarism.

Overall, presenters, including CIT Director Sean Mooney, were excited to share information and wanted attendees to leave the session with some basic, practical skills and encouraged everyone to get some hands-on time with ChIRP and share feedback.

During the presentation, the ChIRP team provided a brief overview of the evolution of AI and LLMs, walked through the ChIRP interface, and offered tips on prompt engineering, the art of how to give the model instructions that yield the best results and reduce errors. A few quick tips: Start with simple prompts, be specific, and use clear instructions.

Presenters also demonstrated how the chatbot can summarize and mine information from uploaded text and documents, assume a role to provide domain-specific information, generate HTML code, and render graphics. One of the areas where ChIRP shines is analyzing long documents to provide summaries or pull specified information and organize it according to given instructions.

The need for ChIRP

ChIRP was born out of a need to help NIH researchers take advantage of AI technology and concerns around uploading confidential and sensitive information to public AI platforms, which are not necessarily private or secure. Mooney spoke at the launch event about the importance of exploring AI.

"Timely access to advanced AI systems is really critical for advancing NIH research," Mooney said. "ChIRP is a great example of how a pilot for an advanced technology could turn into an operational enterprise AI system to support the NIH."

ChIRP also aligns with industry and government efforts exploring the responsible deployment and use of AI and AI-enabled technologies in the health and human services sector, including research and discovery, drug and device safety, health care delivery and financing, and public health.

CIT's role in developing ChIRP

CIT played an important role in getting ChIRP up and running. CIT staff provided access to GPT-4o models through a cloud-based STRIDES account and supported the development of ChIRP infrastructure in Microsoft's Azure cloud environment.

CIT also played a key role in technical architecture and information security planning and supporting provisional authorization-to-operate, or ATO, efforts for the ChIRP pilot. Additionally, CIT provided communications support for the ChIRP launch, including messaging, video support, and design and graphic expertise for ChIRP-related materials.

A call to action

Feedback from pilot participants is crucial in helping to develop and refine the tool for NIH use and will inform future AI efforts at NIH. After using ChIRP, please provide your candid feedback through the ChIRP User Experience Survey. Feedback through the survey is anonymous.

If you have questions about the pilot, please reach out to the CRISPI team by email at CRISPI-LLM@od.nih.gov. ●

To learn more, check out the recording of the ChIRP launch event at www.scgcorp.com/ChIRP2025/docs/ChIRP%20Launch%20Event.mp4, and see the presentation slides on the event materials webpage at https://www.scgcorp.com/ChIRP2025/PostMeetingMaterials.

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That discovery earned Michael Bishop and Harold Varmus, who became NIH director and then NCI director, the Nobel Prize in Physiology or Medicine in 1989.

While termed a growth factor, TGF-beta is a cytokine—a class of critical proteins that broker communication between cells and coordinate proper immune function. Depending on what's happening in their environment, they dock to specific cellular receptors and can set in motion a cascade of events that modify how genes are expressed and what proteins are produced.

So, in 1983 the NCI scientists took on the challenging task of isolating and purifying high yields of TGF-beta from human blood platelets and distributed it freely to scientists both at NIH and around the globe. What ensued was a new field of research.

"Sporn took TGF-beta and gave it to a lot of different people and said 'you should try this in your biological system. I'm sure it will have an effect,'" said **Lalage Wakefield**, who joined the Sporn lab in 1983 and is now a senior investigator in NCI's Laboratory of Cancer Biology and Genetics.

It soon became apparent that TGF-beta had many functions in regulating biology (PMID: 3871521), and that its activity heavily depended on the context in which it was acting, such as the target cell type and the microenvironment.

According to Wakefield, this notion of contextuality was one of three important concepts that came from the Sporn lab's early research about how growth factors behave. The second was the autocrine hypothesis, which posits that one cell can emit signals that can act back on that same cell and render it somewhat independent from signals in the microenvironment. And third was the notion that a growth factor could be multifunctional.

For example, a dogma in the field is that TGF-beta serves a complex dual role in carcinogenesis: It can function primarily as a tumor suppressor early on and then switch to promoting tumor growth as a cancer progresses.

TGF-beta is also a potent immunosuppressive factor. Investigators in the lab of Anthony Fauci, then director of NIAID, were the first to show TGF-beta's inhibitory action on T cells (PMID: 2871125). The molecule's immune-manipulating mechanisms continue to be studied today to design targeted immunotherapies that could treat conditions such as chronic inflammation, autoimmune disease, and cancer. Such work is underway at NIDCR's Mucosal Immunology Section, led by senior investigator **Wanjun Chen** (PMID: 28423340).

Wound healing and fibrosis are yet more processes with TGF-beta's fingerprints all over them. Pioneering work by Roberts and colleagues demonstrated that the molecule plays an integral part in tissue repair by stimulating collagen production (PMID: 2424019). Roberts continued to contribute extensively to the field and is now the third most cited woman scientist in the world, according to **Michael Gottesman**, senior investigator at NCI's Laboratory of Cell Biology.

Current NIH research expanded on the fibrosis concept, showing a potent effect of TGF-beta signals in promoting adipose tissue fibrosis as a precursor to metabolic diseases such as obesity and diabetes (PMID: 39461664). Indeed, inhibiting TGF-beta's actions in mice improved the deleterious effects of metabolic disease by improving adipose tissue function (PMID: 21723505; PMID: 30100246). "The findings open up a potential utility of anti-TGF-beta therapies for these conditions," said **Sushil Rane**, NIDDK senior investigator and corresponding author on those studies.

As the field matured, several other findings would emerge from NIH labs. Those included the development of one of the first TGF-beta knockout mice, confirming the protein's importance in immunomodulation (Stefan Karlsson); SMAD knockout mice, which lack the gene needed for signaling by TGF-beta (Chuxia Deng); and the solution of the molecular structure of TGF-beta (David Davies).

Modeling the molecule in cancer

"I think of TGF-beta as a sort of fine-tuning knob on the top of other more fundamental biologies," said Wakefield, whose name can be found on many of the original papers describing its myriad functions. Her lab now develops preclinical models to investigate the dual role of TGF-beta in breast cancer.

Her team demonstrated in mice that a lifetime exposure to a TGF-beta antagonist could protect against metastasis without adverse side effects, showing the feasibility of targeting the growth factor in cancer (PMID: 12070308).

"Most of that benefit seems to come from reactivating antitumor immunity," said Wakefield, noting that they've also seen deleterious effects in a small fraction of their models. "We think it relates to taking the brakes off the cancer stem cells. So, we're using these preclinical models to develop predicative biomarkers that allow you to determine whether a patient will respond positively or adversely to these treatment strategies."

Wakefield knows the field deeply, having been in the TGF-beta trenches longer than almost anyone on the Bethesda campus, and her team is excited to share a new tool with colleagues. "The coolest thing we've developed yet is a transgenic mouse that reports on TGF-beta signaling with a green fluorescent protein. You can see all the tissues that the TGF-beta pathway is active in lit up in green," she said. As you might imagine, there's a lot of green.

Transgenic mice are mice that have had DNA from another source put into their DNA. The foreign DNA is put into the nucleus of a fertilized mouse egg. The new DNA becomes part of every cell and tissue of the mouse. These mice are used in the laboratory to study diseases. Learn more: https://pmc.ncbi.nlm.nih.gov/articles/PMC4095860.

All in the superfamily

From an evolutionary perspective, TGF-beta is thought to have evolved when animals were becoming more complex and was perhaps needed to coordinate among all the different cells that had to function together. It's a founder molecule for a much bigger superfamily that includes structurally similar bone morphogenetic proteins (BMPs) and activins, all of which play key roles in modulating normal development and maintaining homeostasis.

Uncovering how those molecules regulate development is **Mihaela Serpe**, senior investigator in NICHD's Section on Cellular Communication, who exudes a zest for diving into the deep end of the basic science behind complex cellular signaling. A biochemist by training, Serpe has been involved in TGF-beta research since her postdoctoral days when, coincidentally, she shared a cab ride back to the airport with Anita Roberts—along with a cherished conversation about cellular signaling.

Today, her lab studies the interplay between various BMP signaling pathways and the development of neuromuscular junctions using the fruit fly *Drosophila melanogaster*. "Drosophila became a darling in basic science for TGF-beta because of fewer signaling components and powerful genetics," said Serpe. Teasing these pathways and their different biological outcomes is important because they overlap with those in humans and are critical in maintaining the integrity of cellular junctions.

They defined a novel and nuanced positive feedback mechanism involving BMP signaling pathways whereby active neurotransmitter receptors signal to their controlling motor neuron that they are working hard: Consequently, those synapses receive reinforcement. It's a sort of "use it or lose it" phenomenon (PMID: 26815659). Furthermore, the BMP components engaged in that synapse-strengthening signal become unavailable for retrograde signaling, which controls growth. In essence, motor neurons use different BMP signals to balance their act: They sample their surroundings then choose between building more synaptic junctions or reinforcing the existing ones.

Such discoveries hint at therapeutic targets for a group of human diseases that disrupt cell–cell integrity and can result in malformed brain or heart vessels. "If a disease is due to skewed BMP signaling, you need to figure out first what kind of BMP signaling is perturbed," said Serpe. "And if we know the specific pathway and how to tamp things down and restore the balance, then we might have a way of solving the problem." Serpe's lab has since identified mutations that unevenly disrupt various BMP signaling pathways (PMID: 32737119), and it is about to study new mutant flies that it has developed to understand the basis of several human diseases that affect the integrity of cellular junctions.

Countering cancer's defenses

Treatment-resistant cancers may have an adversary coming. **Claudia Palena**, a senior investigator at NCI's Center for Immuno-Oncology (CIO), uses preclinical models to find new combinations of drugs that break down cancer's defense mechanisms.

"We're trying to understand what we can do in terms of the mechanisms of resistance that are at play in the tumor microenvironment to improve the response to treatments," she said. CIO preclinical labs work closely with their clinical colleagues toward the goal of bringing those strategies to patients. One of those strategies is inhibiting TGF-beta with agents such as bintrafusp-alfa, a dual-function fusion protein that blocks the PD-L1 protein and captures TGF-beta within a tumor. Some cancer cells express PD-L1 to nullify the body's T-cell attack, and blocking the protein is behind how immunotherapies known as checkpoint inhibitors work. However, they don't work for everyone, and part of the reason might be because of TGF-beta's immunosuppressive influence within some tumors. Foundational research at CIO labs found that bintrafusp-alfa indeed had antitumor properties by making cancers more susceptible to the body's immune defenses and treatments such as chemotherapy (PMID: 32079617).

Bintrafusp-alfa has been discontinued by its manufacturer, but the drug did make it to clinical trials and could inform future therapies. Led by **James Gulley**, codirector of the CIO and NCI clinical director, a first-in-human trial used the compound to treat several types of previously treated advanced solid tumors and showed early signs of efficacy (PMID: 29298798).

CIO clinical teams then expanded the approach with encouraging results. For example, treating human papillomavirus-associated malignancies with bintrafusp-alfa showed promise (PMID: 33323462). "These data suggest a response rate that is about twice the response rate of [a checkpoint-inhibitor alone] in the same patient population," Gulley told the *Catalyst*. In patients with non-small-cell lung cancer, the compound was relatively well tolerated and showed modest clinical benefit (PMID: 36571770; PMID: 38485188). Yet other studies investigated the drug's mechanisms in head and neck tumors (PMID: 32641320).

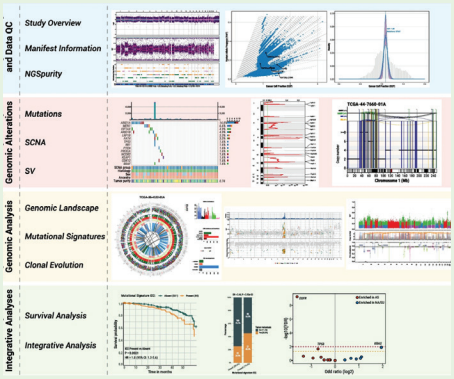
A multiagent strategy looks to be more effective. These are early days for such therapies and research into blocking TGF-beta in the context of immunotherapies continues: Combining several different molecules that disrupt distinct components of cancer's defense arsenal resulted in robust antitumor responses—and even tumor cures—in some preclinical models of breast and lung cancers that were resistant to checkpoint inhibitors alone (PMID: 32188703; PMID: 35230974).

"The interaction between the clinical and the preclinical work is so important," said Palena, whose lab is actively researching new combinations of immunotherapeutic agents. "As we learn more, such as what tumors have high levels of TGF-beta, we can then come up with ideas of how to block it with this multiagent approach. We expect that, hopefully, we keep developing these strategies to eventually bring to the clinic." ●

Intramural Research Briefs

Read About Scientific Advances and Discoveries by NIH Intramural Scientists

NCI: SHERLOCK-GENOME MAKES WHOLE GENOME SEQUENCING DATA USER-FRIENDLY



CREDIT: *BMC GENOMICS*, NCI

NCI: The illustration shows an overview of the four major modules and example visualizations supported by Sherlock-Genome to manage and present whole genome sequencing data in a user-friendly manner.

Comprehensive analysis of an individual's entire genome via whole genome sequencing (WGS) is far from elementary.

Sherlock-Genome, a new interactive web application developed by NCI scientists, aims to streamline how such complex data are analyzed, integrated, shared with others, and visually presented. Among its many uses, WGS has significantly contributed to advancements in the field of cancer genomics. For example, it can precisely detect genetic mutations and complex genomic alterations within a tumor, which can then be used for a personalized approach to cancer treatment.

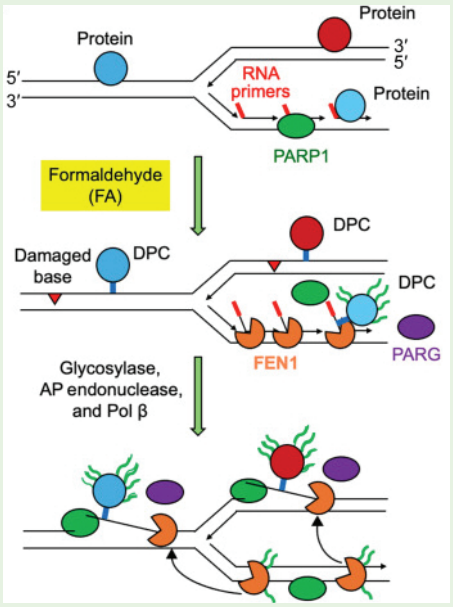
However, the complexity of WGS data poses significant challenges, especially for researchers who don't have a background in bioinformatics or strong programming skills. The NCI team developed Sherlock-Genome to simplify the analysis and visualization of WGS data and to make cancer genomic research more accessible to a wider range of scientists. "It also facilitates the integration of genomic findings with clinical data, bridging the gap between research and patient care," said **Tongwu Zhang**, a Stadtman investigator who led the study.

Sherlock-Genome users can upload and analyze WGS results, integrate their data with other datasets, such as from clinical and epidemiological studies, and generate publication-ready figures. The platform incorporates four major modules for cancer genomic analysis including study summary data, summary of major genomic alterations, reports of advanced genomic analysis, and summary of integrative analyses.

"Sherlock-Genome marks a significant step toward making complex genomic analyses more accessible and interpretable, ultimately advancing human health research," said Zhang. Researchers may access the source code and installation instructions for Sherlock-Genome on Github. (NIH authors: A. Klein, J. Zhong, M.T. Landi, and T. Zhang, PMID: 39819269)

[BY JOHN CARLO J. COMBISTA, NIMH]

NCI, NCATS: NEWLY IDENTIFIED PROTEINS AND PATHWAYS MAINTAIN GENOMIC STABILITY



CREDIT: *SCIENCE ADVANCES*, NCI

NCI, **NCATS**: Illustration showing how a process known as PARylation uses the PARP1 enzyme to mark damaged DNA sites and recruits the FEN1 protein to initiate repair.

DNA-altering environmental pollutants and internal metabolic byproducts, such as formaldehyde, can lead to the development of diseases such as immunodeficiencies, neurodegeneration, and cancer.

Research led by scientists at NCI, NCATS, and the University of Maryland (Baltimore) identified the proteins involved in formaldehyde-induced DNA-protein cross-links (DPCs), a common type of DNA lesion, and discovered a new molecular pathway by which those lesions are repaired.

In a series of experiments, the researchers revealed that the protein FEN1 excises the helix-distorting flap structures that are a hallmark of DPC damage. FEN1 was also found to repair another type of DPC caused by inhibition of the TOP2 enzyme, commonly associated with chemotherapy drugs.

They found that FEN1 works through a DNA repair mechanism regulated by a process known as PARylation, which uses the PARP1 enzyme to tag damaged sites in the genome and recruits FEN1 to initiate repair. In their paper, the authors note that the findings "provide previously unrecognized pieces to the puzzle of DPC repair and a molecular foundation for the etiology of DPC-induced diseases." (NIH authors: Y. Sun, L.M. Jenkins, L.H. El Touny, X. Yang, U. Jo, T.K. Maity, L.K. Saha, S. Saha, K. Cheng, and Y. Pommier, PMID: 39792662)

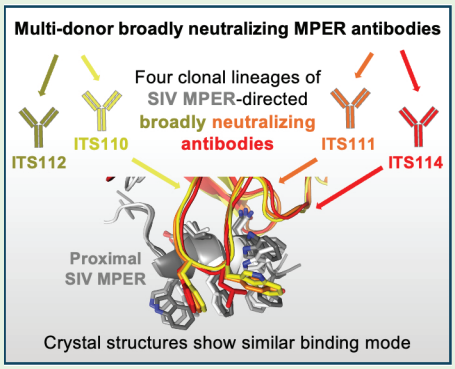
[BY CASEY CARGILL, NEI]

NIAID: BROADLY NEUTRALIZING ANTIBODIES AGAINST SIV IDENTIFIED

Researchers at NIAID's Vaccine Research Center discovered and characterized four lineages of broadly neutralizing antibodies against simian immunodeficiency virus (SIV), expanding scientists' toolkit to design a critically needed vaccine against the closely related HIV.

The scientists homed in on an area of SIV known as the membrane proximal external region (MPER), which allows the virus to merge with and infect a host cell. MPER has been shown in human studies to be a target for broadly neutralizing antibodies against HIV. By screening plasma of multiple SIV-infected rhesus macaques, the investigators identified two animals that could effectively neutralize SIV and isolated 13 antibodies from those animals with specificity to the MPER. The antibodies were found to belong to four distinct, genetically similar lineages that bound in a similar way as broadly neutralizing antibodies against the HIV MPER protein found in humans.

According to **Jason Gorman**, first author on the study, "The results here expand the availability of broad SIV antibody reagents



CREDIT: *CELL REPORTS*, NIAID

NIAID: Four newly discovered lineages of antibodies broadly neutralized simian immunodeficiency virus by binding to the MPER, a region of the virus that could be targeted in vaccine development against the closely related human immunodeficiency virus.

to help facilitate use of the SIV model for studying HIV and can inform HIV antigen design for vaccines targeting the MPER." (NIH authors: J. Gorman, D. Renguang, Y. Lai, A.S. Mohammed, H.A.D. King, K. Song, K. Manalang, C.A. Gonelli, C.A. Schramm, C. Cheng, R. Nguyen, D. Ambrozak, A. Druz, C. Shen, Y. Yang, D.C. Douek, P.D. Kwong, M. Roederer, and R.D. Mason, PMID: 39792559)

[BY TAYLOR FARLEY, NIAID]

NINDS, NIAID: CEREBROSPINAL FLUID BIOMARKER PREDICTS LEWY BODY DISEASES

Early detection of a protein misfolding and aggregation process can act as a screening tool by identifying individuals who might later develop a central Lewy body disease (LBD). The findings come from a prospective longitudinal study at the NIH CC conducted by investigators at NINDS and NIAID's Rocky Mountain Laboratories. LBDs affect more than 1 million people in the United States and are associated with the buildup of abnormal alpha-synuclein proteins in the brain that results in progressive movement disorders and dementia.

One of the factors associated with LBDs, alpha-synuclein seeding activity (SSA), is a process by which a sample of a patient's biofluid triggers alpha-synuclein in a test tube to polymerize and misfold. It is widely thought that the triggering factor in the biofluid is itself misfolded alpha-synuclein. Small chains (oligomers) of alpha-synuclein protein molecules or misfolded alpha-synuclein damages neurons that use catecholamines such as dopamine as the chemical messenger, resulting in manifestations such as Parkinsonism or cognitive dysfunction.

Using an alpha-synuclein seed-amplification assay, the researchers analyzed cerebrospinal fluid from individuals with self-reported risk factors for LBD and followed them for up to 7.5 years. They found that 64% of participants with increased SSA went on to develop an LBD compared with 5% who fell below a cutoff value for SSA activity. Other findings from the study indicated that LBDs involve multiple functional abnormalities in the central nervous system, suggesting targets for future research aimed at delaying or even preventing symptomatic disease.

The addition of multiple tests such as cardiac biomarker assessment by positron-emission scans may prove even more useful. "In at-risk individuals, a combined biomarkers approach that includes cerebrospinal SSA may predict accurately who will go on to develop a symptomatic central LBD during the subsequent several years," said **David Goldstein**, first author on the study. (NIH authors: D.S. Goldstein, P. Alam, P. Sullivan, C. Holmes, J. Gelsomino, A.G. Hughson, and B. Caughey, PMID: 39817492)

NHLBI, NIAID: IMMUNE CYTOKINE SERVES DUAL ROLE IN MEDIATING ALLERGIC RESPONSE

Scientists from NHLBI and NIAID have identified a dual role for thymic stromal lymphopoietin (TSLP), an immune cytokine that can both promote and limit inflammation in type 2 immunity, providing new insight into how the immune response is balanced. The mechanisms behind type 2 immunity are not fully understood and involve a set of inflammation-driven pathways that when dysregulated can contribute to allergic reactions such as asthma.

TSLP is known to activate type 2 helper T (Th2) cells, the immune system's frontline responders that produce type 2 inflammatory cytokines and can also trigger symptoms such as swelling and airway constriction. Blocking that mechanism is behind how current anti-TSLP therapies used to treat severe asthma are thought to work.

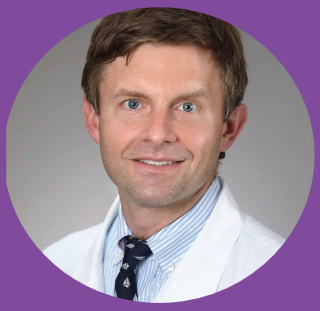
In their study, the investigators found that besides its action on Th2 cells, TSLP also stabilizes regulatory T cells (Tregs), which act as the immune system's peacekeepers to prevent excessive inflammation. Using a mouse model, the researchers genetically deleted the TSLP receptors from both types of T cells, which, as expected, resulted in a muted immune response to an airway inflammation challenge. However, when TSLP receptors were selectively removed from Tregs only, the immune system became dysregulated. Lacking TSLP's stabilizing influence, Tregs not only failed to suppress inflammation but also began driving the process and exacerbated allergic responses. Conversely, when TSLP signaling in Tregs remained intact, the cells maintained their immunosuppressive identity and ability to limit allergic inflammation.

According to the authors, "The results expand the known roles for TSLP and indicate additional points at which TSLP might be targeted to modulate the immune response." (NIH authors: R.K. Gurram, P. Li, J. Oh, X. Chen, R. Spolski, X. Yao, J.X. Lin, S. Roy, M.J. Liao, C. Liu, Z.X. Yu, S.J. Levine, J. Zhu, and W.J. Leonard, PMID: 39792638) ●

[BY ARWAA MEHRAN, NICHD]

Colleagues: Lasker Clinical Scholars

BY BRANDON LEVY, IRP



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SAMIRA SADOWSKI, M.D.
NCI-CCR

Many scientists have a seemingly single-minded focus on their research, but there are considerable benefits to having one foot in the lab and the other in the clinic. Working with patients gives researchers a daily reminder of the people they are working so hard to help and allows them to investigate the effects of promising but still experimental treatments in willing volunteers. That's one of the main reasons why the IRP's Lasker Clinical Research Scholars Program is designed to accelerate the careers of promising early-career physician-scientists.

This year, four NIH researchers began receiving support from the Lasker program, allowing them to dramatically expand their cutting-edge research. From investigating the roots of muscle-weakening genetic conditions to probing the mysteries of rare, hormone-producing tumors, these individuals will make new discoveries that could one day improve lives. Read on to learn more about the exciting research the latest crop of Lasker Scholars is pursuing.

Chris Grunseich: Making sense of neuromuscular disorders

As the calendar turned from 2023 to 2024, Chris Grunseich was also turning a page to a new chapter in his career: Opening his very own lab for the first time.

Grunseich was raring to get started leading new efforts to get to the roots of so-called neuromuscular disorders—a wide range of conditions that damage the motor and sensory nerves that connect the brain and spinal cord to our muscles, leading to muscle weakness.

"It is an exciting time to work in a field with the potential for new discoveries that can be translated back to help patients," he said.

In Grunseich's lab, those discoveries will come primarily from new cellular models of various rare, inherited neuromuscular diseases developed using tissue from patients with those conditions. Using those models, his team can not only probe the molecular aberrations that underlie those diseases but also test new potential treatments to see whether they can correct those problems.

"Some of the diseases we study progress slowly, and having a sensitive way to determine if a drug is working could be very important for the design and cost of clinical studies," Grunseich explained.

Of course, as a physician, Grunseich also spends considerable time with patients, and his work with them has yielded the most intriguing insights of his career. For instance, while conducting a clinical study examining how exercise affects patients with a certain genetic neuromuscular disease, he observed abnormally elevated concentrations of a particular enzyme produced by the liver.

"This enzyme elevation had been previously attributed to abnormal muscle, and I became interested in this and developed a new study to investigate why the liver enzymes were elevated," he recalled.

That study, a collaboration with several other IRP research groups, showed that the patients' liver function was abnormal. Such clinical discoveries happen by working closely with both patients and experienced scientific colleagues with a range of expertise.

Lisa McReynolds: Exploring bone marrow failure

Lisa McReynolds has been interested in medicine from a young age, tracing her passion to an aunt who suffered from a rare autoimmune disease and a seventh-grade teacher whom she describes as "particularly influential." Those experiences growing up set her on a path that has now culminated with her selection as a Lasker Scholar, which allowed her to start her own independent IRP lab in June that uses the tools of epidemiology—the study of populations—to learn about inherited diseases that impair the body's ability to make new blood cells, a condition called bone marrow failure.

"Bone marrow failure research is a fascinating and unique combination of studying blood, the immune system, cancer, and genetics," she said.

One such ailment she has studied is a form of bone marrow failure called Fanconi anemia. People need to have two mutations in a certain gene to develop the disease, but about 6 percent of the general population has at least one of the genetic variants that cause it. In addition to slowing the production of new blood cells, the condition also dramatically raises patients' risk for certain cancers. However, scientists have long wondered whether people who only have one related mutation—so-called carriers—also have a heightened risk for cancer.

McReynolds and her IRP colleagues have conducted research suggesting the answer to that question is, thankfully, "no" for most mutations related to Fanconi anemia.

"Individuals are often identified as single-mutation carriers during genetic testing for other reasons such as tumor testing," she said. "It is important to understand how to counsel these patients."

McReynolds said she was "extremely honored and excited" to be chosen as a Lasker Scholar, viewing it as "a wonderful opportunity to pursue tenure-track research while having strong mentoring and support." She looks forward to making even more new discoveries about Fanconi anemia and other inherited forms of bone marrow failure in partnership with her IRP colleagues.

"NIH is a very collaborative place, and there is almost always someone here who is an expert in what you need, and those experts are willing to share their knowledge and time," she said. "You just have to ask."

Andrea Lisco: Chasing a cancer-causing virus

When Andrea Lisco enrolled in medical school in his home country of Italy, he was "not so much interested in clinical medicine," he said, but instead "fascinated by the mechanistic aspects of biology." His desire to understand the deeper mysteries of the human body eventually narrowed to the way viruses infiltrate and wreak havoc within us, which he attributes to his experience working at an HIV clinic in the mid-1990s, a time when an incredible new treatment for the disease, protease inhibitors, burst onto the scene.

"Those were the drugs that changed the course of HIV infection and made it a treatable disease," he recalled. "I was just a student at the time, but that was what sparked my interest in treating infectious disease."

As a postdoctoral fellow at NIH in the mid-2000s, Lisco began investigating the mechanisms by which HIV weakens the immune system and facilitates disease caused by other viruses, including human papillomavirus (HPV). HPV can cause cancer even in people with fully functioning immune systems, but it finds purchase in the bodies of HIV-positive individuals much more easily, which is why they are far more likely to develop cancer and other serious symptoms when HPV infects them.

"That seemed to me to be the new frontier and a very attractive topic: Cracking the mechanisms that control HPV infection and cells' transformation into cancer, and how you can control not only the infectious process, but also prevent the development of cancers," he said. "That's something for this disease that's incredibly important."

One of the accomplishments he is most proud of is his success working with a particular patient who was experiencing significant symptoms caused by HPV, including cancer, but who was HIV-negative. Lisco and colleagues discovered that the patient had a genetic mutation that was impairing the ability of certain immune cells to combat the virus (PMID: 34469647). After a successful bone marrow transplant, the patient's body began producing normal immune cells that could fight his HPV infection, including the virus-induced cancer.

"That was proof in one patient of the paradigm that the immune system is necessary to control the infection and the cancers that HPV can cause, and that you can change the course of a particular patient," Lisco said. "Of course, now we'd like to expand that to a larger group."

Samira Sadowski: Navigating neuroendocrine tumors

Early in medical school, Samira Sadowski decided that she wanted to be "more hands-on," leading her to choose a career as a surgeon. However, it wasn't long before research caught her eye as well, especially the mysteries of neuroendocrine tumors. These rare tumors stem from cells that have traits of both nerve and hormone-secreting cells, such as certain cells in the lungs, hormone-producing cells in the digestive system, and the cells in the pancreas that release insulin. Because of this diversity, there are varieties of neuroendocrine tumors, "so we can have these tumors kind of everywhere—it's a vast field," Sadowski said.

"What really got me started in research was seeing that it is not as simple as just removing one of these tumors and now the patient is hopefully disease-free. These tumors secrete hormones, and that affects other things in the body. So, when to do surgery and when not to really interested me. Also, we only have one or two of these vital organs like the adrenal glands or the pancreas, so you can't just remove them. The clinical guidelines, to be evidence-based, depend on research."

Unfortunately, scientists currently know relatively little about neuroendocrine tumors because "we have no good models" for them, Sadowski said. For that reason, much of her lab's work focuses on developing cell and animal models that can allow researchers to study neuroendocrine tumors.

At the same time, her research group is investigating the regulation of genes that behave abnormally in those tumors. For instance, she has found that neuroendocrine tumors with abnormally low amounts of a particular receptor, called SSRT2, grow and spread faster than tumors with more of that receptor. Now, as a Lasker Scholar, she hopes to develop a clinical trial testing how increasing the amount of SSRT2 in tumor cells affects the way cancer patients respond to therapy.

"I feel here at NIH I can really focus on the research and the patients that I treat," Sadowski said. "It's amazing. I see the patients that have the disease, and [I] can do lab work to answer all these questions about finding tumor targets and understanding how they are regulated." ●

This article was originally published in the I Am Intramural Blog at irp.nih.gov/blog/post/2024/11/welcoming-nihs-four-newest-lasker-scholars.

Read a longer version online at https://irp.nih.gov/catalyst/33/2.

Preserving History

Book in Progress to Document History of the NIH Intramural Research Program

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

CREDIT: NIH

The NIH perimeter gate

The NIH Intramural Research Program has a storied history but not one that is very well documented. The first and only book dedicated to its history is *NIH: An Account of Research in Its Laboratories and Clinics*, edited by Dewitt Stetten, Jr., and published in 1984. One could argue that a lot has happened since then. For example, there's that whole human genome thing and, oh yeah, cancer immunology. Seems worth documenting.

So, **Michael Gottesman**, former NIH deputy director for intramural research from 1993 to 2022, has teamed up with science writer **Christopher Wanjek** to capture our more recent history, including not just the research but also newer institutes (NHGRI, NIBIB, and more) and our outstanding facilities. What follows is a diverse set of excerpts from the chapter titled "Facilities: The Backbone of NIH Research." The authors hope to finish this book by the end of the year, and they welcome your input in the form of ideas and written contributions. Contact Gottesman for more information.

1987. THE CENTENNIAL ANCHOR: A SHOUT-OUT TO NIH'S MARITIME ROOTS

If you enter the NIH Bethesda campus via South Drive and Rockville Pike, what is now commonly called the main entrance, one of the first historic objects you will see is a large, white anchor. This is the NIH Centennial Anchor, so-named because it came to the NIH coincidentally during NIH's centennial year celebration in 1987.

The story goes that Philip Chen, associate director for intramural affairs, received a call from an official at the Staten Island Marine Hospital, the location where, in 1887, Joseph J. Kinyoun, a physician in the Marine Hospital Service, had set up a one-room laboratory he called a "laboratory of hygiene." This was the direct precursor of the NIH, the Hygienic Laboratory, as it was soon called. In 1987, the Staten Island Marine Hospital was about to be privatized, and the man on the phone told Chen something along the lines of, "Hey, there's a big, heavy anchor here. Do you want it?" Chen jumped at the opportunity and arranged for a flatbed truck to bring it to Bethesda.

Chen had the thing plopped down on a patch of grass, unadorned, at the corner of South and Center Drives. It spent some time there and then on the grass in front of Building 1 before NIH Director James Wyngaarden in 1988 asked for it to be placed in storage. But the anchor stealthily reappeared at its present location of South and Center Drives in 1989, this time with a plaque with a U.S. Public Health Service seal and text prepared by Richard Wyatt and John Eberhart, who both worked with Chen. The text provides a fitting reasoning for the placement of this now iconic landmark of the NIH. It reads, in part: This centennial anchor, originally from a Coast Guard cutter, was presented to the NIH on the occasion of the centennial celebration to commemorate a century of science for health and to symbolize the maritime origins of the Public Health Service.

1990. BUILDING 6: LOTS AND LOTS OF FISH

Additions and renovations are as significant as new buildings, and Building 6B is no exception. Building 6B was added in 1990 to Building 6, which itself is part of the set of historic red brick buildings built on the NIH Bethesda campus in the 1930s. Building 6 opened in 1940 and was the home of NCI, which at that point was separate from NIH (with the addition of NCI in 1944 and other institutes in the following years, the NIH became the National Institutes of Health, plural, in 1948).

CREDIT: I AM INTRAMURAL BLOG

Building 6, 6A, and 6B are easily confused (good thing plans for Building 6C did not come to fruition!) Housed in Building 6 is the massive zebrafish (*Danio rerio*) facility, something that has grown over the years to become one of the largest in the world—housing approximately 20,000 fish tanks with the potential to house more than 100,000 fish on three floors. Such scale is needed because one genetic screen might require as many as 60,000 fish.

Building 6B is a four-story building with a basement and a sub-basement (total: 58,816 square feet). This facility quickly became a destination for breeding transgenic animals for research. The primary tenant on opening was NICHD, but this has since shifted to include NEI and NIAID. Aside from the unique infrastructure that provides for a high level of sterility—protective cages, sterile feed and bedding, air flow, etc.—some vivaria are equipped with sophisticated lighting to allow for studies of circadian rhythm.

2004. THE PERIMETER GATE

Ah, the NIH Bethesda campus. A river runs through it…and a fence runs around it. The river—more of a stream these days—has been there for countless millennia, long used by the Piscataway, members of the broader Algonquian-speaking peoples who inhabited the Bethesda region before the arrival of Europeans. The fence dates to only 2004. One misconception is that the security fence was conceived after the September 11 attacks. But the recommendation to build a perimeter fence, as it is now called, came from the Office of the HHS Inspector General coincidentally a month before 9/11.

Pressure to better secure the NIH campus was building in the late 1990s primarily because of the domestic terrorist truck bombing of the Alfred P. Murrah Federal Building in Oklahoma City in April 1995, as well as other terrorist attacks domestic and abroad. The recommendation became critical when, in 2002, the HHS directed all its agencies to hew to security measures outlined in a DOJ document released in June 1995 titled "Vulnerability Assessment of Federal Facilities."

The NIH had been an open campus since its inception, so the presence of a fence—however essential—was an initial shock to the NIH community. Some cultural elements suffered; evening concerts and lecture events faded away. The National Library of Medicine saw a dramatic decline in visits. But intramural research soldiered on unimpeded. NIH staff rarely has any difficulty entering campus at any hour by car, bike, or foot through the various gates and turnstiles.

The black, metal perimeter fence is approximately 10 feet tall and stretches for about two miles. This is not terribly imposing from the street level and maintains a buffer zone from surrounding neighborhoods, with an additional 100-foot "pedestrian stand-off" zone from NIH buildings, the distance at which someone with a bomb on the outside of the fence could do minimal damage.

Initially, the plan was to keep the entry gates open and unstaffed when the level of security was "green" as determined by the Department of Homeland Security. But today, all staff and volunteers must use their PIV cards for entry. Visitors, by and large, enter through the NIH Gateway Center, Building 66, opened in 2007, where they encounter something akin to airport security. Delivery trucks enter via the Commercial Vehicle Inspection Facility (CVIF), Building 67. The only significant breach of security, it seems, came in June 2014 when a black bear managed to get on campus. This incident was perplexing because the bear did not appear to have its PIV card.

2005. EDMOND J. SAFRA FAMILY LODGE (BUILDING 65): A FOCUS ON HOLISTIC PATIENT CARE

Complementing the Children's Inn is the Edmond J. Safra Family Lodge, for adult patients and their families visiting the Clinical Center. John Gallin, who served as Clinical Center director from 1994 to 2017, relayed the story of how he learned that some of his patients were sleeping in their cars on the NIH campus because hotel rooms in the area were so expensive. The patient volunteers and their families are not billed for medical care, but food and lodging are generally not covered.

So, when he became director, Gallin and his staff focused on creating a lodge for adults. He turned to the Foundation for the National Institutes of Health (FNIH), and they reached out to Lily Safra, a philanthropist married to the banker Edmond Safra, who loved the idea and provided some of the funds.

The Lodge has 34 guest rooms, a library, a business center, a fitness center, a home-style kitchen, a laundry room, social areas, and a lovely garden. ●

CREDIT: NIH CLINICAL CENTER

Edmond J. Safra Family Lodge opened its doors to patient families in 2005.

Colleagues: Recently Tenured

Meet your recently tenured colleagues: **Bizu Gelaye** (NICHD), **Rena Jones** (NCI), **Hendrikje Nienborg** (NEI), **and Natalie Shaw** (NIEHS).

BIZU GELAYE, Ph.D.
NICHD

RENA JONES, Ph.D.
NCI

HENDRIKJE NIENBORG, M.D., Ph.D., NEI

NATALIE SHAW, M.D., M.M.Sc., NIEHS

BIZU GELAYE, NICHD

Senior Investigator and Chief, Epidemiology Branch, Division of Population Health Research

Education: Addis Ababa University, Addis Ababa, Ethiopia (B.Sc. in mechanical engineering); University of Washington, Seattle (M.P.H. and Ph.D. in epidemiology)

Before coming to NIH: Associate professor of epidemiology and psychiatry at Harvard T.H. Chan School of Public Health, Harvard Medical School, and Massachusetts General Hospital, Boston

Came to NIH: In 2024 as branch chief and senior investigator, NICHD

Outside interests: Spending time with family; reading; watching football and basketball with my son (New England Patriots and Boston Celtics fan); walking; playing tennis

Website: https://irp.nih.gov/pi/bizu-gelaye

Research interests: My lab integrates biological, molecular, environmental, social, and structural factors to understand how preconception and perinatal exposures to adversity lead to short- and long-term maternal and offspring health outcomes across generations. We have three main lines of research. First, we have shown how trauma and adversity affect maternal health across the lifespan and extend across generations (PMID: 36776635; PMID: 28905129; PMID: 27173085).

We are now investigating the epigenetic mechanisms, and how the chronicity and timing of maternal trauma affect children's behavioral health intergenerationally, and whether postnatal maternal caregiving sensitivity can buffer these effects.

Our second line of research focuses on understanding the underlying social, economic, and structural drivers of maternal morbidity and mortality. I am one of the key investigators for a NICHD-funded U54 Maternal Health Research Center of Excellence at Jackson State University (Jackson, Mississippi). The overarching objective of the center is to address preventable maternal mortality, decrease severe maternal morbidity, and promote maternal health equity in partnership with the Mississippi Delta communities.

Lastly, our research incorporates novel biomarkers to understand the mechanistic basis of the risk of adverse maternal and child health outcomes. One example biomarker is hair cortisol concentration. Hair cortisol concentration measures long-term systemic cortisol concentrations, providing an integrated measure of hypothalamic–pituitary–adrenal axis activity, one of the main pathways activated in response to stress (PMID: 36893558; PMID: 36841381). Elucidating such biological and molecular mechanisms may lead to novel prevention and treatment strategies.

RENA JONES, NCI

Senior Investigator, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics

Education: University of Massachusetts, Amherst, Massachusetts (B.S. in biology); University at Albany, Albany, New York (M.S. and Ph.D. in epidemiology)

Training: Postdoctoral and research fellow, NCI (2012–2017)

Before coming to NIH: Research scientist, New York State Department of Health, Troy, New York

Came to NIH: In 2012 as a postdoctoral fellow, NCI

Outside interests: Hiking; vegetarian cooking; spending time with family, friends, and pets

Website: https://irp.nih.gov/pi/rena-jones

Research interests: I am an epidemiologist focused on investigating etiologic associations between environmental contaminants and cancer. Fundamental to these studies is high-quality exposure assessment. The development of metrics that adequately reflect human exposure requires understanding exposure pathways, environmental transport and persistence, and exposure determinants, all of which have sources of uncertainty, especially in retrospective studies.

My work leverages Geographic Information Systems (GIS) technologies and novel approaches to assess environmental exposures. I improve long-term exposure estimates by enhancing the spatial accuracy of exposure source locations (PMID: 30302014), characterizing participant mobility and time spent in various microenvironments, and incorporating information from surveys and regulatory monitoring. I also design studies to evaluate the validity and reliability of exposure estimates. In the Los Angeles Ultrafines Study, I am investigating how ultrafine particles (UFP) emitted from vehicle exhaust may influence risk of lung and other cancers. We applied innovative methods to retrospectively quantify exposure to UFP, an unregulated pollutant, and showed a relationship with risk of lung adenocarcinoma (PMID: 37856832).

My drinking water research involves studying cancer associations with agricultural contaminants and disinfection byproducts. I have developed exposure metrics for these contaminants in public water supplies to investigate their relationships with several cancers. Intriguing findings from the Iowa Women's Health Study have motivated efforts to apply similar techniques in two additional cohorts—the Agricultural Health Study and the California Teachers Study. I am also advancing research on persistent water contaminants, including per- and polyfluoroalkyl substances, and their relation to cancer in both children (PMID: 38092046) and adults (PMID: 37902275).

Future directions: In the future, I hope to probe further into the novel associations we have observed between air pollutants and lung cancer. Given the considerable burden of this disease and because screening is recommended only for high-risk individuals such as smokers, understanding the potential environmental causes is of great interest.

[COMPILED BY SEPPIDEH SAMI, CC]

HENDRIKJE NIENBORG, NEI

Senior Investigator, Visual Decision-Making Section, Laboratory of Sensorimotor Research

Education: University of Oxford, Oxford, United Kingdom (M.Sc. in neuroscience); Ludwig-Maximilian University, Munich, Germany (M.D. and Ph.D. in neurophysiology)

Training: Postdoctoral fellow, Salk Institute for Biological Studies, La Jolla, California (2009–12); postdoctoral fellow, NEI (2005–09)

Before coming to NIH: Principal investigator, University of Tübingen, Tübingen, Germany

Came to NIH: In 2019 as an investigator, NEI

Outside interests: Hiking; biking; reading with my family; open water swimming; wood sculpture

Website: https://irp.nih.gov/pi/hendrikje-nienborg

Research interests: I am a systems neuroscientist interested in how vision guides behavior in different contexts. Humans interpret visual information to navigate novel environments, adapt to behavioral or cognitive states, and accomplish various tasks. My research aims to uncover how brain processes support flexible visually guided behavior by integrating computational, behavioral, pharmacological, large-scale electrophysiological, and machine learning approaches to address three key research questions:

1) How are cognitive and sensory signals integrated into the visual cortex (PMID: 34294703)?

2) How do nonvisual factors, such as motivation, behavioral state, movement, or learning, involved in neuromodulatory circuits influence incoming visual signal encoding (PMID: 37828227)?

3) How do these combined signals guide behavior in healthy mammalian brains?

Answering these questions will improve our understanding of how these mechanisms fail in psychiatric and neurological diseases.

Future directions: We plan to target peripheral visual field processing, which is critical for interacting with the world but impaired in common forms of vision loss, and it has been understudied mostly due to technical challenges that can now be overcome.

[COMPILED BY CASEY CARGILL, NEI]

NATALIE SHAW, NIEHS

Senior Investigator, Clinical Research Branch

Education: Cornell University, Ithaca, New York (B.S. in biological sciences); State University of New York at Buffalo School of Medicine, Buffalo, New York (M.D.); Harvard Medical School, Boston (M.M.Sc.)

Training: Intern and resident in pediatrics, Children's Hospital of Pittsburgh, Pittsburgh (2004–2007); clinical fellow in pediatric endocrinology, Boston Children's Hospital, Boston (2007–2010); research fellow in reproductive endocrinology, Massachusetts General Hospital, Boston (2010–2015)

Came to NIH: In 2015 as a Lasker Clinical Research Scholar and tenure-track investigator, NIEHS

Outside interests: Sports and fitness; travel; spending time with friends and family

Website: https://irp.nih.gov/pi/natalie-shaw

Research interests: I am a pediatric endocrinologist, clinical and translational investigator, Lasker Clinical Research Scholar, and principal investigator of the Pediatric Neuroendocrinology Group within the Clinical Research Branch at NIEHS. My research program aims to understand the genetic and environmental control of human reproductive development. To this end, I conduct physiological studies in healthy, pubertal participants and translational studies in patients with a rare form of hypogonadism.

My group's three main research aims are the following:

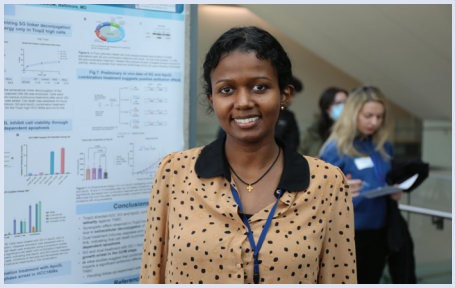
1) To investigate the contributions of body weight, abnormal sleep patterns, and other environmental (for example, per- and polyfluoroalkyl substances or microbiome) and lifestyle factors to irregular menstrual

CONTINUED ON PAGE 15

The 21st Annual NIH Graduate Student Research Symposium

Tomorrow's Scientists Fill Halls of Natcher with Latest Research

BY *THE NIH CATALYST* STAFF



CREDIT: DIEGO ARENAS, IRP

Recipient of the **Pharmacology/Clinical and Translational Science/Structural Biology Research Award,** Yonit Addissie (NCI, University of Maryland School of Medicine), mentored by Stanley Lipkowitz, presented "Synergistic Lethality of Combination Treatment with Trop2-directed Antibody-drug Conjugate (IMMU-132) and Apo2L/TRAIL in Triple Negative Breast Cancer."

The annual NIH Graduate Student Research Symposium was held February 13 at the Natcher Conference Center on the Bethesda campus. Each year, graduate students who participate in the NIH Graduate Partnerships Program display their dissertation research in a research poster presentation format. Over 100 presenters, and their mentors, were showcased this year.

CONGRATULATIONS TO THE RECIPIENTS OF THE 2025 NIH GRADUATE STUDENT RESEARCH AWARD:

Biochemistry/Cell and Molecular Biology/Genetics
Kathryn McDaniel (NINDS, Brown University)
Christopher Shults (NIDCD, University of Maryland)

Bioinformatics/Biostatistics/Epidemiology
Nina Friedman (NIMH, University of Maryland)
Mihirkumar Prajapati (NHLBI, University of Maryland)

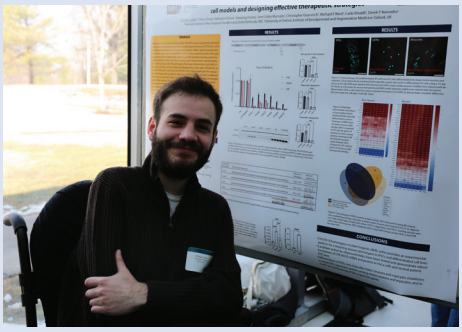
Immunology/Virology/Microbiology
Jack Dorman (NIAID, Johns Hopkins University)
Nathan Santiago (NIAID, University of Alabama)

Neuroscience/Behavioral Sciences/Psychology
Christian Lantz (NINDS, University of Oxford)

New Proposal
Isabella Horton (NIBIB, University of Maryland)
Ava Platt (NINDS, Brown University)
Olivia Molano (NIDCD, Brown University)
Douglas Fritz (NIAID, University of Cambridge)

Elevator Pitch Competition
1st place: Douglas Fritz (NIAID, University of Cambridge)
2nd place: Mitchell Sun (NCI, University of Oxford)
3rd place: Shakira Rodriguez-Gonzalez (NIDDK, Johns Hopkins)

Outstanding Mentor Award:
Chris Baker (NIMH)
Fadila Bouamr (NIAID)

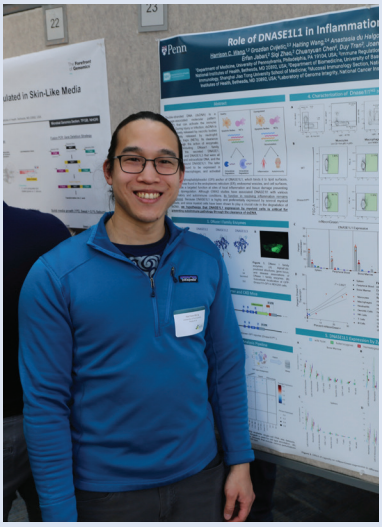


CREDIT: DIEGO ARENAS, IRP

Christian Lantz (NINDS, University of Oxford), mentored by Derek Narendra, presented "Elucidating CHCHD10 Mutant Phenotypes in iPS Cell Models and Developing an Antisense Oligonucleotide Therapy."

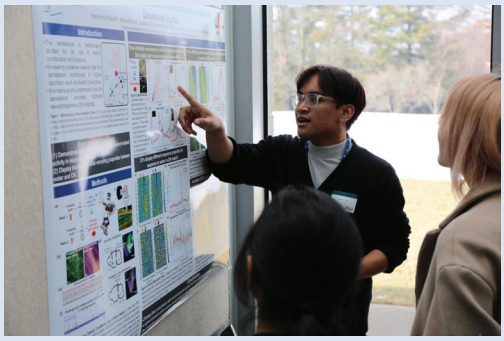
Jemma Strauss (left) answers attendee questions about her poster titled "CRAC Channel Inhibition as a Therapeutic Target for Psoriasis." Strauss DeFilipp (NIEHS, North Carolina State University) is mentored by Anant Parekh.

CREDIT: DIEGO ARENAS, IRP



CREDIT: DIEGO ARENAS, IRP

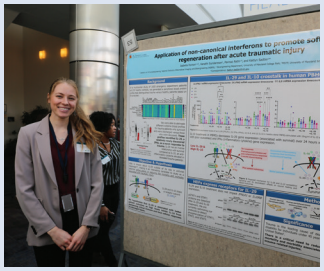
Harrison Wang (NIDCR, University of Pennsylvania), mentored by Roxane Tussiwand, presented "Role of DNASE1L1 in Inflammation and Autoimmunity."



CREDIT: DIEGO ARENAS, IRP

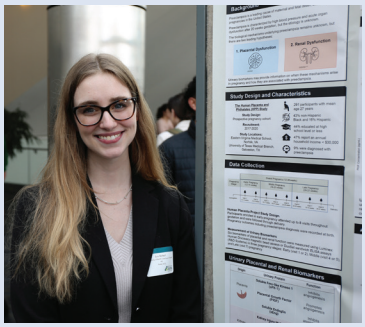
Benjamin Filio (NINDS, Brown University), mentored by Mark Wagner, presented "The Cerebellum Encodes Non-Motor Reward Signals."

For more information, the full event program is available at www.training.nih.gov/documents/45/OITE_GPP25.pdf.



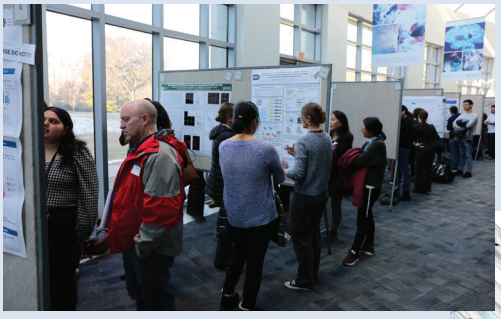
CREDIT: DIEGO ARENAS, IRP

Isabella Horton (NIBIB, University of Maryland), mentored by Kaitlyn Sadtler, presented "Application of Non-canonical Interferons in Acute Traumatic Injury to Promote Soft Tissue Regeneration."



CREDIT: DIEGO ARENAS, IRP

Erin McNell (NIEHS, University of North Carolina at Chapel Hill), mentored by Kelly Ferguson, presented "Associations of Urinary Biomarkers of Placental and Renal Dysfunction with Preeclampsia."



The annual symposium brings together scientists from all ICOs to celebrate the next generation of discovery.

CREDIT: DIEGO ARENAS, IRP

cycles in adolescent girls during the first few years after menarche (a girl's first period). Although irregular menstrual cycles are a common part of female development, a subset of teens never make the critical transition to normal menstrual cycles. By investigating the physiologic and pathophysiologic underpinnings of irregular menstrual cycles in adolescent girls in the one to two years after their first menses, we intend to identify those girls who are at high risk for reproductive dysfunction as adults.

2) To determine the influence of obesity, and genetic and environmental factors on pubertal timing and reproductive hormones in boys and girls. We initiated the NIEHS Body Weight and Puberty Study to investigate pubertal development in girls with obesity vs. normal weight using breast ultrasonography, dual-energy X-ray absorptiometry (for body composition), hand X-ray (for bone age), transabdominal (pelvic) ultrasounds, and anthropometrics such as height, weight, body-mass index, and waist-hip ratio (PMID: 33630047). Through a collaboration with NCATS, we have also identified environmental factors that affect pubertal timing via a high-throughput screen of the Tox21 10K compound library in HEK293 cells and hypothalamic neurons derived from induced pluripotent stem cells (PMID: 39254333).

3) To determine the genetic architecture of Bosma arhinia microphthalmia syndrome, a rare syndromic form of hypogonadism. Patients with Bosma syndrome are born without an external nose (arhinia) and with small or absent eyes (microphthalmia or anophthalmia). They also do not undergo puberty and are infertile (hypogonadotropic hypogonadism). We discovered the genetic cause of Bosma syndrome (mutations in *SMCHD1*; PMID: 28067909) and are now studying patient-derived cranial placode cells to determine the underlying pathophysiology (PMID: 36800423). ●

[COMPILED BY HÉCTOR CANCEL ASENCIO, NINDS]

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PHOTOGRAPHIC MOMENT

CREDIT: DONA JONES, NINR

The NIH Medical Simulation Program recently added simulation-based health care training and research to its repertoire of innovative clinical and translational simulation trainings. Mabel Gómez, lead facilitator and educator, demonstrates how best to manage respiratory emergencies with one of six manikins used by the simulation team to train health care practitioners. The program is jointly supported and managed by the CC's Office of Clinical Research Training and Medical Education and the Office of Nursing Professional Development. ●

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