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Blood, Sweat, and Tears

May 13–14 Conference Explores New Frontiers in Liquid Biopsies

BY JENNIFER HARKER, *THE NIH CATALYST*

When NIH scientists use the phrase "blood, sweat, and tears," they mean it. Literally. In fact, we can join them on May 13–14 to learn more about all the ways in which scientists at NIH and around the world are exploring blood, sweat, tears, and other bodily fluids as liquid biopsies to travel to new frontiers for human health and disease.

"We really accomplished our goal of bringing together a diversity of ideas that span from maternal fetal genetics to almost every liquid biopsy modality you can imagine," said **Adam Sowalsky**, senior investigator in NCI-CCR's Prostate Cancer Genetics Section and one of the conference organizers. "So, there are talks about blood serum and plasma, amniotic fluid, cerebral spinal fluid, saliva, tears, sweat—all the minimally invasive liquids that people have figured out how to co-opt for monitoring disease, diet, disease detection, and of course, precision medicine."

Each of these liquid biopsy applications will be featured during panel discussions and research poster presentations at the two-day conference sponsored by NCI-CCR and NHLBI, to be held at the Natcher Conference Center (Building 45) on the Bethesda campus.

Among the conference highlights is an international roster of speakers, including the opening keynote lecture on Monday, May 13, which will feature Dennis Lo, professor of medicine at the

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President Biden Requests $12B for Research on Women's Health

NIH Is Poised to Perform

BY *THE NIH CATALYST* STAFF

CREDIT: WHITE HOUSE

President Biden signed a Presidential Memorandum to establish the White House Initiative on Women's Health Research.

President Biden signed the most comprehensive set of executive actions ever taken to advance women's health research on March 18. The Executive Order, and a State of the Union request to Congress for a "bold, transformative investment" of $12 billion, came on the heels of a November Presidential Memorandum that charged every federal agency engaged in health research to develop a plan for advancing women's health research.

"I have always believed in the power of research to save lives and to ensure that Americans get the high-quality health care they need. To achieve scientific breakthroughs and strengthen our ability to prevent, detect, and treat diseases, we have to be bold. That's why today, we're establishing a new White House Initiative on Women's Health Research so that my Administration—from the National Institutes of Health to the Department of

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Technologies

They Work for Us (Not the Other Way Around)

BY NINA F. SCHOR, DDIR

When I was an undergraduate student, I spent my entire senior year doing chemistry research in the laboratory of Julian Sturtevant. We discerned the 3D structure of proteins using circular dichroism spectroscopy and the thermodynamics of protein unfolding after disulfide bond reduction using a calorimeter made in Moscow by Peter Privalov that had the serial number 00003.

We did not have personal computers or cell phones or even pocket-sized calculators. In fact, in a wonderful cartography course, I used punch cards for the first time to generate maps!

> "Technology moves very fast, sometimes faster than ethics and analytics can keep pace."

When I was a graduate student in the laboratory of Anthony Cerami, I ran hydrolyzed protein samples on an amino acid analyzer that spanned a whole wall in a large room and took overnight to run my samples. I analyzed the dot matrix printout it generated using a handheld planimeter. I packed my own gas-liquid chromatography columns and poured my own acrylamide gels by hand.

As a medical student, I saw one of the very first computed tomography (CT) scans of the head. The pixels were so large and so few that it looked like a child's jigsaw puzzle!

As a resident physician, I bunched up all my elective time at the end of my final year so I could spend six straight months in the lab of Manfred Karnovsky.

I bought my first pocket-sized calculator and used an Apple II-C computer and a program called Cricket Graph to make figures for publication.

CREDIT: APPLE

The Apple II-C was released April 24, 1984, and was considered a portable computer at the time.

By the time I was a new assistant professor, "technology" meant having a PC and a dot matrix printer on your desk and a magnetic resonance imaging scanner in your Department of Imaging Sciences. By the time I was a professor, transcriptomic chips had 40,000 cDNAs on them and most adults had a cell phone.

Technology moves very fast, sometimes faster than ethics and analytics can keep pace. Now, I feel as if I am the only person left on earth who does t-tests and Mann-Whitney U-tests by hand. Doing so makes me think deeply about whether I am doing the right test for the question I am asking; whether the results make sense; and what the results mean beyond statistics into the biology and chemistry of the system.

I have read more than I think is good for me about artificial intelligence and large language models. I am deeply fearful of what they will convince us we know that we do not, and what they will make us think we understand that we have wrong. We are sharing datasets generated without a driving hypothesis and publishing post hoc analyses before generated hypotheses are tested.

This issue of the *NIH Catalyst* is about emerging technologies. They are alluring and exciting and filled with potential. But they are tools, and their value is not intrinsic. What they enable us to understand, and what we do with that understanding, are what matters.

It feels as if the cutting-edge technologies described in this issue can expand our research efforts to boundless frontiers, but we must think about and use these innovations wisely, cautiously, and thoughtfully, while leveraging our creativity and our ethics as we work to extend the health span of all people everywhere. ●

reddit

Join the NIH Intramural Research Program for a Reddit "Ask Me Anything" (AMA) event featuring Megan Majocha, NCI on May 7, noon to 2 p.m. https://www.reddit.com/r/askscience/

A Remarkable Mechanism of Pain Insensitivity

Wife–Husband Dinner Conversations Open Up New Pathway to Combat Pain

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

Mike Iadarola and Karen Berman

A few years ago, NIMH Clinical and Translational Neuroscience Branch Chief **Karen Berman** began seeing alarming reports from parents about their children in a clinical trial she was conducting. The children appeared to be insensitive to pain that would have others shrieking.

One child presented with skin red from hot bath water. Another boy was severely bitten by a dog, but he didn't feel pain, even while receiving stitches. Yet another child got banged in the jaw, lost a tooth, but complained only of the bitter taste of the blood in his mouth.

Aside from apparent pain insensitivity, these children share one other trait: They have a rare genetic alteration called Dup7, which is short for 7q11.23 duplication syndrome. The condition is related to, but in some ways the polar opposite of, Williams syndrome, which stems from the same chromosome region.

Berman and her team in NIMH study both Williams syndrome and Dup7, the latter of which was first described only about 20 years ago. When they and their colleague Carolyn Mervis at the University of Louisville in Kentucky heard these first-hand reports of incredible—if not dangerous—pain insensitivity, they couldn't help but wonder if there was a deeper, biological connection.

As chance would have it, Berman is married to an NIH pain researcher, **Michael Iadarola**, a senior research scientist in the CC's Department of Perioperative Medicine. Over many an evening dinner and drive to campus, they would talk about this rare pain insensitivity. The conversations drove Iadarola to search for an underlying genetic mechanism within the 7q11.23 region, which contains 25 genes.

And bam! The reason popped out almost instantly. Combined efforts between the Berman and Iadarola groups found that people with Dup7 also have an overexpression of syntaxin-1A (STX1A), a protein involved in the release of neurotransmitters specifically in pain-sensing sensory neurons. Too much syntaxin essentially smothers pain-signal synaptic transmission. Iadarola, Berman, and their colleagues published this finding in January (PMID: 38261410).

But this story is just getting going.

A special pair of cohorts

Berman has studied Williams syndrome for 15 years and has examined scores of volunteers with the syndrome. She first encountered the syndrome while in medical school many years earlier, when it was referred to in textbooks as elfin facies syndrome, because one external characteristic is a person's fairylike face, kindly demeanor, and gregarious behavior.

However, serious conditions include mild to moderate intellectual disability; visual-spatial disabilities; and due to an underexpression of the protein elastin, a narrowing of the aorta just above the aortic valve; low muscle tone; and hernias. The rare Williams-elfin facies syndrome, affecting 1 in 7,500 to 20,000 individuals, is caused by a deletion of genetic material on the chromosomal region 7q11.23.

Dup7, as the name implies, occurs when the same section on the chromosome is duplicated, and this duplication is equally as rare. So, whereas Williams syndrome stems from hemideletion of a section of chromosome 7 (leaving one copy of affected genes, instead of the typical two copies), Dup7 results from duplication of the same section of chromosome 7 (resulting in three copies of the same genes).

People with Dup7 can have characteristics closer to some individuals with autism, such as social avoidance, social anxiety, attention-deficit/hyperactivity disorder, and language delays. Yet they have relative strength in spatial skills, including math.

Berman also has seen scores of Dup7 individuals. Many study participants with both Dup7 and Williams syndrome, along with their families, have returned every two years for over a decade to engage with ongoing research study protocols. Berman and her team also work closely with Duplication Cares, an advocacy group for families of individuals with Dup7.

Michael Gregory, a staff clinician in the NIMH Clinical and Translational Neuroscience Branch, was among the first to note the similarities that Dup7 individuals had in regard to pain insensitivity, as reported by their parents. Pain insensitivity is not something that was easy to test in the clinic (i.e., they would not want to deliberately induce pain), but the anecdotal stories began to pile up. Some stories would give you the shivers: Think, car door slam followed by a child saying, "Hey, Mom. Look!"

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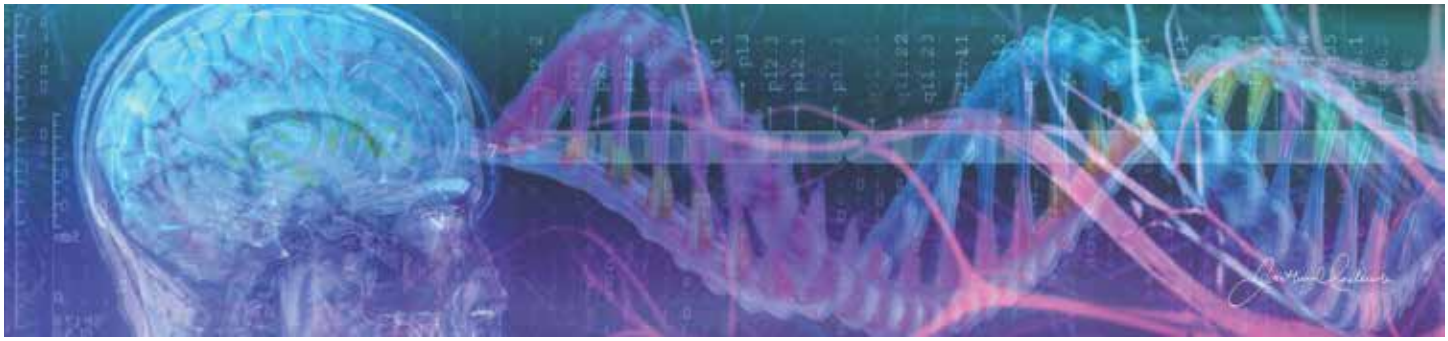


All in the family: This illustration was created by Jonathan Iadarola, Iadarola and Berman's son. It depicts a digital collage showing the relationship between genes, neurons, brain, and behavior. The DNA double helix surrounds chromosome 7, the site of the Dup7 syndrome genetic alteration; this, in turn, is surrounded by an axon bundle to depict the idea of a neuronal circuit, and the ensemble emerges from a brain within the profile of a person.

Add a dash of pepper

And so, with morsels of information fed to him over dinners at home through Berman's table talk about what Gregory and others were hearing from Dup7 parents, Iadarola began to formulate a research project to identify a cause for this profound insensitivity.

His expertise in pain and pain management dates back to 1986, when he first came to the NIH with a background in opioid neuropeptides. He then led the NIDCR Neurobiology and Pain Therapeutics Section, where his research focused on basic and translational research on pain mechanisms, pain molecular neurobiology, and the development of new treatments.

"We always joke that I study things from the neck up, and he studies things from the neck down," Berman said about her research compared with her husband's. "Our work overlaps enough that we understand what each other does, but not enough to drive each other crazy."

Iadarola reasoned that the diversity of organ systems involved in these anecdotal reports (e.g., inflamed intestines, broken bones, lost teeth, lacerated skin) implied that the inability to sense pain in people with Dup7 must be a whole-body phenomenon.

He also understood that pain insensitivity, exceedingly rare but seen in some people without Dup7, usually results from loss-of-function mutations in genes expressed in pain-sensing dorsal root ganglion (DRG) neurons that connect the body to the spinal cord.

Using a dash of capsaicin, the chemical in chili peppers that makes them spicy, Iadarola set out to induce pain signals in a culture of rat cells genetically modified to have the 7q11.23 Williams syndrome/Dup7 swath.

He hypothesized that the candidate insensitivity gene in the 7q11.23 region would exhibit enriched expression in the pain-sensing population.

> "Turning this into a medicine is a challenge, but that doesn't mean it can't be done."

With next-generation sequencing machines at the NIH Intramural Sequencing Center, Iadarola's lab analyzed every gene expressed in pain-sensing and non-pain-sensing dorsal root ganglion neurons.

The aha moment came when he plotted gene expression concentrations in the two populations. One gene stood out like a nail through a plank, STX1A, which yielded a sixfold expression of the pain-sensing neurons compared with the non-pain-sensing population.

"What was most amazing," he said, was that "this particular gene made intrinsic sense; somehow, overexpression was inhibiting synaptic transmission, interrupting communication with the next neuron in the pain pathway."

Specifically, his team was looking at transient receptor potential vanilloid 1 (TRPV1)–expressing neurons because, from one of their clinical trials, they knew that interrupting transmission from TRPV1 neurons produced potent and long-lasting analgesia.

Their experiments showed that overexpressing STX1A in cultured DRG neurons inhibited transmitter release from TRPV1 neurons. Syntaxin 1A is part of the "SNARE" complex that captures and opens synaptic vesicles to cause transmitter release upon stimulation.

Follow-up studies using human dorsal root ganglion tissue, recovered from organ donors, indicated that human nociceptive neurons naturally contain both TRPV1 and syntaxin. The TRPV1-STX1A genes' co-localization places STX1A directly in the same neuron in humans, further implying that too much syntaxin is well positioned to mute pain in humans, as seen—albeit not yet tested directly—in the Dup7 population.

"[Syntaxin] must be very effective to make people like the child with the dog bite and the others insensitive to pain," Iadarola said.

Pathway to pain relief

Pain is both a blessing and a curse. Although unpleasant, the pain sensation serves as an essential bodily function

to help us avoid danger, seek care, and promote healing.

For the Dup7 children, there is no treatment on the horizon that would restore sensitivity to pain.

For now, this discovery by the Berman and Iadarola labs have raised awareness in the Dup7 community for parents to be diligent about any irregularity such as fever, an unusual gait, or clamminess that might indicate internal tissue damage.

There is hope that the syntaxin pathway could lead to the discovery of nonopioid analgesic treatment strategies, although that path is not straightforward, Iadarola said.

Through a simple injection, certain opioids and the calcium channel blocker ziconotide can act at the same synaptic site at which an overabundance of syntaxin is assumed to act, although via different mechanisms. But for syntaxin to work to relieve chronic pain, a type of localized gene or protein interaction therapy would need to be administered.

"Turning this into a medicine is a challenge, but that doesn't mean it can't be done," Iadarola said.

He added that the molecule syntaxin has been known for quite a long time as part of the synaptic vesicle machinery, but no useful medical phenotype has been associated with it until now.

Berman noted that the deletion and duplication of 7q11.23, causing Williams syndrome and Dup7, respectively, involve the same genes in nearly 96% of affected individuals, and thus is very well defined.

Studies of these populations hold great promise for numerous studies of the syndromes' other characteristics, such as changes in cognition, which Berman's lab also is pursuing. ●

In our 1995 January–February issue of the *NIH Catalyst*, a 2.5-page article highlights scientific couples across the NIH. Visit the link below and scroll to page 6 for a youthful snapshot of Berman and Iadarola.

The link to the 1995 *Catalyst* article is https://irp.nih.gov/system/files/media/file/2022-01/NIH_catalyst_v03i1_1995-Jan-Feb.pdf.

Keeping the "I" in DEIA for AI, ML

Keeping Diversity, Inclusion Top of Mind When It Comes to Tech in Health Care

BY TAYLOR FARLEY, NIAID

In 1955, John McCarthy, a computer scientist then at the Massachusetts Institute of Technology (Cambridge), coined the term "artificial intelligence" (AI), creating language for the concept of using computers to mimic the capabilities of humanity's greatest evolutionary asset—the mind.

Today, the future McCarthy and his colleagues envisioned is upon us with all its promise and perils. In health care in the United States, this technology has already reached 78% of patients. While mostly limited to drafting physician notes or providing care insights, AI is being eyed as the next-generation diagnostic tool.

Despite this potential, experts also warn that AI and machine learning (ML), if not properly vetted, could inadvertently amplify health disparities.

Bias in, bias out

Like human intelligence, AI, and thus ML, require the study of data entered into a system. Just as humans read to gain knowledge, so too does AI. That knowledge then can be used to train machines to consume large datasets and use those datasets to create predictive models on which we base our science.

A job that would take the human mind days, weeks, months, or even years to compute could take a properly trained AI or ML model just moments. But in their elemental form, AI and ML are math, not mind, and predictions are based on the study material supplied by humans, which comes with biases.

"The techno-chauvinistic perspective tells us that AI or computational solutions are 'objective' or 'unbiased' or 'superior,' but it quickly becomes clear that the problems of the past are reflected in the data," said Meredith Broussard, a data journalist and New York University professor. "The problems of the past are things like discrimination, racism, sexism, ableism, structural inequality, all of which unfortunately occur in the world, and all of these patterns of discrimination are reflected in the data we have used to train these systems." Broussard delivered a lecture in March, titled "How Can Cancer Help Us Understand Algorithmic Bias" as part of NLM's Science, Technology, and Society Lecture series, during which she highlighted various ways AI and ML can exacerbate prejudice by continuing to make predictions and suggestions based on past patterns.

> "We have an amazing opportunity to correct disparities and biases of the past, and improve health care for all."

Similarly, Marzyeh Ghassemi, an assistant professor at MIT, specializes in the health of the machine learning algorithms and conducts research identifying how easily this technology can inadvertently exacerbate preexisting biases in medicine. Ghassemi explained how biases exist within electronic health records at an advisory council meeting at NIEHS.

Ghassemi's group trained a model to identify whether a chest X-ray had concerning signs of disease that would require further evaluation (PMID: 34893776). The goal was to train the system to assist with triaging patients—can the patient return home, or do they require priority care?

When trained on three publicly available datasets, including one from the NIH, the model disproportionately misdiagnosed female, Black, and Hispanic patients, those under 20 years old, and those with Medicaid insurance, an imperfect proxy for socioeconomic status. For individuals with intersectional identities, these disparities were even more pronounced. Meaning, if this tool rolled out in emergency rooms today, some patients would be sent home without proper care.

Concerning trends of misdiagnosis for marginalized communities are widespread in American health care today. At the precipice of the new age of medicine, we have an opportunity to correct the shortfalls of the past, but it means we must move forward with intention.

NIH efforts to diversify data

Improving these systems will require training data that are more diverse, and the NIH has already established programs to tackle this ongoing limitation.

One NIH-partnered initiative aimed at expanding heath databases through purposeful inclusion of individuals from underrepresented communities is the *All of Us* Research Program. Another effort, the NIH Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and Research Diversity (AIM-AHEAD) Program aims to address inequities in AI and ML research and application through four areas: partnerships, research, infrastructure, and data science training.

Sameer Antani, a tenure track investigator in the Computational Health Research Branch at NLM, conducts research on improving the performance and reliability of novel image-based and multi-modal AI and ML for various diseases. He suggests greater effort should be devoted toward minimizing apparent hubris in the technology and enabling acknowledgment of uncertainty. For example, designing the AI to project its degree of confidence in predictions, based on the training data characteristics, could help improve collaboration between the technology and humans, helping it actively learn to address the gaps, and reduce the potential for bias over time.

"Through appropriate development of this technology, we have an amazing opportunity, a second chance, to correct disparities and biases of the past, and improve health care for all," Antani said.

CREDIT: NLM

Sameer Antani

As with any novel technology, it can be enticing to run in the direction of innovation and ignore the potential negative consequences. But when it relates to the health of our world, we must continue to ask ourselves: Is it helping us all equally in the process. ●

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

CREDIT: CHIA-CHI CHARLIE CHANG

Vinton Cerf, father of the internet, was the 2024 J. Edward Rall Cultural Lecture featured speaker. The Rall lecture is an installment of the Wednesday Afternoon Lecture Series (WALS).

Rall Lecture Featured Famed Father of the Internet

BY MEAGAN MARKS, NIAAA

The annual J. Edward Rall Cultural Lecture featured Vinton Cerf, oft coined a "father of the internet," who delighted hundreds of attendees in Masur Auditorium on March 19 with his humor and quick wit.

Cerf sat down with NIH Director **Monica Bertagnolli** for a fireside chat focused on a matter top-of-mind for NIH's new leader: The future of AI and ML in health care.

The duo discussed how recent advances in AI might influence biomedical research and the future of health care delivery. They answered NIH audience questions that broadly asked:

- Can AI make health care truly evidence-based?
- How should providers preserve, protect, collect, regulate, and diversify the health data of patients?
- What are the most practical and reliable uses of large language model technology such as ChatGPT (if any) in medicine?

Answers explored how AI might aid in 24/7 patient monitoring and how ML could one day lead to personalized medicine and personalized treatment; and the pair estimated the immense potential of electronic health records.

"I hope you recognize what an opportunity NIH has to improve the state of health care with the kind of research that you are doing and the attempt to exercise these powerful computing tools that are emerging," Cerf said to the audience in his closing remarks. "You have an opportunity to make a lot of progress…and if I were in your shoes, I would be sitting here thinking, 'Boy, do we have a lot of work to do and a huge amount of opportunity to do good.'" ●

Experience the full discussion and Cerf's intelligently detailed responses by viewing the lecture in its entirety at https://videocast.nih.gov/watch=54305.

Chinese University of Hong Kong, who was a 2022 recipient of the Lasker~DeBakey Clinical Medical Research Award. Lo will provide an introductory talk on efforts to detect cancer earlier by measuring DNA that freely circulates in blood plasma.

What are liquid biopsies?

Liquid biopsies offer an alternative to tissue sampling for diagnosing, treating, and monitoring disease. Liquid biopsies can be analyzed for various biomarkers including cell-free DNA (cfDNA), extracellular vesicles such as exosomes, and circulating tumor cells (CTCs), to name a few (PMID: 37716353).

Scientists are discovering new ways in which tumors or even transplanted organs shed various biomarkers into the bloodstream, or into other body fluids, that offer enough information to enable reduction of traditional tissue sampling. This process reduces the need for risky procedures in difficult-to-reach areas and lowers the risk of infections or even stress that patients experience from invasive tissue sampling procedures.

Monitoring metastasis

Some cancers and conditions can be partially diagnosed using a liquid biopsy, but the true value of liquid biopsies is in its monitoring capabilities. For example, monitoring CTCs reveals that there really is strength in numbers.

Breast cancer mortality is almost always due to metastasis, so understanding how cancer cells survive the march from primary tumor to metastasis has grown to become a very important research aspect for **Esta Sterneck**, head of the Molecular Mechanisms in Development Section at NCI-CCR and conference co-organizer.

"We monitor circulating tumor cells that travel as groups termed 'clusters' because they are deemed more likely to seed metastasis compared to single tumor cells," she explained, adding that she is

studying how cell-to-cell adhesions may enhance tumor cell survival and might, therefore, be targeted for therapeutic intervention. Toward this aim, Sterneck's lab also uses an unconventional 3D cell culture paradigm for mechanistic molecular studies (PMID: 36757813) and uses mouse cancer models to validate findings by use of liquid biopsies.

One might liken the usefulness of these findings to planning a war strategy: Attack while the enemy is on the move and most vulnerable. "It has been shown that circulating tumor cells surge during surgery or even biopsy, so these are times in patient care during which one might want to particularly target circulating tumor cells to minimize the spread that could accompany these interventions," she said.

"The hope is that one day liquid biopsies can become a complementary diagnostic tool to identify cancer cells in the body, but right now, it is really for monitoring current states of cancer and how it progresses in the body: What is happening now, how the secondary sites are occurring, and how it is travelling within the body."

Sterneck said she hopes the conference will help to connect basic and clinical researchers and thereby contribute to new research directions and collaborations among attendees.

Real-time therapeutic response

Liquid biopsies as a diagnostic tool don't always make sense, as Sowalsky might tell you. His first attempt at investigating circulating tumor DNA paired with a hypothesis that put a liquid biopsy approach up against the existing prostate-specific antigen (PSA) blood test.

"Ultimately, we published my first negative data paper saying that it is just not there, we could not detect it (PMID: 31528835). So far, that has been the experience of almost everyone else we have talked to, and they are glad that we published the negative data paper because it sets the stage for what we cannot do and now we can focus our efforts on something else."

Those efforts have led to NIH clinical studies in which patients with progressed disease receive combination immunotherapy, inhibitor treatments, or other trial drugs (PMID: 30514390, PMID: 33023952; see also, PMID: 36179684, PMID: 33422353). Sowalsky's team tracks patient progress during these treatments using serial blood samples.

"We thought we could try a number of different types of analyses to understand the basis for response," Sowalsky said. "So, we asked, is there something about the circulating tumor DNA or the cfDNA from those patients that would tell us that they would respond or why they did not respond?" The research team examined the liquid biopsies for tumor evolution and monitored whether patients experienced clinical progression.

"We figured out a number of different ways we can approach these questions. One way is looking at mutations and somatic mutations, somatic copy number of alterations, actual structural things that happened to the DNA itself. For example, there could be a mutation and therefore a change in the clonal abundance of the tumor. So, something that was insignificant early in the disease became more important later, and that is what may have driven resistance to the therapy. Or there could have been intrinsic resistance where the patient had a certain combination of mutations that rendered that patient resistant, initially. We did not

know any of these things going into the clinical trial, but having this information now will be useful for the next stage of clinical interrogation."

Less invasive transplant rejection monitoring

Liquid biopsies reduce the number of invasive needle or tissue biopsies. For lung transplant patients, liquid biopsies are making rejection monitoring much less painful and expensive.

Sean Agbor-Enoh, a Lasker clinical research scholar at NHLBI who specializes in pulmonary transplant medicine, grew deeply concerned about patients during the COVID-19 pandemic, not only about the possibility of their contracting the deadly virus but also because of the lack of access to safe health care procedures to monitor for the first signs of organ rejection after transplant.

Traditionally, lung transplant patients undergo seven or more invasive lung biopsy procedures over the first two years post-transplant. These expensive biopsy procedures required anesthesia and a hospital stay, which became risky during the pandemic.

So, Agbor-Enoh partnered with industry professionals and other federal agencies to develop a cfDNA liquid biopsy that can detect rejection two to four months earlier than the traditional tissue biopsy. The cfDNA liquid biopsy approach distinguishes between the host and the organ donor DNA, and as long as the donor DNA stays at a low concentration, the patient's prognosis remains positive (PMID: 30692045).

These patients now can be monitored via a monthly blood draw and the alarm signals (increase in donor DNA) can be identified sooner, medications can be adjusted quicker, and secondary infection rates from invasive procedures are minimized. This procedure has resulted in an 85% reduction of the traditional tissue biopsy for lung transplant patients (PMID: 35063338), and upward of 60–75% of transplant centers now use the liquid biopsy test. According to Agbor-Enoh, it is quickly becoming the standard of care for other types of transplanted organs as well (PMID: 38380175, PMID: 38026221).

"This is quite a paradigm shift," he said. "With just one milliliter of blood from a blood draw not only can one do a diagnosis, but also a prognosis, with quite some degree of accuracy. Importantly, these principles could be broadly applicable in non-transplant diseases [PMID: 38165046, PMID: 36004627, PMID: 38117233]. So, as you can imagine, this could completely change the way we practice medicine."

From SIG to an international exchange of ideas

As with most scientific discoveries, there is a long and storied history, but long story short is that Sowalsky, Sterneck, and Agbor-Enoh joined forces through the Liquid Biopsies Scientific Interest Group (SIG) to spearhead the New Frontiers in Liquid Biopsies conference.

"I wanted to develop a disease-agnostic international intellectual network of individuals who were interested in sharing ideas, technologies, method development, best practices—and not just sharing research achievements but the nitty gritty things like what methods you've used and how did you get it to work, what challenges you encountered along the way, what didn't work, and what should we or should we not try," said Sowalsky about his thoughts behind both the NIH SIG and the May 13–14 conference.

"We have all been working in silos in our own smaller corners," added Agbor-Enoh. "I do lung transplant; Adam does prostate cancer; Esta works with preclinical mouse models; we all do exciting things with different types of liquid biopsies; but

Conference co-organizers:
Esta Sterneck, NCI-CCR
Sean Agbor-Enoh, NHLBI
Adam Sowalsky, NCI-CCR

can you imagine if you bring all of us into the same sandbox such that we can talk about what we do and learn from each other? It could be an even bigger course in the field of liquid biopsy. That's the excitement in the conference. We expect that participants coming to the conference will learn a great deal and then can take that information back to their respective corners and increase what they know while fostering collaborations."

Other conference co-organizers include Aadel Chaudhuri at the Mayo Clinic (Rochester, Minnesota), Alexandra Miller at New York University Langone Health (New York), Aaron Newman at Stanford University (Palo Alto, California), Bruna Pellini at the Moffitt Cancer Center (Tampa, Florida), Antoinette Perry at University College Dublin (Belfield, Dublin, Ireland), and Ignatia Barbara Van den Veyver at Baylor College of Medicine (Houston, Texas).

"The conference will be a great exchange of knowledge and ideas, and our intent is for it to serve as a platform for new collaborations," said Sowalsky. ●

RESEARCH IN ACTION
Read more about Agbor-Enoh's work and view a recent video interview, available online at https://irp.nih.gov/our-research/research-in-action/safeguarding-a-second-chance-at-life

Women's Health Research

CONTINUED FROM PAGE 1

Defense—does everything we can to drive innovation in women's health and close research gaps," said President Biden in the official White House fact sheet on the Presidential Memorandum.

"Never before has there been such a comprehensive effort from the federal government to spur innovation in women's health research," said Carolyn Mazure, who chairs the initiative. "This is a huge opportunity for transformative change that can improve the health and the lives of women across this country." Mazure is the Norma Weinberg Spungen and Joan Lebson Bildner professor in women's health research and professor of psychiatry and psychology at Yale School of Medicine (New Haven, Connecticut). She is taking leave from her duties at Yale to work alongside First Lady Jill Biden, in collaboration with the White House Gender Policy Council, to establish and advance this new White House Initiative on Women's Health Research.

NIH is well prepared

NIH is, of course, at the forefront of this charge. An agency-wide effort will be launched to close gaps in women's health research across the lifespan. The NIH has committed $200 million in the FY25 NIH budget to support this work and President Biden's budget request includes funding to double the current budget for the NIH Office of Research on Women's Health (ORWH), which is led by **Janine Austin Clayton**.

CREDIT: ROBERT LISAK

Carolyn Mazure chairs the White House Initiative on Women's Health Research.

Expounding on the five key areas of this executive order, NIH will embark on a biomarker discovery effort, begin its first ever Pathways to Prevention Series on menopause and the treatment of menopausal symptoms, and engage in an effort to identify and develop new common data elements that are specifically related to women's health. Moreover, menopause has just been added as a research category to the NIH Research, Condition, and Disease Categorization.

> "Women deserve better, and now we are going to get it."
> — First Lady Dr. Jill Biden

"The Biden women's health initiative will galvanize our intramural investigators around efforts to understand, treat, and prevent disorders that disproportionately affect women and to recognize the unique clinical presentations of disorders common to people of both sexes," said **Nina Schor**, deputy director for intramural research. "Every NIH institute has a role to play in this initiative because of their already robust efforts focused on such disorders as autoimmune conditions, migraine, multiple sclerosis, preeclampsia, and postpartum depression, which are more frequently seen in women than in men, and on the unique ways in which heart injury and lung dysfunction, for example, present in women."

A central fund for women's health research at the NIH to advance interdisciplinary science also is being requested, according to Mazure. In addition, this White House Initiative hopes to fund the creation of a new nationwide network of research centers of excellence and innovation.

"We know that healthy women contribute to healthy families, healthy communities, healthy cities, healthy economies, and so much more, and that benefits everyone. NIH is excited and prepared to help leverage the recent executive order to accelerate research that will provide much needed answers and tools to help prevent, diagnose, and treat conditions that affect women uniquely, disproportionately, and differently," said **Tara Schwetz**, deputy director of Program Coordination, Planning, and Strategic Initiatives, at the 60th meeting of the NIH Advisory Committee on Research on Women's Health (ACRWH), April 9.

CREDIT: CHIA-CHI CHARLIE CHANG

Pictured left to right is NIH Director Monica Bertagnolli, Jodie Haydon of Australia, and First Lady Jill Biden during a visit to the NIH Clinical Center in October 2023.

At that meeting, experts in women's health research gathered to discuss the new initiative, as well as disturbing trends in the reduced life expectancy of Americans, and especially women. As NIH Director **Monica Bertagnolli** pointed out during her talk, "Among our main guiding principles at NIH, the very first one is that our work is not finished when we deliver scientific discoveries. Our work is finished when all people are living long and healthy lives."

Making inroads

Mazure accompanied the First Lady at numerous listening sessions across the country after the initial November Presidential Memorandum to hear from a wide range of stakeholders about the health concerns of women. Together, they toured laboratories and held community listening sessions where they heard from patients,

CREDIT: WHITE HOUSE

NIHers at the signing of the President Biden's Executive Order in March included NIH Director Monica Bertagnolli; Tara Schwetz, deputy director for Program Coordination, Planning, and Strategic Initiatives; Janine Austin Clayton, ORWH director; and Vivian Ota Wang, ORWH deputy director.

health care providers, researchers, advocacy groups, and others in the public and private sectors. Among the prominent themes that arose was the need to translate critical research findings into the marketplace in a timelier manner.

Progress is already being made. The Advanced Research Projects Agency for Health, or ARPA-H, Sprint for Women's Health $100 million funding initiative, which just launched in March, will accelerate discoveries from early-stage proof of concept to products ready to be commercialized, according to Mazure. "Although technologies capable of diagnosing and possibly treating diseases across all ages and stages of a woman's life are increasingly possible, very few are affordable and are currently available in the marketplace or are easy to use," she noted.

Moreover, last August, the NIH's Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) Initiative established 10 maternal health research centers of excellence across the country. Bertagnolli said these institutions are working together to design and implement research studies that address the biological, behavioral, environmental, sociocultural, and structural factors that can lead to or help prevent pregnancy-related complications and death.

"To fully realize this opportunity, we need to work together across sectors and industries to ensure that all of U.S. government, research centers, advocacy organizations, philanthropy, and the private sector are doing everything we can to close research gaps in women's health. Thanks to First Lady Dr. Jill Biden's leadership, this initiative will continue taking action to advance women's health research so that women get the answers they need when it comes to their health," Mazure said in her closing remarks.

Sex differences matter

A concept clearance for sex differences in autoimmune disease also was presented at the April 9 ACRWH meeting.

Mazure noted that 80% of those with autoimmune disorders in the United States are women. Women have a greater likelihood of developing chronic conditions as well as multiple disorders that occur at the same time. "Conditions affect women differently than men, such as those found in heart disease and in most brain-based disorders," Mazure explained.

"Whether it's smoking or epilepsy or multiple sclerosis; wherever we look, we find that sex differences matter." ●

CATALYTIC EVENTS

A smattering of catalytic events happening around the NIH in May and June

MAY

5/8 Florence Mahoney Lecture on Aging: From Policies to pTau: Exposing Social and Structural Drivers of Alzheimer's Disease and Opportunities for Brain Health Justice, Jennifer Manly, 2 p.m., VideoCast: https://videocast.nih.gov/watch=53831

5/13–14: New Frontiers in Liquid Biopsies, Natcher Conference Center

5/13–17: National Women's Health Week

5/15: 8th annual Vivian W. Pinn Symposium, 1-5 p.m.

5/16: Future Directions in Menopause Research: Optimizing Midlife Health of Women, 11 a.m. to 12:45 p.m.

Learn more at https://orwh.od.nih.gov/our-work/events

5/15: Robert S. Gordon Jr. Lecture: Addressing Health Disparities in Diabetes: Intersection of Structural Racism, Social Determinants, and Racial/Ethnic Disparities, Leonard Egede, 2 p.m., VideoCast: https://videocast.nih.gov/watch=53833

5/17: NIH Artificial Intelligence Symposium, 9 a.m. to 5:30 p.m., Masur Auditorium, Building 10

5/22: WALS: Type 2 Diabetes Among Asian-Americans: Elevated Prevalence and Novel Risk Factors, Maria Rosario (Happy) Araneta, 2 p.m., VideoCast: https://videocast.nih.gov/watch=51114

5/29: WALS: Coronavirus Activation and Antagonism of Interferon Signaling Pathways: from MHV to SARS-CoV-2, Susan Weiss, 2 p.m., VideoCast: https://videocast.nih.gov/watch=52621

JUNE

6/3 Kuan-Teh Jeang Memorial Lecture: The Broad Impact of Innate Immune Receptors in Viral Infection, Cancer, and Autoimmunity, Jenny Ting, 2 p.m., Lipsett Amphitheater, Building 10

6/5 WALS: Brain-Wide Silencing of Prion Protein and Treatment of Prion Diseases by AAV-Mediated Delivery of CHARM an Engineered Compact Epigenetic Editor, Jonathan Weissman, 2 p.m., VideoCast: https://videocast.nih.gov/watch=52301

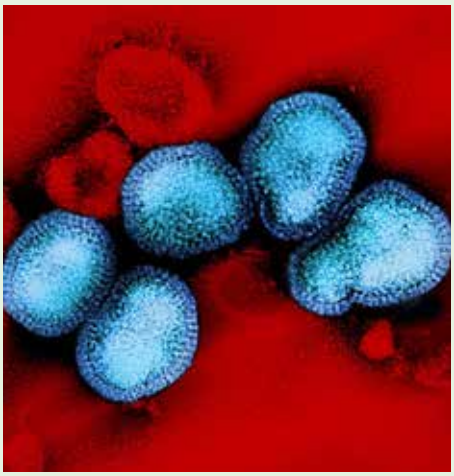
6/5 Barmes Lecture: Global HIV/AIDS Response: Then, Now, Future, Natcher Conference Center, 1–2 p.m. Register online: https://mregs.nih.gov/fic/v2bp-v143302

6/12 WALS: Quantitative Proteomics for Understanding Epigenetics Mechanisms, Benjamin Garcia, 2 p.m., VideoCast: https://videocast.nih.gov/watch=51137

Intramural Research Briefs

Read about Scientific Advances and Discoveries by NIH Intramural Scientists

NIAID: "DARK SIDE" OF INFLUENZA VIRUS PROTEIN OFFERS NEW TARGET



CREDIT: NIAID

NIAID: Colorized transmission electron micrograph of influenza A virus particles.

A new flu-fighting target was uncovered by a research team at NIAID's Vaccine Research Center. Because influenza mutates and generates new strains, there is a constant need to develop new vaccines that remain effective against the rapidly evolving virus. Investigators targeted a conserved region of a glycoprotein called neuraminidase (NA), an essential surface protein of the influenza virus. The underside of the NA protein head, termed the "dark side," is believed to be hidden from the immune system and thus understudied in influenza research. However, the region is less susceptible to mutations and remains relatively unchanged between different virus strains.

The scientists isolated human antibodies against viral epitopes—part of the viral protein which can be recognized by the host immune system—located within the dark side region of NA from people who recovered from influenza infection. These antibodies were able to prevent lethal infection in mice when administered before and after exposure to H3N2 influenza.

Cryogenic electron-microscopy analysis of the antibodies bound to NA revealed that they targeted nonoverlapping epitopes of the dark side region, suggesting that targeting that area could be helpful in designing broadly protective influenza vaccines. (NIH authors: J. Lederhofer, Y. Tsybovsky, L. Nguyen, J.E. Raab, A. Creanga, T. Stephens, R.A. Gillespie, H.Z. Syeda, B.E. Fisher, M. Skertic, C. Yap, A.J. Schaub, R. Rawi, P.D. Kwong, B.S. Graham, A.B. McDermott, S.F. Andrews, and M. Kanekiyo, PMID: 38430907)

[BY DEVIKA BOSE, NEI]

NIA: TWO PROTEINS COLLABORATE TO MOUNT A PATHOGEN-TAILORED IMMUNE RESPONSE

NIA scientists found that the coordinated actions of two inflammatory signaling proteins, RelA and c-Rel, enable immune cells to determine the presence of specific microbes before engulfing them. RelA and c-Rel help these immune cells, called macrophages, distinguish the microbes via their shed pieces, known as ligands. This action produces a response appropriate for the specific pathogen. These two proteins are important components of the nuclear factor kappa B (NF-kappa-B) signaling pathway, which is responsible for regulating the immune response of a mouse or human to pathogens or cellular damage. NF-kappa-B is also broadly involved in all inflammatory conditions.

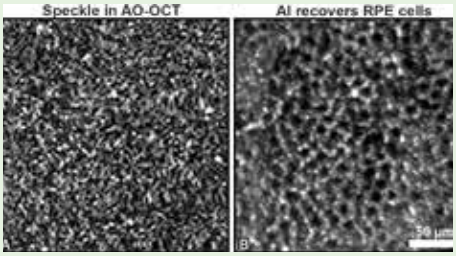
The research team led by **Myong-Hee "Mia" Sung**, an NIA tenure-track investigator, made the discovery by monitoring live macrophages from fluorescent double-knockin reporter mice the group had previously generated for quantitative single-cell studies. The live-cell imaging showed that RelA and c-Rel conveyed more information about ligands than either subunit alone.

Based on this signaling information, Sung and colleagues used machine learning to predict to which microbial ligand macrophages were binding so that they could mount an immune response against a pathogen.

The authors state that the coordinated signaling between RelA and c-Rel may have developed during evolution, and their finding provides insight into how NF-kappa-B proteins mediate a wide range of microenvironmental cues in immune cell communication. (NIH authors: S.M.T. Rahman, M. Aqdas, and M.H. Sung, PMID: 38483906)

[BY ROBIN ARNETTE, NIA]

NEI: AI-ASSISTED RETINAL IMAGING SAVES TIME, IMPROVES RESOLUTION



CREDIT: VINEETA DAS, NEI

NEI: A) AO-OCT provides a more detailed image of the RPE layer, but the cells are obscured by speckle. B) There is a remarkable improvement in RPE cell visualization gained by applying AI to the speckled AO-OCT image. Each dark area represents a single RPE cell.

Clinicians routinely image retinal pigment epithelial cells (RPE), which are crucial to maintaining vision, to detect and treat eye diseases. A recent study found that combining AI with one of those imaging methods, adaptive-optics optical-coherence tomography (AO-OCT), made the process 100 times as fast and improved image contrast 3.5-fold compared with previous methods. AO-OCT is a powerful tool that can produce 3D retinal images at the cellular scale; however, the imaging process creates noise known as speckle, which necessitates that hundreds of images be manually averaged together to improve contrast.

A team led by **Vineeta Das** and **Johnny Tam** in NEI's Clinical and Translational Imaging Section created a deep learning algorithm that efficiently despeckled a single image capture comparably with the manual method while also improving contrast. "Thinking about AI as a

part of the overall imaging system, as opposed to a tool that is only applied after images have been captured, is a paradigm shift for the field of AI," said Tam in a press release. (NIH authors: V. Das, F. Zhang, A.J. Bower, J. Li, T. Liu, N. Aguilera, B. Alvisio, and J. Tam, PMID: 38600290)

NIAID, NCI: MULTI-OMIC PROFILING OF FOLLICULAR LYMPHOMA TUMORS

Lymph nodes are one of the most diverse sites for cancer and metastasis. Located throughout the body, they are connected to many organ systems via lymphatic circulation. In some cases, B cells housed in lymph nodes can become malignant, resulting in B-cell lymphoma. A research team led by NIAID's **Andrea Radtke** and NCI collaborators took a deep dive into a generally incurable form of this disease, called follicular lymphoma (FL), and uncovered some of the genomic, transcriptional, and proteomic factors that contribute to the diverse clinical outcomes observed among FL patients.

Within the tumor environment of FL patient samples, the investigators found enhanced cell signaling and changes in the stromal cells that make up the connective tissue of tumors. The researchers designed an approach that integrated single-cell RNA sequencing and IBEX (iterative bleaching extends multiplexity) imaging, which is an advanced spatial imaging method developed by NIAID investigators that can analyze multiple targets with immunolabeling. This analysis revealed more stromal and myeloid cells than in previous studies in which the tumor was not left intact.

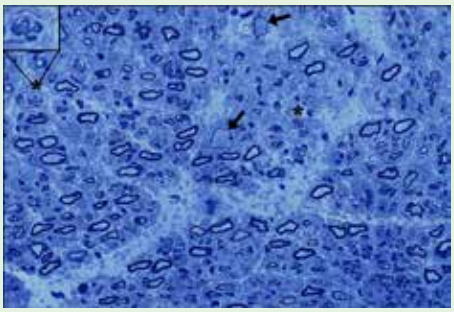
The researchers then analyzed FL samples from patients who had early relapse of disease after beginning therapy. Changes in those samples included further transcriptional differences in B-cell receptor signaling, extracellular matrix remodeling, and glutaminergic receptor activities that can drive tumor growth. Furthermore, distinct architectural changes in the lymph node follicles were found in patients 20 months prior to first progression and relapse.

According to the authors, this study provides a key insight into FL biology and may help physicians and researchers predict disease behavior and improve patient outcomes. (NIH authors: A.J. Radtke, Z. Yaniv, B.C. Lowekamp, E. Speranza, S. Pittaluga, A.L. Shaffer 3rd, J.D. Phelan, T. Davies-Hill, D.W. Huang, M. Kelly, J. Muppidi, J.L. Davis, J.M. Hernandez, W.H. Wilson, E.S. Jaffe, L.M. Staudt, M. Roschewski, and R.N. Germain, PMID: 38428410)

[BY STEPHEN ANDREWS, NCI]

NINDS, CC, NEI, NIAID: INTRATHECAL GENE THERAPY SLOWS PEDIATRIC NEUROPATHY SYMPTOMS

CREDIT: BONNEMANN LAB, NINDS



NINDS, CC, NEI, NIAID: Biopsy of a sensory nerve from a participant in the GAN gene therapy trial (arrows indicate giant axons; regenerating nerve cluster in upper left).

A first-in-human intrathecal gene therapy for the treatment of giant axonal neuropathy (GAN) in children is able to slow symptom progression, according to a recent collaborative NIH study.

GAN is a rare, inherited, and rapidly progressive neurodegenerative disorder caused by the absence or loss of function of gigaxonin. The disease is typically fatal by 30 years of age, and symptoms typically begin as sensory and motor deficits occurring as early as two years old.

In this study, clinicians administered an adeno-associated virus containing a functional GAN gene intrathecally, that is, by injection into the spinal fluid.

The investigators administered one of four intrathecal doses of the therapy to 14 pediatric participants who had also been enrolled in a natural history study at the NIH. Among the various dose groups, motor function scores at one year showed the treatment seemed to slow the rate of motor decline, and six participants regained some sensory nerve activity. The treatment was generally well tolerated with one serious adverse event, a fever, linked to the therapy.

The authors plan to continue dosing with the investigational therapy for the treatment of GAN and note that the study might inform other gene therapies that could be delivered intrathecally. (NIH authors: D.X. Bharucha-Goebel, J.J. Todd, D. Saade, A.R. Foley, P. Mohassel, G. Norato, T. Lehky, J.D. Heiss, M. Jain, M. Waite, W.M. Zein, L.A. Huryn, E.M. Kang, and C.G. Bönnemann, PMID: 385077652)

[BY JOHN CARLO JADORMEO COMBISTA, NIMH]

NLM, NICHD: MYSTERY SOLVED AS RESEARCHERS IDENTIFY KEY ENZYME THAT BREAKS DOWN BILIRUBIN

The complete process of breaking hemoglobin down to urobilin is essential for clearing our bodies of cellular waste, and issues with this breakdown process can lead to health problems such as jaundice. While much of this process was already well understood, the identity of the enzyme that turns bilirubin into urobilinogen remained a mystery.

That is, until recently. **Xiaofang Jiang**, a principal investigator at NLM, and her collaborators used a combination of modern comparative genomics analyses and novel biochemical assays to identify bilirubin reductase, a key enzyme in the human gut microbiome that is responsible for the bilirubin-to-urobilinogen reduction process.

After this discovery, data were analyzed from previous studies and found that while healthy adults almost always had this enzyme, it was often missing in infants who were susceptible to jaundice as well as over 30% of adults with inflammatory bowel disease.

"Now that we've identified this enzyme, we can start investigating how the bacteria in our gut impact circulating bilirubin levels and related health conditions," said Jiang. And because the gut microbiome has been linked to other diseases and conditions, these findings can potentially guide future work to understand the gut microbiome's role in human health even better.

According to Jiang, what they've discovered is "just the tip of the iceberg." (NIH authors: K. Dufault-Thompson, A. Zhong, and X. Jiang, PMID: 38172624) ●

[BY FELICITY FOX, NLM]

Being There

A Case for In-Person Lecture Attendance

BY CHRISTOPHER WANJEK, *THE NIH CATALYST*

Multitudes of scientific breakthroughs have been born of chance encounters. Katalin Karikó and Drew Weissman met for the first time in 1997 while both were waiting to use a photocopier at the University of Pennsylvania (Philadelphia) and conversed about seemingly idle concepts that ultimately would lay the foundation for mRNA COVID vaccines and earn them a Nobel Prize.

Similarly, Emmanuelle Charpentier and Jennifer Doudna met at a conference in 2011 in San Juan, Puerto Rico, and got to chatting about bacterial genetics and biological chemistry, the seeds of the CRISPR-Cas9 method. And, if we can trust the veracity of certain television commercials in the 1970s, the Reese's Peanut Butter Cup came about when two inattentive individuals—one eating chocolate and the other, inexplicably, eating peanut butter—collided on the street and inadvertently combined their foodstuffs.

Unfortunately, in a world of virtual meetings and remote lectures, chance encounters are rare these days, aside from with your IT support. And that's a problem. Although there's no way to quantify this, we are likely missing out on all those people, places, and things in your peripheral vision, and in front of your face, that spur new ideas and spark the insights so critical to the advancement of science.

We actually have a vehicle at the NIH for chance encounters. It's called the Wednesday Afternoon Lecture Series (WALS), initiated by former NIH Director Harold Varmus 30 years ago. Varmus envisioned a set time to gather with colleagues to hear about fantastic science, regardless of the discipline, and to be inspired.

"We are all slaves to our schedules and creatures of habit, so I am glad to be able to block out Wednesdays at 3 p.m. for the coming academic year to listen to the wonderful people who have agreed to tell us about their latest work," he told the *NIH Record* in 1994.

A Nobel laureate himself, Varmus attended most WALS talks during his tenure as NIH director. We have since moved WALS to 2 p.m. at the Lipsett Amphitheater because, frankly, we seldom attract a sizable crowd to the Masur Auditorium. Can you imagine this grand venue with only 35 audience members?

What has caused the decrease in lecture attendance, and what are the ramifications? I have pondered this question.

Clearly, the COVID pandemic has "changed everything." The convenience of remote viewing (and remote work) appears to be eclipsing the desire to attend events in person. Yet, the decline in attendance started before the pandemic as science has become increasingly balkanized. Many who are focused on one discipline—be it neurobiology, immunology, or evolutionary biology—are now less inclined to hear a lecture on a topic outside of their expertise. That's a pity. Varmus saw equal value in just getting out of the lab to hear new ideas. Like Varmus, NIH Deputy Director for Intramural Research **Nina Schor** attends most WALS talks, as did **Michael Gottesman** before her.

Statistics do show that total WALS attendance has remained nearly the same as five years ago, but the crowd once in the auditorium is now in front of their computer. We must question this level of engagement, though. It's analogous to watching a movie at a theater or at home. At the theater, you are invested and absorbed; at home, you may be inclined to check email, text a friend, or move about the house and not fully appreciate the movie.

As for the lack of a chance encounter, the ramifications, as noted, are profound. Consider the trainees and what they may be missing if they are largely confined to their labs, among only their peers, and are rarely exposed to the diversity of ideas that define the NIH. Indeed, at the NIH, much like at the famed Bell Labs in Murray Hill, New Jersey, home to ten Nobel Prize winners, you are all but guaranteed to have meaningful chance encounters. What is the value of an NIH trainee experience if not to explore the NIH as a physical entity?

In addition to WALS, the Office of Intramural Research hosts the Demystifying Medicine courses from January to May, another cross-disciplinary lecture series that offers continuing medical education credits (CMEs). The 2024 season was crazy good with **Francis Collins** interacting with a patient with progeria, Tom Insel and **George Koob** discussing the mental health crisis, and **Nora Volkow** sharing the stage with a recovery coach speaking about fentanyl.

The series wraps May 7 in Lipsett with a talk on "Artificial Intelligence in Scientific Publishing" by Holden Thorp, editor of the *Science* family of journals, and Vardit Ravitsky from the Hastings Center. Join us—you will have no problem finding a seat.

Chance favors the prepared mind. I am confident that the NIH is filled with prepared minds. Why not take a chance and join us for a live lecture? ●

For more information about WALS and to view the 2024 calendar, visit https://oir.nih.gov/wals.

NCATS Taps Matthew Hall as New Scientific Director

Translational Scientist Champions Team-based Approach, NIH-wide Partnerships

BY TERRY RUDD, NCATS

CREDIT: NCATS

NCATS Scientific Director Matthew Hall

It's a riddle even renowned Victorian-era physician and crime-fiction creator Sir Arthur Conan Doyle might struggle to solve: What do Sherlock Holmes, rugby, and translational science have in common?

The answer is elementary: They're all passions of the new NCATS scientific director, **Matthew Hall**.

Hall's love of rugby and his status as an avowed "Sherlockian" are a synergistic fit with his professional pursuits as a translational scientist. Just as rugby rewards collaborative hard work by a team of diversely talented individuals, translational science tackles perplexing research challenges by uniting individual creativity with team science, while demonstrating a Sherlockian knack for uncovering innovative solutions.

As NCATS' scientific director, Hall will lead the Division of Preclinical Innovation (DPI). DPI conducts collaborative preclinical research projects for common and rare diseases, and it develops new methods and technologies that speed translational research. Hall succeeds **Anton Simeonov**, who guided DPI to an array of translational science achievements and partnerships.

"Matt brings an exceptional combination of NIH research experience and leadership skills to his new role," said NCATS Director **Joni Rutter**. "His team-first mindset and broad scientific expertise will continue to speed the translational process of turning scientific discoveries into health interventions."

Hall, who began his new role in January, is committed to strengthening the center's role as a world-class translational science hub.

"I am excited to continue our culture of teamwork to bring new therapies to people, particularly in underserved areas like rare diseases," Hall said. "I also look forward to building partnerships with other NIH institutes and centers, including NIH extramural partnerships. There's incredible opportunity to create integrated research environments from multiple ICs on the intramural side. I'd like to find the best way to tackle scientific challenges, and a big part of that is building working relationships across NIH. I think conversations can lead to innovation for patients."

Hall earned his bachelor's degree in chemistry, molecular pharmacology, and toxicology and his doctorate in chemistry from the University of Sydney (New South Wales, Australia). Before joining NCATS, he served as a research fellow and then became a staff scientist at NCI's Laboratory of Cell Biology. While at NCI, Hall led collaborative research programs on the clinically challenging phenomenon of cancer multidrug resistance.

After joining NCATS in 2015 as a biology group leader in what became NCATS' Early Translation Branch (ETB), he later served as ETB director. Hall's recent achievements include two NIH Director's Awards for his work on the Antiviral Program for Pandemics team and the Accelerating COVID-19 Therapeutic Interventions and Vaccines team. He also won an HHS Secretary's Award for Meritorious Service for his work on the OpenData Portal, which offers real-time information about how individual SARS-CoV-2 variants may respond to known therapeutics.

> "Conversations lead to innovation for patients."

Hall's research covers a range of human pathologies and diseases, with a rare disease emphasis, and most of it has been in partnership with a chemistry group led by **Samarjit Patnaik** and a cheminformatics group led by **Min Shen**. Hall has published more than 190 peer-reviewed papers, including one on the collaborative discovery of a small-molecule class [YC-1] that selectively targets intrahepatic cholangiocarcinoma and hepatocellular carcinoma (PMID: 36914816).

"My favorite scientific projects have all been deep collaborations," said Hall. "The YC-1 collaboration with Nabeel Bardeesy [Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston] is a nice example. The compound was found through screening, but screening hits are only curiosities. It took several years of close partnership to discover the mechanism of YC-1, and that understanding is a start point for finding promising molecules with therapeutic potential. We're working on several very rare diseases where we hope to develop molecules that can be useful for treating patients."

Hall's NIH colleagues welcomed the news of his new appointment.

CONTINUED ON PAGE 21

Escaping the Bounds of Biology

Computational and Experimental Techniques Converge to Reshape Research

BY MICHAEL TABASKO, *THE NIH CATALYST*

A SEA CHANGE IS UNDERWAY IN biomedical research. Lifted by a tide of new experimental lab techniques, scientists are merging innovative technologies with synthetic methods like artificial intelligence (AI) and machine learning (ML). It's a synergistic approach that is accelerating our understanding of human health and disease and building completely new biology to tackle difficult diseases.

Other computational tools are gleaning fresh insight from existing medical data to enhance diagnostic and prognostic methods across diverse patient populations. ML is also proving a useful partner in human genomics by finding previously unknown genetic drivers behind disease.

Rewiring cells

Consider an immune cell engineered to kill cancer by recognizing multiple antigens; or cells reprogrammed to deliver drugs to specific sites in the body.

These ideas are the realm of generative biology, according to pioneer Wendell Lim, professor at the University of California at San Francisco (UCSF). On March 13, Lim delivered a Wednesday Afternoon Lecture Series talk titled "Generative Biology: Learning to Program Cellular Machines." With the help of ML techniques that comb through genomic data to model how a reengineered cell might behave, Lim and his team can create purpose-built cells to carry out specific therapeutic tasks to help fight against some cancer, autoimmune, and neurodegenerative conditions.

In contrast to small-molecule drugs, which can result in whole-body side effects, Lim likens his lab's rewired cells to powerful machines that can be designed to execute precise, targeted effects.

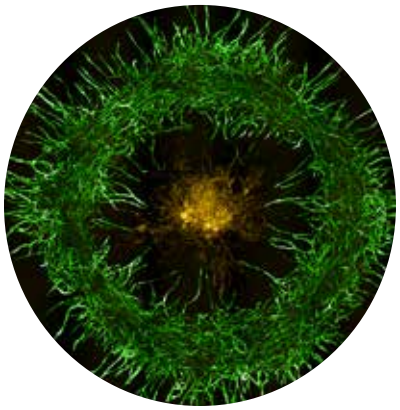
One such technology is synthetic notch (synNotch) chimeric antigen receptor (CAR) T cells. In mice, Lim's team showed how these cells can be programmed to recognize a combination of multiple antigens unique to a particular tumor, and then activate only in that target tissue. For example, they can target glioblastoma in the brain by creating a "controlled blast radius" whereby the tumor cells are killed while healthy tissues elsewhere are largely spared (PMID: 33910979). By tweaking the combination of antigens to target, synNotch can be navigated toward other locations in the body or other diseases by acting as a cellular GPS to deliver a therapeutic payload precisely where it is needed.

Synthetic cell-adhesion molecules are another intriguing technology that uses the existing rules of biology to create something new. They can be customized to orchestrate cells into self-organized assemblies that resemble natural tissue or even completely novel ones (PMID: 36509107).

In one example, Lim's team showed how rewired cells assembled and drove stem cells to differentiate into a heartlike structure that beats, complete with a central cavity and peripheral vasculature. He hints that such choreographed behaviors might someday be harnessed to reconstruct damaged nerves or organs.

Optimizing T cells at NIH

Constructing computational models of the immune response can serve as a roadmap to design better immunotherapies against tumors. The lab of **Grégoire Altan-Bonnet**, senior investigator at NCI's Laboratory of Integrative Cancer Immunology (LICI), created a robotic platform that streamlines



CREDIT: YEN-TING TUNG, NCATS

Shown here is a 3D bioprinted neurovascular unit tissue model surrounding patient-derived glioblastoma (GBM) cells using human brain microvascular endothelial cells (green), pericytes, astrocytes, and patient-derived GBM cells (yellow).

and automates how CAR T cells are tested on samples from both mouse studies and clinical trials. In close collaboration with Paul François's group at the Quebec Artificial Intelligence Institute (known as Mila), the LICI team uses supervised ML to analyze the unfolding immune dynamics in those samples and uses that data to create models of how immunotherapies might work. That new platform discovered six classes of antigens that elicited distinct T cell responses (PMID: 35587980).

Importantly, LICI's immune models are tuned to pick up on signals coming from healthy tissue as well as diseased tissue. That method better reflects the complex immune environment and ideally results in safer therapies when a drug moves to clinical trials. "At this stage, we know it is more critical to actively shut down the response in the healthy tissue while boosting your response in the tumor," said Altan-Bonnet, who tempers the exuberance currently surrounding AI and ML with cautious optimism. "We must do it right. There's a lot to be done in terms of doing the proper ML [that] connects to the proper biology and being able to use it."

Better drug screening platforms

Once a shiny new therapeutic is created, testing it for safety and efficacy begins. That's where wet-lab programs such as

NCATS' intramural 3D Tissue Bioprinting Laboratory led by **Marc Ferrer** can come in. The lab is a cross-disciplinary group that biofabricates in vitro complex cellular models for drug discovery and development.

The hope is that these models are better at predicting how effective or toxic a drug may be in humans compared with simple cell lines. "In the body, different cells talk to each other, and these models mimic how cells behave in human tissues and organs, and therefore drugs should respond more like in the body," said Ferrer.

The bioprinting process begins with mixing a hydrogel of the right viscosity with human cells. For example, a mixture of keratinocytes and fibroblasts are used to make a human skin model. Software is used to design the shape of the tissue, which is then crafted by extrusion of the gel into specific layers of different cell types that will soon resemble real tissue. Nature then takes over and the model matures, secreting other components such as collagen and other support proteins in the case of skin tissue.

Once Ferrer's team validates the healthy model, they can make a diseased one and then test drugs on it. The approach can complement or provide an alternative to animal models and has broad application. For example:

- A bioprinted model of the retina was used to test a clinically approved antibody for age-related macular degeneration (PMID: 36550275).
- A disease model of atopic dermatitis in human skin successfully showed how JAK inhibitors reversed the disease state (PMID: 32059197).
- A 3D bioprinted neurovascular unit model demonstrated how glioblastoma tumors grow in a brainlike environment and can be used to test anticancer drugs (PMID: 38394389).

"Establishing validity and predictability of these tissue models is very important," said Ferrer, who added that these models are used in preclinical studies to allow investigators to look closely at the mechanisms underlying both the disease and how a drug might work for that disease.

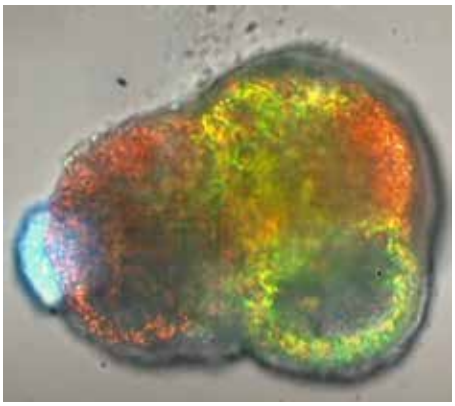
CREDIT: GRÉGOIRE ALTAN-BONNET, NCI

At NCI's Laboratory of Integrative Cancer Immunology, an automated robotic platform tests T cells on samples from mouse studies and clinical trials. Then, supervised machine learning helps model the unfolding immune dynamics to inform the design of new tumor-specific T cells.

AI-powered predictions

Back in the synthetic space, investigators are using AI to decipher big data and unearth clinically significant insights. "We now have computational ways to predict causal mutations for all complex diseases," said **Ivan Ovcharenko**, senior investigator at NLM, whose research spans Alzheimer's disease, ovarian cancer, and glaucoma.

CREDIT: WENDELL LIM, UCSF



Lim and colleagues designed synthetic organizer cells that directed the assembly of a heartlike structure that beats, complete with a cavity and peripheral vasculature. Lim serves as director of UCSF's Center for Synthetic Immunology, an NIH IOTN-i3 Center supported by NCI, NIA, and NIBIB.

"This opens doors for more diagnostics, screenings, and studies to find new drug targets," he said. His group uses deep learning methods (DL) to computationally mutate every single disease-associated nucleotide in a process known as "in silico mutagenesis" and predict which ones are causative. Then, they collaborate with other labs that confirm those digital findings using biochemical techniques.

In one such example, a DL method applied to a genome-wide association study of type 2 diabetes found nearly triple the number of known causative genes in pancreatic islet cells compared with traditional methods (PMID: 37603758).

Ongoing work at Ovcharenko's lab is using AI to identify silencers in the human genome. Silencers are compact clusters of noncoding genetic material that act to shut off gene expression in nearby coding regions. They act like an architect to trim the activity of enhancer regions. Without them, a gene can be expressed somewhere it should not and lead to carcinogenesis or other diseases.

Validating those computational predictions on real biology is the next step. Scientists such as **Laura Elnitski**, senior investigator at NHGRI, and **Ben Afzali**, a Stadtman investigator from NIDDK, then do the wet-lab work using biochemical techniques that analyze how genes express from in vivo and in vitro samples after CRISPR modification.

Work by the Elnitski group showed that silencers do indeed influence gene expression in specific tissues (PMID: 30886051), and ongoing studies are testing how alterations in genome regulation could cause B-cell lymphomas or ovarian tumors. The computational models and lab experiments are aligning. "The validation testing tells us the models are working," she said. "Predictions from integration of data reveal dynamic biological processes."

An upcoming collaborative study from those labs aims to demonstrate that large clusters of silencers are a critical component of cellular development and disease regulation.

"I think this is going to have a huge impact on our understanding of genetic predisposition to diseases," said **Richard Scheuermann**, scientific director at NLM.

Learn more about how NIH is using AI to dig deeper into DNA differences in the latest SciBites episode: https://irp.nih.gov/scibites/using-ai-to-diagnose-rare-diseases.

Colleagues: Recently Tenured

Meet your recently tenured colleagues: **Lauren Atlas** (NCCIH, NIMH, NIDA), **Aaron Cypess** (NIDDK), **Rasika Mathias** (NIAID), **Fasil Tekola-Ayele** (NICHD), **Anish Thomas** (NCI-CCR), and **Achim Werner** (NIDCR)

LAUREN ATLAS, PH.D.

Senior Investigator, Affective Neuroscience and Pain Laboratory, NCCIH, NIMH, NIDA

Education: University of Chicago (B.A. in psychology); Columbia University, New York (Ph.D. in psychology)

Training: Postdoctoral fellow, Department of Psychology, New York University, New York (2011–2014)

Came to NIH: In 2014 as a clinical investigator, NCCIH

Outside interests: Stained glass; scuba diving; bird watching; samba dancing

Website: https://irp.nih.gov/pi/lauren-atlas

Research interests: I am a psychologist and cognitive neuroscientist who is interested in how expectations shape pain, emotional experience, and clinical outcomes (e.g., placebo effects). My lab integrates experimental psychology, neuroimaging, computational approaches, and psychophysiology to understand how psychological and contextual factors influence subjective experience. We pursue three main lines of research.

First, we measure how subjective pain is linked to nociception and whether individual differences modulate these relationships. We have shown that autonomic responses are more related to subjective pain than noxious input (PMID: 31107415) and that pain sensitivity is more stable across visits in women than in men (PMID: 35189353).

Our second line of work addresses the brain mechanisms by which expectations shape pain, and we have identified dissociations between effects of verbal instructions and associative learning (PMID: 36317867; PMID: 27171199).

Finally, we ask how social factors influence pain and expectations, both in terms of patient-provider relationships (PMID: 34126294) and health disparities in pain (PMID: 37293681). Current work includes the role of nonverbal reactions to pain (i.e., facial expressions), whether we can reduce biases in pain assessment, and whether brain mechanisms of pain modulation are unique to pain or shared across areas of affect and emotion.

AARON CYPESS, M.D., PH.D.

Senior Investigator, Chief of Translational Physiology Section, Diabetes, Endocrinology, and Obesity Branch, NIDDK

Education: Princeton University, Princeton, New Jersey (B.A. in chemistry); Rockefeller University, New York (Ph.D. in biochemistry); Cornell University Medical College, New York (M.D.)

Training: Internal medicine intern and resident, Beth Israel Deaconess Medical Center (BIDMC), Boston (2001–2003); endocrinology clinical and research fellow, BIDMC Joslin Diabetes Center (2003–2006); clinical investigation fellow, BIDMC Harvard-MIT Division of Health Sciences and Technology (2006–2008)

Before coming to NIH: Assistant professor of internal medicine, Harvard Medical School (Boston); staff physician, Joslin Diabetes Center and BIDMC

Outside interests: Biking; hiking with my wife and kids; Shabbat meals with family and friends

Website: https://irp.nih.gov/pi/aaron-cypess

Research interests: The goal of my research group is to understand the roles of brown and white adipose tissue (BAT and WAT) in human physiology and identify approaches to turn that knowledge into treatments for obesity-related metabolic diseases (PMID: 35196429).

Until recently, BAT was thought to be nonexistent and metabolically irrelevant in adult humans in part because there were no methods to localize and quantify BAT mass and measure its activity.

Using a combination of molecular techniques and whole-body imaging, we showed that BAT is present in women and men in defined anatomical depots and has an activity that correlates inversely with age and obesity, suggesting several physiological roles for BAT in adult human metabolism (PMID: 19357406). In parallel with these advances, our group is developing a pharmacological approach to treat obesity-related metabolic disease through the activation of the beta-3 adrenergic receptor (AR). The beta-3 AR has a distinct tissue

expression in humans, with particularly high amounts in the BAT, the WAT, and the hepatobiliary system.

Over the past decade, we pioneered the use of the beta-3 AR agonist mirabegron (Myrbetriq) in the setting of metabolic research (PMID: 25565203). We recently showed in a clinical trial that chronic mirabegron treatment increased BAT metabolic activity and resting energy expenditure, and it led to higher plasma concentrations of several typically beneficial metabolites, including high-density lipoprotein, total bile acids, and the adipokine adiponectin. Moreover, mirabegron increased insulin sensitivity, glucose effectiveness, and insulin secretion (PMID: 31961826). These discoveries have opened up several new areas of research as we determine the mechanisms underlying mirabegron's effects and the physiological roles of human BAT as both a thermogenic and an endocrine organ.

Going forward, the translational research projects in the group will focus on human BAT and WAT structure and function at the molecular, genetic, and anatomical levels; beta-3 AR physiology and therapeutics; and metabolic imaging.

RASIKA MATHIAS, SC.D.

Senior Investigator, Chief of Genomics and Precision Health Section, NIAID

Education: Stella Maris College, Chennai, India (B.Sc. in zoology); Johns Hopkins Bloomberg School of Public Health, Baltimore (Sc.D. in genetic epidemiology)

Training: Postdoctoral fellow, Inherited Disease Research Branch, NHGRI

Before coming to NIH: Professor of medicine, Johns Hopkins School of Medicine, Baltimore

Came to NIH: In 2024 as a senior investigator, NIAID

Outside interests: All things food; travel; photography

Research interests: I recently joined the Laboratory of Allergic Diseases where I have established the Genomics and Precision Health Section (GPHS). The section will work on bringing together genomics, transcriptomics, and epigenetics to understand disease risk, severity, and trajectory, with an emphasis on health disparities and clinical translation in precision health.

My primary interest is to look across the allergic diathesis of atopic dermatitis, asthma, and food allergy, because we have shown that there is a high degree of overlap in the genetic underpinnings of these related allergic diseases (PMID: 32777389). We will integrate genetics seamlessly with additional -omics, and do so by leveraging expansive preexisting resources in conjunction with new initiatives to deliver on the promise of genetic risk prediction and the ultimate translation of genetics into clinical practice for allergy. My lab has demonstrated the importance of allergen exposure and context-dependent genetic determinants of allergy (PMID: 34981778), and we will continue to focus on these factors for allergy risk and response to interventions like immunotherapy.

My research also places special emphasis on the inclusion of individuals representing the African Diaspora in research programs because often they bear a major burden from health disparities in these disease areas that is further compounded by the existing inequalities stemming from their lack of inclusion in biomedical research. One of the major programs that I have led for over a decade is the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA). In CAAPA, we have forged close collaborations with scientific teams in Nigeria, Brazil, Barbados, and Honduras, which I will continue to build upon at GPHS. CAAPA is the single largest multi-omics study on asthma in African ancestry populations and has made numerous inroads into dissecting the molecular underpinnings of the allergic diathesis in this group that bears significant prevalence and morbidity (PMID: 27725671).

FASIL TEKOLA-AYELE, PH.D.

Senior Investigator, Epidemiology Branch, Division of Population Health Research, NICHD

Education: Debub University, Ethiopia (B.S. in public health); Addis Ababa University, Addis Ababa, Ethiopia (M.P.H.); Brighton and Sussex Medical School, Universities of Brighton and Sussex, Brighton, England (Ph.D. in genetic epidemiology)

Training: Postdoctoral fellow, NHGRI (2010–2014); research fellow, NHGRI (2014–2016)

Before coming to NIH: Doctoral student at Brighton and Sussex Medical School

Came to NIH: In 2008 as predoctoral fellow; returned in 2010 as postdoctoral fellow, NHGRI

Outside interests: Jogging; gardening; spending time with family and friends

Website: https://irp.nih.gov/pi/fasil-tekola-ayele

Research interests: The early life period is critical for long-term health. Fetal growth abnormalities and cardiometabolic diseases are interconnected and cause a high burden of morbidity.

CONTINUED ON PAGE 20

Understanding the complex genetic and environmental factors that underlie these relationships is crucial to developing preventive and therapeutic interventions for maximizing health across the life span. The placenta is critical for fetal development and potentially underlies later-onset diseases, but it is understudied. Moreover, to date, perinatal genomic studies have failed to capture human ancestral diversity, which impedes biological understanding of diseases and could fuel disparities in genomic-informed health care in the future. In the genetic epidemiology research group, we study genetic mechanisms of fetal growth variations at the maternal-placental-fetal interface and their links with cardiometabolic outcomes in diverse human populations. Our studies so far demonstrated that genetic and epigenetic processes that regulate fetal development and placental response to maternal metabolic and psychosocial factors may offer mechanistic insights to early origins of cardiometabolic diseases in later life.

Highlights of our contributions include the following.

1) Identifying multiancestral as well as African- and Amerindigenous- ancestry-related genetic loci associated with fetal growth (PMID: 32407400; PMID: 33590300).

2) Identifying high-priority genes in placenta that affect fetal growth via epigenetically and transcriptionally altered mechanisms, filling a major gap in functional understanding of birthweight genome-wide association study loci (PMID: 35501330).

3) Developing a genome-wide atlas of placenta-specific variably methylated regions, elucidating their regulatory functions, and demonstrating the importance of gene-environment integration in advancing phenotypic relevance of placenta research (PMID: 34155504).

4) Offering evidence on placental aging "clock" epigenome, and transcriptome as a potential link between maternal cardiometabolic status, fetal growth, and offspring risk of cardiometabolic diseases (PMID: 32078381; PMID: 33926514).

In our future research, we hope to identify potential molecular intervention targets for promoting long-term health and reducing health disparities.

ANISH THOMAS, M.D.

Senior Investigator, Developmental Therapeutics Branch, NCI-CCR

Education: St. John's Medical College, Bangalore, India (MBBS and M.D.)

Training: Research assistant, State University of New York (SUNY) Upstate Medical University, Syracuse, New York (2006–2010); internal medicine resident, SUNY Upstate Medical University (2007–2010); medical oncology and hematology fellowship, NCI and NHLBI (2010-2013)

Came to NIH: June 2010 as a postdoctoral fellow, NCI and NHLBI

Outside interests: Spending time with family

Website: https://ccr.cancer.gov/staff-directory/anish-thomas

Research interests: I am a medical oncologist and physician-scientist specializing in the care of patients with lung cancer, specifically small-cell lung cancer (SCLC), the most fatal form of lung cancer. Over the past decade, I have dedicated my efforts to establishing a cutting-edge translational research program at the NIH aimed at advancing our understanding and treatment of SCLC. The overarching goal of my group is to develop innovative strategies that improve the quality of life and outcomes of patients with this aggressive form of lung cancer.

Our approach integrates personalized patient care, clinical trials, in-depth tumor molecular profiling, and laboratory-based research to discover and evaluate new treatment approaches for SCLC. Using a bed-to-benchside approach (PMID: 35561672), we learn from individual patients. For example, we investigate the reasons behind the considerable variability in tumor responses among patients, aiming to predict outcomes at the individual level, and investigate the determinants leading to the preference of specific metastatic sites in certain patients.

Overall, our findings have contributed to the understanding that SCLC is not just one disease but comprises many subtypes, each with its own characteristics and risk factors. We have also identified vulnerabilities that are unique to these subtypes. Key insights from our work include:

1) Replication stress is a transformative vulnerability of SCLCs characterized by high neuroendocrine differentiation (PMID: 33848478).

2) Notch signaling is a driver of intrinsic immunity, which renders low neuroendocrine SCLC more sensitive to immunotherapy (PMID: 34162872).

3) Ataxia telangiectasia and Rad3 related (ATR), a key mediator of replication stress, is a tractable SCLC target. Targeting ATR improves overall survival of relapsed SCLC patients over standard therapies (PMID: 29252124; PMID: 37824137; PMID: 37227187).

4) Germline genotype defines a novel SCLC subset characterized by improved responses to DNA repair targeted drugs (PMID: 33504652).

5) Extrachromosomal DNA amplification contributes to MYC-driven SCLC heterogeneity and is associated with worse outcomes (PMID: 36715552).

6) SCLC subtypes can be profiled noninvasively using histone modifications in plasma circulating free DNA, providing a comprehensive view of the tumor gene expression patterns, as well as cell and tissue of origin (https://doi.org/10.1101/2022.06.24.497386).

We plan to continue to advance novel therapies for the benefit of SCLC patients and nurture the next generation of scientists and clinicians.

ACHIM WERNER, PH.D.

Senior Investigator, Stem Cell Biochemistry Section, NIDCR

Education: University of Lübeck, Germany (B.S. in molecular biotechnology); University of Göttingen, International Max Planck Research School for Molecular Biology, Germany (Ph.D. in molecular biology)

Training: California Institute of Regenerative Medicine postdoctoral fellow, Department of Molecular and Cell Biology, University of California at Berkeley (2012–2017)

Before coming to NIH: K99 postdoctoral fellow, University of California at Berkeley

Came to NIH: In 2017 as a Stadtman tenure track investigator, NIDCR

Outside interest: Volleyball; tennis; running; watching TV shows. *The Big Bang Theory* is my all-time favorite.

Website: https://irp.nih.gov/pi/achim-werner

Research interests: My lab studies the molecular principles of how cell-fate decisions are determined during development.

We focus our studies on ubiquitylation, an essential posttranslational modification that is required for cell division, differentiation, and migration in all metazoans. We leverage the unique environment of the NIH intramural program and combine our core expertise in human pluripotent stem cell culture, proteomics, and ubiquitin biochemistry with animal models, clinical genetics, and human disease cohorts.

This integration has allowed us to establish a collaborative research program that has identified previously unrecognized diseases manifesting with brain and craniofacial defects (PMID: 33523931) or autoinflammation (PMID: 33108101) and has uncovered molecular principles of how ubiquitylation regulates diverse aspects of neuroectodermal development (PMID: 37495603) and hematopoietic differentiation (PMID: 35793467; PMID: 38360993).

We believe that our studies will continue to determine pathogenic variants in undiagnosed disease patients and will facilitate the development of novel therapies for diseases of dysregulated ubiquitylation. ●

NCATS Taps Matthew Hall as SD

CONTINUED FROM PAGE 15

"I could not be more pleased about this outstanding appointment," said **Michael Gottesman**, chief of NCI's Laboratory of Cell Biology and Hall's first NIH PI. "To say he was always a creative, independent, and extraordinarily effective scientist from the very beginning would be an understatement. He was a magnet for outstanding trainees, and he has continued at NCATS to recruit excellent scientists, to pursue important projects, and to catalyze networks of scientists working in teams to enhance public health."

Amy Newman, NIDA's scientific director and a long-time collaborator with Hall, said she welcomes him among the director-level ranks.

"Matt is keenly attuned to the translational potential of science in the intramural program and has already created strong ties with a broad array of institutes," she said, adding, "NCATS provides the link between basic research and medication development across diseases, and Matt is clearly ready to take the lead."

What does Hall do in his extramural hours when he's not in the stands at Old Glory DC's pro rugby games or home reading Victorian detective works?

"This is all very awkward—I'm a member of multiple Sherlock Holmes groups," he admits. He also applies his research talents to Hall family genealogy and the written histories of Australia's early European convicts and settlers. ●

Terry Rudd is a technical writer-editor at NCATS.

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The Closer

NCI's Technical Laboratory Manager Anna Trivett on Closing Labs and Rolling with the Changes

BY ANNELIESE NORRIS, NCI

CREDIT: ANNELIESE NORRIS, NCI

Anna Trivett in her NCI Frederick office. The plaque that commemorates the group 2021 NCI Award she earned is displayed on her top shelf.

Anna Trivett, an NCI technical laboratory manager (TLM), has seen a lot of changes.

Currently, Trivett works in the Cancer Innovation Laboratory (CIL) with Daniel McVicar, principal investigator and NCI-CCR deputy director. And she was among the CCR's TLM recipients of a group 2021 NCI Award for their "instrumental role in identifying, communicating, and solving emerging challenges related to NIH efforts to safely reopen intramural research facilities during the COVID-19 pandemic," according to the citation.

Yet perhaps ironically, Trivett is better known for something opposite of that—closing labs due to retirements, reassignments, or reorganizations.

Trivett is a longtime Frederick native and a graduate of the University of Maryland at College Park and Hood College (Frederick, Maryland). She has worked at the Frederick NCI campus more than 20 years, having first arrived as a summer college student trainee in the Mouse Cancer Genetic Program (MCGP). "It was a wonderful experience, and I really loved the people there," Trivett reminisced.

After graduation, Trivett worked at the company MedImmune in the vaccine production plant. That is, until one fateful phone call came informing her that a technician was needed at the MCGP.

She happily returned to NCI, but the thrill was short-lived. Soon after her return, Neal Copeland and Nancy Jenkins, the PIs with whom she was to work, moved to Singapore.

Trivett became a displaced federal employee, a time in her career she recounts as "exciting and a little terrifying."

From "jumping genes" to cellular immunology

Trivett ended up in David Symer's program, which focused on "jumping genes," or transposons, in mammals. She quickly became fluent in sequencing repetitive elements, and her contribution to the Symer laboratory led Trivett to coauthoring papers on retrotransposition. After two years in Symer's lab, she once again became a displaced federal employee when Symer moved to Ohio.

Joost "Joe" Oppenheim, a senior investigator and head of the Cellular Immunology Section, was conducting interviews for a new technician. Trivett was one of the youngest to be interviewed and landed the job, which lasted over 10 years. "It worked out wonderfully and was a great position," she said. When Trivett transitioned to CIL as a TLM, Oppenheim was the first to congratulate her, and they remained working together until his passing in 2022.

Rolling with change

While Trivett no longer works in the laboratory, she characterizes the role of a TLM as quite dynamic. Recently, she has become the key contact for closing labs, tapping into her experience of being twice displaced.

Her new mantra is highlighting the need to "clearly label" anything that is not to be thrown away. "That's my nightmare: That I am going to discard something that is really important," explained Trivett.

After cleaning out several laboratories, Trivett suggests the following:

1) You should never reach into a drawer without looking. "There is always something sharp, and usually at the bottom," she warned.

2) Do not tape down bench coats and layer them, as she is the person who must peel layer upon layer off!

Occasionally Trivett finds mystery objects. In a recent lab close-out, she found a device that sharpens the tool used to cut a hole in stoppers. "No one knew what it was," said Trivett.

And when Howard Young retired, he made sure that Trivett saved part of the original window frame from Building 560. All these objects Trivett fondly keeps labeled in her office as "Building History."

When she's not working, you might find Trivett in her garden. She serves on NCI Frederick's Green Team, she is involved in a plant swap at the Fort Detrick Spring Research Festival, and she serves on the Birdhouse Committee, which recently built and hung birdhouses around the NCI Frederick campus.

Some of Trivett's roles as CIL TLM include coordinating the service maintenance agreements for all laboratories, being a key contact for the Animal Care and Use Committee, and serving as a radiation room safety officer. She is a server owner, the key contact for property, and a safety expert and is coordinator for moving laboratories, ordering supplies, managing staff, budgeting, and providing general support to principal investigators. Trivett does it all—all in a day's work! ●

NIHers Race to Raise Awareness for National Minority Health Month

BY SEPPIDEH SAMI, NIMHD, CC

The NIH community came together on April 11 on the front lawn of Building 1 on the Bethesda campus to participate in the NIH Minority Health Walk/Run/Roll 5K event. The annual event, sponsored by NIMHD and ORS, was held in observance of National Minority Health Month (NMHM) to raise awareness about the importance of improving the health of racial and ethnic minority communities and reducing health disparities.

The event was made possible through the unrelenting support and the coming together of various members of the NIH community including the race participants, water station sponsors, exhibitors, volunteers, NIH Events Management, NIH police, NIH emergency medical technicians, and the 5K planning committee. What better way to embody the 2024 NMHM theme: Be the Source for Better Health: Improving Health Outcomes Through Our Cultures, Communities, and Connections.

CREDIT: CHIA-CHI CHARLIE CHANG

Captain Tarsha Cavanaugh, principal deputy director of the HHS Office of Minority Health, and Eliseo J. Pérez-Stable, NIMHD director (not shown), greeted participants and delivered inspiring remarks.

CREDIT: CHIA-CHI CHARLIE CHANG

Over 500 people registered for the NIH Minority Health Walk/Run/Roll 5K event, sponsored by NIMHD and ORS.

CREDIT: WILLIAM CEFALU

Colleagues at NIDDK joined the festivities by conducting a walk event at their location on Democracy Boulevard.

CREDIT: CHIA-CHI CHARLIE CHANG

5K volunteers pose for a photo. On the far left is Seppideh Sami, 5K coordinator on detail from the Clinical Center to NIMHD and volunteer writer for the *NIH Catalyst*.

NIH ABBREVIATIONS

CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
FAES: Foundation for Advanced Education in the Sciences
FelCom: Fellows Committee
FDA: Food and Drug Administration
FNIH: Foundation for the NIH
FNL: Frederick National Laboratory
IRP: Intramural Research Program
HHS: U.S. Department of Health and Human Services
NCATS: National Center for Advancing Translational Sciences
NCBI: National Center for Biotechnology Information
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
OD: Office of the Director
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health

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PHOTOGRAPHIC MOMENT

CREDIT: AIXIA ZHANG

On April 8, NIHers across the Bethesda campus emerged from their labs, switching from goggles to NASA-approved protective eyewear, to enjoy the afternoon solar eclipse. Pictured here are postbaccalaureate trainees (left to right) **Miranda Alaniz** and **Amanda Brewer,** members of **Gisela Storz**'s NICHD Section on Environmental Gene Regulation lab; and **Julia Silberman** and **Ryan Fishman,** members of **Philip Adams**' NICHD Group on Gene Regulation in Bacterial Pathogens. The next solar eclipse visible in the United States will occur in 2044. ●

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Address correspondence to:
Building 1, Room 160, NIH
1 Center Drive
Bethesda, MD 20892

phone: 301-201-1106
email: catalyst@nih.gov

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