

'THE LEAST OF US'

Quinones Sequel Examines Changing Addiction Crisis

BY DANA TALESNIK

For more than 20 years, a societal epidemic was lurking and burgeoning. It has wreaked havoc on communities across the country, tearing apart families, impoverishing people and killing by the tens of thousands each year.

This national crisis was born out of the misuse and addiction of opioids—prescription pain relievers, heroin and synthetic opioids such as fentanyl. From April 2020–2021 in the U.S., more than 75,000 people died from opioid overdoses, a nearly 30 percent increase from the previous year.

As the crisis was unfolding, author Sam Quinones was living in Mexico and has since interviewed many affected on both sides of the border, from people who are addicted to families who lost loved ones, from imprisoned drug traffickers to prosecutors.

A former *Los Angeles Times* reporter, Quinones chronicles the rise of black-tar



Author Sam Quinones

heroin from Mexico in his 2015 book *Dreamland*. His new book, *The Least of Us: True Tales of America and Hope in the Time of Fentanyl and Meth*, delves into the

emergence of synthetic drugs in the massive quantities seen today, a topic he discussed during a recent virtual NIDA Director's Special Lecture.

Roots of a Crisis

It began with the lure of a quick fix for pain and the mistaken belief that prescription opioid painkillers such as oxycodone were non-addictive. Meanwhile, an illegal opioid that yields similar effects was infiltrating the U.S. Heroin, arriving from Latin America, was a game-changer.

"That heroin got here every year cheaper and every year more potent," said Quinones. "And that is a big reason why we saw the opioid epidemic go from pain pill addiction to heroin addiction."

As their tolerance to pain pills grew, people found a convenient substitute in heroin. "It awakened the sleeping giant of

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NIDCR director shares leadership insights, p. 3.

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VACCINATING AGAINST ADDICTION Janda Discusses Treatments for Substance Abuse Disorders, Drug Overdose

BY AMBER SNYDER

Can we train the immune system to treat harmful drugs like foreign invaders? Are drug vaccines viable solutions for opioid and nicotine addictions?

Dr. Kim Janda of the Scripps Institute is working on just that. In his recent lecture, "A Vision Engaging Pharmacokinetic Strategies to Treat Substance Abuse Disorders and Overdose," Janda discussed



Dr. Kim Janda

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Seminar Examines Structural Determinants of Health Disparities

BY ANDREW ERON AND SHELLY POLLARD



Dr. Karen Winkfield

People who live in rural communities comprise nearly one-fifth of the U.S. population. No single profile encapsulates rurality and health outcomes vary significantly between regions. While all rural residents experience higher rates of all-cause mortality, certain issues are more prevalent within specific racial and ethnic rural populations.

During a recent Rural Health Seminar, speakers highlighted the structural-level

SEE RURAL, PAGE 8

UNITE Launches Staff Resources

The UNITE Initiative launched two resources for NIH staff.

The Ending Structural Racism (ESR) employee intranet page features a suite of staff resources on advancing diversity, equity, inclusion and accessibility (DEIA) at NIH and within biomedical research. Visit <https://employees.nih.gov/pages/ending-structural-racism/>.

The ESR Data Dashboard provides cross-tabulations of NIH workforce data by sex, race/ethnicity and career stage. Visit <https://www.nih.gov/ending-structural-racism/data-dashboard>.

For more information about UNITE's progress, visit <https://www.nih.gov/ending-structural-racism/unite-milestones-progress>.

Rare Disease Day Set for Feb. 28

Rare Disease Day at NIH will be held virtually on Monday, Feb. 28 from 10 a.m. to 6 p.m. ET.

This year's event will feature panel discussions, rare diseases stories, virtual exhibitors and scientific posters. It seeks to bring together a broad audience including patients, patient advocates, caregivers, health care providers, researchers, trainees, students, industry representatives and government staff. It is free and open to the public.

Rare Disease Day takes place worldwide, typically on or near the last day of February each year, to raise awareness among policymakers and the public about rare diseases and their impact on patients' lives. NCATS and the Clinical Center sponsor Rare Disease Day at NIH as part of this global observance.

Each year, the slogan for NIH's event has been "Patients & Researchers—Partners for Life." This slogan aligns with NCATS's philosophy that researchers must work closely with patients, families, caregivers and advocacy groups to maximize the chances for success in advancing rare diseases research.

Since rare diseases often are difficult to diagnose, it can take years to obtain an accurate diagnosis. Even after a proper diagnosis, treatment often is unavailable, because fewer than 5 percent of rare diseases have a treatment approved by the FDA.

Rare Disease Day at NIH aims to raise awareness about rare diseases, the people they affect, and NIH collaborations that address scientific challenges and advance research for new treatments.

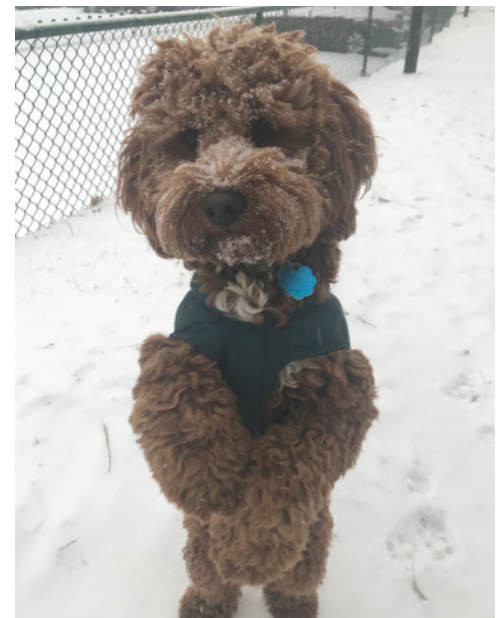
Learn more about the event, view the agenda and register at <https://ncats.nih.gov/news/events/rdd>.



New Access Road Paved

It may look vaguely like the yellow brick road from the *Wizard of Oz*, but it's the new access road for Bldg. 60, the Mary Lasker Center (a.k.a. the Cloister).

Once the gate on Old Georgetown Road and Center Drive closes for construction of the new Clinical Center wing, the only access to Bldgs. 60 and 61 will be to take a hard left at the main campus's Old Georgetown Road and South Drive entrance. The new access road runs between the perimeter fence and the red brick wall that surrounds Cloister grounds.—**Michele Lyons**



Self-care enthusiast Colter Bock, intern to *NIH Record* assistant editor Eric Bock, takes a break to frolic in a recent snowfall.

Wanted: Self-Care Strategies

Readers, the *Record* is tapping into the department of self-care. Share your best self-care strategy—whether it's a yoga break, a nature walk or attempting a new recipe. If it's helped see you through a tough time, or if it's part of your regular routine, we want to know about it. Send us a few sentences to share widely with others.

Prefer to show us? Submit an original drawing, painting, photo or graphic. Send us a selfie to go with, too. We'll publish the best we get over the next few issues. Email nihrecord@nih.gov.



‘SHARED VISION’

D’Souza Reflects on Career, First Year as NIDCR Director

On Oct. 13, 2020, Dr. Rena D’Souza was sworn in as the new director of the National Institute of Dental and Craniofacial Research by NIH director Dr. Francis Collins.

D’Souza reflected on her career journey, mentorship, leadership, inaugural year as NIDCR director and advice for the Asian-American, Native-Hawaiian and Pacific Islander community in an interview published by NIH’s chapter of the Federal Asian Pacific American Council.

A licensed dentist and scientist, D’Souza—a former NIH grantee who has served on the advisory committee to the NIH director—is recognized for her

research in craniofacial development, genetics, tooth development and regenerative dental medicine. She is deeply committed to NIDCR’s mission to advance fundamental knowledge about dental, oral and craniofacial health and disease and translate these findings into prevention, early detection and treatment strategies that improve overall health for all individuals and communities across the lifespan.

D’Souza became NIDCR director during the Covid-19 pandemic. The crisis underscored the fact that the groups most adversely affected by the pandemic were the same ones who struggle to access oral health care. This reinforced the urgency of addressing health disparities to improve oral health for all.

In the interview, D’Souza highlights the importance of being proactive in one’s career

Celebrate ‘Wear Red Day’


Friday, Feb. 4, is National Wear Red Day. Join Americans nationwide in wearing red to show support for women’s heart disease awareness. This year, Dr. David Goff, director of NHLBI’s Division of Cardiovascular Sciences, will join NIH fitness instructor Shannon Oussoren for a live online stretching and yoga session. They will open with remarks on the importance of self-care in protecting heart health and go through a series of exercises to help viewers stretch and relax.

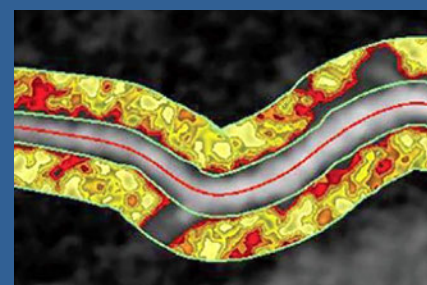


For more information about Wear Red Day and American Heart Month resources and live events, visit www.nhlbi.nih.gov/HeartMonth or follow The Heart Truth on Facebook at <https://www.facebook.com/hearttruth>.

and setting goals in 5-year increments. Her leadership style is to be consultative, open, transparent and to value the uniqueness of individuals. As a leader, she recognizes the importance of uniting people towards a shared vision.

Family is the center of D’Souza’s life. She loves the outdoors, walks, yoga, Pilates and music. She loves people and entertaining, having met many new friends since moving from Utah.

For the full interview, visit <https://www.fapac.org/resources/Documents/Newsletters/FAPAC%20Headlines%202021%20Winter%20Edition.pdf>. —Starsky Cheng, Phalla Messina and Catherine Evans 



ON THE COVER: *Computerized tomography image of a diseased blood vessel from a person with psoriasis after treatment with a promising biologic therapy for the condition. Psoriasis can lead to inflamed vessels and heart disease. February is American Heart Month.*

IMAGE: NEHAL MEHTA, NHLBI

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Opioids

CONTINUED FROM PAGE 1

the Mexican drug trafficking world to the new market that we had created with our pill-prescribing policies.”

Moving Production Inside

Mexican traffickers began shifting from plant-based drugs such as cocaine and marijuana to synthetic drugs such as methamphetamine and fentanyl in the 2000s. These traffickers, descended from farmers and ranchers, had a deep connection to the land but found a new way to do business.

“Meth teaches them that if you can make your own drugs, you don’t need land,” said Quinones. “You don’t care about the seasons

★ ★ ★

“It’s a dangerous situation where we have more of these extraordinarily damaging, deadly, dangerous drugs than we’ve ever seen before.”

-SAM QUINONES

★ ★ ★

or irrigation. You don’t have to employ farmers. You can [do this] indoors.”

And with access to shipping ports, they could import the chemicals and make these drugs year-round.

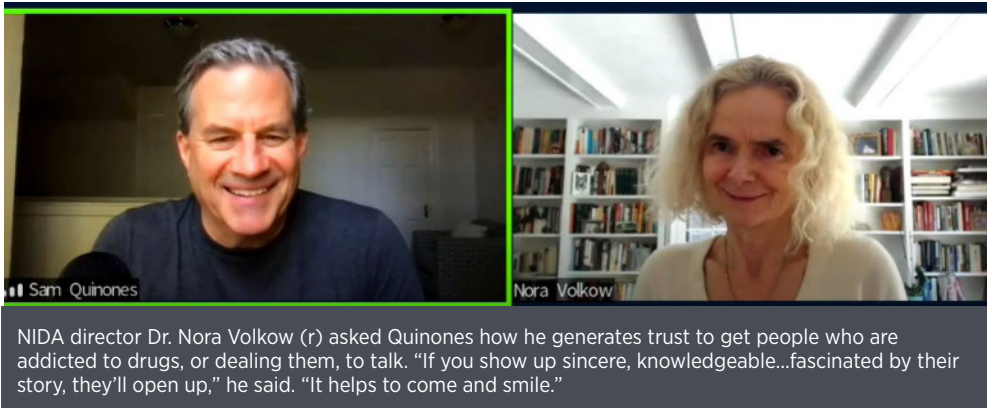
Cooking Fentanyl: From Powder to Pill

In the early 2000s, as the Mexican government began cracking down on ephedrine, a meth cook in Toluca switched to fentanyl.



Illicit synthetic drugs such as fentanyl and methamphetamine have marched across the country with alarming speed.

PHOTO: SHUTTERSTOCK/TIM GRAY



At first, the infamous Sinaloa cartel was unhappy; they had never heard of it.

“They soon realized he’s created this enormously potent profit center they didn’t even know existed,” Quinones said.

When that fentanyl reached the U.S. in 2005, thousands died before the ring got busted, setting off the first mass

fentanyl-related overdose deaths.

By 2014, the fentanyl industry took off. Mexican traffickers began buying and exporting fentanyl, at first in powder form. Early on, U.S. narcotics agents—alarmed by many clusters of overdose deaths—got tipped off by an unusual spike in sales of a common kitchen product: mini blenders. People were trying to mix fentanyl in Magic Bullet blenders, creating a lethal mix.

By 2017, traffickers got sophisticated and began making fentanyl pills, “what we’re seeing now by the millions,” noted Quinones. “Part of the attraction was, by then we were cutting back on doctors prescribing pain pills, and people were still addicted to them.” This synthetic narcotic was filling the ongoing demand.

“Traffickers never really had access to that deep love affair that Americans have with pills,” he said. “Fentanyl offered them that access.”

In 2017, U.S. drug enforcement officials confiscated thousands of fentanyl pills. In 2021, officials had seized more than 9 million pills. “Just staggering,” said Quinones, “and that means probably 10 times more than that were getting through.”

The March of a New Meth

At the same time, the methamphetamine business was changing. Undeterred by crackdowns on ephedrine, a cartel leader started tinkering with a new way to make the psychostimulant, called the P2P method.

Ephedrine meth was cheaper and easier to cook, noted Quinones. But P2P meth could be made in many ways with many different chemicals that are abundant and legal, but also toxic.

P2P meth causes severe symptoms. Hallucinations. Schizophrenia. Paranoia.

“Mentally, the P2P meth is destroying the brain, creating mental illness very quickly,” Quinones said. “It’s a drug where you live in your brain. You isolate.”

There’s so much supply, the price collapses. “The supplies of meth begin to explode, the same as with fentanyl,” he said. “You begin to see it marching across the country. It’s a dangerous situation where we have more of these extraordinarily damaging, deadly, dangerous drugs than we’ve ever seen before.”

‘Anybody Can Be a Kingpin’

The rise of synthetic drugs has stretched the illegal drug trade beyond cartels. “Now, anybody can be a kingpin,” Quinones said.

He tells of a 19-year-old who bought a pill press and a quarter-kilo of fentanyl online. The teen made hundreds of thousands of pills a week, raking in \$25,000 a day for a year before he was busted.

“You don’t have to be very smart or savvy

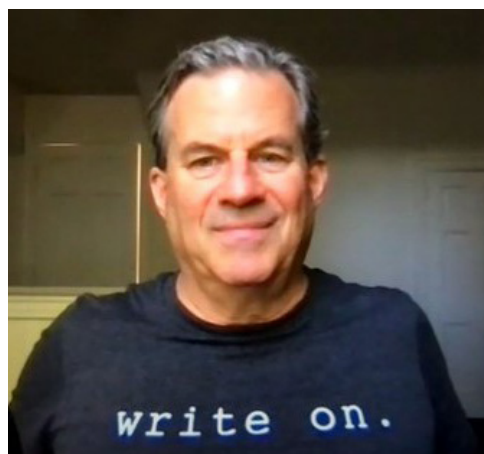
to [enter the business] and make a lot of money,” Quinones said. All it takes is a laptop and an internet connection.

Who are ‘the least of us?’

Everyone. “We all have this capacity for addiction. We all can be that addict eating from the trash,” said Quinones. “The least of us lies within us all.”

The deeper he dove into his research, Quinones kept circling back to a misguided cultural ideal driving the crisis.

“One of the reasons we got into the pill problem,” he said, “is we wanted one answer for every single human being for our very complex issues of pain.”



Quinones has written two books on the rise of synthetic opioids, *Dreamland* and *The Least of Us*.

This ideal was set against the backdrop of growing isolation and the withering of community. In Ohio, a swimming pool called Dreamland—the title of his previous book—once held a community together. In Indiana, tool and die shops once dotted Muncie, places important to the town and its energy, where workers proudly toiled daily. But communities have been disintegrating and sites of vibrant public gatherings, like Dreamland, are disappearing.

Quinones tells stories of community repair, of ordinary people reaching out and coming together to make a difference in small ways. Little by little.

“I think the opioid epidemic, and the [Covid] pandemic certainly as well, have taught us that we’re only as strong as the most vulnerable,” he said. “We’re only as strong as the least of us.” **R**

STUDIED THE NEXUS OF ORAL HEALTH, INFECTIOUS DISEASE

Webster-Cyriaque Named NIDCR Deputy Director

Dr. Jennifer Webster-Cyriaque joined NIDCR as its new deputy director on Dec. 6. Previously, she served as a faculty member for 21 years at the University of North Carolina schools of dentistry and medicine, where she practiced dentistry and studied the role of viruses like HIV and herpes simplex virus in oral lesions and cancers.



Dr. Jennifer Webster-Cyriaque

“As a beneficiary of the NIDCR training pipeline, I have always been drawn to NIDCR’s mission, and to the tremendous impact I know the institute can have by translating scientific discoveries and reducing oral health disparities,” said Webster-Cyriaque. “As someone who has studied the nexus of oral health and infectious disease, NIDCR’s focus on understanding the oral health implications of Covid-19 leave me eager to play a role in the developing science around emerging infectious diseases.”

Webster-Cyriaque served as a tenured full professor at the UNC schools of dentistry and medicine, where she also served as the attending on clinical service at UNC Hospital’s dental clinic. While there, she led research into a potential etiologic agent for salivary gland disease in patients living with HIV, assessed the oral microbiome and its implications for cancer-causing viruses and studied the impact of the oral microbiome and oral health on HIV outcomes.

“As a dentist-scientist, educator and passionate mentor, Dr. Webster-Cyriaque brings a wealth of expertise to our institute,” said NIDCR director Dr. Rena D’Souza. “She is a natural leader whose talent and insights are matched by her impressive understanding of the science and of the people and processes that make it possible.”

In addition to her research pursuits, Webster-Cyriaque has held leadership roles as the chair/vice chair of the Oral HIV/AIDS Research Alliance, research director at the National Dental Association Foundation, director of postdoctoral CTSA training, along with multiple positions within the American Association for Dental, Oral and Craniofacial Research and the International Association for Dental Research.

Since 2004, she has led the UNC Malawi project and provided assistance in founding Malawi’s first dental school in 2019.

Webster-Cyriaque earned her Ph.D. in microbiology/immunology from the University of North Carolina-Chapel Hill in 1998, her D.D.S. from SUNY Buffalo in 1992 and her B.A. in biology and interdisciplinary social science from SUNY Buffalo in 1988.

his work on developing heroin, fentanyl and nicotine vaccines/biologics. His research uses a pharmacokinetic (PK), treatment strategy that targets the drug molecule itself, which aims to reduce drug concentrations at the site of action thereby reducing the drug's pharmacodynamic effects.

There are FDA-approved therapeutics for opioid use disorder, Janda shared, but frequently they leave room for improvement. Psychotherapy and cognitive behavior therapy are often insufficient on their own. Substitution therapy, such as methadone and buprenorphine (in which the illicit drugs are replaced with medically prescribed opiates), is expensive and can perpetuate dependence. And antagonist drugs such as naltrexone can have unpleasant side effects.

Vaccines may be preferable to these already existing treatments for numerous reasons: They reduce overdose risk, are inexpensive and suitable for use in low- and middle-income countries (LMICs), and do not require daily compliance.

Drugs such as opioids are not naturally antigenic, meaning they do not create an immune response like a cold or flu virus (or

flu vaccine) would do. Janda had to build a molecule that would stimulate an immune response against the target drug.

When creating a drug vaccine, he said, "it's not just the amount of antibody you create, but also the quality" of those antibodies. Drugs, and opioids in particular, have high affinity for the receptors that they bind to in the body, so the antibodies that are created need to have even higher affinity to sequester the drug from its targeted receptor(s).

Janda discussed his heroin vaccine first. Heroin is a semi-synthetic opioid derived from morphine. Janda formulated vaccines that resembled heroin and morphine and tested them in the lab. His intention was to "preserve the drug-like structure as much as possible" while still allowing for the additives needed to formulate the vaccine. It was administered in animal trials and showed promise in mitigating both addiction and the physical effects of opioid use.

In one study that measured heroin self-administration in rats, formerly addicted animals that were vaccinated either ceased use altogether or maintained their level of drug tolerance. Janda also showed a video of two rats—one vaccinated and one unvaccinated—who were given heroin. The unvaccinated rat was very lethargic ("heroin sedation") while the vaccinated rat was very active. "When these vaccines are working well, they can work extremely well," Janda said.

Another goal was to make the vaccine stable at room temperature. After tweaking the formulation, Janda

came up with a vaccine that "is stable for months at room temperature," making it ideal for use in LMICs that may not have the ability to refrigerate vaccines in regions that most need them.

He emphasized, though, that the vaccines still need more work. "I'm not sure how well they're going to hold up in the clinic," he confided. He's looking next to explore deuteration, an isotope of hydrogen that has



When creating a drug vaccine, "it's not just the amount of antibody you create, but also the quality" of those antibodies.

-DR. KIM JANDA



shown some early positive benefits over the previous version of heroin vaccines.

Janda also wanted to make a vaccine that would target fentanyl, a fully synthetic opioid that is a major contributor to rising opioid overdose deaths.

Fentanyl has a lot of different analogues, so Janda wanted to create a broadly neutralizing vaccine that could target many of these. Janda based the vaccine on 6-7 fentanyl derivatives, including ones that have been made by clandestine laboratories.

The fentanyl vaccines worked much better than the heroin vaccines.

"We were really able to keep the drug out of the brain...[and] basically control it in the blood," Janda explained. When tested in an animal model, the vaccine fully protected against fentanyl overdose.

Janda is also exploring the possibility of a heroin-fentanyl combination vaccine, although he thinks the two original vaccines would have to be approved before the focus can shift to a "Heroin Street" shot. "The individual drug [vaccines] work better than the combo," Janda found, "but the combo works reasonably well."

Monoclonal antibodies (mAbs) have become more widely known recently due to their use as Covid-19 treatments, and they also show potential as overdose treatments. Janda obtained human fentanyl mAbs by vaccinating a transgenic mouse and then going through a novel single B-cell sorting technique. These mAbs, like the opioid

Active Vaccines Against Drugs of Abuse

Adjuvants

Carrier Protein

Hapten/Linker Design

The Development of Active Vaccines is Interdependent Upon Three Critical Aspects

Janda discusses the main components of a drug vaccine.

vaccines, sequester the drug in the blood, and could be more effective at treating overdoses than naloxone (Narcan). This was demonstrated using plethysmography as he showed head-to-head data between these two treatments with a critical dose of carfentanil. [Plethysmography measures changes in volume in different areas of the body.]

Janda was particularly impressed by the mAbs P1A4 that bound well to both fentanyl and carfentanil (an incredibly potent fentanyl analogue): “This is like the Guinness World Records with regard to antibody affinity to small molecules, so this is as good as you’re going to get here.”

Finally, he discussed his research on nicotine, which is a less dangerous drug than opioids but notoriously difficult to quit. Janda is not the first person to attempt a nicotine vaccine.

“There’ve been probably 20 nicotine vaccines that have hit clinical trials,” he shared, “and all of them have failed.”


It comes down to the chemistry of the drug, he says. Antibodies will sequester the drug in the blood, but the drug eventually must be processed. Again, this comes down to a PK/PD dilemma ideally, he thought, a better scenario would be to both sequester and degrade the drug.

Pseudomonas putida, a bacterium that lives in the soil under tobacco plants, may hold the key. It uses nicotine as its sole source of carbon and hydrogen, and avoids nicotine toxicity by degrading it with an enzyme termed NicA2.

Importantly this approach could be useful in treating pediatric nicotine toxicity (caused by ingesting liquid nicotine such as vape fluid), for which there are currently no treatments.

Janda’s research shows many exciting opportunities for treatment of substance abuse disorders. However, he is realistic about the potential for drug vaccines:

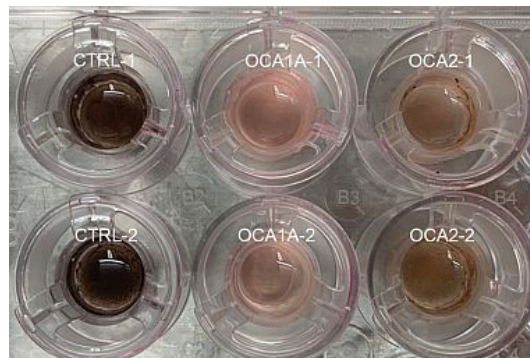
“I always tell people...I’m not selling you on ‘this will cure everybody.’ And I don’t think these vaccines will be helpful for all drugs of abuse,” Janda concluded. “I think you have to pick and choose your battles.”

The archived lecture can be viewed at <https://videocast.nih.gov/watch=43773>. 

First Patient-Derived Stem Cell Model Developed for Eye Conditions Related to Albinism

BY CLAUDIA COSTABILE

Researchers at NEI have developed the first patient-derived stem cell model for studying eye conditions related to oculocutaneous albinism (OCA).



Researchers reprogrammed skin cells from individuals without OCA and people with the two most common types of OCA into iPSCs.

IMAGE: NEI

“This ‘disease-in-a-dish’ system will help us understand how the absence of pigment in albinism leads to abnormal development of the retina, optic nerve fibers and other eye structures crucial for central vision,” said Dr. Aman George, a staff scientist in the NEI Ophthalmic Genetics and Visual Function Branch, and lead author of a report describing the model’s development.

Stem Cell Reports published the article in its January edition.

OCA is a set of genetic conditions that affects pigmentation in the eye, skin and hair due to mutation in the genes crucial to melanin pigment production.

In the eye, pigment is present in the retinal pigment epithelium (RPE), and aids vision by preventing the scattering of light. The RPE is located right next to the eye’s light-sensing photoreceptors and provides them nourishment and support.

People with OCA lack pigmented RPE and have an underdeveloped fovea, an area within the retina that is crucial for central vision. The optic nerve carries visual signals to the brain.

People with OCA have misrouted optic nerve fibers. Scientists think that RPE plays a role in forming these structures and want to understand how lack of pigment affects their development.

“Animals used to study albinism are less than ideal because they lack foveae,” said NEI clinical director Dr. Brian P. Brooks, chief of the Ophthalmic Genetics and Visual Function Branch. “A human stem cell model that mimics the disease is an important step forward in understanding albinism and testing potential therapies to treat it.”

To make the model, researchers reprogrammed skin cells from individuals without OCA and people with the two most common types of OCA (OCA1A and OCA2) into pluripotent stem cells (iPSCs). The iPSCs were then differentiated to RPE cells. The RPE cells from OCA patients were identical to RPE cells from unaffected individuals but displayed significantly reduced pigmentation.

Researchers will use the model to study how lack of pigmentation affects RPE physiology and function. In theory, if fovea development is dependent on RPE pigmentation, and pigmentation can be somehow improved, vision defects associated with abnormal fovea development could be at least partially resolved, according to Brooks.

“Treating albinism at a very young age, perhaps even prenatally, when the eye’s structures are forming, would have the greatest chance of rescuing vision,” said Brooks. “In adults, benefits might be limited to improvements in photosensitivity, for example, but children may see more dramatic effects.”

The team is now exploring how to use their model for high-throughput screening of potential OCA therapies.



Above, Dr. Aman George, a staff scientist in the NEI Ophthalmic Genetics and Visual Function Branch. Below, branch chief Dr. Brian P. Brooks





Collaboration with Navajo Nation communities to sample water from unregulated wells was cited as a successful engagement concept.

IMAGE: LINDSEY JONES

Rural

CONTINUED FROM PAGE 1

determinants of rural health disparities, the unique health burdens facing rural communities and how they intersect with other structural determinants, and the need for community-driven and -engaged research. Participation by staff and directors from several institutes and centers, as well as from then-NIH director Dr. Francis Collins, emphasized the agency’s commitment to improving rural health.

Improving the health of individuals in rural areas spans the missions of multiple institutes. Dr. Eliseo Pérez-Stable, director of the National Institute on Minority Health and Health Disparities, opened the seminar by explaining that underserved rural residents—such as persons from racial and ethnic minority groups, less privileged socioeconomic backgrounds and sexual and gender minority groups—often experience health disparities. He dispelled the myth that “bad behavior” engenders these disparities, offering instead that structural factors are the primary cause.

Subsequently, Dr. Richard Hodes, director of the National Institute on Aging, discussed NIA’s life course approach to studying rural health and rural health disparities. Dr. Rick Woychik, director of the National Institute of Environmental Health Sciences, introduced structural elements that have increased dangerous environmental exposures on rural communities. He discussed NIH-wide efforts to support research, partnering with rural communities, to address these exposures.

Keynote speaker Dr. Karen Winkfield of Wake Forest University urged the audience to examine the geographic disparities in

health and to tailor engagement strategies to specific communities. She and other presenters stressed the need to move beyond analyzing the existence of disparities to “working on the ground” toward community-engaged interventions.

Tom Morris of the Health Resources and Services Administration then

explained effects from structural determinants of health on health and disease in rural communities. These ongoing disparities include high rates of opioid misuse and overdose, Covid-19 hospitalizations and deaths and maternal mortality and morbidity from lack of obstetric care.

Many factors impact the health outcomes of all communities, from income and job opportunities to access to unpolluted water and healthful foods. Other panels focused on the impact of sociocultural and economic determinants of health and physical environment on rural communities. Afterward, early-stage investigators presented research describing interventions and multilevel frameworks tailored to, and developed in collaboration with, local communities of underserved populations.

Another session considered optimal methods of evaluation and measurement of rural health disparities to guide public policy.

Continuing the theme of collaboration, Dr. Melody Goodman of NYU’s School of Global Public Health emphasized the importance of rigorously evaluating stakeholder engagement, moving beyond “tokenism” to true partnership.

These and other best practices—like honoring and leveraging local cultural wisdom—will be incorporated into new rural health resource hubs, like the one Dr. Brian Rivers is developing at Morehouse School of Medicine.

Examples of successful engagements were highlighted in the work of several presenting investigators, in collaboration with American Indian/Alaska Native (AI/AN) communities.

Dr. Jani Ingram of Northern Arizona University discussed her work with the Navajo Nation communities to sample water from unregulated wells contaminated with uranium and arsenic, reporting the levels—and their expected effect on health—back to the communities.

Further illustrating the structural barriers to healthy physical environments, Dr. Tony Ward of the University of Montana discussed his work researching indoor wood smoke exposures, leading to poor air quality throughout winters, in remote and underserved areas of AI/AN reservations and villages.

Dr. Arleen Brown of the University of California-Los Angeles charged the audience to strive for specific opportunities to improve rural health, including adaptive models of care like telehealth, greater understanding of environmental pollutant sources, research on policy implications and greater diversity in the investigator workforce.

“There should be more opportunities for conducting interdisciplinary and multisectoral work...thinking about a different type of workforce, including community members who can serve these navigator or translator roles in a way that no academic investigator will ever be able to,” she said.

View an archived recording of the workshop at <https://videocast.nih.gov/watch=43942>.

The seminar was supported by NIMHD, NIA, NIEHS and the National Institute of Allergy and Infectious Diseases.



Dr. Tony Ward discussed his research on indoor wood smoke exposure.

IMAGE: EMILY WEILERURE

Awoniyi Is New Director of NIH Ethics Office

Tonia Awoniyi joined NIH as the new director of the Ethics Office. She oversees the NIH Ethics Program, after serving as the director of advice and education since 2014 for the U.S. House of Representatives committee on ethics and heading the primary office that provides counsel and education on ethics to members of Congress and their staff.

Awoniyi spearheaded programs in efficiency and transparency, working to ensure that both the parameters and the responsibility of ethical conduct were effectively communicated and understood.

Before the House post, she was director of education and training for the Senate select committee on ethics, where she gained distinction as the first-line advisor on ethical concerns. In addition to overseeing the federal ethics education of Senate members and their staff, she also assessed and met the training needs of external stakeholders such as the representatives of lobbying groups.

Awoniyi brings nearly 17 years of experience counseling, training and leading on the statutes and regulations governing ethical conduct within the federal government.

A *cum laude* graduate in political science from Morgan State University, Awoniyi also holds an M.S. in management information systems from the University of Baltimore and a J.D. from the University of Maryland School of Law.

Hunter Serves as OBSSR Acting Director

OBSSR deputy director Dr. Christine M. Hunter began serving as acting NIH associate director for behavioral and social sciences research and director of the Office of BSSR, following the retirement of Dr. Bill Riley in December.

A captain in the Public Health Service, Hunter previously was director of behavioral research focused on obesity and diabetes prevention and



Tonia Awoniyi

treatment at NIDDK. Her research interests are on advancing precision health and the application of rigorous but varied methods and designs in the behavioral and social sciences across the translational spectrum. NIH has begun a nationwide search to replace Riley.

Staff Scientist Falk Retires After 38 Years at NCI

Roni Falk, staff scientist in the Metabolic Epidemiology Branch (MEB), retired from the Division of Cancer Epidemiology and Genetics in December, after 38 years of distinguished service to the National Cancer Institute. She played a pivotal role in numerous epidemiologic studies that improved the understanding of circulating hormones and cancer risk.

“Roni was a founding member of MEB and shared her expertise in hormonal carcinogenesis, hormone measurements and her particular skills in developing robust quality control plans for many of our projects,” noted MEB chief Dr. Christian Abnet. “I relied heavily on Roni when she served as the branch coordinator for MEB’s first site visit in 2018. Roni is a lifelong learner and her wide scientific interests are evident in her active participation in several DCEG working groups. I’ll miss Roni’s contributions to our work and her keen insights gleaned from the early days of DCEG.”

Throughout her career, Falk made critical contributions to research in DCEG often as part of international consortia, including the Male Breast Cancer Pooling Project, Pooled Analysis of Smoking and Breast Cancer Risk and the Biomarkers and Breast Cancer Risk Prediction in Younger Women.

Critical to the success of these endeavors was the emergence of the study of biomarkers. Falk guided the design, implementation, analysis and

peer-reviewed journal articles, commentaries and reviews.

In addition to her research contributions, she served on the faculty of the DCEG molecular epidemiology course and was a dedicated mentor committed to the growth and success of her trainees.

“When I joined DCEG as a postdoctoral fellow I had the good fortune of working with Roni on a nested case-control study of estrogen metabolism and breast cancer risk,” reflected Dr. Gretchen Gierach,



Staff scientist Roni Falk retired from NCI’s Division of Cancer Epidemiology and Genetics after 38 years of distinguished service.

chief and senior investigator in the Integrative Tumor Epidemiology Branch. “Over the years, she taught me many important lessons about

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“I’ll miss Roni’s contributions to our work and her keen insights gleaned from the early days of DCEG.”

—DR. CHRISTIAN ABNET

• • •

interpretation of laboratory studies of estrogens, androgens, growth factors, vitamin D, cytokines, angiogenic factors and adipokines. She played a key role in developing methods to assess the validity and reproducibility of assays to measure estrogen, androgen and progesterone metabolites using state-of-the-art technology and statistical approaches.

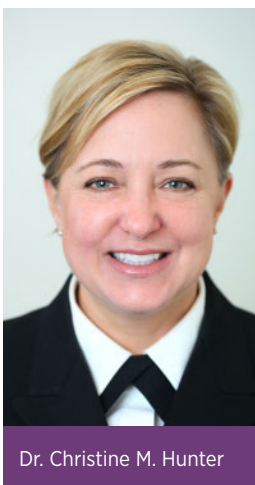
In 2009, Falk received an NIH Merit Award in recognition of this work. These methods have since been used as a model for evaluating the feasibility of new molecular markers.

Falk made significant efforts to advance the field of epidemiology and is an author of more than 140

integrating quality control regimens into biomarker studies. While she will be sorely missed, I know the wisdom Roni has imparted will be long-lasting in DCEG and beyond.”

“In my time as a trainee, and now as a senior scientist in the division, Roni inspired each of us with her meticulousness and innate understanding of the data,” said Dr. Mia Gaudet, senior scientist in the Trans-Divisional Research Program. “She is a treasured colleague and surrogate mother to many of us. The world of cancer epidemiology is indebted to her.”

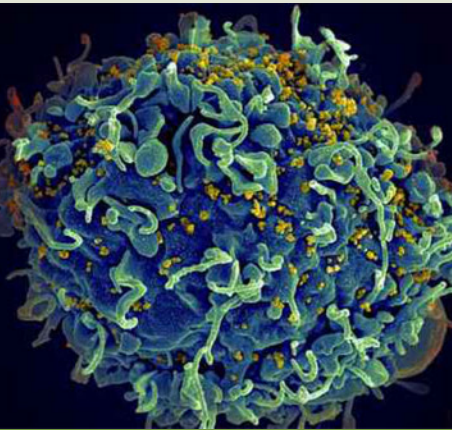
Following her retirement, Falk will serve as a special volunteer to the division. **R**



Dr. Christine M. Hunter

Experimental HIV Vaccine Shows Promise

A team led by NIAID's Dr. Paolo Lusso developed and tested an mRNA HIV vaccine in animals. Study results were published in *Nature Medicine*.



Human cell (blue) infected with HIV (yellow), the virus that causes AIDS.

IMAGE: SETH PINCUS, ELIZABETH FISCHER AND AUSTIN ATHMAN, NIAID

Messenger RNA, or mRNA, is a molecule that instructs the body to make proteins. mRNA vaccines teach cells to make proteins from a virus or other microbe, which then trigger the body's immune response, protecting the body from infection if the real virus enters.

The first two mRNA vaccines available to the public are Covid-19 vaccines, but researchers have studied mRNA technology for other uses for decades.

The experimental HIV vaccine is injected into muscle, where it instructs the body to make two key HIV proteins, Env and Gag. Muscle cells assemble these two proteins into virus-like particles studded with many copies of Env on their surface. These virus-like particles cannot cause infection or disease because they lack the complete genetic code of HIV. Yet they provoke immune responses similar to natural HIV infection.

The researchers first tested the vaccine in mice. After two injections, it elicited antibodies in all animals that could neutralize HIV, producing a response that closely mimicked natural infection.

They then tested the vaccine in rhesus macaques. Monkeys received a priming vaccine followed by several booster inoculations. By week 58, all vaccinated macaques had developed measurable levels of antibodies that could neutralize many diverse HIV strains. The experimental vaccine also induced other important immune responses, like helper T cells, which aid other immune cells.

The macaques were then exposed weekly to simian-human HIV (SHIV), a form of the virus used for modeling human HIV in monkeys. Overall, vaccinated monkeys had a 79 percent lower per-exposure risk of SHIV infection than unvaccinated animals.

The vaccine course was well-tolerated with only mild side effects. These results showed that the novel HIV vaccine was safe and prompted immune responses against an HIV-like virus. The team plans to conduct a phase 1 trial of the mRNA HIV vaccine in healthy adult volunteers after further refinement and testing.—adapted from *NIH Research Matters*

Offering Buprenorphine to Inmates Has Hopeful Results

A study conducted in two rural Massachusetts jails found that people with opioid use disorder (OUD) who were incarcerated and received buprenorphine, a medication approved to treat OUD, were less likely to face rearrest and reconviction after release.

After adjusting the data to account for baseline characteristics such as prior history with the criminal justice system, the study revealed a 32 percent reduction in rates of probation violations, reincarcerations or court charges when the facility offered buprenorphine to people in jail compared to when it did not. The findings were published in *Drug and Alcohol Dependence*.

The study, conducted by the Justice Community Opioid Innovation Network (JCOIN), a program to increase high-quality care for people with opioid misuse and OUD in justice settings, was funded by NIDA through the Helping to End Addiction Long-term (NIH HEAL) initiative.

"Studies like this provide much-needed evidence and momentum for jails and prisons to better enable the treatment, education and support systems that individuals with an opioid use disorder need to help them recover and prevent reincarceration," said NIDA director Dr. Nora Volkow. "Not offering treatment...can have devastating consequences, including a return to use and heightened risk of overdose and death after release."

Offering evidence-based medications to treat OUD—such as buprenorphine, methadone and naltrexone—is not currently standard-of-care in U.S. jails and prisons; most jails that do offer them are in large urban centers.

While previous studies have investigated the impact of buprenorphine on overdose rates, risk

for infectious disease and other health effects among the incarcerated, this study is one of the first to evaluate the impact specifically on recidivism, defined as additional probation violations, reincarcerations or court charges.

The researchers recognized an opportunity to assess this research gap when jails in two neighboring rural counties in Massachusetts both began to offer buprenorphine to adults in jail, but at different times. Franklin County began offering buprenorphine, in addition to naltrexone, in 2016. Hampshire County started in 2019.

"There was sort of a 'natural experiment' where two rural county jails located within 23 miles of each other had very similar populations and different approaches to the same problem," said study author Dr. Elizabeth Evans of the University of Massachusetts-Amherst.

Researchers observed the outcomes of 469 adults who exited 1 of the 2 participating jails between Jan. 1, 2015 and Apr. 30, 2019, during which time Hampshire County was not yet offering buprenorphine. Most observed individuals were male, white and around 35 years old.



A recent NIDA study shows giving buprenorphine to inmates with opioid use disorder put them on the road to recovery.

PHOTO: SHUTTERSTOCK/NEW AFRICA

The researchers found that 48 percent of individuals from the Franklin County jail recidivated, compared to 63 percent of individuals in Hampshire County. The rate of reincarceration in the Franklin County group was 21 percent, compared to 39 percent in the Hampshire County group.

Additional research is underway in both urban and rural jails across more diverse populations, including women and people of color.

"Though this study was done with a small sample, the results show convincingly that providing these medications in jail can break the repressive cycle of arrest, reconviction and reincarceration that occurs in the absence of adequate help and resources," said senior study author Dr. Peter Friedmann. "That's huge."

Survival Rate Increases for Extremely Preterm Infants

The survival rate of extremely preterm infants born from 2013 through 2018 in a large network of U.S. research centers improved to 78.3 percent, compared to 76 percent for infants born in the



Survival rates of extremely preterm infants improved in a recent NICHD study.

PHOTO: SHUTTERSTOCK/PETER BAKO

network from 2008 to 2012, according to NIH-funded researchers.

Their study included more than 10,000 infants born at 22 to 28 weeks of pregnancy at 19 centers of the Neonatal Research Network funded by NICHD. The

results appear in the *Journal of the American Medical Association*.

In the study, survival was greater for infants born later in pregnancy, with 94 percent of those born at 28 weeks surviving to hospital discharge and roughly 11 percent born at 22 weeks surviving to discharge. Survivors were assessed at 2 years corrected age—a child's chronological age, minus the number of weeks the child was born preterm.

Slightly more than 8 percent had moderate to severe cerebral palsy, 1.5 percent had vision loss in both eyes, 2.5 percent needed hearing aids or cochlear implants and 15 percent required mobility aids such as braces, walkers or wheelchairs. Nearly 49 percent had no or only mild neurodevelopmental impairment. About 29 percent had moderate neurodevelopmental impairment and roughly 21 percent had severe neurodevelopmental impairment.

The causes of preterm birth are only partially understood. The researchers noted the infants were treated at academic medical centers and their health outcomes may not reflect those of the whole U.S. preterm population.

SARS-CoV-2 May Cause Fetal Inflammation

A small NICHD-led study showed that a SARS-CoV-2 infection during pregnancy may cause inflammatory immune responses in the fetus, even if the virus does not infect the placenta.

Researchers describe unique maternal, fetal and placental immune responses among pregnant women with Covid-19. The findings detail changes in antibodies, immune cell types and

inflammatory markers in maternal blood, umbilical cord blood and placental tissues. The study is published in *Nature Communications*.

Women who are pregnant are at a higher risk for severe illness from Covid-19. The virus during pregnancy also increases the risk for preterm birth, stillbirth and preeclampsia.

The study evaluated 23 pregnant women: 12 were positive for SARS-CoV-2. Of them, 8 were asymptomatic, 1 had mild symptoms and 3 had severe Covid-19. After delivery, the researchers compared immune responses between mothers and their newborns by comparing maternal blood and umbilical cord blood. Inflammatory immune responses triggered by the virus were observed in women, their neonates and placental tissues regardless of whether the mothers had symptoms. The study team described the following observations:

- Pregnant women with SARS-CoV-2 had a reduction in an immune cell type called T-cells, which helps drive antiviral responses.
- Mothers with SARS-CoV-2 infection developed antibodies against the virus regardless of whether they had symptoms, and some of these antibodies were found in the umbilical cord blood.
- Infected mothers had a higher level of immune activity markers (i.e., cytokines) in blood regardless of symptoms. The elevated cytokines are interleukin-8, interleukin-15 and interleukin-10.
- Infants born to infected mothers, even if the mother had no symptoms, had an inflammatory response reflected by higher levels of interleukin-8. This elevation was observed even though the fetus presumably did not have Covid-19.

• While SARS-CoV-2 virus was absent in placentas, the placentas from infected mothers had altered ratios of immune cell types. The researchers also found altered immune activity in the placenta and cord blood of infants born to infected mothers. These findings indicate that the neonatal immune system is affected by maternal infection by SARS-CoV-2 even if the virus is not detected in the placenta.

Overall, the findings will help researchers better understand Covid-19 during pregnancy.



In small study, infants born to Covid- infected mothers had an inflammatory response.

PHOTO: SHUTTERSTOCK/ TITIKUL_B

Adults with Diabetes Wanted

NIDDK researchers seek adults with type 2 diabetes to join a study. Doctors will investigate physiology of vitamin C in red blood cells of diabetic subjects as a function of the presence of glucose in the blood, with and without vitamin C supplementation. Compensation is provided. For details, contact the Clinical Center Office of Patient Recruitment at (866) 444-2214 (TTY users dial 711) or ccopr@nih.gov. Refer to study #14-DK-0060. Online: <https://go.usa.gov/xyTaY>.

People with AUD Needed

People with alcohol use disorder (AUD) have trouble controlling their drinking and cravings for alcohol. Studies have found a relationship between ghrelin, commonly called the hunger hormone, and alcohol cravings for those with AUD. Researchers at NIDA are now testing an investigational drug, GLWL-01, to change the activity level of this hormone and determine whether it can help decrease craving for alcohol. If you are 18-70 years old, have moderate to severe alcohol use and are willing to quit, you may qualify to join. The study includes a 21-day stay at the clinical research unit on the Johns Hopkins Bayview campus in Baltimore. Compensation for participation will be provided at completion. To learn more and see if you qualify, contact the Clinical Center Office of Patient Recruitment at (866) 444-2214 (TTY users, dial 711) or email ccopr@nih.gov and reference NIH study #19-DAN075. Online: <https://go.usa.gov/xM6CF>.

Volunteers with Type O Blood Sought

NIAID is looking for volunteers with type O blood to create a supply of malaria-rich blood for future malaria research. Volunteers will be infected with a mild case of malaria, donate their blood for future research and then be treated with a highly effective malaria treatment. Participants may experience mild, flu-like symptoms but will be monitored closely and treated quickly. Volunteers will receive compensation for participating. For details, call (866) 444-2214 or email ccopr@nih.gov. Refer to study #000212-1 or visit <https://go.usa.gov/xejfb>.

Do You Have a RASopathy Syndrome?

RASopathies are rare disorders caused by a genetic change often diagnosed in infancy or early childhood. People with RASopathy syndromes may have developmental issues, cognitive and congenital disabilities and poor growth, and may also have an increased risk of developing cancer. An NCI study will look to better understand medical conditions in individuals with RASopathies. If you or a relative have been diagnosed with a RASopathy syndrome and want to know how to enroll in the study, contact the Clinical Center Office of Patient Recruitment at (866) 444-2214 (TTY users dial 711) or email ccopr@nih.gov and reference study #20-C-0107 Online: <https://rasopathies.cancer.gov>.

SCIENTIFIC SINGERS
Nerds in Harmony Still Going Strong

BY AMBER SNYDER

“CRISPR Cas-9, bring me a gene ...”

NIH’s resident acapella group, Nerds in Harmony, recently sang their own version of the Chordettes’s *Mr. Sandman* in front of a large Christmas tree outside of the Anthropologie in Bethesda. *CRISPR Cas-9* wasn’t a typical Christmas carol, but it brought smiles and laughter from the crowd.



Top: Nerds in Harmony recently sang at the Maryland ZooLights event in Baltimore. Middle: The pandemic forced the group to collaborate from a distance. Below, a flyer for their ‘Music at the Metro’ series

Nerds in Harmony is a musical ensemble with a unique challenge: the only instruments they use are their own voices. It was formed in 2004 by a group of Intramural Research Training Award fellows. The group first went by “IRTApella,” then “The Cytochromatics.” Nerds in Harmony became the official group name in 2010.

“It’s a really nice community, especially when you’re new to the area,” said Barbara Benowitz, a second year postbac at NCCIH who also manages the group’s social media. “We share [a love of] science, but we also share a love of music.” She is also a founding member of the Post-Bachs, another music ensemble for NIH employees, and is one of several NIH’ers who belong to both groups.

“We think music is another way of healing, really, and it can be really therapeutic for people and the scientists and trainees at NIH,” explained Brandon Levy, a health communications specialist in the NIH Intramural Research Program and the administrator for Nerds in Harmony. “It can be a really stressful

environment... [so] it’s really nice for us to have something else going on.”

In normal times, Nerds in Harmony performs for both NIH and public audiences, and has begun to hold outdoor concerts again in the latter half of 2021. They have a “Music at the Metro” series held outside the Medical Center Metro Station, and perform at various locations around Bethesda.

Pre-pandemic, they sang in events ranging from retirement parties to Zoo



“At first, we were really afraid that the group would go defunct and never really start up again when we were allowed to come back in person,” Levy recalled. “So, fortunately, we had a really tech savvy then-grad student (now postdoc).” Members learned their parts virtually using Google Drive and MuseScore and then recorded their performances, which were edited into the split-screen performance videos that are available on the groups’ social media.



“We think music is another way of healing, really, and it can be really therapeutic for people and the scientists and trainees at NIH.”

-BRANDON LEVY



Lights at the National Zoo in D.C. On-campus indoor performances are currently limited because of restrictions on gathering and the heightened risk of Covid-19 transmission when singing.

The early months of the Covid-19 pandemic posed a huge obstacle to musical

groups of all sorts due to safety measures put in place for in-person gatherings.

Alex Zhu, a postbac at NIDDK, is the current director of Nerds in Harmony. He grew up playing the violin and always wanted to try acapella but worried about his lack of experience. Zhu was pleasantly surprised to find that “it’s a great group for anyone who wants to sing, regardless of their experience.”

“I had never sung in a group before [either],” Benowitz added, but “all these wonderful people have helped me learn how to read vocal music.”

“It’s a lot of fun,” she concluded.

For details on the group, visit <https://sites.google.com/view/nerds-in-harmony>.

