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Resistance to the Plague May Be a Double-Edged Sword

BY ETHAN SMITH, NINR

Evolutionary pressure to survive the bubonic plague may have selected for genetic mutations that protect certain Mediterranean populations from being infected by the infamous *Yersinia pestis*, the bacterium behind the plague. But evolution isn't perfect. Being able to survive the plague may also be the reason for today's prevalence of another ancient disease—familial Mediterranean fever (FMF)—National Human Genome Research Institute (NHGRI) researchers recently reported in *Nature Immunology* (*Nat Immunol* **21:**857–886, 2020).

FMF, an autoinflammatory disease that mainly affects people of Mediterranean and Middle Eastern descent, is caused by mutations in the *MEFV* gene. The gene encodes pyrin, a protein involved in the inflammatory response. In healthy people, pyrin helps immune cells fight infection by increasing inflammation and producing inflammation-related molecules. In FMF patients, though, pyrin is activated without being triggered by an infection and can cause episodes of hyperinflammation: fever, chest pain, arthritis, and abdominal pain so bad it can be mistaken for appendicitis. Without treatment, FMF can lead to renal failure and death. People with two copies of the mutated *MEFV* gene are predisposed to FMF; those with only one copy of the mutated gene may develop FMF, but at a lower frequency.

But it turns out that having one or two

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NHGRI Scientists Study Ancient Dog Breed

New Guinea Singing Dogs May Hold Clues to Human Vocalization

BY NATALIE HAGEN, NCATS

CREDIT: JAMES K. MCINTYRE, NEW GUINEA HIGHLAND WILD DOG FOUNDATION

Studying the New Guinea highland wild dog, the original New Guinea singing dog, may help scientists understand how human vocalization developed. Shown: a male New Guinea highland wild dog.

The New Guinea singing dog, whose harmonious wolf-like howls sound eerily like whale songs, was thought to have been extinct in the wild for some 50 years. But researchers at the National Human Genome Research Institute (NHGRI) reported, in the *Proceedings of the National Academy of Sciences*, that their genome analysis has confirmed that this breed still roams the New Guinea Highlands. Moreover,

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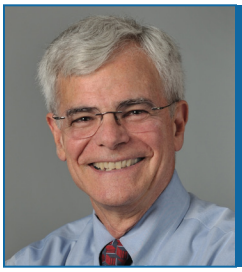


A Wonderful October Surprise for the NIH

Harvey Alter Wins the Nobel Prize

BY MICHAEL GOTTESMAN, DDIR

Unless you have been on Mars, which incidentally is closer to Earth than it will be for next 15 years and is easily visible as an orange orb in the southeast sky after sunset, you know that early Monday morning, on October 5, 2020, our own **Harvey Alter**, senior scientist in the NIH Clinical Center, got a call from Sweden notifying him that he was sharing this year's Nobel Prize in Medicine or Physiology for his pioneering work on defining and detecting the hepatitis C virus. Although this work had previously been recognized by the Lasker Prize in 2000 and the Canada Gairdner International Award in 2013, the NIH had pretty much given up hope that the Nobel Prize committee would recognize Harvey's critical contribution to what has since become the potential eradication (through drug treatment) of this virus in infected individuals, and the elimination of a public-health plague.

To be clear, Harvey's work had made it possible to cleanse the blood supply of the agents that caused hepatitis (both B and C) through blood transfusions. His work was instrumental in leading to the development of new diagnostic and therapeutic agents and providing the scientific basis for instituting blood-donor screening programs that have decreased the incidence of transfusion-transmitted hepatitis to near zero.

But hepatitis C could still be transmitted in other ways such as shared needles among intravenous-drug users. One continuing consequence of hepatitis C infection is cirrhosis of the liver and the eventual development of liver cancer in a high percentage of chronically infected individuals. So treatment of all infected patients has become a goal of public-health experts. Harvey continues to study the natural history and outcomes of hepatitis C infection and is collaborating with **Marc Ghany** and others in the Liver Diseases Branch (in the National Institute of Diabetes and Digestive and Kidney Diseases) to conduct long-term follow-up studies of patients to see if cirrhosis is prevented or goes away after treatment.

There is probably no one at NIH whose work has had more impact on improving the public health, and so it seems appropriate to ask how this work came to be in the intramural research program (IRP). How did Harvey himself come to be in the IRP? Like many "Yellow Berets" (including myself), he was invited by the federal government in the 1960s to report for military duty. We sought instead to provide service to our country by working at NIH; Harvey chose to work at the NIH Clinical Center. (The term "Yellow Beret" came about because those who came to NIH to fulfill the selective service obligation for every male physician—or, as some said, to avoid the draft—were initially perceived as cowards, the opposite of the brave U.S. Army Special Forces called the Green Berets. Later, however, most considered "Yellow Beret" to be a badge of pride.)

Harvey's choice precipitated a series of events that clarify why the IRP continues to be the source of innovative and high-impact scientific discoveries. Consider how the IRP:

• Provides opportunities to collaborate with world-class scientists: Trained as a hematologist, Harvey began to work in the NIH Clinical Center Blood Bank and became interested in detecting antigens in blood (using a standard technique) that might contribute to transfusion reactions. This work was stimulated by a long-term collaboration with **Baruch Blumberg**. Harvey and Baruch discovered the Australia Antigen, which turned out to be the hepatitis B antigen. Baruch Blumberg received the Nobel Prize for this work.

• Offers researchers the ability to do long-term studies that are hypothesis-generating: Harvey has commented about how the NIH IRP enabled him to collect and store longitudinal samples from cardiac-surgery patients, who had about a 30% incidence of hepatitis related to the clinically required transfusions, and pursue his research interests over many years without having to write grants. It soon became clear that only 25% of post-transfusion hepatitis was due to hepatitis B and none due to hepatitis A virus. Hence, the vast majority of cases were due to a new infectious entity that the research team cautiously called non-A, non-B hepatitis.

Harvey, **Bob Purcell**, **Steve Feinstone**, and **Patrizia Farci** set out to discover the missing agent. Harvey says he doubts that these studies could have been done anywhere other than NIH. Only the intramural program would have supported his large blood repository and his chimpanzee studies, both of which proved critical to the discovery of hepatitis C, or funded the "nondirected" research when it wasn't clear where the research was going. The actual cloning of the hepatitis C viral genome was

accomplished by a group led by Michael Houghton at Chiron (with whom this year's Nobel Prize was shared along with NIH-supported researcher Charles Rice at Rockefeller University in New York). But Harvey's pioneering work defining the existence of this virus and his establishment of a repository of coded blood samples that included non-A, non-B hepatis proved critical for the discovery.

• Recognizes unusual talent: No one is more self-effacing, more generous, and more able to see the humor in most situations than Harvey. But his pleasant exterior masks a very sharp, persistent, and intuitive intellect that is apparent to all of us who have gotten to know Harvey well. He is a very serious and effective scientist who just happens to be able to laugh at himself and his life's work and along the way earn the support of his colleagues and supervisors. I like to think that NIH has a good eye for talent. Harvey's career here illustrates that quality.

CREDIT: ERNIE BRANSON

Harvey Alter shared the 2020 Nobel Prize in Medicine or Physiology for the "discovery of Hepatitis C virus."

• Allows researchers to take advantage of special resources: The NIH Clinical Center is a unique resource. Harvey's career at NIH reflects the optimal use of this resource, which provides access to an unusual patient population; supports the ability to do studies over several decades; and has the capacity to collect and characterize clinical samples and data from patients.

• Dedicates itself to the public health: At its core, Harvey's work is about defining an important public-health problem (hepatitis-virus-contaminated blood), doing research to understand the nature of the problem, and applying knowledge to alleviate the public-health consequences. This dedication is written into the mission statement for the NIH and its Clinical Center and underlies much of the work done at the NIH.

So please join me in congratulating Harvey Alter and the NIH for this wonderful recognition of a life's work dedicated to the public health, and let us redouble our efforts to preserve the environment here that enabled our latest Nobel laureate's lifesaving work. ●

There are now six Nobel laureates who did the entirety of their award-winning research at the NIH as federal scientists: **Marshall Nirenberg**, **Julius Axelrod**, **Christian Anfinsen**, **D. Carleton Gajdusek**, **Martin Rodbell**, *and* **Harvey Alter**. *For a complete list of NIH Nobel laureates including those who trained or worked extensively in one of NIH's intramural laboratories, visit https://irp.nih.gov/about-us/honors/nobel-prize.*

NIH ABBREVIATIONS

CBER: Center for Biologics Evaluation and Research, FDA
CC: NIH Clinical Center
CCR: Center for Cancer Research, NCI
CIT: Center for Information Technology
DCEG: Division of Cancer Epidemiology and Genetics, NCI
DIPHR: Division of Intramural Population Health Research, NICHD
FAES: Foundation for Advanced Education in the Sciences
FARE: Fellows Award for Research Excellence
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
OITE: Office of Intramural Training and Education
OIR: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women's Health
OTT: Office of Technology Transfer

From the Fellows Committee

Taking Control of the Job Search During the Pandemic

BY CRAIG MYRUM, NIA

Even in normal times, applying for academic faculty positions is time-consuming, and the competition is fierce. Throw in a pandemic, your chances of snagging that long-sought-after position in academia may feel hopeless. Currently in the midst of my own job search, I have experienced difficult moments, but I have also fortunately found ways to alleviate the anxiety.

Structured around the academic calendar, academic job postings typically peak between September and November. So, in March, when I heard about colleges and universities beginning to implement hiring freezes and rescinding new faculty offers, I was worried about my rapidly approaching faculty search in the fall. And on top of that, nonessential laboratory research had come to a standstill as NIH shut down all but mission-critical functions. My plans of submitting one last paper before the job search quickly became unrealistic.

When in-person professional trainings swiftly switched to virtual Zoom and WebEx sessions, I attended a handful of workshops arranged by the Office of Intramural Training and Education (OITE). As an introduction to many of these sessions, the OITE staff reminded attendees that many things about the pandemic were out of our control, but more importantly, that there were still a great number of things that we could control. We could prepare our job packets. We could attend to our career development. We could attend to our science. And we could control our own thoughts and behaviors. With that thought in mind, I got to work.

Since my career aspiration has long been to become a faculty member at a selective liberal arts college, my job packet would need a solid "Teaching" statement. I dusted off a draft that I had written in NIH's "Scientists Teaching Science" (https://www.training.nih.gov/sts_main_page) course five years ago. (As a side note, I highly recommended this course!) Now with four years of adjunct teaching (at a couple of local universities) under my belt, I reflected on my experiences and identified what I personally believe about teaching and learning and got those thoughts down on paper. And as required of all academic positions, I would also need a solid publication record. In the absence of new data being generated in the lab during the COVID-19 lockdown, I wrote a solid draft of a review that I had thought about for a long while. I drafted cover letters, I updated my CV, and with the backdrop of persistent racial injustice in the news, I drafted the all-important "Diversity and Inclusion" statement. I identified what I could control, and I did what I could to control it.

While I would generally consider myself an optimist, I am also a realist. I guess that makes me a realistic optimist. So with the already-tough job market in academia compounded by the economic crisis resulting from the COVID-19 outbreak, I decided that I needed to consider a Plan B. A backup. Reminded of a Career Spotlight Series session at my institute a couple of years back, I decided to look into what it would take to become a Medical Science Liaison (MSL). I read about the roles and responsibilities of an MSL, learned more about how clinical trials work through the NIH Office of Clinical Research (which I reasoned was important to know regardless), and did informational interviews. I even wrote an article about it for the May–June 2020 issue of the *NIH Catalyst* (https://irp.nih.gov/catalyst/v28i3/the-training-page).

But if I thought that getting a job in academia was hard, getting an MSL position is almost certainly tougher. Nevertheless, if spring rolls around and I am still without an academic job, I will muster up all of the optimism I have left and again make a plan to control what I can control.

That resilience would not be possible without a little self-care. For myself, that means going on runs, exploring new places in the region (since traveling via plane does not sound reasonable at the moment), and maintaining relationships—even if that sometimes requires staying six feet apart. Both physical and mental wellness are imperative during this period of ups and downs. If that's something that you need to work on, the OITE fortunately has a whole host of resources to get you started. Remember—you are also in control of your own thoughts and behaviors.

If you're also on the job hunt, I wish you the very best! ●

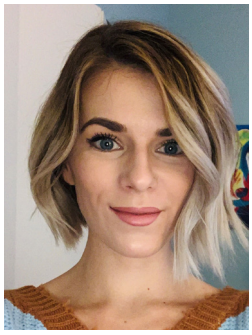
Craig Myrum has been a postdoctoral fellow at the National Institute on Aging's Laboratory of Behavioral Neuroscience since 2015. He works in the Neurocognitive Aging Section, where he studies the intersection of memory, aging, and sleep. When his training is complete in 2021, he hopes he will have landed a job at a liberal arts college where he can both teach and continue his research. He has been overseeing and contributing to this page since 2016.

Highlighting NIH's Outstanding Women Fellows

10th Annual Women Scientists Advisors Scholars Symposium

BY FRANCES FERNANDO, NICHD

Ever since 2011, the outstanding research achievements of NIH women postdocs have been recognized at the Annual Women Scientists Advisors (WSA) Scholars Symposium. On October 5, 2020, postdoctoral fellows **Alix Warburton** and **Ida Fredriksson** presented their work. They had been selected as WSA scholars from among the 95 women recipients of the 2020 Fellows Award for Research Excellence (FARE).



ALIX WARBURTON

IDA FREDRIKSSON

ALIX WARBURTON (NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES)

Education: Ph.D. in molecular and clinical pharmacology from the University of Liverpool (Liverpool, England)

Mentor: Alison McBride, Chief of NIAID's DNA Tumor Virus Section

Talk: "Mechanisms of Tandem Repeat Formation at HPV Integration Sites in Cervical Carcinoma Cells"

Interested in how human papillomavirus (HPV) genomes are integrated into cellular chromatin in HPV-associated cancers, Warburton investigates the role and mechanism of the HPV integration locus in oncogenic progression. She studies the clonal selection of integration events that sustain oncogene expression and the role of hijacking cellular enhancers at HPV-integration loci in cervical cancer, with emphasis on alterations in common fragile sites in the gemome. In cervical cells, she showed that integrated HPV16 could result in the formation of a super-enhancer-like element that drives transcription of the viral oncogenes (*PLoS Genet* **14:**e1007179, 2018).

When asked about unexpected findings in her research, Warburton commented on how "interesting it is that each integration locus is fundamentally unique, which has different implications for cancer progression, and the translational potential of applying basic mechanistic understandings to other human viruses." She mentioned a need for further study of the effects of silencing tumor suppressors or amplifying oncogenes.

IDA FREDRIKSSON (NATIONAL INSTITUTE ON DRUG ABUSE)

Education: Pharm.D. from Uppsala University (Uppsala, Sweden); Ph.D. in neuroscience from the Karolinska Institute (Solna, Sweden)

Mentor: Yavin Shaham, Chief of NIDA's Behavioral Neuroscience Research Branch and of the Neurobiology of Relapse Section

Talk: "Incubation of Oxycodone Craving After Conflict-induced Voluntary Abstinence"

To better understand the clinical problem of high relapse rates during abstinence from addictive drugs, Fredriksson decided to study rats to determine the mechanisms of incubation (the time-dependent increases in drug-seeking behavior) of oxycodone craving during abstinence. After a period of drug self-administration, rats experienced an increase in their drug-seeking behavior during a forced drug abstinence period in the home cage (the classical incubation of drug-craving model). However, this model does not mimic the human condition in which abstinence is self-imposed despite drug availability, and relapse may involve conflict (arguments with other people).

Fredriksson's solution was to use an electric barrier model to imitate voluntary abstinence, which involves introducing adverse consequences (such as punishment) of continued drug self-administration. The most unexpected finding was that the electric-barrier-induced abstinence *increased*, rather than *decreased*, oxycodone craving and seeking behavior, suggesting that abstinence induced by negative consequences (discipline, punishment, incarceration) in humans might paradoxically increase relapse vulnerability (*Neuropsychopharmacology* **44:**465–477, 2019).

Current projects include using whole-brain imaging in rats to identify neural projections that are activated during relapse; and functional magnetic-resonance imaging to monitor neural-circuit mechanisms. ●

The NIH WSA Scholars Symposium was sponsored by WSA and the NIH Office of Research on Women's Health. The WSA committee aims to advance the scientific careers and scientific contributions of women at NIH. Each year, the WSA selects two or three awardees from the pool of female FARE winners for this special recognition and gives them the opportunity to present their research to the NIH community. To learn more about the history and activities of the WSA, visit https://sigs.nih.gov/wsa.

Frances Fernando is a postbaccalaureate fellow in the National Institute of Child Health and Human Development. After completing her training in 2021, she plans to pursue a doctorate in public health to work on integrative global health issues and human rights.

Access to the National Death Index Made Easy

Centralized Database Now Available to NIH-supported Researchers

BY SUNITA CHOPRA, NCI

For many long-term clinical studies, it is critical for investigators to know whether patients have died, and if so, when, where, and how. Unfortunately, this information—especially if the patients died outside the research hospital—has often been difficult and expensive to obtain. Recently, NIH has made it easier—and free—for NIH-supported epidemiologists and other health and medical researchers to access a centralized database of death-record information held by state vital statistics offices.

It can be incredibly hard to study the natural history of a disease without patient data that show whether people have died and the causes of death, said **John Gallin**, chief scientific officer of the NIH Clinical Center and NIH associate director for clinical research. He's been studying a genetic immunodeficiency disorder called chronic granulomatous disease for almost 40 years. Although he and other NIH-supported researchers (both intramural and extramural) could access death records through the Social Security Administration or the Center for Disease Control's National Center for Health Statistics (NCHS)—which provided access to the National Death Index (NDI)—the process was becoming more difficult, he said. Not only was the process unwieldy, but the information was often incomplete. In addition, researchers had to pay for access. For example, the cost of accessing 1,000 patient records for a 10-year period is about $1,850. But the costs quickly escalate when researchers need information on thousands of patients, depending on the size of the study.

Intramural investigators do have other means of obtaining death information, but only for patients on protocols at the NIH Clinical Center: the Biomedical Translational Research Informatics System (BTRIS), which is fed data from the Clinical Center's electronic medical record called the Clinical Research Informatics System (CRIS). But both BTRIS and CRIS are of limited use because their records do not show the cause of death for patients who died outside the Clinical Center, explained **Jon McKeeby**, chief information officer and chief of the Department of Clinical Research Informatics at the NIH Clinical Center. The NDI, however, does show the cause of death no matter where the patient died.

So NIH decided to explore ways to help both intramural and extramural researchers access the NDI more easily. Led by the Office of Behavioral and Social Sciences Research (OBSSR), NIH entered into an agreement with the NCHS that became effective in January 2020. Now PIs can more easily request access to NDI data. What's more, NIH will bear the expense.

Staff scientist **May A. Baydoun** (National Institute on Aging), who frequently needs to access the NDI database for her studies on dementia and Alzheimer disease, was excited to have the NDI made available for free to researchers like herself.

The NDI assists investigators in determining whether people in their studies have died and provides the names of the states where the deaths occurred, the dates of death, and death-certificate numbers. Investigators can make arrangements with the appropriate state offices to obtain copies of death certificates or specific statistical information such as cause of death. Or to make things even easier, the "NDI Plus" service can provide cause-of-death codes. Records go back to 1979, and new death records are added to the NDI file annually.

Under the new NIH-NDI agreement, it will be also easier for investigators to share the NDI-linked data with their NIH-funded collaborators as well as with those who are not funded by NIH, according to OBSSR Director **William T. Riley**.

To submit an NDI application, PIs go to the NDI Portal (https://www.cdc.gov/nchs/ndi/portal.htm) and follow the step-by-step instructions. The website includes information on eligibility requirements, rules for obtaining NDI information, criteria for approval, and more. The NDI data can only be used for statistical purposes in public health and medical research. Once PIs are sure their projects meet the criteria, they fill out an online form requesting an electronic application and then wait less than a week for an email with instructions directing them to the electronic application. After they submit the application and supporting documents, there's a two-to-three month wait for NDI processing and approval. A PI can make up to four requests in a calendar year; any request exceeding $100,000 needs to be pre-approved by the NIH.

For more information about the application process and other details about the National Death Index, go to https://www.cdc.gov/nchs/ndi/index.htm. ●

Sunita Chopra is a visiting postdoctoral fellow in the National Cancer Institute, where she studies radiation-responsive coding and noncoding RNA signatures in the blood of whole-body-irradiated animal models.

NIDA Scientists Invent Mobile-Health Platform

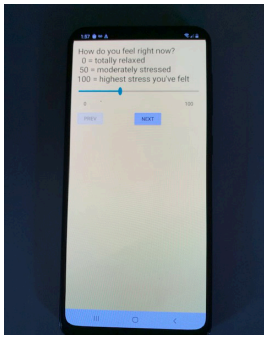
Mobile Technologies Revolutionize Care for People with Substance–Use Disorders

BY DIPTADIP DATTAROY, NCI

Mobile-health technology (mHealth) lets health-care providers collect data on handheld electronic devices such as cell phones or tablets and use those data to predict the optimal timing for delivering treatments and health-education messages to patients. Researchers at the National Institute on Drug Abuse (NIDA) have developed an mHealth platform for promoting psychological wellbeing in people suffering from opioid-use disorders: Mobile devices can monitor a patient's location and intermittently ask questions about their psychological status, predict psychosocial stress, and deliver warnings and automated therapeutic messages that can help prevent a recovering addict from relapsing into drug use.

The journey to this innovation began in 2005 when NIDA Senior Investigator **Kenzie L. Preston** (recently made scientist emeritus) and her team began using a sort of real-time electronic diary—called ecological momentary assessment (EMA)—for 114 opioid-abusing outpatients being treated with methadone to report their activities and moods for up to 20 weeks. EMA had been used to study tobacco addiction but rarely opioid addiction. The researchers reported that the individuals used the mobile devices to provide self-reported data daily and that the data revealed behavioral patterns that led up to drug craving and use. The findings were published in the *Archives of General Psychiatry* (*Arch Gen Psychiatry* **66:**88–94, 2009).

In another study, published in 2014, Preston's team collected time-stamped Global Positioning System (GPS) data and Ecological Momentary Assessment ratings of mood, stress, and drug cravings at random times over 16 weeks of 27 urban drug misusers receiving methadone treatment. The participants were given PalmPilots that they used to answer questions about drug cravings, stress, and their location; and carried small GPS devices. The researchers also used a novel tool, the Neighborhood Inventory for Environmental Typology, to evaluate data in relation to environmental cues (*Drug Alcohol Depend* **134:**22–29, 2014).



Kenzie Preston (left) has invented a mobile health technology that uses mobile devices to deliver warnings and therapeutic messages to help prevent recovering addicts from relapsing into drug use.

These initial experiments led to developing a tool that can unobtrusively collect data on smartphones and use them to predict drug cravings in people recovering from substance-use disorders before it's too late. In 2015, Preston along with NIDA researchers **David H. Epstein**, **Matthew Tyburski,** and **Massoud Vahabzadeh** developed an mHealth platform that uses machine-learning technology and smartphones to continuously collect and monitor patient-specific ambulatory data, process it in a cloud-based server, predict a user's psychological status, and deliver automated interventions when needed. Such interventions include warning a patient in recovery when they are at especially high risk of experiencing a negative event that might cause them to relapse. Through numerous repetitions of processing such information, the mHealth platform became increasingly accurate over time. A U.S. provisional patent application and an international patent application were filed on this technology in 2015 and 2016, respectively. In 2017, a U.S. patent application was filed on the same invention.

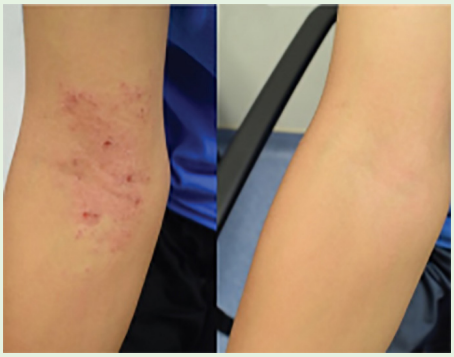
In a recent clinical study, Preston and her team tested a prototype of this mobile app on 189 outpatients being treated for opioid-use disorders and analyzed the data using NIH's High-Performance Computing facility Biowulf. The mHealth platform accurately predicted the probability of opioid craving or stress up to 90 minutes before the craving began (*NPJ Digit Med* **3:**26, 2020).

This mHealth technology could revolutionize clinical care for patients diagnosed with substance-use disorders, posttraumatic stress disorder, depression, or other mental-health disorders. Preston hopes that this mHealth platform would drastically reduce health-care costs and improve patient outcomes. This tool could also be used to study the effect of nongenetic influences, such as environmental exposures, on human health. NIDA is seeking licensing and/or codevelopment partners to further develop and commercialize this mHealth platform.

To learn about technology transfer activities at NIH, go to https://www.ott.nih.gov. In addition, you can read the *NIH Catalyst* story on Tech Transfer (May–June 2019 issue) at https://irp.nih.gov/catalyst/v27i3/news-you-can-use-technology-transfer.

Diptadip Dattaroy was a postdoctoral fellow in the National Institute of Diabetes and Digestive Diseases and an NCI Technology Transfer Ambassador. He is now a fellow in NCI's Technology Transfer Center.

Intramural Research Briefs



CREDIT: NIAID

NIAID: Inner elbow of a child with eczema before *Roseomonas mucosa* therapy (left) and after four months of treatment (right).

NIAID, NCI, NCATS, NIEHS: EXPERIMENTAL TREATMENT FOR CHILDREN WITH ECZEMA

NIH researchers found that an experimental treatment, with *Roseomonas mucosa,* modifies the skin microbiome, safely reduces the severity of atopic dermatitis (eczema), decreases amounts of *Staphylococcus aureus*, a bacterium known to exacerbate eczema, and increased quality of life for children as young as three years old. Eczema, affects about 5% to 25% of children worldwide and is linked to an increased risk of developing asthma, hay fever, and food allergy. The researchers found that specific lipids produced by *R. mucosa* strains isolated from healthy skin can induce skin-repair processes and promote the turnover of skin tissue. (NIH authors: I.A. Myles, et. al., *Sci Transl Med* **12:** issue 560, eaaz8631, 2020)

[BY AMRITA MANDAL, NICHD]

NICHD: OPIOID USE MAY BE LINKED TO PREGNANCY LOSS

Though physicians often prescribe opioids to women of reproductive age, including after a cesarean or vaginal delivery or following a miscarriage, little is known about the effects of the periodic use of such drugs in women who were previously pregnant and wish to conceive again. Researchers in NICHD examined the trends of conception and miscarriage in 1,228 women and monitored prescription opioid use through urine samples and self-reporting. For women who used opioids while trying to conceive, there was a 29% reduced likelihood of achieving conception. Among the women who became pregnant, those who used opioids around the time of conception were 1.5 times as likely to have a miscarriage as women who had not. (NICHD authors: K.S. Flannagan, S.L. Mumford, L.A. Sjaarda, J.G. Radoc, N.J. Perkins, V.C. Andriessen, J.R. Zolton, and E.F. Schisterman, *Epidemiology* **31:**844–851, 2020)

[BY MEGAN KALOMIRIS, NIAID]

NHLBI: STUDY SHOWS DECLINE IN AWARENESS, TREATMENT, AND CONTROL OF HIGH BLOOD PRESSURE

In the past 15 years, there's been a downward trend in awareness among Americans about hypertension (high blood pressure) and how to control and treat it, according to an NHLBI-funded study that included one intramural investigator. The study analyzed data from the National Health and Nutritional Examination Survey of more than 18,000 American adults 18 and older with hypertension. The researchers found 70% of participants were aware of their condition in 1999–2000; awareness increased steadily to 85% in 2013–2014 but declined to 77% in 2017–2018. Of adults with high blood pressure, the number who controlled their condition increased from 32% in 1999–2000 to 54% in 2013–2014, but then declined to 44% in 2017–2018. (NHLBI author: L.J. Fine, *JAMA* **324:**1190–1200, 2020)

[BY EMMA ROWLEY, NIAID]

NCCIH, NIMH, NINR, NINDS: POST-EXERTIONAL MALAISE IN CHRONIC FATIGUE SYNDROME

Myalic encephalitis/chronic fatigue syndrome (ME/CFS) is a debilitating, chronic disease characterized by pain, cognitive difficulties, and severe fatigue. One of its major symptoms is post-exertional malaise (PEM), the worsening of symptoms after physical or mental activities. NIH researchers conducted a study in which 43 ME/CFS patients, divided into nine focus groups (including five groups of people who experienced PEM after a cardiopulmonary exercise test), described their experiences.

The study found that,compared to ordinary activities, the exercise test triggered a faster onset of PEM, it lasted longer, and was more severe. More research is needed to identify PEM subtypes, which may help guide the development of targeted treatments. (NIH authors: B. Stussman, A. Williams, J. Snow, A. Gavin, R. Scott, A. Nath, and B. Walitt, *Front Neurol* **11:** article 1025, 2020; DOI:10.3389/fneur.2020.01025)

[BY DEBOLEENA MITRA GUHARAY]

CC, NICHD: MIGLUSTAT MAY DECREASE RISK OF PNEUMONIA AND DEATH IN CHILDREN AND ADOLESCENTS WITH NIEMANN-PICK DISEASE TYPE C1

A drug called miglustat seemed to stabilize swallowing problems in children and adolescents with Niemann-Pick disease type C1 (NPC1) and decrease the risk of pneumonia caused by the aspiration of food or drink, according to an NIH study. NPC1, which has no FDA-approved therapy, is a rare genetic disorder that causes a progressive decline in neurological and cognitive functions. The researchers used video fluoroscopy—a digitized X-ray movie—to examine the ability of miglustat to improve the swallowing function in 50 children and adolescents with NPC1. By the end of the three-year study, 36 patients had been prescribed miglustat and 24 had not. A longitudinal analysis found that, compared with those not taking miglustat, those who took the drug had a 91% lower risk for deterioration of swallowing and a 72% lower risk of aspiration. The findings add to growing clinical evidence demonstrating the efficacy of miglustat for treating NPC1. (NIH authors: B.I. Solomon, A.C. Smith, A.C., N. Sinaii, N. Farhat, M.C. King, L. Machielse, and F.D. Porter, *JAMA Neurol,* 2020)

[BY THU-LAN LILY NGUYEN, NCI]

Read more at: https://irp.nih.gov/catalyst/v28i6/research-briefs.

COVID-19 Timeline at NIH (September–October 2020)

September 1: NIH launches a study to track the prevalence and impact of SARS-CoV-2 infection among approximately 16,000 pregnant women in seven low- and middle-income countries.

September 2: NIH announces $129.3 million in manufacturing support for new COVID-19 testing technologies as part of its Rapid Acceleration of Diagnostics (RADx) initiative.

September 9: NIH Director **Francis Collins** and U.S. Surgeon General **Jerome M. Adams** testify on vaccines at a Senate Health, Education, Labor, and Pensions Committee hearing.

September 10: NIH ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) initiative launches two of three adaptive clinical trials of blood-clotting treatments for COVID-19.

September 11: NIH Director **Francis Collins's** email to staff mentions that AstraZeneca phase 3 investigational COVID-19 vaccine trial was paused because of an adverse event in the United Kingdom. He also announces the launch of a brief survey to determine how many employees have telework situations that are not ideal and would like to work on-site.

September 14: NIDA Director **Nora D. Volkow** coauthored a study that found that people with substance-use disorders are more susceptible to COVID-19 (*Mol Psychiatry* 2020).

September 14: Clinical Center begins offering saliva testing for asymptomatic employees.

September 15: NIH awards contracts to develop digital health technologies for COVID-19.

September 16: NIH funds community engagement research efforts in areas hardest hit by COVID-19.

September 22: NIH expands clinical trials to test convalescent plasma against COVID-19.

September 23: Fourth large COVID-19 vaccine trial, to evaluate a single-dose vaccine, begins.

September 23: NIAID Director **Anthony Fauci** testifies at a U.S. Senate Health, Education, Labor, and Pensions Committee hearing on an update to the COVID-19: federal response.

September 23: The Office of Research Services announces that NIH staff on campus can use an app to order and pay for food from two cafeterias. Food truck services continue, too.

September 24: NIH scientists and others announce their discovery of the genetic and immunologic underpinnings of some cases of severe COVID-19 (*Science* **370:**eabd4570, 2020; *Science* **370:**eabd4585, 2020).

September 29: NIH reports that the phase 1 trial of Moderna's investigational vaccine, which was codeveloped with NIAID, shows that the vaccine generates an immune response in adults over 70 years old (*N Engl J Med* 2020).

September 30: As part of RADx, NIH awards nearly $234 million to improve COVID-19 testing for the underserved and vulnerable.

October 2-5: On October 2, President Donald Trump announces that he and First Lady Melania Trump have tested positive for COVID-19. He is admitted to Walter Reed Medical Center on October 3 and receives one dose of experimental monoclonal antibodies, a several-day course of remdesivir, and the steroid dexamethasone. He is released on October 5.

October 5: **Harvey Alter** is awarded the 2020 Nobel Prize in Physiology or Medicine for his contributions to the discovery of the hepatitis C virus that led to curative treatments and keeping the blood supply safe for transfusions.

October 5: **Anthony Fauci** is celebrated as the Service to America Medal 2020 Federal Employee of the Year. **Ira Pastan** is named the 2020 winner of the Paul A. Volcker Career Achievement Award for his discovery of drugs that successfully treat a rare form of leukemia and holds promise for other cancers.

October 6: The NIH RADx initiative advances six new COVID-19 testing technologies.

October 8: NIAID announces the start of a phase 3 clinical trial to test whether remdesivir plus a highly concentrated solution of antibodies that neutralize SARS-CoV-2 virus is safe and effective in hospitalized patients.

October 8: NCI announces the launch of the Serological Science Network for COVID-19 (SeroNet), which aims to quickly increase antibody testing capacity.

Oct 8: A final report confirming remdesivir benefits for COVID 19 is published (*N Engl J Med* NEJMoa2007764, 2020).

October 12: Johnson & Johnson announces that it is pausing its phase 3 vaccine trial due to an unexplained illness in one participant (trial resumes October 23). Also paused is the ACTIV-3 trial testing the Eli Lilly monoclonal antibody. The AstraZeneca phase 3 clinical trial remains on hold in the United States but has resumed in other countries.

October 12: NIAID launches the phase 2 ACTIV-5 Big Effect Trial, which is designed to determine whether certain approved therapies or investigational drugs in late-stage clinical development show promise against COVID-19.

October 16: An NCATS-coordinated phase 3 ACTIV-1 trial starts; it will evaluate safety and efficacy of three immune modulator drugs in hospitalized adults.

October 16: NIH opens an exceptions process to allow federal employees who are teleworking under challenging circumstances to apply to voluntarily return to the physical workspace.

Week of October 19: Moderna announces that it has reached its phase 3 vaccine trial enrollment goal of 30,000 participants, with 42% of those from high-risk groups.

October 23: Maryland's Montgomery County Chamber of Commerce announces that the 2020 Visionary of the Year Award goes to NIH.

October 28: *Cell* paper reports that NHLBI researchers discovered a biological pathway that the novel coronavirus uses to hijack and exit cells as it spreads through the body.

October 29 and 30: The NIH/FDA COVID-19 Research Workshop, held virtually, highlights NIH's and FDA's extensive work on COVID-19.

October 31: In a virtual celebration, NIH marks the 80th anniversary of President Franklin Roosevelt's October 31, 1940, dedication of the NIH campus.

Read more at: https://irp.nih.gov/catalyst/v28i6/covid-19-timeline-at-nih-september-october-2020

Bringing Precision Medicine to Neuroscience

Profile: Andrea Pfeifer

BY MICHAEL TABASKO

CREDIT: AC IMMUNE

Andrea Pfeifer, who trained at NIH, is now chief executive officer of AC Immune SA, a Swiss biopharmaceutical company that she helped launch in 2003.

One of Andrea Pfeifer's mottos comes from Carl Zuckmayer, a German writer who said, "One-half of life is luck; the other half is discipline–and that's the important half, because without discipline you wouldn't know what to do with your luck." In a career that arcs from the lab to corporate leadership and back again, Pfeifer knows a bit about what it takes to write your own success story.

The 1980s saw the dawn of precision medicine in oncology. At the National Cancer Institute (NCI), **Curt Harris's** Laboratory of Human Carcinogenesis was at the forefront of molecular epidemiology. They were pioneering novel approaches to understand what factors make human cells mutate into cancer cells. Walking the halls of building 37, you would find Nobel laureate **Michael Bishop**, whose groundbreaking discovery of oncogenes had already changed the course of cancer research, or Lasker Award winner **Robert Gallo**, whose work associated retroviruses with certain leukemias and lymphomas. The idea that cancer was a multifaceted disease deserving of targeted interventions was gaining traction. Meanwhile, over in Germany at the University of Würzburg, a bright young scientist was considering where to start her career.

As luck would have it, two of Harris's respected colleagues at the university had been mentoring Andrea Pfeifer to a Ph.D. in toxicology and cancer research: Professor Hans Günter Neumann, the chair of the university's Institute of Toxicology and Pharmacology and a pioneer in the field of chemical carcinogenesis; and Professor Dietrich Henschler, an expert in pharmacology and toxicology. They encouraged Pfeifer to explore a postdoctoral experience at NIH.

Up to that point, Pfeifer's studies were founded on a chemically based model of treating chronic diseases. She had a different vision however, and her career trajectory began to tilt toward a more precise molecular approach. "I wanted to link oncology with molecular biology and this is why I choose Curt's lab," said Pfeifer. In 1984 she secured a grant and a fellowship, and she joined the NIH family as a postdoctoral fellow.

Growing up in Germany, Pfeifer was exposed to the more technical aspects of life: "I changed tires, adjusted valves, and ran cars with my brothers." She also had an uncle at the University of Würzburg, Professor Otto Volk, a physicist who stimulated and supported her curiosity in science.

At age 11, things changed for Pfeifer when her father was diagnosed with lymphoma, which ultimately pushed her toward the medical sciences. "It made me resilient, a survivor, made me a leader simply because early on in life I had to take on greater responsibility," she recalled. Studying pharmacology and toxicology led to working on what mattered most to her—coming up with ways to diagnose and treat incurable diseases.

She remembers her time at NIH fondly. "We worked like crazy, days and nights, for this unique opportunity to generate papers, feeling like there were no limits," she explained. "You could go out into the corridor and discuss your project with a Nobel Prize–winning scientist such as Michael Bishop. It was an incredible experience, the openness and sharing. I've never seen anything like that again."

At NIH, Pfeifer helped create the first immortalized human cell lines used as models for studying lung and liver cancer. These intentionally mutated cells divide indefinitely and are still in use today and are licensed for applications ranging from medical research to drug testing. Pfeifer would later work for the food and beverage company Nestlé. In 1990 she set up a Cooperative Research and Development Agreement with NIH to further develop those cells for use in food-safety testing.

"She was very creative, rigorous with her scientific method, and had this inventive spark," recalled Harris, who became Pfeifer's scientific mentor and close friend. He joked, "She was also very communicative and an instigator of parties."

Harris's lab celebrated its 25th anniversary in 2006, long after Pfeifer had left NIH. But she helped to organize the event, bringing in alumni from across the globe. She recalled, "We decided to gift Curt a painting by Swiss artist and physician-scientist Peter Cerutti for the party." (Before pursing an art career, Cerutti was internationally recognized for his work in cancer research and aging.) "The painting was bigger than any airline would allow and I had to persuade a

German government delegation to help me bring it from Switzerland to NIH."

In 1989 Pfeifer left NIH having published 26 papers (she now has over 200). She returned to Europe to be with her ailing father and joined Nestlé at their Research Center in Lausanne, Switzerland, rising rapidly to become head of Nestlé Global Research as she brought her knowledge of molecular diagnostics to the food industry. Over the next 13 years she would transform the company's research direction from chemistry to biology. Pfeifer's team sequenced the genome of the bifidus bacterium, resulting in the first probiotic yogurt. "We discovered how food can influence genetics, from skin health to allergy prevention–all going in the direction of precision nutrition," she said.

She was translating science into business. Using her multinational network Pfeifer expanded Nestlé's research collaborations with universities around the world. She cofounded a venture capital fund to bring new projects into the company, exposing her to the world of start-up financing. It was around this time where she met the men who would be the cofounders of her future company: Nobel laureate Jean-Marie Lehn, Claude Nicolau, Fred Van Leuven, and the late NIH scientist and Lasker Award winner, **Roscoe Brady** (National Institute of Neurological Disorders and Stroke).

The four scientists approached Pfeifer with a potential game-changer in the world of neuroscience. "They introduced a technology that has the capability to target plaques and tangles in the brain caused by misfolding proteins," she explained. The researchers were mainly studying prions, proteins that can trigger neighboring proteins to misfold abnormally. A hallmark of several neurodegenerative diseases, mutated proteins can spread in a virus-like manner throughout the brain and are linked to cognitive decline.

While prion diseases (such as Creutzfeldt-Jakob disease) are rare, the scientists recognized the same mechanism of action in Alzheimer disease (AD) involving amyloid-beta and tau proteins. Nearly 50 million people suffer from dementia worldwide, and AD is the leading cause. Without an effective treatment, Pfeifer saw a huge unmet need and an opportunity to improve millions of lives. She left Nestlé and returned to her roots in medical research.

Pfeiffer and her cofounders launched AC Immune, a Swiss biopharmaceutical company, in 2003. They now have three diagnostic and nine therapeutic product candidates to diagnose and treat neurodegenerative diseases. With a focus on early detection and accurate diagnosis, the company leads the industry with their tau protein programs. Brain-imaging techniques, such as positron emission tomography (PET) scans, can detect abnormal tau concentrations decades before AD symptoms start. For example, a PET tracer (a radioactive drug used for diagnostic purposes) can identify abnormal tau which could then be treated with an appropriate vaccine, small molecule, or antibody. AC Immune's diverse pipeline continues to evolve through ongoing clinical trials.

Much like targeting specific oncogenes, the door is now open to identify neurodegenerative diseases before they start. Pfeifer is reminded of her days at NCI. "We are at a crossroads because we can finally apply a precision approach in neuroscience as we did 30 years ago in oncology," she said. "We can look into the brain, identify the underlying pathology, and then actually treat [neurodegenerative diseases] according to that pathology."

In an NIH-funded study on healthy individuals, AC Immune is testing whether the drug crenezumab can prevent the onset of AD in a high-risk population in the Aburrá Valley of Columbia who are genetically predisposed to AD. If the treatment works, it would be the first to show how AD might be prevented.

CREDIT: AC IMMUNE

Lab at AC Immune (Lausanne, Switzerland), a company with diagnostic and therapeutic product candidates to diagnose and treat neurodegenerative diseases.

Pfeifer will tell you that she never wanted to be a role model. But with time, she realized that the success story around her career became an inspiration to other women. Woman are vastly underrepresented in the biopharmaceutical industry, yet Pfeifer excelled. Her secret? She credits remaining authentic, having honest mentors, and never compromising the quality of her science. Staying true to herself has been a source of strength. "I worked extremely hard, and maintained my [traditionally] feminine qualities, like working with people and bringing people together," she said. AC Immune is currently 52% women, well above the biopharma industry average.

From scientist, to businesswomen and entrepreneur, Pfeifer has had a truly remarkable journey. "It really goes back to NIH," she said. "I was exposed to multicultural approaches where many friendships and collaborations were formed that still exist. They are still a source of inspiration today." ●

Resistance to the Plague

CONTINUED FROM PAGE 1

Dan Kastner was a co-author of a study that found that genomic variants that cause familial Mediterranean fever may also confer increased resistance to the bubonic plague.

copies of the mutated *MEFV* gene may be a secret weapon against the bubonic plague. Normally *Y. pestis* represses the function of pyrin in healthy individuals and in so doing suppresses the body's inflammatory response to the plague. But the mutated *MEFV* genes prevent the ability of *Y. pestis* to interfere with the normal function of pyrin.

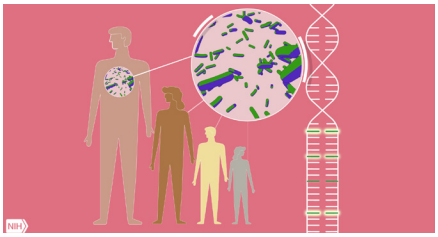
NHGRI Scientific Director **Dan Kastner**, a senior author on the paper, has studied FMF since 1985 when, as an NIH rheumatology fellow, he treated an Armenian patient who had the disease. Kastner's group first considered that natural selection played a role in today's prevalence of FMF because of its unusually high carrier frequency (proportion of people in a population who have only one copy of a mutant gene). The carrier frequency of *MEFV* mutations in Mediterranean populations is about 10%.

"It was in Jewish populations, Arab, Turkish, [and] Armenian," said Kastner. "It didn't seem like something that would happen just by chance." If it did, the carrier frequency would be much lower.

To provide evidence for natural selection, the researchers analyzed the genomes of 2,313 Turkish people and 352 ancient archeological samples including 261 from before the Christian era. Kastner's team used mathematical modeling to estimate that two FMF-causing mutations in the *MEFV* gene arose more than 2,000 years ago. They also found that people with the same mutations had stretches of identical DNA flanking the mutation site. This set of DNA variants tends to be inherited together and is called a haplotype. According to evolutionary theory, if there is a selective pressure such as an infectious disease, a haplotype with mutations that protect humans in some way is conserved over the course of multiple generations. But if there is no selective pressure, the haplotype is no longer useful and is lost over time. In people with the normal *MEFV* gene, the researchers didn't find a conserved haplotype.

But this evaluation didn't explain what was causing the natural selection to increase the frequency of *MEFV* mutations in Mediterranean populations.

Kastner's group suspected *Y. pestis* as exerting a potential selective pressure on mutations in the pyrin gene because 1) *Y. pestis* releases a toxin called YopM that inactivates pyrin—it makes sense that humans would evolve a mutation in the pyrin gene that increases its resistance to YopM; 2) *Y. pestis* was an incredibly strong selective pressure—the bubonic plague wiped out a third of Europe's population in the 14th century; and 3) *Y. pestis* has been able to shape the human genome for an incredibly long time—it was around during the 6th century Justinian plague and the 14th century Black Death.



E. DEL AGUILA III, NHGRI

An illustration depicting specific genomic variants passed down to succeeding generations.

The researchers found that, compared with cells from healthy control subjects, the immune cells isolated from the blood of people with FMF produced more interleukin 1-beta (an inflammation-causing protein) in response to *Y. pestis* infection. In addition, immune cells from people with only one copy of the mutated *MEFV* gene (and who usually do not develop FMF) were also resistant to *Y. pestis* infection. Even mice that were genetically altered to have two mutated *MEFV* genes had a clear survival advantage when infected with *Y. pestis*.

The findings demonstrate the double-edged sword that is evolution. "This is certainly not the first example of a mutation in a recessive disease gene being protective against an infectious agent…on the one hand…but on the other hand causing a human disease," said Kastner.

Another example of a genetic mutation that is protective yet causes disease is the beta-globin gene, which when mutated causes sickle-cell anemia but also confers resistance to malaria.

Still, evolution has done what is best for humans. Despite a small number of people having two mutant *MEFV* copies and developing FMF, more have only one copy and are resistant to the bubonic plague.

Moving forward, Kastner plans to consider how interactions between hosts and microbes influence the evolution of other genetic diseases. "The host is just half of the equation," said Kastner. "There's this whole other world, the microbial world." ●

Ethan Smith, a postbaccalaureate fellow in the National Institute of Nursing Research, is working on clinical studies involving biomarkers for traumatic brain injury. When he completes his training in 2021, he expects to attend graduate school for social work.

Glimpses of History through Uniform Patches and Coloring Books

Two New Exhibits at the NIH Clinical Center

BY DEVON VALERA, OFFICE OF NIH HISTORY

Two fairly new exhibits in the NIH Clinical Center (CC)—one on uniform patches and another on coloring books—reveal the more colorful side of the CC's history.

Patches: Thanks to **Margaret Conant** (in CC's Radiological and Imaging Sciences Department), who donated patches to the Office of NIH History and Stetten Museum, more than 50 uniform patches are now on display. The exhibit is on the first floor of Building 10 at the end of the central corridor near the Phlebotomy/EKG Clinic.

A familiar sight on lab coats and uniforms, these patches identified different departments and units that operated within the CC. Patches were designed either by the Medical Arts branch or by NIH employees competing in design competitions and revealed the personalities and perspectives of the divisions they represented.

The patches are vibrant, playful, thoughtful, and, at times, mysterious. Anesthesiology's patch takes the phrase "counting sheep" literally and features two fluffy white sheep leaping over a fence. The patch for the National Cancer Center's (NCI's) Hyperthermia Unit shows a crab being boiled, referencing both Maryland's culinary specialty as well as the zodiac sign Cancer in a clever visual pun. More curiously, though, the CC itself is represented by, of all things, a duck. Why? We're not quite sure ourselves. If you have any insights into this mysterious duck's meaning, please let **Michele Lyons** know (lyonsm@od.nih.gov). We'd be delighted to include its history alongside these patches.

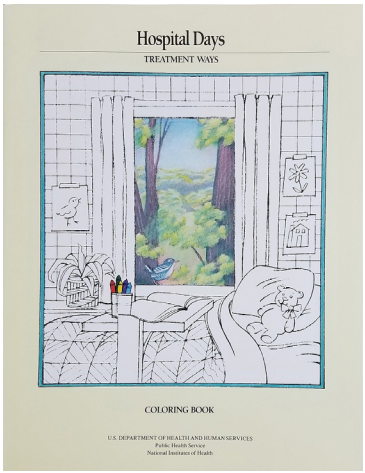
Coloring books: The second exhibit, on the second floor near the cafeteria, considers the history of a familiar object–the coloring book. From explaining the roles of doctors and nurses to illustrating what operating rooms look like, these books not only introduced children to complicated ideas but can also aid historians in understanding changing attitudes and perspectives at the NIH throughout history.

Coloring books have been prevalent at NIH since at least the 1960s. The oldest on display, *The Friendly Clinical Center Coloring Book*, introduced children to the NIH and potentially foreign concepts such as medical clothing, hospital rooms, and occupational therapy. Despite the commendable intentions of this coloring book, it unfortunately reveals the biases of the time. Diversity wasn't a consideration back then—children were all presumed to be white and the doctors exclusively referred to as "men." This lack of diversity changed, however, with the introduction of *The Clinical Center Coloring Book* published nearly 30 years later. It was created by **Wendy Schubert** of the CC's Patient Education Working Group and represents a more diverse panel of both patients and clinicians.

Another noteworthy coloring book is *Hospital Days, Treatment Ways: Hematology–Oncology Coloring Book*, written and illustrated by Jenene Warmbier and Ellen Vassy. Warmbier began illustrating the book in 1975 when her two-year-old daughter was diagnosed with neuroblastoma, a cancer that targets early nerve cells. When her daughter was being treated at the Ohio State University Children's Hospital (Columbus, Ohio), Warmbier began to draw what she saw around her, compiling images of the potentially scary things that children can encounter during cancer treatment. Warmbier created a remarkably compassionate and friendly image of the hospital featuring a diverse representation of races, sexes, and abilities. Ellen Vassy, a nurse at the Children's Hospital, contributed text. This book was first used at the Children's Hospital before being modified and reprinted by NCI in 1982. (Sadly, Warmbier's daughter died 20 months after her diagnosis.)

These stories and many more are tucked within the halls of the Clinical Center. We invite you to explore these two new exhibits as well as the many others the Office of NIH History and Stetten Museum has installed throughout the NIH campus. ●

Mark Riewestahl, an exhibit intern at the Office of NIH History and Stetten Museum, near the display of Clinical Center patches that he designed.



BOTH: MICHELE LYONS, OFFICE OF NIH HISTORY

One of the coloring books in the display in the NIH Clinical Center: *Hospital Days, Treatment Ways: Hematology-Oncology Coloring Book*.

Singing Dogs

CONTINUED FROM PAGE 1

Elaine Ostrander's team confirmed via genomic analysis that there is an ancestral relationship between the New Guinea highland wild dog and the New Guinea singing dog, long thought to be extinct in the wild.

studying these dogs may help scientists understand how human vocalization developed.

"One of the cool things about genomics is that once you do the genome sequence of something, you can go back to that data over and over and over to look at different traits," explained **Elaine Ostrander**, NIH Distinguished Investigator and senior author of the paper. "We went to it to test and see if these were, in fact, the New Guinea singing dogs. But we can go back to it again and see if we can find the genes responsible for vocalization."

The New Guinea singing dog was first studied in 1897. In the late 1960s, when it was clear that the breed was endangered, eight of the dogs were brought to the United States for conservation purposes. There are 200–300 of these dogs in captivity today, but the effects of inbreeding in such a small pool of individuals for many generations has resulted in loss of genomic variants that existed in their wild counterparts.

More recently another wild dog population, called the "New Guinea highland wild dog," has been sighted. It is physically similar to and thought to be the predecessor of the singing dogs. In 2016, the New Guinea Highland Wild Dog Foundation, in collaboration with the University of Papua (West Papua, Indonesia), led an expedition to Indonesia and found 15 highland wild dogs. In a follow-up field study in 2018, blood samples were collected from three of the dogs and analyzed by Ostrander's lab in NHGRI. The DNA analysis revealed an ancestral relationship between the highland wild dog and the New Guinea singing dog. They are essentially the same breed, according to the researchers. The genomes are not identical, however, because the populations have been physically separated for several decades and due to inbreeding among the captive New Guinea singing dogs.

"There's an opportunity to reinvigorate the conservation populations and bring back the true New Guinea singing dog" by establishing breeding programs, said Ostrander. "It's one of the many examples of how the Human Genome Project benefits a lot more than just humans."

Heidi Parker and her dog Hattie. Parker led the genomic analysis in the study. The discovery of free-living highland wild dogs may provide greater insight into the genomics of vocalization, a field that has previously relied on the study of birdsongs.

Moreover, the discovery of free-living highland wild dogs may provide greater insight into the genomics of vocalization, a field that has previously relied on the study of birdsongs. According to **Heidi Parker**, an NHGRI staff scientist who led the genomic analysis, it is believed that dogs developed barking as a means to mimic human speech after they were domesticated. This belief is supported by the fact that wolves do not bark, and neither do highland wild dogs, which seldom encounter people. The highland wild dogs are unique in that they neither bark nor howl but have developed a completely different form of vocalization with their singing, the purpose of which is yet unknown.

"We think that this could be a really great comparison [with] both wolves and [with] modern dogs to understand what changed in [the highland wild dogs] to change the tones, basically to hold these very sort of musical notes versus a barking sound," said Parker. The genome sequences collected in this study can be searched for the genes responsible for vocalization and those genes can be compared with the ones found in the human genome; the differences and variations could reveal more about what these genes do. "It could even give us some indication of how people sing."

The researchers also hope that their studies will provide insights into how deficits in human vocalization occur and offer clues that could lead to treatments. ●

Journal article referred to in the article: *Proc Natl Acad Sci USA* 117:24369-24376, 2020; DOI:10.1073 (https://www.pnas.org/content/117/39/24369).

Natalie Hagen, a postbaccalaureate research fellow in the National Center for Advancing Translational Sciences, is performing pharmacokinetics studies of novel drug candidates. In 2021, she plans to pursue a Ph.D.

Joan Steitz's WALS Lecture on Viral Noncoding RNA

Taking RNA from Historic Origins to Modernity

BY FRANCES FERNANDO NICHD

Yale professor Joan Steitz delivered a virtual WALS lecture on "Viral Noncoding RNAs: Approaching Answers."

Joan Steitz leads and inspires by example, with her infectious passion for all things RNA. As a young college student, she had seen female medical doctors but never a female professor heading a lab. She did not anticipate building a career as a woman molecular biologist.

Her interest in molecular biology began in the 1960s when she was a work-study intern in **Alex Rich's** laboratory at the Massachusetts Institute of Technology (MIT, in Cambridge, Massachusetts). Rich, who played an important role in the discovery of nucleic acid hybridization, had worked with Nobel laureate Francis Crick to solve the structure of collagen.

Steitz earned her undergraduate degree in chemistry in 1963 (from Antioch College in Yellow Springs, Ohio) and then went on to train with two Nobel laureates herself—Crick and **James Watson**, who together had first described the DNA double-helix structure in 1953 and won the Nobel Prize in Physiology or Medicine in 1962. She was the first female graduate student to join Watson's lab at Harvard University (Cambridge, Massachusetts) and completed a Ph.D. in biochemistry and molecular biology in 1967. Her postdoctoral training in cell biology was with Crick at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England.

Incidentally, both Rich and Watson had NIH ties: Rich as a section chief in physical chemistry (1954–1958) and Watson as the first director of the National Center for Human Genome Research (1989–1992).

Today, Steitz is a Howard Hughes Medical Institute Investigator and the Sterling Professor of Molecular Biophysics and Biochemistry at Yale. She's won numerous awards including the 2018 Lasker-Koshland Special Achievement Award in Medical Science for "pioneering discoveries in RNA biology, generous mentorship of budding scientists, and vigorous and passionate support of women in science."

Exploring RNA: Steitz has been studying RNA since the field's nascency in the 1960s and has loved seeing the developments and exciting questions answered since. "The RNA field did not exist, and [I] was privileged enough to be one of the committee of people who established the RNA Society," said Steitz who was its first vice president and president-elect in the 1990s when the society was established.

She has contributed to monumental advancements in the RNA field through multiple discoveries, notably of the sites, sequences, and mechanisms for mRNA binding to ribosomes and of single-nucleotide ribonucleic proteins and their role in splicing systems. From this basic RNA research comes exciting and tangible payoffs in medicine because 60% of genetic diseases have splicing-system defects.

WALS lecture: On September 23, 2020, Steitz's gave a virtual lecture on her research on viral noncoding RNAs (ncRNAs), which play critical roles in the regulation of gene expression. Her focus has been on gamma-herpesviruses such as Kaposi sarcoma-associated herpesvirus (KSHV, the cause of the most common cancer afflicting AIDS patients), Epstein-Barr virus (which can cause mononucleosis), and others. Her investigations of polyadenylated nuclear (PAN) RNA, which is in cells infected by KSHV, has led to the realization that it contains an RNA element (called the element for nuclear expression, or ENE) that's needed for the nuclear accumulation of RNA transcripts.

Her group discovered that ENE elements prevent the degradation and decay of PAN RNA by engaging the end section called the polyA tail. One of Steitz's postdocs later determined that the structure forming the RNA was the longest stretch of triple helix ever documented in RNA. Steitz told the story of how three NIH investigators—**Gary Felsenfeld**, **David Davies**, and her mentor, Rich—predicted exactly this structure…back in 1957.

Steitz believes that further structural and molecular understanding of RNA will be critical in the field's future of elucidating RNA's diverse functions. With her pioneering RNA work, she has enthusiastically forged paths forward for new scientific discoveries, medical contributions, and women in science. ●

To watch Joan Steitz's WALS talk, go to https://videocast.nih.gov/watch=38678 (HHS only).

Frances Fernando is a postbaccalaureate fellow in the National Institute of Child Health and Human Development. After completing her training in 2021, she plans to pursue a doctorate in public health to work on integrative global health issues and human rights.

Cyber Health Checkup: Don't Be Phish Food!

NIH Cyber Safety Awareness Campaign

BY SUSAN CHACKO, CIT

Cybersecurity is one of those annoyances that your institute's information technology (IT) people take care of, right?

Wrong. That might have been the case a decade or two ago, but now, keeping NIH's employees, patients, and systems safe from cyberattacks is a responsibility for *everyone* who accesses NIH data and systems. Did you know than more than 99% of the emails coming into NIH are spoofing or phishing attempts (messages that masquerade as a trusted entity and try to trick recipients into sending money or clicking malicious links) or spam (unsolicited advertising email)? Every day, 23 million emails are blocked by the central NIH email filters and 36 million web connections to suspicious sites are stopped at the NIH firewall.

Last year, one spoof didn't get blocked: Several employees received an email purporting to be from NIH Director **Francis Collins** asking them to use their government purchase cards to buy gift cards that supposedly would be distributed for employee recognition awards. Luckily, a careful recipient alerted the NIH IT Service Desk. The NIH information security team confirmed the spoof, removed the email from the inboxes of hundreds of employees, and determined that the director's email had not been hacked. Without this alert, thousands of federal dollars might have been scooped up by the cyber criminals.

It's not just taxpayer money that is at stake but also patient medical records, personal employee information, and vital research data.

Cyber risks don't just come from the outside. One seemingly minor infraction is sharing login credentials with a friend or colleague. The potential for damage—to systems, to personnel, and to biomedical research—is huge. A few years ago, a peer reviewer at a university shared their NIH grant-review login information with a grant applicant, who was then able to access reviews and identify the reviewers of their own grant application. NIH takes the confidentiality and integrity of its vast grant-review process very seriously, and there are consequences from such misbehavior. When the breach was discovered, the resulting investigation led to the resignation of both researchers from their institutions.

NIHers may have noticed an increasing number of emails, announcements, and articles about cybersecurity at NIH over the past few months. These are part of the NIH Cyber Safety Awareness Campaign, an Optimize IT Security initiative, which aims to raise awareness of the real-life risks to NIH if cybersafe behaviors are not implemented and embraced.

Cybersecurity and research: Many scientists have seen IT security as an obstacle to research but are beginning to understand that the barriers are necessary for the protection of their work and NIH resources, said NCI staff scientist **Art Shaffer**. As a member of the Optimize IT team, he brings a bench researcher's perspective to the work. Before COVID-19 forced many NIH employees to work from home, interactions between scientists were face-to-face with little cyber risk. Now "I can't just take a flash drive with my two gigabytes of data over to my buddy's computer at the other end of the lab," said Shaffer. Instead, the data need to be transferred securely over the NIH network using a tool such as NIH Box.

Data sharing "is fundamental to the NIH mission, but we need to be able to do that safely," reiterated **Robert Balaban**, the scientific director of the National Heart, Lung, and Blood Institute, during a recent virtual panel discussion about cyber safety and COVID-19. "The important thing to realize is that we are a connected community, and [anyone] could end up being one of the breaks in the system."

Scientists might feel that a security-monitoring program, or "agent," running on their laptop is slowing the computer down or that they are being spied on, said **Ryan Dale**, a senior scientist at the National Institute for Child Health and Human Development (NICHD). He certainly understands the pressure to get research done, but as NICHD's scientific information officer, he also appreciates the importance of protecting the big cyber target that is the NIH. Thousands of vulnerabilities—old, unsafe operating systems, poorly configured software, and suspicious downloaded material—are identified each day by NIH's security agents.

Collaborating safely: There are a lot of collaboration tools for sharing photos and data, but they are not all NIH approved or safe to use. The NIH Technology Availability Guide (NTAG) provides a list of approved tools that will enable research collaborations while protecting NIH digital assets. NIH has a robust set of collaboration and file-sharing tools that are approved and available for use including Box, Skype for Business, Jabber, Microsoft Teams, and Zoom. Using collaboration or file-sharing platforms that have not been approved for use by your information system security officer (ISSO) and are not listed on the NTAG may expose NIH to cyber threats, breaches, or data loss and should not be used. If you don't already have access to a tool listed on NTAG, contact the NIH IT Service Desk for assistance. Before using any collaboration or file-sharing tool that is not listed on NTAG, contact your ISSO to ensure it is safe to use. If emailing sensitive or confidential information, encrypt the emails or send them via NIH Secure Mail. And if

you need a collaboration tool that is not on the NTAG list, work with your ISSO to discuss your needs and have tools properly assessed before use. A single cybersecurity incident has the potential for widespread consequences; do not compromise your data or that of others, use NIH approved tools, and when in doubt, reach out to your ISSO for guidance.

Report anything suspicious: In general, "Don't be afraid to report something" that seems unusual, said **Jothi Dugar**, chief information security officer at the Center for Information Technology, who is leading the Cybersecurity Awareness Campaign. Be on the lookout for suspicious emails, or computers acting weird (crashing frequently or showing popup ads, for example). "We're not going to be coming after you for clicking on a link. We want to take care of the situation and provide guidance and training."

Cyber safety needs to be a priority for all employees, integrated into their day-to-day jobs. The "protective shell of IT infrastructure armors NIH against cyberattacks on a daily basis," said Schaffer. But all of us have a part to play as well. ●

To find resources mentioned in this article go to NIH Cyber Safety Awareness Campaign website, go to https://ocio.nih.gov/InfoSecurity/Pages/CyberSafety.aspx. To reach the NIH IT Service Desk go to https://myitsm.nih.gov or call 301-496-4357, 866-319-4357 (toll-free), or 301-496-8294 (TTY).

Susan Chacko, who is a scientist on the Biowulf cluster staff at the Center for Information Technology, came to NIH as a postdoc in 1992. She leads a team of scientists who install and maintain scientific programs on Biowulf, helps intramural researchers implement large-scale computational research projects, and provides one-on-one support.

New SIG: Sexual and Gender Minority (SGM) Health Scientific Interest Group

The recently established Sexual and Gender Minority Health Scientific Interest Group (SGM Health SIG) is interested in supporting a range of biomedical, clinical, behavioral, and social science research to advance the health of all sexual and gender minority (SGM) populations, with a specific interest in the disease areas and health conditions that affect these individuals.

The SIG will 1) connect individuals trained in different scientific disciplines engaged or interested in conducting SGM health research; 2) provide intramural researchers and trainees a venue to share and receive feedback on their research and discuss publications related to SGM health; and 3) provide opportunities for career development, networking, and community engagement.

SGM populations include but are not limited to individuals who identify as lesbian, gay, bisexual, asexual, transgender, Two-Spirit, queer, and/or intersex; individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development; and those who do not self-identify with one of these terms but whose sexual orientation, gender identity or expression, or reproductive development is characterized by nonbinary constructs (not identifying as either man or a woman) of sexual orientation, gender, and/or sex.

The SGM Health SIG is a partnership among the NIH institutes, centers, and offices, the Intramural Research Program (IRP), and the Sexual and Gender Minority Research Office (SGMRO) in the Office of the Director. While regular activities for this SIG will be led by members of the IRP, the SGMRO will provide guidance by selecting and inviting extramural scientists to present scientific lectures to the group. SGMRO will also assist IRP researchers leverage resources to better engage in SGM health research and help identify mentors for trainees.

The SGM Health SIG is open to all (including NIH intramural and extramural investigators, as well as people from other federal agencies and area universities). The SIG will have regularly scheduled meetings every two to three months and hold an annual retreat. Meetings will feature presentations by invited NIH staff, extramural researchers, and SIG members, and discussions about research ideas and relevant publications.

For more information and to join the SGMHEALTH_SIG LISTSERV email list, which will share meeting announcements and other information, go to https://oir.nih.gov/sigs/sexual-gender-minority-health-scientific-interest-group. For questions, contact the chair, **Erik Rodriquez** (erik.rodriquez@nih.gov). ●

NIH Scientific Interest Groups (SIGs) are assemblies of scientists with common research interests; communicate via LISTSERVs; sponsor symposia, poster sessions and lectures; provide mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; and more. Most SIGs welcome interested non-NIH scientists, too . For more information and a list of SIGs, go to https://oir.nih.gov/sigs.

Recently Tenured


CHRISTINA ANNUNZIATA, NCI-CCR


T.C. "KELVIN" CHOI, NIMHD


TAE-WOOK CHUN, NIAID


HEIDI H. KONG, NIAMS


DA-TING LIN, NIDA

CHRISTINA ANNUNZIATA, M.D., PH.D., NCI-CCR

Senior Investigator and Head, Translational Genomics Section, Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute

Education: Georgetown University College of Arts and Sciences, Washington, D.C. (B.S. in biology, Ph.D. in pathology); Georgetown University School of Medicine, Washington, D.C. (M.D.)

Training: Resident, Department of Internal Medicine, Georgetown University School of Medicine; Medical Oncology Fellow and later Research Fellow, Medical Oncology Branch, NCI

Came to NIH: In 2002 for training

Outside interests: Cooking; cycling; and doing yoga

Website: https://irp.nih.gov/pi/christina-annunziata

Research interests: Ovarian cancer accounts for more deaths than any other cancer of the female reproductive system, resulting in over 15,000 deaths annually. Most patients respond to platinum-based chemotherapy, but more than 70% of people with advanced ovarian cancer relapse within 24 months. My lab has identified a subset of ovarian cancer cell lines that are dependent on the NF-kappa-B signaling pathway for growth and survival. NF-kappa-B is a protein complex that controls DNA transcription, cytokine production, and cell survival. Aberrant NF-kappa-B signaling has been identified in tumors of epithelial origin including breast, colon, lung, and ovarian carcinomas.

My lab's genomic profiling and functional screens identified both downstream targets and upstream regulators of this pathway, defining subgroups of patients whose cancers depend on NF-kappa-B and opening up possibilities for novel therapies to treat ovarian cancer. I am conducting several clinical trials to better understand both predictive and pharmacodynamic markers of treatment response. One of my earlier clinical trials used a synthetic small molecule called birinapant to block NF-kappa-B signaling and induce apoptosis in ovarian cancer (*Cancer* **122:**588–597, 2016). This study led us to identify other pathway inhibitors that are synergistic in killing ovarian cancer cells. We are about to open a new clinical trial with the combination of small molecules that inhibit two pathways.

A second focus of my lab and clinic is immunotherapy for ovarian cancer. I participated in a recent study to assess the efficacy and safety of avelumab in 125 women with previously treated recurrent or refractory ovarian cancer. We found that avelumab demonstrated antitumor activity and acceptable safety in these patients (*JAMA Oncol* **5:**393–401, 2019).

More recently, we have focused on enhancing the innate immune system to overcome the immune-suppressive environment of the abdominal cavity, where ovarian cancer grows. We completed a phase 1 clinical trial using interferons alpha and gamma to stimulate monocytes that we injected directly into the patients' abdomens (*J Transl Med* **16:**196, 2018). This therapy is very promising in that it could be a platform on which to layer personalized immunotherapy approaches.

Ongoing studies of patient samples from this trial will help us to design the next steps in improving this therapy as well.

T.C. "KELVIN" CHOI, PH.D., M.P.H., NIMHD

Senior Investigator, Social and Behavioral Group, National Institute on Minority Health and Health Disparities

Education: The Hong Kong Polytechnic University, Hong Kong (B.Sc. in physiotherapy); University of Minnesota at Minneapolis (M.P.H. in community health education and Ph.D. in epidemiology)

Training: Attended training institutes through NIH's Office of Behavioral and

SUSAN L. MOIR, NIAID

KEISUKE (CHRIS) NAGAO, NIAMS

JOHN NGAI, NINDS

KANDICE TANNER, NCI-CCR

STEPHEN WHITEHEAD, NIAID

Social Sciences Research and NIDA; Fundamentals of Team Science and the Science of Team Science through the National Science Foundation and the University of Central Florida

Before coming to NIH: Various positions including assistant professor at the University of Minnesota School of Public Health, Division of Epidemiology and Community Health; clinic manager and physiotherapist, Cosmo Physiotherapy Center (Hong Kong)

Came to NIH: In 2013 as a Stadtman Investigator in NIMHD

Outside interests: Enjoying nature (hiking, biking, canoeing, and camping) and being the father of a synchronized ice skater

Website: https://irp.nih.gov/pi/kelvin-choi

Research interests: I am interested in the interconnected and potentially reciprocal relationships between the social determinants of health and tobacco exposure and use, and the social and environmental factors that explain these relationships. For example, we found that smoking influences sleep quality in youth, which can affect their academic performance and subsequent college enrollment. We also found that cigarette smoking during the high school years is associated with a lower likelihood of enrolling in post-secondary education, especially four-year college programs. In another study, we found that youth exposure to secondhand smoke was associated with later lower academic performance (*Am J Prev Med* **58:**776–782, 2020).

My team is also investigating how tobacco companies' marketing strategies cultivate and foster tobacco use among adolescents and adults and how the effects differ by demographics and socioeconomic status (SES). In one study, we found that adults of lower SES were more likely to be exposed to tobacco discount coupons, and this exposure was related to the progression and continuation of smoking (*Nicotine Tob Res* **20:**1095–1100, 2018). We are also investigating the physiological and neurological responses to tobacco-marketing materials among smokers; what we learn will inform both how best to regulate these materials and design anti-tobacco messages.

In addition, we are examining how to leverage marketing principles (including price, placement, promotion, and products) to reduce tobacco-use disparities, particularly among young adults. I am currently working with collaborators to develop a computer simulation that can forecast the potential impact of tobacco–marketing regulations on tobacco-use disparities.

The knowledge gained from these investigations will be used to construct more effective anti-tobacco interventions and messages that are tailored to smokers of disadvantaged populations, and public-health interventions for other health-risk behaviors.

TAE-WOOK CHUN, PH.D., NIAID

Senior Investigator and Chief, HIV Immunovirology Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases

Education: California State University at San Bernardino, California (B.S. in biology); Johns Hopkins University School of Medicine, Baltimore (Ph.D. from the Biochemistry, Cellular and Molecular Biology Graduate Program)

Training: Research fellow, Laboratory of Immunoregulation at NIAID

Came to NIH: In 1997 for training; became a staff scientist in 2001, an associate scientist in 2009, and an Earl Stadtman Investigator in 2016

Outside interests: Hanging out with Canada Geese on campus and Panda Cam watching

Website: https://irp.nih.gov/pi/tae-wook-chun

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Recently Tenured

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Research interests: Although antiretroviral therapy reduces the amount of human immunodeficiency virus (HIV) in blood, it does not completely eradicate the virus in infected individuals. Persistently infected CD4 T-cell reservoirs have long half-lives and could contribute to viral rebound when antiretroviral therapy is interrupted. Treatment for HIV, therefore, has to be continued through life. My group's research focuses on 1) delineating the role of viral reservoirs in the pathogenesis of HIV disease; 2) examining host and viral factors that contribute to the maintenance of HIV reservoirs; and 3) developing therapeutic strategies aimed at achieving durable virologic control in infected individuals in the absence of antiretroviral therapy.

We conduct comprehensive genetic, immunologic, and virologic analyses of T cells in diverse cohorts of HIV-infected individuals. In so doing, we are addressing fundamental pathogenic questions, such as elucidating mechanisms of viral persistence; examining the role of the host immunity in containment of viral replication; and evaluating promising novel therapeutic agents in both ex vivo and in vivo settings (*J Infect Dis* jiaa270, 2020); *J Clin Invest* **129:**4832–4837, 2019; *PLoS Pathog* **14:**e1006792, 2018).

In addition to our bench research, we have conducted several phase 1 clinical trials in close collaboration with the NIAID HIV clinic, with the ultimate goal of developing safe, effective, and scalable therapeutic strategies that would allow HIV-infected individuals to control viral replication without having to use antiretroviral drugs daily. Among the multiple therapeutic trials we have conducted over the past several years, two were directed at blocking HIV by using monoclonal antibodies that bind either the virus or the human receptor for the virus, CD4 (*N Engl J Med* **375:**2037–2050, 2016; *N Engl J Med* **380:**1535–1545, 2019).

Additional clinical trials are currently being developed to explore the possibility of achieving complete remission of HIV in infected individuals through the administration, twice a year, of a combination of long-acting anti-HIV antibodies and antiretroviral drugs.

HEIDI H. KONG, M.D., M.H.SC., NIAMS

Senior Investigator, Cutaneous Microbiome and Inflammation Section, Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases; Adjunct Investigator, Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute

Education: Stanford University, Stanford, California (B.S. in biological sciences); Baylor College of Medicine, Houston (M.D.); Duke University, Durham, North Carolina (M.H.Sc.)

Training: Residency and chief residency in Dermatology, Duke University; clinical research fellow, NCI's Dermatology Branch

Came to NIH: In 2005 for training

Outside interests: Spending time and traveling with family; baking; reading

Website: https://irp.nih.gov/pi/heidi-kong

Research interests: My group integrates advanced genomics and translational research expertise in dermatologic disorders to study human skin microbes and gain insights into the pathogenesis of inflammatory skin diseases. My lab's work has advanced our understanding of human skin microbial communities.

In particular, we study the diversity and complexity of bacterial, fungal, and viral communities in healthy skin and in eczema from patients with atopic dermatitis and with primary immunodeficiencies. We have demonstrated how the skin microbial communities can vary based on the specific location on the body. We found that despite the skin's exposure to the external environment, its microbial communities were largely stable over time.

In addition, we know that the skin microbiome can be distinguished in certain skin diseases and with specific immunodeficiencies. While we found that disease flare-ups in patients with atopic dermatitis are linked with higher percentages of *Staphylococcus aureus* or *Staphylococcus epidermidis*, patients with a rare primary immunodeficiency (DOCK8, or dedicator of cytokinesis 8, deficiency) have higher proportions of DNA viruses on their skin.

These studies highlight how the host shapes, and in turn may be shaped by, the skin microbiome. Our current efforts are focused on deeper investigations of these host-microbial interactions.

DA-TING LIN, PH.D., NIDA

Senior Investigator and Chief, Neural Engineering Section, Behavioral Neuroscience Branch, National Institute on Drug Abuse

Education: University of Science and Technology of China, Hefei, China (B.S. in biology); University of Texas Health Science Center at San Antonio, San Antonio, Texas (Ph.D. in cell biology)

Training: Postdoctoral fellow, Department of Neuroscience, Johns Hopkins University (Baltimore)

Before coming to NIH: Assistant professor, The Jackson Laboratory (Bar Harbor, Maine) and Department of Medicine, Tufts University School of Medicine (Boston)

Came to NIH: In 2013 as chief of NIDA's Optical Imaging Core

Outside interests: Playing soccer

Website: https://irp.nih.gov/pi/da-ting-lin

Research interests: I am studying the neural circuit mechanisms involved in long-term drug addiction and relapse. My laboratory is developing and applying in vivo optical imaging methods, as well as computational methods for data analysis, to measure neural-circuit dysfunction that may lead to long-term substance abuse and cause patients in recovery to relapse.

Neuroscientists and engineers are increasingly interested in studying neuronal activities at the microcircuit level and are pushing the limits in developing miniature in vivo imaging systems. This interdisciplinary effort has led to a widespread use of wearable miniature microscopes, which are constantly improving in size, cost, spatial and temporal resolutions, and signal-to-noise ratio.

Right now my group is developing imaging systems that can visualize neural activity from deep-brain regions in animals. Such systems are becoming more important for understanding neural-encoding mechanisms underlying cognitive functions. We independently developed a miniScope (a miniature fluorescence microscope), an imaging system that allows the simultaneous recording of activity of hundreds of neurons in deep-brain regions of freely behaving mice. The miniScope expands the realm of possible behavioral experiments for in vivo imaging studies (*Neuron* **92:**202–213, 2016 and *Neuron* **100:**700–714.e9, 2018). We are continuing to explore in vivo deep-brain imaging of neuronal circuit activity and refining techniques to measure neuronal dysfunction.

SUSAN L. MOIR, PH.D., NIAID

Senior Investigator and Chief, B-Cell Immunology Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases

Education: University of Guelph, Guelph, Ontario, Canada (B.S. in biological science, minor in biotechnology); Université du Québec, Institut Armand-Frappier, Laval, Québec, Canada (M.Sc. in virology and immunology); Université Laval, Québec City, Québec, Canada (Ph.D. in microbiology and immunology)

Training: Postdoctoral visiting fellow, NIAID

Came to NIH: In 1996 for training; became staff scientist in 2006, associate scientist in 2010, and Stadtman Investigator in 2015

Outside interests: Spending time with her family; enjoying outdoor activities; and being inspired by market-to-table-style cooking to share meals with others

Website: https://irp.nih.gov/pi/susan-moir

Research interests: The primary focus of my research program is to study the role of B cells in the pathogenesis of human immunodeficiency virus (HIV) disease, with the ultimate goal of filling gaps in knowledge about humoral immunity against the virus. This knowledge is critical to the development of an effective antibody-based vaccine and for the advancement of immunotherapeutic interventions in HIV-infected individuals. My group's approach involves assessing transcriptional, phenotypic, and functional attributes of B cells that circulate in the peripheral blood and those that reside in tissues, particularly lymph nodes and bone marrow.

A major focus of our research also includes identifying and characterizing various subsets of B cells—in the blood and tissues of healthy individuals—that are overexpressed at various stages of HIV infection. We have shown that several of these subsets may be responsible for various manifestations associated with HIV disease, including hypergammaglobulinemia (excess globulins in the blood), inadequate response to vaccination, altered homeostasis associated with lymphopenia (lower than normal number of lymphocytes) that occurs in late HIV disease and AIDS, reduced responsiveness of B cells due to immune exhaustion and other inhibitory effects, and inefficient antibody responses due to altered maturation of B cells in lymphoid tissues (*Nat Rev Immunol* **9:**235–245, 2009; *Nat Immunol* **19:**1001–1012, 2018; *Sci Transl Med* **11**:eaax0904, 2019).

Another long-term goal is to apply our knowledge of B cells in HIV to other immune-mediated diseases, particularly primary immune deficiencies in which B cells play a pathogenic role.

KEISUKE (CHRIS) NAGAO, M.D., PH.D., NIAMS

Senior Investigator and Head, Cutaneous Leukocyte Biology Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases

Education: Keio University School of Medicine, Tokyo, Japan (M.B., M.D., Ph.D. in microbiology)

Training: Residency in dermatology, Keio University School of Medicine, and in anesthesiology, Tokyo Dental College Hospital, Tokyo, Japan; visiting fellow, Dermatology Branch, Center for Cancer Research, National Cancer Institute

Before returning to NIH: Senior assistant professor, Department of Dermatology, Keio University School of Medicine

Came to NIH: In 2005–2008 for training; returned in 2014 as Stadtman Investigator

Outside interests: Reading; exercising

Website: https://irp.nih.gov/pi/keisuke-chris-nagao

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Recently Tenured

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Research interests: I am a dermatologist with a longstanding interest in skin immunology and immune-mediated diseases. My research program aims to advance our knowledge on how the skin functions as an immunological organ. We study mechanisms that underlie skin immunity and host-microbiota crosstalk during health and inflammatory diseases. Over recent years, we have identified hair follicles as control towers of skin immunity: the follicles guide the localization of skin-resident leukocytes and enhance their survival by producing chemokines and cytokines. In turn, leukocytes, such as the innate lymphoid cells, communicate with hair follicles to tune the balance of the microbiota on the skin surface.

We have also determined that the alteration of the host-microbial relationship drives atopic skin inflammation. The skin of atopic dermatitis (AD) patients is commonly colonized with *Staphylococcus aureus*. For decades, scientists have debated whether this bacterium contributes to AD pathophysiology. By generating an AD mouse model that recapitulated *S. aureus* susceptibility in humans, we demonstrated *S. aureus* to be a crucial driver of skin inflammation, thereby providing an answer to a longstanding question.

We leverage advances in sequencing technologies to understand disease pathophysiology directly in humans. Diseases of interest include primary immunodeficiencies and intractable immune-mediated diseases such as severe drug hypersensitivities in which we use single-cell RNA sequencing to tailor personalized medicine. We will continue to use approaches in experimental models and expand our studies on human diseases to understand core and translatable mechanisms that regulate skin immunity and facilitate host-microbial symbiosis.

JOHN NGAI, PH.D., NINDS

Senior Investigator, National Institute of Neurological Disorders and Stroke; Director of NIH BRAIN Initiative

Education: Pomona College, Claremont, California (B.A. in chemistry and zoology); Harvard Medical School, Boston (Program on Cell and Developmental Biology); California Institute of Technology, Pasadena, California (Ph.D. in biology)

Training: Postdoctoral fellow, California Institute of Technology and Howard Hughes Medical Institute/Columbia University College of Physicians and Surgeons (New York)

Before coming to NIH: Professor of Neurobiology, Department of Molecular and Cell Biology, and Coates Family Professor of Neuroscience, Helen Wills Neuroscience Institute, University of California at Berkeley (Berkeley, California)

Came to NIH: In 2020

Outside interests: Doing photography; enjoying food and wine

Website: https://www.ninds.nih.gov/About-NINDS/Who-We-Are/staff/John-Ngai

Research interests: The generation of cellular diversity in the nervous system requires the specification and differentiation of a multitude of cell lineages from multipotent progenitor cells. The regulatory programs governing this process remain incompletely characterized, however, in part because of the difficulty in studying neuronal progenitor cells in their native environments. My lab uses the mammalian olfactory epithelium as a model for addressing this challenge.

Primary sensory neurons in the olfactory epithelium are continuously regenerated throughout adult life via the proliferation and differentiation of multipotent neural progenitor cells. Upon severe injury, these adult tissue stem cells are activated and go on to reconstitute all of the cellular constituents of this sensory epithelium. The regenerative capacity of the olfactory epithelium therefore presents a powerful and experimentally accessible paradigm for elucidating the mechanisms regulating neural stem-cell function.

We are using a variety of approaches to unravel the molecular and cellular mechanisms regulating olfactory stem cells and olfactory neurogenesis in the mouse. For example, we use conditional genetic knockouts to investigate the roles of certain transcription factors and intracellular signaling pathways in promoting stem-cell self-renewal, proliferation, and differentiation.

As a complementary approach, we also apply single-cell transcriptomic and single-cell epigenomic analyses to identify the genetic and epigenetic programs that both define and regulate olfactory neurogenesis during regeneration.

Our studies provide a model for understanding the mechanisms regulating neural stem cells and lay the groundwork for the future development of treatments and therapeutics to ameliorate tissue damage and degeneration in the nervous system.

KANDICE TANNER, PH.D., NCI-CCR

Senior Investigator and Head, Tissue Morphodynamics Section, Laboratory of Cell Biology, Center for Cancer Research, National Cancer Institute

Education: South Carolina State University, Orangeburg, South Carolina (B.S. in electrical engineering technology and physics); University of Illinois at Urbana-Champaign, Urbana, Illinois (M.S. in physics; Ph.D. in physics)

Training: Postdoctoral fellowships at University of California at Irvine (Irvine, California), University of California at Berkeley (Berkeley, California)/Lawrence Berkeley National Laboratory (Berkeley, California)

Came to NIH: In 2012 as a Stadtman Investigator

Outside interests: Kickboxing; running; reading

Website: https://irp.nih.gov/pi/kandice-tanner

Research interests: My lab focuses on understanding the metastatic traits that allow tumor cells to colonize secondary organs. Some exciting findings in the field of mechanobiology have demonstrated that biophysical properties such as cell shape, mechanical phenotype, topography, hemodynamic forces, and pressure can modulate how genes are activated and silenced in key processes involving cell growth, migration, invasion, and metabolism. We have developed biophysical tools and novel animal models to understand how physical cues from the tissue microenvironment drive organ-specific metastasis. We aim to understand what drives organ targeting and secondary-tumor outgrowth.

In one study, we discovered that the physical properties of blood vessels regulate organ selectivity in vivo. We combined intravital imaging, vessel-topographical analysis, and mechanical mapping—and the use of home-built optical tweezers—in a zebrafish model. This work was the first demonstration that physical properties of blood vessels can regulate how metastasizing tumor cells in vivo select organs to migrate to (*Cell Syst* **9:**187–206.e.a6, 2019).

We also found that after tumor cells leave the circulation, they must adapt to a tissue environment of different properties from that of the primary tumor. Using 3D culture models, we have uncovered a novel mathematical formulation that decribes the coupling of 3D microscale cell extracellular-matrix mechanics (*Proc Natl Acad Sci U S A* **116:**14448–14455, 2019). Moving forward, we wish to leverage our understanding of tissue biophysics to define a biomarker that will be predictive of the site of the secondary lesion.

STEPHEN WHITEHEAD, PH.D., NIAID

Senior Investigator and Chief, Arbovirus Vaccine Research Section, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases

Education: Brigham Young University, Provo, Utah (B.S. microbiology; M.S. in microbiology); Oregon State University, Corvallis, Oregon (Ph.D. in microbiology)

Training: Postdoctoral fellow, Rockefeller University (New York) and NIAID; senior staff fellow, NIAID

Came to NIH: In 1995 for training; became a staff scientist in 1999

Outside interests: Loves spending time with his family; working in the garden; and cooking. He holds a certificate in Chinese cuisine.

Website: TBD

Research interests: My lab is developing and evaluating vaccines against mosquito-borne flaviviruses, which include dengue virus (DENV), Zika virus (ZIKV), West Nile virus, and Japanese encephalitis virus (JEV). We are particularly focused on developing a tetravalent dengue vaccine called TV003. Because previous infection with one DENV serotype can increase the risk for serious disease after infection with a different serotype, a successful vaccine will need to protect against all four DENV serotypes.

I have long-standing collaborations with investigators from Johns Hopkins University (JH, Baltimore) and the University of Vermont (UVM, Burlington, Vermont). Among our many studies of the dengue vaccine TV003, one was a pivotal clinical demonstration showing that TV003 elicited complete protection against DENV in a human challenge model: 21 vaccine recipients were protected and 20 placebo recipients were not (*Sci Transl Med* **8:**330ra36, 2016). In another clinical study with JH, UVM, and NIAID colleagues, we demonstrated that TV003 was fully potent as a single-dose vaccine (*J Infect Dis* **214**:832–835, 2016); and we also showed that TV003 is well tolerated and highly immunogenic in subjects with flavivirus exposure before vaccination (*PLoS Negl Trop Dis* **11:**e0005584., 2017). In addition to recent clinical studies in Thailand and Taiwan, a key phase 3 study of TV003 is nearing completion in Brazil. The vaccine technology has been licensed to seven companies and institutes across the world for further development and commercialization.

My group has also made important advancements with other flaviviruses. For example, we are developing live attenuated ZIKV and JEV vaccines that are compatible with the DENV vaccine, thus enabling simultaneous vaccination against DENV and either ZIKV or JEV. Novel vaccine candidates for ZIKV are being developed with **Alexander Pletnev** in NIAID's Laboratory of Infectious Diseases.

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PHOTOGRAPHIC MOMENT

Award–Winning Fish (Photo)

CREDIT: DANIEL CASTRANOVA, NICHD

This beautiful image of a juvenile zebrafish won first place in the 2020 Nikon Small World Photomicrography Competition. The creator was aquatic research specialist **Daniel Castranova**, assisted by postbac **Bakary Samasa**, while working in the lab of **Brant Weinstein** in the National Institute of Child Health and Human Development. Using confocal microscopy and image-stacking, Castranova stitched together more than 350 individual images to create this visual of a dorsal view of the head of the fish with fluorescently "tagged" skeleton, scales (blue), and lymphatic system (orange).

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH.

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