THE NIH CATALYST

A PUBLICATION ABOUT NIH INTRAMURAL RESEARCH

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That Record-breaking Sprint to Create a COVID-19 Vaccine

BY MELISSA GLIM

At the end of 2019, most people were looking forward to an exciting 2020, a new decade starting with those magic numbers, 20-20, that denote a sharpness of vision. There would be the Summer Olympics in Japan and the U.S. presidential election. Meanwhile, intramural scientists at the National Institute of Allergy and Infectious Diseases' Vaccine Research Center (VRC) were designing vaccines for several coronaviruses using a promising, new platform based on messenger RNA (mRNA).

Everything changed on a Saturday morning in early January. Chinese scientists had isolated a new coronavirus that was causing a serious epidemic in China's Wuhan province and released its genetic sequence to the scientific community around the world. **Barney Graham**, director of the VRC's Viral Pathogenesis Laboratory (VPL), and VRC research fellow **Kizzmekia Corbett** dropped everything and began using this mRNA platform to develop a vaccine for the illness that would become known as COVID-19.

"Dr. Corbett was directing a team doing coronavirus work, and we had relationships with three or four really good academic collaborators and had been having monthly conference calls for years," Graham said. "We also had our industry collaborators [at Moderna], and we had a strategy and all the technology, so we were ready to go."

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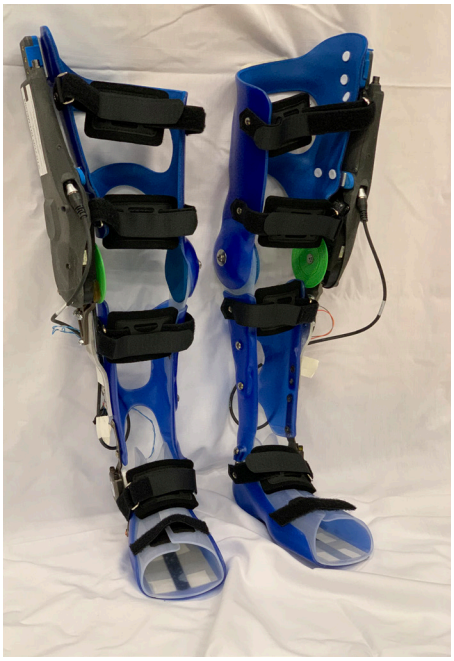
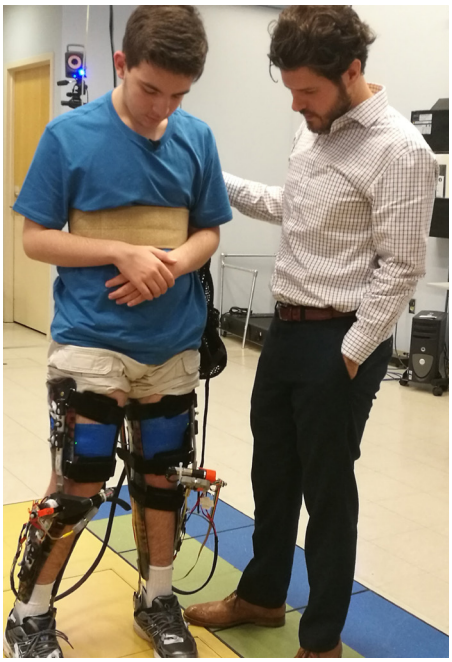
The Intersection of Man and Machine

Bionics Gives New Hope to Those Living With Physical Disabilities

BY MICHAEL TABASKO, OD





CREDIT: THOMAS BULEA (LEFT); NIH CLINICAL CENTER (RIGHT)

(Left) The NIH pediatric exoskeleton for children with cerebral palsy and other movement disorders uses custom actuators from Agilik developed as part of a cooperative research and development agreement with NIH, along with embedded sensors and microcontrollers, to provide overground gait training while worn. (Right) Alexander Theodorakos, a participant in a research protocol at the NIH Clinical Center that is evaluating the new pediatric exoskeleton, and Thomas Bulea, the study's principal investigator, discuss how the device changes the way the legs move when walking.

If popular culture is any indication, the notion that bionic technology will someday redefine the boundaries of human function has long held our collective fascination. "We can rebuild him; we have the technology," began the 1970s classic television series *The Six Million Dollar Man*. Massachusetts Institute of Technology (MIT) Professor Hugh Herr has the technology and is building bionic limbs to end physical

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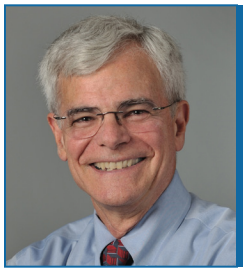

Looking Back: Knowing I Could Make a Difference

BY MICHAEL GOTTESMAN, DDIR

Michael Gottesman, who has been the Deputy Director for Intramural Research since November 1994, recently announced that he would be stepping down from that position, but will continue as chief of NCI's Laboratory of Cell Biology, where his research is focused on multi-drug resistance in cancer cells. The following is a reprint of his first essay in The NIH Catalyst *and appeared in its January 1994 issue. He was acting DDIR at the time and was eloquent in describing his passion for making a difference for the intramural research program. Still passionate about NIH's intramural research program, he plans to remain as DDIR until a replacement is found. A national search will begin soon.*

"Intramural Research Program Review Update"

[1994]

While driving to the laboratory the other night at 2:00 a.m. to deal with a freezer alarm that predicted impending meltdown, I had a chance to ponder the sanity of my decision to divide my time between supervision of research on multidrug resistance in the Laboratory of Cell Biology in NCI and the management of the Intramural Research Program (IRP) at NIH. A major part of this decision was the persuasiveness of our new Director, Dr. **Harold Varmus**. I had also become involved as Co-chair of the Internal Working Group on the Intramural Program, which has been helping the External Advisory Committee (EAC) to make recommendations to Dr. Varmus about the IRP. The review process has convinced me of the paramount importance of the quality of research at NIH, and the Deputy Director for Intramural Research (DDIR) is the person most responsible for maintaining excellence in our IRP. Knowing that I could make a difference convinced me to accept the job of Acting DDIR.

Another important consideration was that I would become Acting DDIR with the help of my good friend and colleague **Lance Liotta**, who applied his considerable energy, enthusiasm, and love for the IRP to initiate a series of changes to improve the lot of the bench scientists at NIH. One of his many achievements was developing the NIH tenure-track system which guarantees, for up to six years, the resources needed to cultivate the intellectual independence of our brightest young scientists. The tenure system has now been initiated, and every scientist at NIH should now know his or her status with respect to the tenure process.

Much of my time in the first few weeks on the job has been devoted to co-chairing (with **Jay Moskowitz**) the Internal Working Group on the Intramural Program, which acts as a fact-finding committee for the EAC. The internal and external committees were set up in July and September to respond to a congressional mandate in the 1993 NIH Appropriations Bill to redefine the "role, size, and cost" of the IRP. This review was prompted in part by the impending expenses related to the needed rejuvenation of the Clinical Center research and hospital facilities, and in part by a perception in the extramural community that the review of intramural research is not as stringent as the review of individual extramural research grants.

The EAC, co-chaired by Dr. Paul Marks of the Memorial Sloan-Kettering Cancer Center in New York and Dr. Gail Cassell of the University of Alabama at Birmingham, has asked us to provide data in three major areas: 1) review of all intramural research, 2) allocation of resources between the intramural and extramural programs of the institutes, and 3) organizational and administrative disincentives to the conduct of top-quality science. Scientists at NIH have been asked to provide written comments on these issues, and I hope you have all taken the time to do this. In addition, we have been assembling options for the renovation or reconstruction of the Clinical Center for review by the EAC.

In assembling this information, our committee has learned a great deal about the IRP and the differences in style and substance among our various institutes, centers, and divisions. Members of the EAC say they have been impressed by the effort and cooperation of everyone involved in the IRP review, and we are

looking forward to their suggestions, which will be contained in a report to Dr. Varmus early in 1994.

Many researchers have expressed concern about increasing limitations on positions and funding for the IRP. Many institutes have had full-time-equivalent staff positions (FTEs) frozen for many months, and Health and Human Services has just instituted a temporary total freeze on new hiring. There is no question that the rapid growth of the IRP has ended for now, but that does not mean that we cannot continue to strengthen our scientific programs and encourage young scientists to come to NIH to develop their laboratory and clinical research ideas. The new tenure-track system reflects a new emphasis by our Scientific Directors on providing a supportive environment for talented new scientists and setting aside resources as they become available for competitive, wide-open recruitment of outstanding investigators. The counsel of the EAC will be extremely useful in ensuring research at NIH remains first-rate, and that we can rejuvenate the institutes, despite limitations on resources.

On campus, Dr. Varmus and I intend to encourage grass-roots efforts by intramural scientists to improve the intellectual atmosphere at NIH. One way we are doing this is by encouraging the development of trans-NIH scientific interest groups to complement the existing groups. For example, the new Cell Biology Interest Group is preparing a catalog of research activities of its members and has launched a seminar series similar to that of the existing Structural Biology, Immunology, and Glycobiology groups. Groups interested in neurobiology and genetics will be coalescing, and plans for an NIH Director's Seminar Series, consisting of general lectures by recently tenured and tenure-track staff, are underway. To highlight lectures of general interest of this type, the "Yellow Sheet" is undergoing a facelift with some changes in typography and format.

On a more personal note, I would like to tell you how privileged I feel to be able to represent the intramural research community. My respect and affection for this community, my sense of justice and desire for fair treatment of all NIH researchers, my experiences as a bench scientist, and my conviction that no better model for the conduct of creative science exists will guide my future actions.

Incidentally, a little dry ice temporarily solved that problem with the freezer. I also drafted a memo specifying that my colleagues in the laboratory be given priority when it came to late-night calls (we call this "delegation of authority" in Building 1). I wish you all a happy new year, and look forward to working with all of you. ●

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

Creative Activities Can Reduce Stress and Enhance Work Performance

BY ERICA WYNNE-JONES, NIAID

During the COVID-19 pandemic, many of us turned to creative activities to provide comfort and entertainment. Some people took on activities that were completely new to them, such as baking, which led to many spectacular pandemic baking fails shared on social media, including deflated sourdough, burnt messes, and fused megacookies. No matter the final outcome, the process of undertaking creative activities can have a positive influence on mental health. One recent study showed that participating in creative activities in lockdown during the COVID-19 pandemic helped people to build resilience.

During the pandemic, some people also returned to their former creative hobbies, which brought with them a sense of nostalgia. Nostalgia can be a huge source of comfort during times of stress and can help to combat feelings of loneliness. Speaking to the *New York Times*, Clay Routledge, a psychologist who specializes in nostalgia, hypothesized that people unknowingly turned to nostalgia during the COVID-19 pandemic as a stabilizing force and reminder of what they cherish most.

Creative activities have benefits beyond stress relief and can even improve work performance. Critical scientific skills such as innovation and problem-solving are enhanced through creative activities. Performative activities, like improvisation (improv), can also help to improve teamwork, communication, and presentation skills at work.

Creative activities can also offer relaxing breaks from work which are beneficial for work performance.

Choosing the creative activity that's right for you is also important. Setting off the fire alarm while trying to cook in a dodgy oven is unlikely to bring about positive mental health for anyone. The NIH Office of Intramural Training and Education (OITE) has recently run several wellness activities for trainees that incorporate creativity, such as painting, cooking, and even science improv. These activities are not only fun but can also bolster a sense of community within the NIH. There are also a range of free creative activities in the community, such as classes at your local library. The Labs at District of Columbia Public Library and the Montgomery County Public Library currently offer classes in cake decorating, clothing repair, and knitting. Online learning platforms such as LinkedIn Learning can be accessed for free through many public libraries and offer a range of courses on creative skills such as graphic design and video editing.

The COVID-19 pandemic isn't over yet, and it is unlikely to be the last stressful and traumatic event we will encounter in our own lives. As we return to normal work, it's important to continue to think about how we are managing our stress. Incorporating nonwork creative activities into our day-to-day lives can help us to not only cope with stress but also build critical scientific skills and enable us to work more effectively. ●

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OITE wellness events and resources:

- https://www.training.nih.gov/events/upcoming.
- Wellness website https://www.training.nih.gov/wellness.

Erica Wynne-Jones is a former visiting postdoctoral fellow (from Australia) in the National Institute of Allergy and Infectious Diseases. She left NIH in September 2021 for a job with Takeda Pharmaceutical Company and is studying immune-targeting oncology drugs that only become active once they are in a tumor.

New SIG: Resilience Research Scientific Interest Group

The Resilience Research Scientific Interest Group (RR-SIG) was established to advance resilience research across NIH and partnering agencies by fostering communication, collaboration, and the sharing of resources. The concept of resilience encompasses the capacity to resist, adapt to, recover, or grow from a challenge.

The RR-SIG aims to facilitate the harmonization of definitions, experimental design protocols, and frameworks for identifying and measuring resilience outcomes; the coordination and sharing of data resources for the development, testing, and validation of computer models and animal models that might advance the prediction of resilience health outcomes and responses to various stressors or treatment and prevention strategies; and the linkage of longitudinal data on healthy individuals to clinical trial data such that a broader range of baseline characteristics and long-term outcomes that might be associated with factors related to resilience can be achieved.

NIH staff are welcome to join the group which meets the first Tuesday of every month at 11:00 a.m.–12:00 p.m. Individuals from organizations and agencies outside of NIH may join by invitation only. All individuals with an interest in resilience research are invited to participate in the quarterly seminar series or other public events. The RR-SIG chair is **LaVerne L. Brown**; the intramural advisor is **Ann Berger**. For more information about the RR-SIG and instructions for joining the LISTSERV e-newsletter (to keep informed of the SIG's activities), go to https://oir.nih.gov/sigs/resilience-research-scientific-interest-group or contact LaVerne L. Brown (laverne.brown@nih.gov).

New SIG: Biomedical Engineering Scientific Interest Group

The Biomedical Engineering Scientific Interest Group (BME-SIG) seeks to fill a void in bioengineering interest within the NIH community. Initially spearheaded by the National Institute of Biomedical Imaging and Bioengineering and the National Cancer Institute with clinical advisors from the National Institute of Allergy and Infectious Diseases, the SIG focuses on community-building and resource knowledge of engineers and scientists in the NIH intramural research program. The subdisciplines represented include biomaterials, regenerative medicine, in vitro systems, immunoengineering, fabrication, tissue biomechanics, nanoformulations, drug delivery, materials science, and cancer therapeutics.

There will be several educational and outreach programs including seminars from invited speakers aimed at increasing the visibility of bioengineering and biomaterials and feature tech-transfer and patent law; regulatory processes such as FDA's investigational new drug applications; and pathways for bringing technologies to commercialization. The BME-SIG will host a technology-demonstration day in partnership with the NIH Library and feature 3D printing, nanoparticle synthesis, microfiber electrospinning, microencapsulation, organ-on-a-chip and microfluidic platforms, hydrogel biomaterials, and organoid modeling. The BME-SIG will provide career talks and teas so fellows can chat with members of the external bioengineering community.

For more information about the BME-SIG and instructions for joining the LISTSERV, go to https://oir.nih.gov/sigs/biomedical-engineering-scientific-interest-group.

New SIG: Innovation-Driven Enhancements for Advancement

The Innovation-Driven Enhancements for Advancement Scientific Interest Group (IDEA-SIG) provides a platform and safe space for the development of creative ideas through the exchange of information among NIH employees who have training and/or an interest in leadership, management, or business acumen. The group offers NIH faculty, staff, and trainees an opportunity to network and problem-solve and to gain access to business and management ideas, approaches, and analyses that can be used to address current challenges at the NIH and beyond. Techniques the group will use include the three-lenses approach, five-forces analysis, catalytic questioning, cooperative conversations, go-and-see approach, understanding the jobs-to-be-done, question bursts, dynamic work design, collaborative iteration, adaptable visions, and challenge-driven leadership for transformational change.

The full group will meet every other month via Zoom and on the NIH Bethesda campus (when in-person meetings are allowed) and maintain a LISTSERV e-newsletter for more frequent communication between meetings. Smaller project-based working groups are advised to meet as needed. Presentation formats and topics may include leadership and management strategies and approaches; case studies; guest speakers; and panel discussions. The group is open to all NIH employees and trainees. For more information, go to https://oir.nih.gov/IDEA-SIG or email **Jessica Chertow** (Jessica.chertow@nih.gov).

For a full list of NIH scientific interest groups, go to https://oir.nih.gov/sigs.

What It's Like to Be a Patient in an NIH Clinical Trial

Interview with Alexandra Ambrico

INTERVIEWED BY LAURA S. CARTER

Alexandra Ambrico, the Administrative and Special Projects Manager at the International Biomedical Research Alliance and former research technician at Cold Spring Harbor Laboratory, is a "healthy volunteer" participating in the NIH clinical trial "Brain Dopamine Function in Human Obesity." The trial is measuring dopamine activity in the brain to determine how it relates to body weight and eating behavior and is being conducted by Senior Investigator Kevin Hall (National Institute of Diabetes and Digestive and Kidney Diseases) and Valerie Darcey, a postdoc in his lab. Here Alexandra answers a few questions about what it's like to be part of the trial. Her responses have been lightly edited.

How did you find out about the trial?

I found the trial on Twitter last year. I have been following the NIH Clinical Center on Twitter for years and was excited about participating in trials as a healthy volunteer.

What was your understanding of what the trial was about?

The trial is designed to understand aspects of brain function and how it relates to body weight and weight change. The researchers would use PET and MRI scans and different radiotracers to measure dopamine activity in regions of the brain involved in reward processing and feeding behavior. The researchers would also track my weight (I would weigh myself daily) and physical activity (via a wearable activity monitor) throughout the year as well as my body composition and brain structure at a one-year follow-up visit.

What concerns, if any, did you have before entering the trial?

I truly did not have any concerns because all of my questions were answered ahead of time. I was able to work remotely throughout my inpatient stay and organize my day since I was given the schedule in advance.

What were your biggest motivators for participating?

My biggest motivation was to give back to science. Having a background in science, especially research—and knowing what it takes to write a protocol and outline a study—provided a perspective that I wished to share. I was very motivated to be able to share my story with colleagues and friends, in the hopes that they too would participate in more trials and give back to science.

Can you briefly describe what you had to do for the trial?

I had a blood draw, electrocardiogram, and physical. I also met with a nutritionist prior to the start of the trial to establish a baseline and create the meal plan. During the first outpatient portion of the trial, I was put on a five-day diet-stabilization meal plan with meals prepared by NIH's metabolic kitchen. I could not drink or consume anything else during this time.

Following the outpatient study, I then checked into the NIH Clinical Center for a five-day inpatient stay. I was given activity-monitoring devices to wear on my ankle, wrist, and waist during my inpatient stay and for two weeks afterwards.

During my inpatient stay, I had blood draws, continuous glucose monitoring, body composition analysis, MRIs, PET scans, iPad questionnaires and computer tasks, the diet-stabilization meal plan, and my vitals were taken daily. I could not exercise during the study.

How was your regular routine affected by the trial and how did you adapt?

Not being able to exercise was more difficult than I expected. Living in Washington, D.C., my main method of transportation is walking. I also do an exercise class online every day. I was grateful this restriction was only for a few days.

I thought it would be hard to stick to the diet, however, I did not have any urge to eat any foods that weren't part of the study. I found it harder to eat all of the food provided, especially during my inpatient stay. I don't usually eat large meals in one sitting; I normally eat smaller amounts throughout the day.

Was there anything surprising or unexpected that happened?

During the end of the trial, I experienced some stomach issues. I later found out that I had higher sensitivity to certain foods that I was consuming throughout the study. The doctors and nurses were monitoring me closely and made sure I felt okay. I cannot stress enough how incredible the staff was at the NIH Clinical Center. They provided me their contact details and told me to reach out if I had any questions or concerns.

Is there anything important that you think others considering participating in a clinical trial should know?

I would say the most important thing to do is ask questions and get to know the researchers on the study. I felt comfortable asking questions and relaying how I felt, which made me feel at ease. ●

Read more online at https://irp.nih.gov/catalyst/v29i5/what-it-s-like-to-be-a-patient-in-an-nih-clinical-trial.

Casting the NET Wide: How Neutrophils Shape Chronic Autoimmune and Inflammatory Diseases

Mariana Kaplan Is Discovering New Ways to Fight Lupus

BY NATALIE HAGEN, NCATS

Mariana Kaplan, M.D.

Known as the "disease with a thousand faces," systemic lupus erythematosus is a lifelong autoimmune disease with a wide range of symptoms and signs—fatigue, fever, joint pain, facial rash and skin lesions, shortness of breath, and more. It may develop suddenly or slowly and be mild or severe, with people affected going through periods of flare up and remission of their symptoms. Lupus affects mostly women of childbearing age and causes widespread inflammation, damage to organ systems, and premature cardiovascular disease.

Previously, it was believed that white blood cells called lymphocytes were the predominant drivers of this disease. Recent discoveries and technical advances, however, have suggested that neutrophils—another type of white blood cell—may also play an important role in immune dysregulation.

NIH Senior Investigator **Mariana Kaplan** is exploring how neutrophils wreak havoc on the immune system in lupus and other autoimmune disorders. Her interest in immunology was piqued when, as a medical student at the National Autonomous University of Mexico's School of Medicine (Mexico City), she began seeing patients with lupus. "The idea that someone's body starts attacking itself...I thought that was a really fascinating problem," said Kaplan, who is chief of the Systemic Autoimmunity Branch in the National Institute of Arthritis and Musculoskeletal and Skin Diseases and is also involved in lupus clinical trials in the NIH Clinical Center.

Kaplan has identified several mechanisms, including a role for neutrophils, associated with the development and prevention of premature atherosclerosis in people with lupus. She presented her research on neutrophils and their role in autoimmunity on June 9, 2021, at the annual G. Burroughs Mider Lecture, part of the Wednesday Afternoon Lecture Series.

Neutrophils undergo a process called NETosis: The neutrophils extrude nuclear material bound to cytoplasmic proteins in a meshwork called neutrophil extracellular traps (NETs) that can then capture and kill pathogens. Kaplan determined that this process also causes the neutrophils to release autoantigens—such as host DNA and histones and other proteins.

A subset of proinflammatory neutrophils from patients with lupus, compared with those from patients without, are more likely to form NETs with a greater potential for developing an immune response, increased inflammation, and vascular damage.

There are also sex differences in how immune systems work. Females have a stronger immune response than males, which may explain why women tend to react better to vaccines and infections. However, that enhanced immune response also makes females predisposed to inflammatory and autoimmune diseases such as lupus. Kaplan has found that sex hormones modulate neutrophil metabolism: Female neutrophils are significantly more active than male ones and have an enhanced ability to form NETs and respond to inflammatory insults. In one experiment, she showed that when male neutrophils are treated with the female sex hormone estradiol, they acquire the bioenergetic profile and behavior of female neutrophils. (*Proc Natl Acad Sci U S A* **117:**16481—16491, 2020).

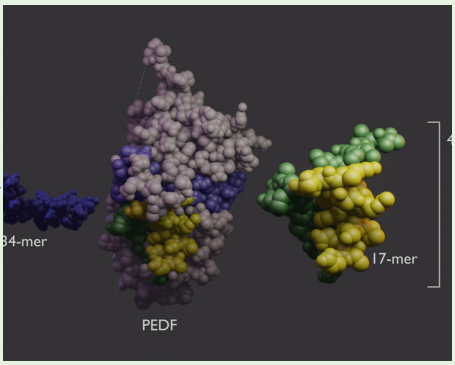
Current treatments for lupus that suppress numerous immune cells can have serious side effects. Kaplan's findings have implications for the development of new individualized, sex-specific therapies that target neutrophils. Furthermore, strategies that suppress the aberrant NET formation seen in lupus—without hampering other important antimicrobial functions—could prove a useful approach for autoimmune and chronic inflammatory diseases that involve neutrophil dysregulation.

"While in some patients, lymphocytes may be the main players in lupus, there may be other patients [in whom] neutrophils are playing a very important role," she said. "So if you treat these patients the same way, you're probably not going to get the same therapeutic response." ●

To watch a videocast of Mariana Kaplan's June 9, 2021, WALS lecture, "Casting the Net Wide: The Role of Neutrophils in Chronic Diseases," go to https://videocast.nih.gov/watch=41601.

Natalie Hagen is a postbaccalaureate research fellow in the National Center for Advancing Translational Sciences, where she is performing pharmacokinetics studies of novel drug candidates. Upon completion of her fellowship in 2022, she is planning to pursue a Ph.D.

Intramural Research Briefs



CREDIT: LESLEY EARL, NEI

NEI: PEDF protein (center) has two domains with different functions. The 34-mer (blue, left) has anti-angiogenic properties. The 44-mer (green and yellow, right) protects and stimulates neurons. The 17-mer (yellow) is a smaller region of the 44-mer with the same function.

NEI: PROTEIN FRAGMENTS PROTECT AND STIMULATE RETINAL NEURONS

In an NEI-led study, researchers found that small protein fragments known as peptides serve distinct functions in protecting neurons found in the light-sensing layer of the retina. These peptides are components of pigment epithelium-derived factor (PEDF), which prevents cell death as well as the invasion of blood vessels and inflammation, hallmarks of eye diseases such as age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy.

The investigators cultured immature rat retinal cells. These cells were isolated in a nutrient-deprived environment in which researchers tested the protective function of each PEDF fragment. They discovered that two closely associated peptides (44-mer and 17-mer) prevented premature cell death and promoted the growth of new connections between neurons. One other peptide, 34-mer, lacked such retinal protective property, but it is known for stopping abnormal blood vessel growth in the eye, as shown in a previous study.

"We're hoping that we can harness some of these protective effects in a peptide-based therapeutic approach in the near future," said lead author **Patricia Becerra**. (NIH authors: G. Michelis, R. Villasmil, and S.P. Becerra, *J Neurochem* 2021; DOI:10.1111/jnc.15454)

[BY SATABDI NANDI, NIA]

NCI: STUDY FINDS GENETIC RISK FACTORS FOR RARE CHILDHOOD CANCER

An international consortium of scientists, led by NCI, has discovered new genetic risk factors for rhabdomyosarcoma (RMS), a rare cancer that forms in soft tissues and most often affects children. RMS treatment has historically been guided by clinical factors such as tumor size, location in the body, and the presence of *PAX-FOX01*, a fusion gene associated with poorer survival. These new findings emerge from the largest genomic profiling effort of RMS tumors to date and establish links between genetic risk and clinical outcomes so that treatment can be better tailored to the individual.

The researchers used next-generation sequencing to analyze 641 tumor samples from children with RMS. The results revealed that patients with mutations in the genes *TP53*, *MYOD1*, and *CDKN2A* had worse outcomes than children without these mutations. Moreover, the investigators identified a median of one mutation per tumor and found that patients with two or more mutations per tumor might also have poorer survival outcomes.

"These discoveries change what we do with these patients and trigger a lot of really important research into developing new therapies that target these mutations," said NCI's **Javed Khan**, who led the study. (NIH authors: J.F. Shern, R. Patidar, H-C. Chou, Y.K. Song, M.E. Yohe, S. Sindiri, J. Wei, X. Wen, K. Jones, B. Hicks, and J. Khan, *J Clin Oncol* 2021; DOI:10.1200/JCO.20.03060)

[BY HENRY DIECKHAUS, NINDS]

NHGRI, NIEHS: MANY PATIENTS CHANGE THEIR MIND ABOUT RECEIVING SECONDARY GENOMIC FINDINGS

A small minority of patients undergoing genome sequencing elect not to know whether their results uncover any secondary genetic findings (SFs). SFs are known, actionable DNA variants associated with serious diseases that are unrelated to the primary reason for an individual's medical care or participation in a study. "Because these genomic findings can have life-saving implications, we wanted to ask the question: Are people really understanding what they are saying 'no' to?" said lead author **Benjamin Berkman**. "If they get more context, or a second opportunity to decide, do they change their mind?"

The investigators recruited 231 participants from a large NIEHS study who initially accepted or refused to be notified of any SFs that came out of their genome sequencing. Each respondent completed an online survey that asked questions about their decision-making process and included an intervention–more detailed information about SFs and the option to change their original decision: Nearly half of the initial refusers changed their mind. Surprisingly, 45.8% of refusers thought they had initially agreed to receiving SFs (compared with 6.8% of acceptors who thought they had refused). Among the persistent refusers, the most common reason for refusing was concern about becoming worried or sad. Based on these results, the researchers suggest considering a transparent default of returning secondary findings without soliciting participant preferences. Alternatively, subjects could be provided with detailed information about SFs and allowed multiple opportunities to revise their decision. (NIH authors: W. Schupmann, S.A. Miner, J.E. Hall, S.H. Schurman, and B.E. Berkman, *Genet Med* 2021; DOI:10.1038/s41436-021-01271-1)

[BY ETHAN SMITH, NINR]

NIAID, NCI: ANCIENT VIRUSES, BACTERIA, AND HOST IMMUNE SYSTEM PARTICIPATE IN "MULTIKINGDOM DIALGOUE"

Collectively known as microbiota, billions of microbes inhabit the human body and play an important role in immunity, digestion, and other aspects of host physiology. This symbiotic relationship extends not just to microbes such as bacteria and fungi, but to endogenous retroviruses (ERVs)—remnants of viruses that infected our ancestors and became integrated into the human genome. In a recent NIH-led study, scientists found that some of

these ERVs mediate an alliance between the microbiota and the host immune system.

In mouse and in vitro experiments, the researchers discovered that the common skin bacterium *Staphylococcus epidermidis* promoted expression of several ERVs in skin cells known as keratinocytes. This response was associated with maintaining protective tissue immunity and promoting tissue healing. These processes were impaired when the scientists inhibited expression of ERVs.

Conversely, a high-fat diet in the mouse model triggered an inflammatory response to the microbiota. This pro-inflammatory reaction was controlled with an antiretroviral treatment, suggesting that certain nutritional conditions can change how ERVs communicate with the microbiota. The findings shed new light on the mechanisms behind diseases such as obesity and inflammatory skin disorders. (NIH authors: D.S. Lima-Junior, S.R. Krishnamurthy, N. Bouladoux, N. Collins, S. Han, M.G. Constantinides, V.M. Link, A.I. Lim, M. Enamorado, C. Cataisson, L. Gil, I. Rao, T.K. Farley, G. Koroleva, S.H. Yuspa, and Y. Belkaid, *Cell* **184:**3794–3811.e19, 2021)

[BY NATALIE HAGEN, NCATS]

NINDS, NIMH: TAKING SHORT BREAKS MAY HELP BRAIN LEARN NEW SKILLS

In a recent study, NIH scientists explored how wakeful conversion of learned experiences to long-term memory was reinforced by neural replay, a memory-consolidating process in which the brain automatically replays a skill in a compressed time frame. The NINDS-led team found that skill improvements were largely explained by substantial jumps in performance after a brief period of rest between practice sessions, as opposed to improvements during actual practice.

Investigators asked subjects to type a five-digit numeric sequence on a response pad as many times as they could with their nondominant hand. A 10-second practice session was followed by a 10-second rest period and repeated 36 times. To analyze how each subject processed the new skill, researchers measured brain electrical activity using magnetoencephalography.

They found that neural replay of the skill during the rest interval was temporally compressed by approximately 20-fold relative to the practiced behavior. On average, subjects replayed the sequence about six times more than they practiced it. Furthermore, subjects who replayed the sequence more often during rest periods performed the sequence faster in the following practice session compared with those who replayed it less frequently. The findings suggest that taking structured breaks may aid in learning new skills. "Overall," said senior author **Leonardo Cohen**, "our results support the idea that manipulating replay activity during waking rest may be a powerful tool that researchers can use to help individuals learn new skills faster and possibly facilitate rehabilitation from stroke." (NIH authors: E.R. Buch, L. Claudino, R. Quentin, M. Bönstrup, and L.G. Cohen, *Cell Reports* **10:**109193, 2021; DOI:10.1016/j.celrep.2021.109193)

[BY ERIN SNYDER, NCI]

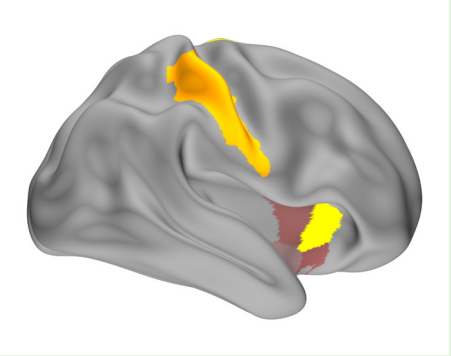
NIAID: ANTIBODY EFFECTIVE AGAINST MALARIA INFECTION

A recent small clinical trial led by NIAID scientists found that a single dose of a monoclonal antibody safely prevents malaria infection for up to nine months. Malaria infection occurs when mosquitos infected with the plasmodium parasite inject an immature form of the parasite known as sporozoites into the bloodstream. These sporozoites travel to the liver to mature and multiply, ultimately resulting in severe illness or death. The new laboratory-produced antibody, called CIS43LS, was developed to remain present within the bloodstream over time and neutralize sporozoites before they invade the liver.

Investigators first administered one dose of CIS43LS to 21 healthy subjects by either intravenous infusion or subcutaneous injection, with each dose varying between 5 and 40 milligrams per kilogram of body weight. Over the next six months participants were followed to ensure that treatment was well tolerated and that plasma antibody concentrations remained durable.

In the second part of this study, 15 participants (nine who had received CIS43LS and six control participants) were subjected to a carefully monitored exposure to malaria from infected mosquitoes. None of the volunteers receiving the antibody developed malaria, whereas five of the six control participants did (and were promptly treated to eliminate the infection). Among those who received an infusion of CIS43LS did so at time points ranging from 1 to 9 months before being exposed to malaria, demonstrating how antibody treatment could be a safe and effective way to prevent the disease. A larger phase 2 clinical trial is currently underway in Mali to evaluate CIS43LS in adults living under malaria endemic conditions. (NIH authors: M.R. Gaudinski, [see online version for complete list]...J.R. Mascola, J.E. Ledgerwood, and R.A. Seder for the VRC 612 Study Team, *N Engl J Med* 2021; DOI:10.1056/NEJMoa2034031)

[BY LEANNE LOW, NIAID]

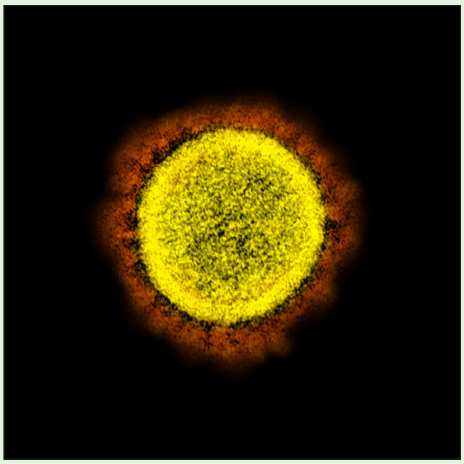


CREDIT: COHEN LAB, NINDS

NINDS: In a study of healthy volunteers, NIH researchers discovered that our brains may replay compressed memories of learning new skills when we rest. Above is a map of the memory replay activity observed in the study.

Read longer versions of these briefs at: https://irp.nih.gov/catalyst/v29i5/research-briefs.

COVID-19 Timeline at NIH (July–August 2021)



CREDIT: NIAID

Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

July 2: NIH funds five projects to identify ways of safely returning students and staff to in-person school in areas with vulnerable and underserved populations. The awards are part of the NIH Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) program.

July 5: NIH Clinical Center CEO **Jim Gilman** updates the NIH Clinical Center visitor policy: Adult inpatients may have one adult visitor during hospital visiting hours and pediatric inpatients may have up to two adult visitors; inpatients at the end of life may have two adult visitors; adult outpatients may have one adult visitor accompany them and pediatric outpatients may have up to two adult visitors.

July 6: The Employee Asymptomatic Testing Center changes its days of operation to Tuesdays and Fridays. All employees are eligible to be tested for SARS-CoV-2.

July 8: An NIH-supported study finds that nanobodies—specialized antibodies produced by the immune systems of llamas, alpacas, and camels–can be used to effectively neutralize SARS-CoV-2 variants. (*Nature* **595**:278–282, 2021; DOI:10.1038/s41586-021-03676-z)

July 8: The FAES Coffee Bar and NIH Federal Credit Union Branch reopen in Building 10.

July 8: An NIH-led study finds that strain placed on hospitals during surges in COVID-19 caseloads between March and August 2020 may have been responsible for one in four deaths and diminished benefits gained from emerging treatments. The findings suggest that bolstering preventative measures and supporting surging hospitals could save lives. (*Ann Intern Med* 2021; DOI:10.7326/M21-1213)

July 9: In his all-staff email, NIH Director **Francis Collins** updates staff on statements issued by Johnson & Johnson and Pfizer that reported both of their vaccines are effective against current SARS-CoV-2 variants, including the highly contagious delta variant. Additionally, the NIH RADx-UP program announced new awards as the second installment of the Safe Return to School Diagnostic Testing Initiative, which addresses the needs of children with unequal access to COVID testing as well as those facing barriers to attending school remotely.

July 16: NIH Director **Francis Collins** highlights a new NIH-supported study that found the protective effects from mRNA vaccines against COVID-19 may last for years. (*Nature* 2021; DOI:10.1038/s41586-021-03738-2)

July 20: A study funded in part by NIDA finds that more than 1.5 million children around the world are estimated to have lost at least one caregiver who lived with them due to death related to COVID-19 during the first 14 months of the pandemic. (*Lancet* 2021; DOI:10.1016/S0140-6736(21)01253-8)

July 20: NIH Director **Francis Collins** highlights an international study that identified gene variants that may influence who becomes infected with SARS-CoV-2 and how sick they will become. (*Nature* 2021; DOI:10.1038/s41586-021-03767)

July 20: President Joseph Biden signs an executive order requiring all federal employees, contractors, and visitors to wear masks and physically distance when on government property.

July 23: In his all-staff email, NIH Director **Francis Collins** points to efforts to fight misinformation about COVID-19 and vaccines, highlighting recent estimates that the delta variant now accounts for 83% of all COVID-19 cases and that 99.5% of COVID-related deaths occur in unvaccinated people. NIH continues to operate in a state of maximum telework, and Group C staff are not yet approved to return to the physical workplace.

July 26: HHS and the Department of Justice jointly publish guidance on how disability nondiscrimination laws apply to people with long COVID and other post-COVID conditions.

July 27: Given new evidence on the delta variant, the CDC updates its mask guidance and recommends that fully vaccinated people wear a mask in public indoor settings in areas of substantial or high transmission; and universal indoor masking for all teachers, staff, students, and visitors to schools, regardless of vaccination status.

July 28: After the CDC masking update, HHS announces that all employees, contractors, and visitors, regardless of their vaccination status, will be required to wear masks when in HHS facilities. NIH's indoor masking requirement remains unchanged.

July 29: President Joseph Biden announces that all federal employees and contractors must be vaccinated against COVID-19 or be required to be tested once or twice weekly.

July 29: NIAID researchers demonstrate proof of aerosol transmission of SARS-CoV-2 in a hamster model. (Preprint on *BioRxiv* 2021; DOI:10.1101/2021.07.26.453518)

August 4: A worldwide clinical trial, supported in part by NHLBI, finds that full-dose blood thinners reduce the need for organ support in moderately ill COVID-19 patients but not in critically ill patients. (*N Engl J Med* 2021; DOI:10.1056/NEJMoa2103417; *N Engl J Med* 2021; DOI:10.1056/NEJMe2111151)

August 5: The Office of Research Services announces new food service additions on the Bethesda NIH Campus: Daily breakfast served at the Eurest food trailer; Chef's Tables in Building 35 will offer made-to-order lunchtime specials Tuesdays, Wednesdays, and

Thursdays. The outdoor barbecue will return on the south lawn of Building 10 and continue every other Wednesday.

August 6: In his all-staff email, NIH Director **Francis Collins** announces a virtual Town Hall on September 10 to update staff on the changing pandemic landscape as the delta variant causes a rise in COVID-19 cases.

August 6: A panel of experts convened by NIH recommends standardized criteria to define infection of the placenta with SARS-CoV-2, the virus that causes COVID-19. The recommendations aim to help streamline research on SARS-CoV-2 infection during pregnancy and optimize clinical care. (*Am J Obstet Gynecol* 2021; DOI:10.1016/j.ajog.2021.07.029)

August 10: A NIAID-led team finds that a nasal spray of the Oxford-AstraZeneca COVID-19 vaccine protected hamsters and monkeys against serious disease and reduced the amount of virus in the nose. (*Sci Transl Med* 2021; DOI:10.1126/scitranslmed.abh0755)

August 10: NIAID launches a pilot study to assess the antibody response to a third dose of an authorized COVID-19 mRNA vaccine in kidney-transplant recipients who did not respond to two doses of the Moderna or Pfizer-BioNTech COVID-19 vaccine.

August 12: The FDA amends the emergency-use authorizations for both the Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for an additional dose in certain immunocompromised individuals.

August 12: HHS announces a mandatory COVID-19 vaccination policy for all HHS staff who have contact or potential contact with patients. At NIH, the policy covers everyone who works inside Building 10 at the Bethesda campus and all clinical sites in other locations.

August 16: The Building 10-B1 Cafeteria and Dining Room on the Bethesda campus reopens.

August 16: The Employee Asymptomatic Testing Clinic increases its operations to three days: Mondays, Tuesdays, and Fridays.

August 16: NEI and NIDCR researchers develop a faster COVID-19 test using direct RNA detection. (Preprint *ISCIENCE* 2021; DOI:org/10.1016/j.isci.2021.102960.)

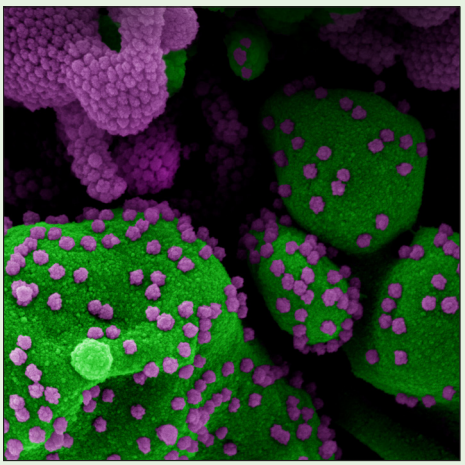
August 17: NIAID scientists publish a study that details how different routes of SARS-CoV-2 virus exposure are linked to disease severity. They found that airborne transmission is associated with more-severe disease and is markedly more efficient than exposure from contaminated surface contact. (*Nat Comm* **12**:article number 4985, 2021; DOI:10.1038/s41467-021-25156-8)

August 18: An NHLBI-supported study reports that COVID-19 convalescent plasma did not prevent disease progression in a high-risk group of outpatients with COVID-19 when administered within the first week of their symptoms. (*N Engl J Med* 2021; DOI:10.1056/NEJMoa2103784)

August 18: NIH Director **Francis Collins** and NIAID Director **Anthony Fauci** join several HHS public health and medical experts to announce the need for booster shots to maximize vaccine-induced protection. Individuals will be eligible for a third dose of the Pfizer and Moderna mRNA vaccines starting 8 months after receiving their second dose.

August 20: In his all-staff email, NIH Director **Francis Collins** updates staff on this week's vaccine booster recommendations. He announces that the Safer Federal Workforce Task Force has approved the voluntary return of NIH staff who perform critical laboratory and clinical activities that must be done on site. Due to the surge in COVID-19 cases from the delta variant, all non-mission-critical travel is on hold. He ends with a note of gratitude to staff and volunteers at the Office of Research Services and Occupational Medical Service for their commitment to keep the NIH family safe during the pandemic.

August 23: The FDA approves the Pfizer-BioNTech COVID-19 vaccine, which will now be marketed as Comirnaty, for the prevention of COVID-19 disease in individuals 16 years of age and older.



CREDIT: NIAID

Colorized scanning electron micrograph of an apoptotic cell (green) heavily infected with SARS-COV-2 virus particles (purple), isolated from a patient sample. Image at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.

August 27: NIAID supports a phase 2 clinical trial to assess antibody response to an extra dose of an authorized or approved COVID-19 vaccine in people with autoimmune disease.

August 30: NIH opens the application process to allow federal employees, fellows, and trainees to apply to voluntarily return to the physical workspace if they perform laboratory and clinical activities that must be done on site (and they are not already reporting on site).

August 31: HHS Secretary Xavier Becerra and Deputy Secretary Andrea Palm host a virtual Town Hall for the HHS community to answer frequently asked questions about the evolving COVID-19 pandemic and how it will affect the future workplace. They are joined by NIH Director **Francis Collins**, CDC Director Rochelle Walensky, FDA Acting Commissioner Janet Woodcock, and HHS Secretary of Administration Cheryl Campbell. ●

Read a more detailed version of this timeline, complete with links, https://irp.nih.gov/catalyst/v29i5/covid-19-timeline-at-nih-july-august-2021.

Eyes on Fire

Profile: Charles E. Egwuagu, Ph.D.

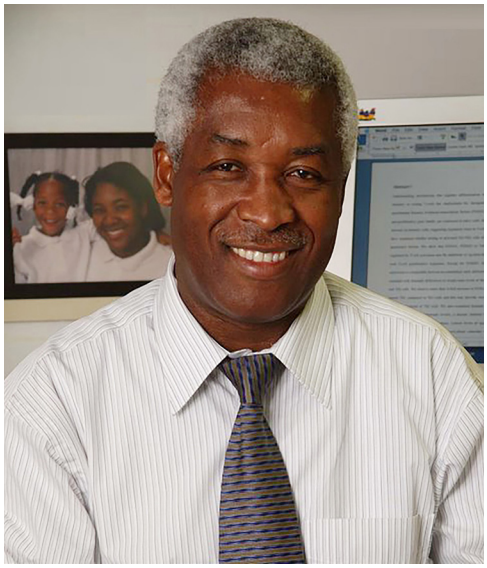
BY ETHAN SMITH, NINR

There's a high demand for new treatments for uveitis, an intraocular inflammatory disease that destroys eye tissues and can even render a person blind. Uveitis can be of autoimmune or infectious etiology and may affect the front of the eye (anterior uveitis), back of the eye (posterior uveitis), or all layers of the eye (pan uveitis). Corticosteroids and immunosuppressive agents are often used to treat the disease, but they can also shackle the immune system's ability to defend the body, leaving patients more vulnerable to cancer and other infectious diseases.

Charles Egwuagu, a senior investigator at the National Eye Institute (NEI), is working to develop new treatments for uveitis that don't have the side effects of other therapies. His approach is a unique cell-based therapy using immune cells called regulatory B cells (Bregs). Bregs were first described in the late 1990s for their ability to suppress inflammation, and, since then, many subpopulations of Bregs have been described in various inflammatory diseases.

Long before he took on Bregs, Egwaugu established that Th17 cells (a type of T-helper immune cells that protect the body from bacteria and fungi) play a crucial role in driving inflammation in human uveitis. He published his findings in *Nature Medicine* in 2007 (*Nat Med* **13:**711–718, 2007).

Then he shifted his focus toward developing biologics (drugs produced using a biological source). For example, the insulin that stabilizes blood sugar in diabetes is mass produced using *Escherichia coli*. Egwaugu's goal was to treat uveitis using a biologic that could selectively inhibit Th17 cells and other inflammatory immune cells without suppressing the whole immune system. In particular he was interested in what the



Charles Egwuagu, Ph.D.

immune-regulatory protein interleukin 35 (IL-35) could do. He and his team produced IL-35 in insect cells using baculovirus, injected it into mice, and found that IL-35 suppressed uveitis. But no one expected that the IL-35 would also cause the growth of a new population of Breg cells that could suppress autoimmune disease.

"We found out IL-35 can induce a rare population of B cells that are immunoregulatory," said Egwuagu.

In 2014, he published his discovery in *Nature Medicine* (*Nat Med* **20:**633–641, 2014). Now, he is trying to leverage the immunosuppressive capabilities of IL-35+ Bregs to treat uveitis and other autoimmune diseases such as multiple sclerosis.

Early Exposure

Egwuagu's first interest in science was in hygiene—large-scale practices designed to control and prevent disease. "I come from a place where the burden of disease is too much," said Egwuagu, who grew up in the Southwest region of Cameroon in the coastal city of Victoria (renamed Limbe in 1982). In Victoria, the sanitation department handled mandatory vaccination programs for infectious diseases such as measles and smallpox. He didn't know much else about the department other than one of his dad's friends was the director. "All I knew was that he was the person trying to make everyone healthy," said Egwuagu.

A Brief Foray Into Biochemistry

At the age of 19, Egwuagu traveled to the United States for college, carrying with him the belief that, whatever direction his career took him, it was important that his work be relevant to the community around him.

He earned a B.A. in biology from Kean University (Union, New Jersey), then an M.S. in biochemistry from Rutgers University (New Brunswick, New Jersey). Although he enjoyed synthesizing chemical compounds at the lab bench, he wasn't sure whether he wanted to be a biochemist. He was also still passionate about hygiene, specifically infectious and tropical diseases, so he enrolled in the M.P.H. program at the Yale School of Public Health (New Haven, Connecticut) and in the M.Phil. and Ph.D. programs in epidemiology and microbiology at Yale Graduate School of Arts and Sciences.

An Education in New Haven

Joint matriculation in the Yale programs afforded Egwuagu the opportunity to explore various scientific disciplines, such as physiology, pathophysiology, microanatomy, and cell biology (Yale Medical School); epidemiology, virology, and parasitology (School of Public Health); and immunology and molecular biology (Yale Graduate School of Arts and Sciences).

"I was like a sponge," said Egwuagu. "I would take information from all these

places." He credits the interdisciplinary design of his education in preparing him for a leadership role in biomedicine. "There are few people who have the kind of training and experience that helps you cross-talk with the different scientific and medical communities."

Occasionally, Egwuagu's thesis advisor—then the only Black tenured professor at Yale School of Medicine—would send Egwuagu (also Black) to other labs at Yale and at Smith, Kline & French (now GlaxoSmithKline) to learn molecular cloning and gene-expression techniques. The professor warned him that he might face discrimination at some of these places and advised Egwuagu that, no matter what, he should stay focused on gaining skills that would advance his career.

After Egwuagu earned his graduate degrees, he considered doing postdoctoral training at the Centers for Disease Control and Prevention's (CDC's) Epidemic Intelligence Service so he could pursue his interests in epidemiology and tropical diseases. But he'd had such good training in molecular cell biology and immunology that two of his Yale mentors (one was George Palade, who shared the 1974 Nobel Prize in Medicine or Physiology) advised him to go to NIH for postdoctoral training in immunology or neuroscience. Egwuagu figured there'd always be a chance to go to CDC later (he never went, however).

Because he was eager to explore the latest advancements in medical research, he took his mentors' advice and headed to NIH for further training. "At that time [1980s], there was a revolution in [scientific] thought among young molecular epidemiologists at Yale," said Egwuagu. "The concept of molecular medicine was taking hold."

In 1987, Egwuagu joined the lab of **Igal Gery**, an immunologist who is now a scientist emeritus at NEI. Gery's lab had all the resources Egwuagu needed to gain basic research experience in immunology and study the proteins that were involved in causing eye autoimmune disease. Their cutting-edge work led to the seminal discovery of the molecular basis of susceptibility to organ-specific autoimmune diseases (*J Immunol* **159:**3109–3112, 1997). Less than a year after joining NIH, Egwuagu started his own lab in NEI.

From Point A to Point B

IL-35 is a tricky protein to work with. Making it is "a pain in the neck," said Egwuagu. "For about three liters of culture, you end up with only about one microgram" of purified IL-35. In addition, it's made up of two subunits that need to interlock to become active and exert anti-inflammatory effects. Egwuagu was confident that both subunits were made inside Bregs and that his team could isolate the active form of IL-35 in culture. Yet the same question kept coming up: How do both subunits of IL-35 get out from inside the cell and meet to create the active form that the lab team isolates?

This question had Egwuagu at a loss. He remembers chatting at dinner with his wife **Michele Evans**, a senior investigator in the National Institute on Aging. She works with exosomes, microscopic "bubbles" that contain a variety of molecules, including proteins. After her husband described his dilemma, Evans explained that many cells secrete exosomes and suggested that perhaps Bregs secrete them as well. Egwuagu decided to test his wife's theory in the lab. He and his team found that the Breg population they study did indeed secrete exosomes containing both subunits of IL-35 and that IL-35-containing exosomes grown in the lab have therapeutic effects in an autoimmune mouse model of uveitis. The findings were published in 2020 in *Frontiers in Immunology*. (*Front Immunol* **11:**1051, 2020).

Thanks, in part, to Evans' insight, Egwuagu had shifted his research and found a more clinically feasible, and easier, way to determine the right dose of IL-35 to treat uveitis: Measure the IL-35-containing exosomes instead of the two loosely linked subunits that form the active IL-35. His ultimate goal is to develop Breg immunotherapies for the treatment of CNS autoimmune and neurodegenerative diseases.

In addition to conducting his own research, Egwuagu enjoys mentoring young predoctoral and postdoctoral scientists and tutoring students in the NIH Medical Research Scholars Program (a 12-month residential research immersion program for medical, dental, and veterinary students). "I believe strongly that the mission of NIH is to train young people," he said. His philosophy involves balancing being hands-on while allowing his trainees the independence to work through problems on their own. He encourages his trainees to figure out what it is they want to do in their careers and tailor their training accordingly.

Egwuagu considers his decision to train—and stay—at NIH as one of the best he's made. "Dreams change as you grow up," he said with a laugh. "It all turned out for the best." ●

Ethan Smith, a postbaccalaureate fellow in the National Institute of Nursing Research, is studying biomarkers for traumatic brain injury. He's in the process of applying to graduate programs in clinical psychology.

St. Elizabeths Hospital

How Its Architecture Informs Us of the Past and Present

BY LEANNE LOW, NIAID

In her recent presentation at NIH, historian Sarah Leavitt laid out the evolution of St. Elizabeths Hospital, an institution for people with mental illness, established in 1855.

Once referred to (unofficially) as the "U.S. Lunatic Asylum," St. Elizabeths Hospital in Southeast Washington, D.C., established in 1855, remains open, welcoming and helping patients with serious and persistent mental illnesses. Most people, however, are unaware of the many changes the hospital has undergone both in landscape and in medical practice.

Sarah Leavitt, a former historian in the Office of NIH History (2002–2006) and an expert on the hospital's architectural story, gave a talk on June 24, 2021, as part of the Office of NIH History and Stetten Museum's biomedical history lecture series. She previously worked at the National Building Museum (Washington, D.C.) where she curated its St. Elizabeths Hospital exhibit in 2017. She is now a curator and historian at the Capital Jewish Museum (Washington, D.C.).

Leavitt's interest in the history of medical institutions began when she was an undergraduate at Wesleyan University (Middletown, Connecticut) with an honors thesis on the Connecticut Industrial School for Girls (Middletown, Connecticut) for "vagrant" or delinquent girls. "This started my thinking about institutionalization and what was the right approach," said Leavitt, who went on to get a Ph.D. in American Studies and Civilization at Brown University (Providence, Rhode Island).

Architectural Drawings

By happenstance, she briefly visited St. Elizabeths during her time at NIH, but it wasn't until she joined the National Building Museum that she had an opportunity to view the vast collection of the St. Elizabeths architectural drawings held at the Library of Congress (Washington, D.C.). From there, the story of St. Elizabeths grew and resulted in an exhibit that not only included 20 of the original architectural drawings but various historical elements such as a writing desk on which the first piece of legislation toward the establishment of St. Elizabeths Hospital was written, to the ventilation grills that once graced its inner walls.

Kirkbride Plan

First opened by the federal government in 1855, the conception of St. Elizabeths Hospital was largely pioneered by Dorothea Dix, an early 19th-century activist who advocated improving conditions for the mentally ill. Dix partnered with the hospital's first superintendent, Dr. Charles Nichols, to choose a location and design based on the views of Dr. Thomas Kirkbride, who championed the philosophy of "moral treatment" based on compassion and respect. He believed that architectural landscape and view could "cure" a patient who had mental illness.

The hospital would eventually spread into a 350-acre campus in Southeast Washington, D.C., and its first building—the Center Building—was constructed in the style of the "Kirkbride Plan." It had a characteristic "V" shape in which the central core housed administrative staff and the wings accommodated patients in individual rooms that brought in ventilation and sunlight. Patients were organized based on their symptoms and severity with those suffering from severe symptoms being furthest from the center. Several other hospitals featuring the iconic "V" design were built across the United States between 1848 and 1913, with some 33 buildings—no longer used as hospitals—retaining their original form today.

Although the importance of surroundings was recognized, the "view was often marred by construction," Leavitt noted. "The ideology of this rural and bucolic setting was really punctured…and didn't always have that idealistic quiet."

Segregation of white and Black patients occurred during St. Elizabeths' first 100 years. Leavitt, however, highlighted the differences between architecture: White

patients had accommodations, based on the Kirkbride Plan, that were elaborate and decorative—even the ventilation grates had intricate patterns. In contrast, Black patients lived in less decorative lodges that were not based on the Kirkbride Plan and they slept in dormitory-style rooms.

It was soon apparent that environment alone couldn't cure many mental illnesses and that the Kirkbride vision was insufficient in dealing with the increasing demand for mental-health facilities. The architectural landscape evolved into a cottage and farm-style system in the 1880s, reflecting the belief that patients could be better cared for in smaller, more homelike buildings that specialized in certain mental illnesses. Self-sufficiency also became an important aspect and farming activities soon became part of white patients' therapy programs.

Medical Research

Medical research became important at St. Elizabeths. During the early 20th century, the Blackburn Laboratory, named for neuropathologist Dr. Isaac W. Blackburn (1851–1911), was established. Scientists there made major contributions to neurological research, with particular focus on the study of brains of patients with mental illness.

By the 1950s, the initial hope that provision of moral treatment could help rehabilitate patients had given way to the mindset of needing to have people with mental illness walled away from the general public. An increasing number of patients contributed to overcrowding, with St. Elizabeths population going from 2,000 patients at the beginning of the 1900s and reaching as many as 8,000 patients in the early 1960s. Needed expansion, coupled with decreasing funds, eventually culminated in the creation of utilitarian structures that were

COURTESY OF SARAH LEAVITT

Sarah Leavitt, a former historian at NIH and now a curator and historian at the Capital Jewish Museum, gave a talk recently about St. Elizabeths Hospital, an institution for people with mental illness.

seen as "warehouses for the mentally ill," said Leavitt. These buildings were boxlike and devoid of the intricacies seen in earlier architecture.

From 1967 to 1987, the National Institute of Mental Health (NIMH) had administrative control over the hospital. During this time, the rise of the patient rights' movement, combined with increased medical research and federal reluctance to provide more funding encouraged the ensuing de-institutionalization of St. Elizabeths. Beginning in the 1960s with President John F. Kennedy's proposal to end custodial care and open 1,500 community mental-health clinics, Presidents Richard Nixon and Jimmy Carter aimed to fund this network of clinics; however, the passing of President Ronald Reagan's Omnibus Bill of 1981 led to severe restriction of federal funding for mental-health care. By the late 1970s the St. Elizabeths population had decreased to nearly 2,000 patients.

Today

Once comprising the West Campus and East Campus, the St. Elizabeths hospital facilities were consolidated to a portion of the East Campus and is now operated by the District of Columbia Department of Behavioral Health, which took over administrative control in 1987. (NIMH continued to run a research program there until 1999, when the NIMH Neuroscience Center/Neuropsychiatric Research Hospital was transferred to the NIH Bethesda, Maryland, campus.) The city has redeveloped the rest of the East Campus into residential and entertainment spaces. Several buildings still remain, including the Center Building (on the West Campus), which has been rebuilt and is now home to the Department of Homeland Security headquarters.

Leavitt closed with not only a poignant reminder of society's responsibility toward supporting and funding mental-health programs, but also several lingering questions, such as what were 19th-century moral reformers trying to accomplish by institutionalizing mental patients or why did the reformers do things as they did? More importantly, what should we do now? She posed one final question to consider: "How can we use architecture and landscape moving forward to promote wellness?" ●

To view a videocast of Sarah Levitt's lecture, go to https://videocast.nih.gov/watch=42142.

Leanne Low is a visiting postdoctoral fellow in the Laboratory of Malaria and Vector Research in the National Institute of Allergy and Infectious Diseases, where she is investigating the role of a Plasmodium falciparum *protein in the intracellular development of the malaria parasite.*

Bionics

CONTINUED FROM PAGE 1

CREDIT: MATTHEW SEPTIMUS, MIT

MIT Professor Hugh Herr, who designed his own prosthetics after he lost both legs in a climbing accident, shared his story at a WALS lecture at NIH recently.

disability caused by trauma and disease. Herr heads the Biomechatronics Research Group at MIT's Media Lab (Cambridge, Massachusetts) and co-leads the MIT Yang Center for Bionics. He shared his story, "On the Design of Bionic Limbs: The Science of Tissue-Synthetic Interface," at a recent Wednesday Afternoon Lecture Series (WALS) presentation.

A Life Refocused

As a young man Herr was a rising rock-climbing talent, establishing himself as one of the sport's best. But in January 1982, an ice climb on New Hampshire's Mount Washington altered his trajectory: Herr lost both legs below the knee to frostbite after he and his partner became disoriented in a blizzard and spent four harrowing days stranded on the mountain.

A set of standard prosthetic limbs enabled Herr to walk again, but he was unsatisfied with the rough design and insistent on resuming his climbing career. Herr took to the machine shop and fabricated his own legs that were optimized for the vertical world: Specialized attachments enabled him to adjust his height from five- to nine-feet tall, or balance on razor-thin rock fissures and vertical ice walls. He was able to climb at a more advanced level than ever before. "This was a tremendous lesson for me," said Herr. "Technology has the ability to heal and rehabilitate, and in my own case, extend human capability beyond normal physiological levels."

The Bionic Age

In 2002 Herr went on to invent the world's first powered ankle-foot prosthesis. Known today as the Empower, the device has been fitted to more than 3,000 people who've had lower-extremity amputations. The computer-controlled robotic ankle restores natural gait through a motor, three processors, and 12 sensors. Herr uses the technology himself but saw room for improvement. So, his MIT team set to work linking the nervous system directly to the electromechanics and allowing the device to release feedback to the central nervous system (CNS)—a concept he calls "neuro-embodied design." In order to take full advantage of the sophisticated prosthesis, however, they first needed a new amputation paradigm.

Herr refers to the surgery performed on him as a "Civil War–era amputation." While surgical techniques have advanced, amputations today still tack down muscles in a static position. This disrupts the person's awareness of their limb's position and movement, a sense known as proprioception.

In 2014, Herr led his MIT group in the invention and preclinical development of the agonist-antagonist myoneural interface (AMI) amputation technique. This procedure surgically reconnects natural muscle pairs, or reconstructs new ones, restoring the dynamic link that provides critical proprioceptive feedback. Surface electrodes placed over each AMI pair can then translate voluntary movement (or a computer-generated electrical signal) to a bionic prosthesis, allowing the user to control their new limb.

In 2016, bolstered by this foundational preclinical research from MIT, Brigham and Women's Hospital (BWH) performed a first-in-human amputation using an AMI surgical design under the direction of Matthew Carty, director of the Lower Extremity Reconstruction Program. The first person to receive the AMI procedure was Jim Ewing, who had his left ankle amputated after a climbing accident in the Cayman Islands. Herr designed a robotic ankle with two planes of motion that connected to Ewing's AMI muscle pairs. The results were remarkable. "Jim showed natural mechanics mediated through the electromechanics on steps and slopes, the same involuntary movements that happen in intact biological limbs," said Herr in his talk. In this preliminary study, Ewing's CNS was able to exert both voluntary and involuntary control over his bionic ankle. Subsequent studies on a larger population of persons with an AMI amputation have shown that even when using traditional prostheses, AMI recipients experienced less pain and greater perception of their phantom limb.

Thirty patients have now received the AMI surgical procedure primarily at BWH. In addition, the Walter Reed National Military Medical Center (Bethesda, Maryland) has recruited patients and performed the surgery as well.

Preclinical studies underway at the MIT lab are exploring ways to create seamless bidirectional communication between bionic prostheses and humans, a concept Herr refers to as "closing the loop." Small magnets are being implanted into AMI muscles to precisely track contractions. This technology, called magnetomicrometry, will one day enable the bionic joint to respond in real-time to AMI muscle contractions.

Another neural interfacing technology Herr is exploring is optogenetics. Proprioceptive feedback on prosthetic joint position and force is sent back to the nervous system by optogenetic stimulation: This technology genetically alters neurons in the nerve that innervates muscle to respond to light. The computer in the prosthesis can then activate light emitters to stimulate AMI muscles, effectively letting the brain know exactly how the artificial joint is moving.

Preclinical data collected by Herr's lab has also shown that skin cells grafted to muscle could potentially restore the sense of touch through sensors on the bionic limb. To create a wired, percutaneous connection between the peripheral nervous system and the bionic limb, Herr's lab is using a technique called osseointegration: A titanium rod affixed to the bone bears weight and runs wires from internally implanted electronics directly to the prosthesis. Two patients are currently enrolled in a clinical trial funded by the Defense Advanced Research Projects Agency, and have undergone the procedure at the above-knee amputation level.

Herr ended his talk with dramatic drone footage of Jim Ewing returning to the site of his accident to ascend a seaside cliff using a climbing-specific ankle-foot prosthesis.

From hearing aids to artificial heart valves, many of us are already, in a sense, bionic. We may not be leaping over skyscrapers (yet), but new technology has had a profound impact on the lives of those with physical disability, and is rapidly filling the void between our actual and potential selves. ●

To view the May 5, 2021, videocast of Hugh Herr's WALS lecture "On the Design of Bionic Limbs: The Science of Tissue-Synthetic Interface," go to https://videocast.nih.gov/watch=41586.

NIH's Work Helping People With Movement Disorders

NIH is also investigating how technology can improve the function of people living with movement disabilities, not necessarily from amputation, but as a result of neurologic disorders such as cerebral palsy (CP) and spina bifida. **Diane Damiano**, chief of the NIH Clinical Center's Functional and Applied Biomechanics (FAB) Section has assembled a multidisciplinary team of scientists and engineers, who've been developing wearable robotics and using brain-imaging technologies to assess and train motor coordination and tailor rehabilitation interventions. Much of Damiano's work has focused on children with CP, a condition caused by a brain injury or malformation that occurs before, during, or after birth. CP affects a person's ability to perform motor skills, including walking. Any two children with CP might use completely different parts of their brain to perform such a skill, suggesting that any training strategy should be fit to the individual.

In 2017, the FAB team unveiled the first prototype of a powered lower-limb exoskeleton that improved upright posture and walking speed in children with CP. The wearable device uses external sensors and motors to facilitate the child's natural effort. "We expanded the mechanical design and software to provide multiple modes of assistance and identify the most effective one for each individual," said lead investigator **Thomas Bulea**.

FAB recently partnered with Vancouver, Canada–based Agilik Technologies Inc. to update the original exoskeleton into a streamlined, lightweight, wireless unit. The exoskeleton can also be outfitted with electric stimulators to cue key muscles involved in knee extension during walking, a technique that has begun to show promise.

To determine the effectiveness of the exoskeleton, researchers use electroencephalography (EEG) to record brain activity, electromyography (EMG) to measure muscle response to nerve stimulation, and motion-capture techniques to record movements. This information can be incorporated into personalized software and robotic interventions. "Our software takes information from sensors at 100 times per second on limb position and velocity and deduces what the person is trying to do in real time," said Bulea. "So the robot adjusts to what the person wants to do." His team has begun studies on patients with spina bifida (a birth defect that occurs when the spine and spinal cord don't form properly) and are planning to expand the technology to other conditions such as stroke and incomplete spinal cord injury.

Damiano's current focus is on using new technologies to intervene during the earliest stages of motor development. Her group worked with Ashburn, Virginia–based Aretech, Inc. to modify the company's ZeroG computerized harness system that partially supports a person's weight. The miniaturized design enables infants with CP to learn to move more easily.

A pilot study on infants with CP older than age 1 year found that using the harness system significantly improved mobility skills compared with a control group. Damiano hopes to apply this technology to babies with CP. "There's a brief window of time from 3 to 6 months of age where they may be able to recover [from] the brain injury," she said.

FAB is set to begin a new neurofeedback protocol. They designed a computer interface in which the patient practices a movement while receiving EEG and EMG feedback on what part of their brain they are using. Tactile cues such as resistance or electrical stimulation can then push the patient to recruit different parts of their brain that better control the movement.

FAB continues to discover ways to help people with all kinds of movement disabilities by bringing new interventions to the rehabilitation arena. ●

Read more at https://irp.nih.gov/catalyst/v29i5/the-intersection-of-man-and-machine

COVID-19 vaccine

CONTINUED FROM PAGE 1

Barney Graham's lab is located in NIH's Dale and Betty Bumpers Vaccine Research Center, also known as Building 40.

Graham and Corbett quickly mapped out a plan to begin experiments, assigned roles to team members, and went to work designing an antigen—in this case, a copy of the spike protein found on the surface of the COVID-19 virus, which it uses to infect cells. This antigen molecule, when provided via a vaccine, would trick the body into forming a defensive arsenal against future infection. After years of prior work to unlock the mysteries of coronaviruses and, with their partners at Moderna, perfect a method to coax the body to manufacture antigens via mRNA, they were prepared. Less than 48 hours after the release of the novel coronavirus's genome, the team had designed the protein that their candidate COVID-19 vaccine would use to teach the immune system to fend off the virus. Sixty-five days later, the VRC began clinical trials in collaboration with Moderna and clinical investigators from NIH's Division of Microbiology and Infectious Diseases. Ultimately, the vaccine received emergency use authorization (EUA) from the FDA on December 18, 2020, just one week after a similar vaccine developed by Pfizer was granted an EUA.

In recognition of this groundbreaking success in developing a life-saving COVID-19 vaccine in record time, Graham and Corbett were named finalists for the 2021 Samuel J. Heyman Service to America Medals, also known as the "Sammies." Often referred to as the "Oscars of government service," the Sammies honor exceptional work by government employees.

Although Graham and Corbett have captured the public's attention, they both stressed that there were dozens of other researchers at the VRC and elsewhere that made the NIH–Moderna vaccine a reality.

A Long Road and a Fast Finish

While creation of the specific vaccine for COVID-19 was surprisingly rapid, Graham and Corbett, along with fellow researchers in their field, had been laying the groundwork for decades. As a young chief resident at Vanderbilt University School of Medicine (Nashville, Tennessee), Graham began studying respiratory syncytial virus (RSV), an infectious disease that can be fatal in children. A vaccine made with the inactivated virus had been tested in the 1960s with tragic results—not only did it not work, but the disease worsened in children who received the vaccine.

Eventually, Graham discovered that the original vaccine failed for two major reasons. First, the vaccine induced a response from immune cells called T cells that was more like an allergic response, making a lot of mucus and not effectively clearing the virus from the body. Second, inactivating the virus caused it to change shape to the form it takes once it has already infected and fused with a cell. As a result, the vaccine caused the body to release antibodies that could bind to the virus but could not block infection, making it ineffective. These findings set Graham on a path to create vaccines that could emulate the prefusion form of the virus.

He continued the RSV project in 2000 when he was recruited to NIH to help create the VRC. Eventually, he and **Jason McLellan**, a postdoctoral fellow in the lab of senior investigator **Peter Kwong** isolated and created 3D models of the prefusion virus protein. The new vaccine that used this prefusion version of the virus caused the body to produce antibodies 16 times as potent as the postfusion antibodies elicited by the old vaccine.

"I just wanted to know what the shape of the prefusion protein was [and] how it was folded, and what it looked like," Graham said. "That led to a vaccine approach that looks like it's probably going to work."

In fact, the discovery of the prefusion structure proved foundational to the work Graham's lab subsequently began on coronaviruses like the severe acute respiratory syndrome and Middle East respiratory syndrome (MERS) viruses, both of which had previously caused worrisome outbreaks around the world. Some of this work was

done in continued collaboration with McLellan, who later joined the faculty at the Geisel School of Medicine at Dartmouth College (Hanover, New Hampshire) and now runs a lab at the University of Texas at Austin (Austin, Texas).

"After we had the RSV breakthrough, Dr. McLellan and I decided that coronaviruses were similar enough to RSV and there was no structural information for them," Graham said. "That was a good area to work in because it was a wide-open field and it needed to be done."

At that point, in 2014, Corbett joined the VPL as a senior research fellow and plunged full speed into understanding how the antibodies that bind to different forms of coronavirus spike proteins block infection. She also started developing a way for her team to quickly and reliably develop antigen proteins that could be tweaked to match each virus, as well as a method to deliver the instructions for making these proteins to cells via mRNA. The VRC was already gearing up for clinical trials with Moderna to test an mRNA vaccine against Nipah virus, which the lab had developed in parallel with an mRNA vaccine against the coronavirus that caused the 2012 MERS outbreak. As a result, by the time COVID-19 emerged, the VPL was poised to switch gears to a vaccine for COVID-19 and hit the ground running.

Inspiring Communities

In addition to her work on the Moderna COVID vaccine, Corbett has worked tirelessly on educating the public about vaccination and addressing vaccine hesitancy, particularly in communities of color. For the past year, her spare time has been filled with everything from television appearances and interviews to personally reassuring individuals and answering their questions.

CREDIT: (LEFT) CHIA CHI "CHARLIE" CHANG; (RIGHT) NIH

Kizzmekia Corbett (left) and Barney Graham (right) were named finalists for the 2021 Samuel J. Heyman Service to America Medals for leading NIH's COVID-19 vaccine development effort.

She even accompanied a young man and his mother to get their shots after the man expressed concerns about the vaccine at an MSNBC town hall. Corbett hopes her newfound celebrity might motivate young people—especially women and minorities—to pursue careers in science.

"I try to tell my story because it's not just that I don't even look like a scientist, but my background would suggest I could not be a scientist, ever," Corbett said. "So I hope that people start to see that there's talent in different places."

"20 Years of Work for a Thousand People"

As the frenzied rush to develop a safe and effective COVID-19 vaccine winds down, both Graham and Corbett are planning their futures. Graham recently retired and hopes to devote his time to improving communication and education about science and technology here and around the world. In particular, he'd like to see the establishment of more research capacity in low- and middle-income countries and improved dissemination of information and technology.

In June 2021, Corbett left NIH to lead her own laboratory at Harvard T.H. Chan School of Public Health (Boston), where she'll continue to study coronaviruses and "do work on things that hopefully will surprise people," she said.

She'll have plenty of options. As Graham points out, there are 26 different families of viruses known to infect humans.

"You should pick something within those 26 families that you find really interesting," Graham advised her. "It may end up being the cause of the next big pandemic, or it may not, but there's at least 20 years of work for a thousand people." ●

This story is adapted from one that originally appeared on the NIH "I Am Intramural" blog at https://irp.nih.gov/blog.

Melissa Glim, a science writer and health care communications professional, has written about topics from Alzheimer disease to women's health, covering basic science to patient education to policy and advocacy.

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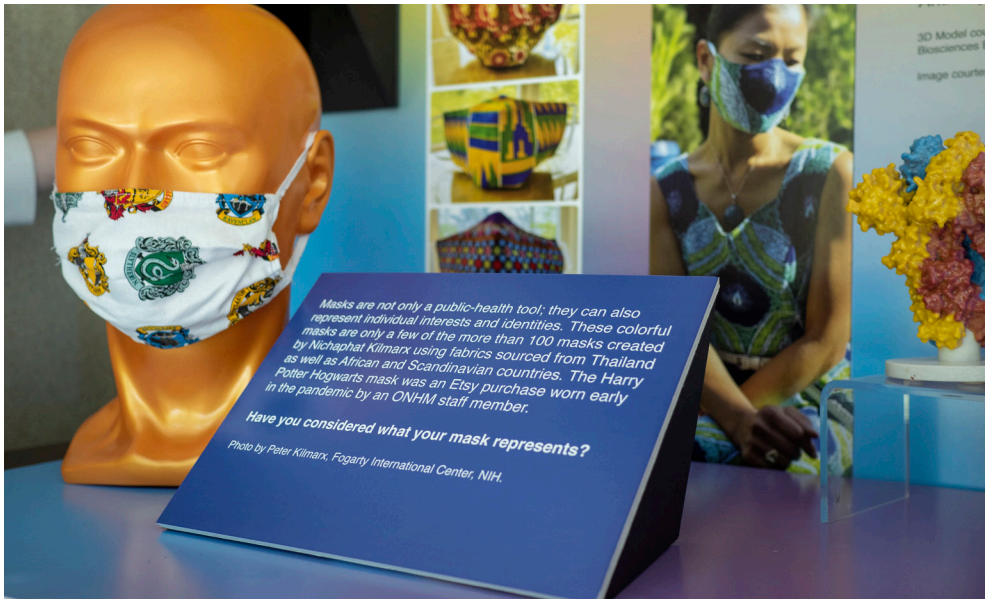
FROM THE ANNALS OF NIH HISTORY

Making History: The COVID-19 Exhibit

BY MARK RIEWESTAHL AND DEVON VALERA, OFFICE OF NIH HISTORY



CREDIT: MARK RIEWESTAHL, OFFICE OF NIH HISTORY

The Office of NIH History and Stetten Museum (ONHM) has installed a new exhibit in the main hallway of Building 31: The "NIH & COVID-19" exhibit showcases NIH's role in the fight against COVID-19. Read all about it at https://irp.nih.gov/catalyst/v29i5/from-the-annals-of-nih-history-covid-19-exhibit. ●