Antibiotic resistance (AR) looms as one of the biggest public health crises of our time. AR occurs when microbes such as bacteria develop the ability to evade the drugs designed to kill them. The Centers for Disease Control and Prevention estimate that over 2.8 million people get an AR infection in the United States each year, resulting in more than 35,000 deaths. AR is rising to dangerous levels worldwide while the pipeline of new antibiotics is running dry, threatening our ability to treat common infectious diseases. But the use of bacteriophages (phages) to treat AR infections caused by bacteria offers a glimmer of hope. Phages are naturally-occurring viruses that invade bacterial cells and replicate. The viral particles eventually burst out, killing the host cell in the process. Phages have coevolved with bacteria and function to keep microbe populations in check: Potency, self-amplification, and specificity make phages an attractive alternative to antibiotics. And phages are everywhere; one can assuredly find them in a lake, sewage water, or farm.

A promising treatment resurfaces
Phage treatment, known as phage therapy, has a colorful history going back a century. After the dawn of small-molecule antibiotics however, interest in the therapy quickly died down, at least in Western medicine.

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[16] Profile: Sean Agbor-Enoh, M.D., Ph.D.
In May, we celebrate Asian American and Pacific Islander (AAPI) Heritage Month. This is a good time to reflect on how researchers from these groups have enriched the NIH Intramural Research Program (IRP). One does not need to look any further than our recent COVID-19 seminar series to see outstanding research presented by Helen Su (National Institute of Allergy and Infectious Diseases, NIAID), Peter Kwong (Vaccine Research Center), and Yogen Kanthi (National Heart, Lung, and Blood Institute). NIH Distinguished Investigator T. Jake Liang, who is chief of the Liver Diseases Branch and deputy director of Translational Research at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), has agreed to take on the new role of executive sponsor and champion for the AAPI Engagement Committee. There are also our National Academy of Sciences members, Wei Yang (NIDDK), Shiv Grewal (National Cancer Institute, NCI), Sankar Adhya (NCI), and Kiyoshi Mizuuchi (NIDDK). We are all fortunate to have such incredible researchers in our midst.

As part of IRP’s celebration, we will continue to co-sponsor, with the NIH Office of Equity, Diversity, and Inclusion, the annual Kuan-Teh Jeang lecture, which takes place this year on May 20, 2021, at 1:00 p.m. This year’s lecturer is Peter Kwong. This lecture series honors the life and legacy of the late Kuan-Teh Jeang, a former senior investigator in NIAID.

This is also a good time to reflect upon the challenges facing Asian American and Pacific Islander scientists. One of the challenges has been recognizing their many different countries of origin and how different their histories are within the United States and at NIH. In particular, the number of Pacific Islander researchers at NIH has always been vanishingly small, with only some modest successes in recruitment through programs such as the NIH Undergraduate Scholarship Program (https://www.training.nih.gov/programs/ugsp). Even though scientists of Asian descent have represented over 15% of the IRP’s senior investigators for several years, they represent only 7% of our lab and branch chiefs and currently hold no scientific director positions.

Fear that we might be missing opportunities to advance individuals with leadership skills was the main driver of the recent changes in our practices for the selection of lab and branch chiefs. Now that these searches are more uniformly open, we encourage all qualified scientists to apply for these key leadership positions. It is also worth noting that we anticipate that there will be no fewer than seven scientific director positions available over the next year. Again, we encourage all qualified researchers to apply for these positions, which will be advertised at the IRP careers website (https://irp.nih.gov/careers/faculty-level-scientific-careers).

We have all been horrified recently by many instances in this country of bias and violence directed toward Americans of Asian descent. As we celebrate the many, many contributions of our Asian American and Pacific Islander colleagues, let us also be sure that NIH remains a civil and inclusive research environment where no one need feel insecure or unappreciated. The incredible tapestry of our cultural, ethnic, and racial heritage is a strength that will sustain the creative force that propels the IRP.

Links to information contained in this essay can be found in the online version at: https://irp.nih.gov/catalyst/v29i3/from-the-deputy-director-for-intramural-research.
“There’s not some sort of magic process that can remove everything we put down the drain.” —David Sedlak, Director of the Institute for Environmental Science and Engineering at University of California, Berkeley (Berkeley, California)

The valuable research and support activities performed at NIH produce an array of waste products. Whether they are hazardous or nonhazardous, all must be managed appropriately. Submitting materials through waste-management services ensures proper disposal and prevents hazardous chemicals from being discharged into the sanitary sewer (system of pipes that carries sewage from labs, bathrooms, sinks, kitchens, etc., to wastewater treatment plants). The NIH waste-management policy requires that all waste be reduced to the greatest extent feasible to limit any potential negative environmental impacts. It’s the responsibility of everyone at NIH to know what can and cannot go down the drain.

Wastewater treatment technologies have advanced over the years. As a result, we have become overly confident in our publicly owned treatment works capabilities to clean the waste we release into the sanitary sewer. Unfortunately, there are still problems: Newly introduced chemicals may interfere with the treatment process or pass through the system entirely untreated. In the 1980s, for example, some states enacted bans on phosphates in laundry detergents because they promoted harmful growth of algae in waterways.

We continue to discover new chemicals in our environment and water supply which defy treatment standards. Substances such as asbestos, PFAs (per- and polyfluoroalkyl substances), and pharmaceuticals—a chief concern as it relates to NIH operations—all pose significant challenges to our waste-management systems.

In cooperation with NIH scientific directors and the National Institute of Environmental Health Sciences, the Division of Environmental Protection (DEP) in the NIH Office of Research Facilities—has developed a Drain Discharge Guide to inform staff which chemicals can be disposed through the sanitary sewer.

• Only chemicals approved for drain disposal by the DEP may be poured down the drain.
• Surplus solid chemicals must be disposed of through the NIH chemical-waste services and not discharged down the sanitary sewer.
• If you are unsure whether a chemical can be disposed of via the drain, or if you do not see the chemical on the list of approved chemicals for drain disposal, do not dispose of via the drain. Instead, call DEP at 301-496-7990 for further guidance.
• Chemicals that are not listed on the approved disposal list within the Drain Discharge Guide may be considered for drain disposal, but you first have to complete an application requesting approval (VPN and NIH credentials required) at https://spapps.od.nih.gov/sites/DEPAuthorizations/SitePages/Home.aspx. Please note that when pursuing this option, disposal via the sanitary sewer can occur only after DEP has reviewed and approved the application.

You can find the Drain Discharge Guide at https://nems.nih.gov/Documents/NIH_Drain_Discharge_Guide.pdf. Any questions regarding the guide should be directed to the DEP by calling 301-496-7990 or emailing depwasteresource@mail.nih.gov. For links to more resources, read the online article at https://irp.nih.gov/catalyst/v29i3/news-you-can-use.

Craig Upson is a Chemical Waste Technical Specialist in the Waste and Resource Recovery Branch, Division of Environmental Protection.
Science communication has never been more important than during the past year. Suddenly, everyone is interested in a category of viruses that scientists have been quietly studying for decades. We all want to know when life will return to normal, and we are searching for answers. Unfortunately, misinformation spreads faster than factual information: People pay attention to simple explanations and sometimes ignore what they do not comprehend. If we want people to trust the science, we have to help them to understand it.

I am a nonscientist who has taught advanced English classes to scientists through the Foundation for Advanced Education in the Sciences since 2017. Many of my students are quite proficient in English, having studied the language in depth, but they want to make better use of their language skills to become more effective communicators. I challenge my students to explain the important aspects of their work more clearly.

Regardless of your native language, it is much easier to speak to people inside your specialty area than to those outside your area of expertise. After all, the people in your field share a common language, full of specialized terms unique to you and your colleagues. But the more you practice speaking to people outside your specialty, the more comfortable you will feel. You’ll be rewarded with interesting conversations while doing your part to educate the public about science.

The first step in getting your audience to understand what you are saying is to get them to listen. Here are some tips that can help when you want to engage in a conversation with someone who knows nothing about what you do:

**Tip 1: Tell your audience what excites you about what you do.**
Do you like the excitement of discovering something before anyone else? Use an analogy to explain how much we have yet to learn about how our bodies work. You can compare what you do to being an explorer. Make identifying a new protein sound as exciting as discovering a new planet.

**Tip 2: Think about your audience’s interests and find a connection.**
How does your specialty area connect to something that the average person can understand? When your audience includes people in the general public, you may need to explain words that are part of your vocabulary as a scientist, but are new to them. For example, describing CRISPR-Cas9 gene editing as genetic scissors can provide a helpful visual. If you are a basic scientist, give an example of how your work is important in providing vital information that leads to treatments and cures for diseases.

**Tip 3: Leave your audience wanting to hear more.**
Give bite-sized pieces of information in the simplest language possible, then pause to let your audience digest it. When your listeners get a taste of what you know and start asking questions, you’ve succeeded in communicating about science.

**Tip 4: Tell a Story.**
People of all ages love stories. One of my students likes to tell her seven-year-old son stories in which the main characters are antibody superheroes. Wouldn’t you prefer to learn about the immune system through her stories instead of a boring PowerPoint presentation?

My students have told me that speaking to members of the public can be both challenging and rewarding. It’s “an exciting challenge because…you can’t use all the [scientific] jargon…when you talk to a general audience,” said postdoctoral fellow Omar Jose (National Institute of Diabetes and Digestive and Kidney Diseases), who gave a short talk recently about vaccines at a community learning event called Celebrating Scientists. “Whenever I give a presentation, I try to make the message as simple as possible without leaving out any critical information. It takes time to develop this ability, but it pays off because it’s an excellent way to engage the audience.”

Remember, if we want people to trust the science, we need to help them understand it. So the next time someone asks what you do or wants to know about your day, think of it as a communications challenge that you’re ready to take on. And if you are asked to speak at your child’s school for career day, say “Yes!” Think of it as a communications challenge, and a challenge that you’re ready to take on.

Jennifer Kagan, a faculty development specialist with NIH’s Foundation for Advanced Education in the Sciences (FAES) [https://faes.org], teaches courses in English communication skills and supports faculty in delivering high-quality, graduate-level courses to the NIH community. Before joining FAES in April 2021, she was English Now!’s Director of Program Development and held a joint appointment with FAES, teaching for English Now! Outside of work, she enjoys biking, playing Scrabble, and spending time with her family.
New SIG: Asian American Pacific Islander Health

The Asian American Pacific Islander Health Scientific Interest Group (AAPI-HSIG) is open to all in the intramural and extramural NIH community who are interested in research related to the health of AAPIs. The SIG provides a forum to foster scientific communication, share and disseminate information, facilitate collaborations, provide education, assess research needs, and make recommendations to NIH leadership that aims to stimulate research and improve the health and well-being of the AAPI population. Regular activities include monthly (or quarterly) meetings as well as research and education seminars (virtual or in-person). Other activities may include holding conferences and lectures in collaboration with other NIH groups and other Federal and non-Federal entities; conducting joint activities with the Federal Asian Pacific American Council; and encouraging extramural program staff to develop grant-funding opportunities. The SIG co-chairs are Dan Xi (NCI) and Phuong-Tu Le (NIMHD). Co-advisors include Kelvin Choi (NIMHD) and Xinzhi Zhang (NCATS). For information, go to https://oir.nih.gov/sigs/AAPI-HSIG or contact Dan Xi (xida@mail.nih.gov).

New SIG: Precision Oncology

Cancer is a constellation of diseases typified by the uncontrolled accumulation of cells. Given the diversity of the cell types that can be transformed, cancer can affect nearly every tissue and organ. Taking into account the variety of genetic variations, epigenetic influences, and environmental factors that drive the development of tumors, one quickly appreciates that any given cancer is essentially a patient-specific disease. From this perspective, precision in the treatment of cancer is essential in providing the best care for patients.

At the NCI-Center for Cancer Research's (CCR's) online PI retreat, held in March 2021, clinicians, pathologists, principal investigators, staff scientists, and staff clinicians expressed an interest in creating a Precision Oncology Interest Group (POIG).

Short-term goals. 1) Discuss, plan, implement, and execute the current CCR initiative to perform standardized genomic analyses (RNA sequencing, exome sequencing, methylation analysis) on a large cohort of NCI patients; 2) Use these data to drive collaborative, predictive, prognostic biomarker discovery, and precision-therapy strategies for improving patient outcomes.

Long-term goals. 1) Discuss and implement best sample-acquisition and management practices; 2) Discuss and implement the best technologies and informatics to help discover candidates for targeted therapies; 3) Rationally design clinical trials in oncology with a focus on precise therapies that have the potential to maximize benefit and minimize side effects.

The POIG aims to foster effective communication across the basic and clinical research oncology communities and to harness NIH’s translational powers to advance cancer precision therapies. This POIG effort, initially proposed by Brigitte Widemann (NCI), will be co-chaired by NCI scientists Padma (Sheila) Rajagopal, Antonios Papanicolau-Sengos, and Art Shaffer; advisors are Eytan Ruppin and Kenneth Aldape. All are welcome to participate and contribute suggestions for discussion topics and speakers (including yourself, of course). For more information and to join the LISTSERV, go to https://oir.nih.gov/sigs/precision-oncology-interest-group.

New SIG: Cancer Metabolism

The Cancer Metabolism Interest Group aims to provide a forum for individuals from NIH and the extramural community to discuss basic, translational, and clinical research related to metabolism and the intersection of metabolism with immunology. The wide scope of seminar topics will reflect the increasing recognition that the study of subcellular, cellular, and whole-body metabolism is relevant for understanding metabolic heterogeneity, drug resistance, diets in cancer, cancer biology, and tumor progression. The group will meet the first Monday of each month (virtually for now). Each meeting will feature one 60-minute presentation from an intramural or extramural senior scientist or two 30-minute presentations from trainees. Senior advisers are Mark Gilbert (NCI-CCR) and Dan McVicar (NCI-CCR). The SIG chair is Mioara Larion (NCI-CCR). For more information, go to https://oir.nih.gov/sigs/cancer-metabolism-interest-group or contact Mioara Larion (mioara.larion@nih.gov).

For a full list of NIH scientific interest groups, go to https://oir.nih.gov/sigs.
The exciting news is that phage therapy is making a comeback; recent case studies have been successful in using phages as an experimental therapy.

The therapy still has a long way to go as it is not yet generally approved by the FDA. And, as with antibiotics, bacteria also develop phage resistance. The evolutionary arms race between phages and bacteria has been going on for billions of years—which is critical to understand for phage therapy to become a success. Two experts, Paul Turner from Yale School of Medicine (New Haven, Connecticut) and Michael Laub from MIT (Cambridge, Massachusetts), shared their research on the evolutionary interaction between phages and bacteria and its significance to phage therapy at the NIH Director’s Wednesday Afternoon Lecture Series (WALS) on March 10 and March 17 respectively.

**Evolutionary trade-offs**

Turner is the Rachel Carson Professor of Ecology and Evolutionary Biology at Yale and a prominent expert on evolutionary trade-offs (he earned his Ph.D. with Richard Lenski, famous for his ongoing 33-year-old long-term evolution experiment on bacteria). A trade-off occurs when natural selection improves one trait at the expense of another. Turner shared his findings that demonstrated how evolutionary trade-offs between AR and phage resistance could be used in phage therapy.

His research team isolated phages that enter a bacterial host by selectively targeting the elements used by the bacteria to develop AR. The idea was simple: If the bacteria evolve phage resistance by modifying these elements, it will compromise their antibiotic resistance, making the bacteria susceptible to antibiotics once again. A synergistic treatment using phages together with antibiotics would leave little chance for the antibiotic-resistant bacteria to escape.

Bacteria often develop AR by expelling drugs through proteins known as efflux pumps. Turner showed how a phage that binds to an efflux pump of *Escherichia coli* (*E. coli*) results in the selection of phage-resistant bacteria that are now sensitive to tetracycline. A similar approach could target virulence factors. For example, his team found a phage that invades *Pseudomonas aeruginosa* by attaching to pili, hair-like appendages on the surface of bacteria to
help in movement and surface adherence during infection. When the bacterium developed phage-resistance by losing the pili, it became avirulent (more vulnerable to the immune system) due to its inability to form biofilms and to move around.

“But there is a cautionary tale, and you should know what you are doing before using phages for therapy,” Turner said. Sometimes, instead of causing a trade-off, mutations cause a trade-up; they confer resistance to both antibiotics and phages.

The last part of Turner’s talk focused on emergency phage therapy. His team was granted FDA approval to treat a patient who developed a chronic AR infection after undergoing an aortic arch replacement. They chose a phage that used an efflux pump for entering the bacteria and predicted that the phage would kill the existing microbe population while exerting selection pressure on the bacteria to develop phage resistance, compromising their ability to maintain AR. Consistent with the evolutionary trade-off theory, a single application of the phage and a previously ineffective antibiotic (ceftazidime) resolved the infection with no sign of recurrence.

In another case, a 22 year-old patient with cystic fibrosis undergoing pulmonary failure had a high concentration of AR bacteria in her sputum. After a phage therapy treatment given via nebulizer, her lung function improved significantly. Interestingly, the treatment resulted in a population of bacteria that became sensitive to almost all antibiotics, opening the door to previously unavailable treatment options.

Turner is hopeful that phage therapy will be used in clinics soon. To date, Yale New Haven Hospital has successfully treated over 13 patients with AR infections using the emergency therapy. And things are moving in the right direction; The hospital was recently granted FDA approval to begin phage-therapy clinical trials.

From proteins to phages
Laub is a professor of biology at Massachusetts Institute of Technology and a Howard Hughes Medical Institute Investigator. He studies the coevolution of proteins and the selective pressures that drive the evolution of bacterial signaling pathways (mechanisms that allow bacteria to process information and respond to environmental changes). But “the coevolution of proteins is dear to my heart”, he said.

Laub’s ongoing work on the coevolution of toxin-antitoxin (TA) protein pairs (referred to as TA systems in bacteria) led to his foray into the world of phages. A TA system consists of a toxin gene and an associated antitoxin. The toxin is always a protein, and the antitoxin can be either a protein or a noncoding RNA. These systems are widespread in the bacterial kingdom, but why bacteria carry them remains a mystery. Laub’s team discovered that cloning the TA systems found in several E. coli strains into E. coli K12 (a widely used laboratory strain of the bacterium) resulted in phage resistance.

Interestingly, the bacteria did not develop broad phage resistance, suggesting that TA systems seem to provide tailored protection only against specific phages. For example, one of the TA systems prevents the production of new viral particles by destroying the phage RNA. These findings establish TA systems in bacteria as another arm of immunity against phages in the ongoing evolutionary arms race.

“Phages fight back,” Laub said. His team identified a phage variant that evolved a counter-defense against one of the TA systems. This phage amplified a region of its DNA that encoded a protein capable of neutralizing the toxin, allowing the phage to propagate.

Both Laub and Turner are exploring concepts with far-reaching implications in phage therapy. Turner also believes that his work may help answer some bigger questions, such as how do we predict the emergence of viruses in new hosts? The investigation into evolutionary trade-offs between phages and bacteria might just reveal some clues.

Subhash Verma is research fellow in NCI’s Laboratory of Molecular Biology. In his spare time, he enjoys exploring nature, playing cricket and volleyball, and biking.
NINDS, NCI, NIAMS, NICH, NEI: DNA DAMAGE “HOT SPOTS” DISCOVERED WITHIN NEURONS

Researchers at NIH and the University of Sussex (Falmer, England) have identified “hotspots,” in neuron genomes that appear to accumulate DNA damage known as single-strand breaks (SSBs)—a finding that has the potential to reshape the way we think about DNA damage and its role in neurobiology.

The scientists found that the most prominent concentrations of SSBs localized to distinct regions of DNA called enhancers, which control nearby gene activity. One way a cell can influence gene expression is by applying a chemical tag known as a methyl group to specific sites on its DNA; SSBs accumulated when the methyl group had been removed.

The researchers proposed that the absence of methyl group resulted in the formation of SSBs. And, at least in neurons, the failure to properly repair DNA damage, not the damage itself, could dysregulate gene expression, thereby contributing to the development of neurodegenerative diseases. (NIH authors: W. Wu, S.E. Hill, W.J. Nathan, J. Paiano, E. Callen, D. Wang, K. Shinoda, N. van Wietmarschen, J.M. Colón–Mercado, D. Zong, R. De Pace, H. Shih, S. Coon, M. Parsadanian, R. Pavani, S. Park, S.K. Jung, C. Chen, R. Casellas, M.E. Ward, and A. Nussenzweig, *Nature* 2021; DOI:10.1038/s41586-021-03468-5) [BY CHARLESICE GRABLE-HAWKINS, OD]

NIH: ENGINEERED IMMUNE CELLS MAY PREVENT CANCER SPREAD

Scientists at NCI have developed a form of immunotherapy that prevents and slows cancer metastasis in mice. They studied mice implanted with rhabdomyosarcoma, a type of cancer that develops in the muscles and spontaneously metastasizes to the lungs. The team first examined immune cell changes in the lungs before metastasis but after muscle-tumor development. They found that several immune cell types—in particular myeloid cells—were attracted to the premetastatic site. However, instead of sending signals to recruit cancer-fighting immune cells, the myeloid cells were actively suppressing the immune response.

The researchers created genetically engineered myeloid cells (GEMys) that produce interleukin 12 (IL-12). The mice treated with GEMys had decreased metastatic cancer and muscle-tumor size and lived longer than control mice. GEMys in combination with other treatments even prevented cancer recurrence.


The NIAD team had previously established a human cerebral organoid system—a small cluster of human brain cells grown in a lab from skin cells. The cerebral organoids have been shown to accurately predict neurotoxicity—and therapeutic benefits—of drug treatments in humans.

The researchers infected the cerebral organoids with pathogenic prions and then tested pentosan polysulfate (an established antiprion compound), which successfully delayed prion propagation when applied both prophylactically and after an established infection. The findings demonstrate the utility of cerebral organoids as a model for screening therapeutic drug candidates to treat human prion diseases. (NIH authors: B.R. Groveman, N.C. Ferreira, S.T. Foliaki, R.O. Walters, C.W. Winkler, B. Race, A.G. Hughson, and C.L. Haigh, *Sci Rep* 11:Article number 5165, 2021) [BY NATALIE HAGEN, NCATS]

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NICH: CAFFEINE DURING PREGNANCY MAY LEAD TO SMALLER BIRTH SIZE

NICHD researchers found that women who consumed as little as the equivalent of a half cup of coffee a day (50 milligrams) had slightly smaller babies than women who did not drink caffeinated beverages.

The study enrolled more than 2,100 nonsmoking women from racially and ethnically diverse backgrounds with no history of health problems. They reported their daily consumption of caffeinated beverages and provided a blood sample between 10 and 13 weeks of pregnancy. Compared with those consuming minimal or no caffeine, women with the highest plasma caffeine concentrations gave birth to babies that were 84 grams lighter, 0.44 centimeters shorter, and had head circumferences 0.28 centimeters smaller. The long-term implications are unclear, but caffeine has been hypothesized to restrict blood supply to the fetus, inhibiting growth, and potentially putting infants at risk for childhood obesity and chronic diseases later in life. (NIH authors: J.L. [BY JENNA SHERFAN, NCATS]
NIAID: ADOLESCENTS MAY DEVELOP ADDICTIONS FASTER THAN YOUNG ADULTS
NIAID researchers reported that the onset of substance-use disorders (SUDs) is associated with the age an individual tried a drug for the first time.

The scientists analyzed data from participants (ages 12-25 years) in the National Surveys on Drug Use and Health, from 2015 to 2018. They compared the prevalence of substance use in adolescents (ages 12-17) and in young adults (ages 18-25). Each group was examined at four intervals after their first use of a drug: less than 12 months, 12-24 months, 24-36 months, and more than 36 months. The study found that adolescents have a 10.7% chance of developing a SUD to cannabis within 12 months of their first experience, compared with 6.4% in young adults. This difference grew to 20.1% in adolescents and 10.9% in young adults in the over-36-month interval. Similarly, an overall higher rate of SUDs were found in adolescents with the misuse of prescription drugs such as opioids, stimulants, and tranquilizers. (NIH authors: N.D. Volkow, B. Han, E.B. Einstein, and W.M. Compton, JAMA Pediatr e206981, 2021)

[BY SUBHASH VERMA, NIA]

NHLBI,CC: CIRCULATING MITOCHONDRIAL DNA TRIGGERS INFLAMMATION IN SICKLE CELL DISEASE
NIH researchers discovered that DNA from the mitochondria triggers inflammation in people with sickle cell disease (SCD). The researchers identified elevated mitochondrial cell-free DNA (cf-mtDNA) in the plasma of SCD patients compared with healthy control subjects. Normally, mature red blood cells do not contain mitochondria. These findings indicate that cf-mtDNA is not only a prognostic biomarker but may also contribute to the pathology of SCD, opening new avenues for investigation and therapeutic intervention. (NIH authors: L. Tumburu, S. Ghosh-Choudhary, F.T. Seifuddin, E.A. Barbu, S. Yang, M.M. Ahmad, L.H.W. Wilkins, I. Tunc, I. Sivakumar, J.S. Nichols, P.K. Read more, and longer, briefs at: https://irp.nih.gov/catalyst/v29i3/research-briefs.

[CREDIT: NIAID]

NIAID, NCI: BACTERICIOPHAGE TREATMENT RESCUES MICE FROM MULTI-DRUG RESISTANT KLEBSIELLA PNEUMONIAE
Scientists from NIAID’s Rocky Mountain Laboratories (Hamilton, Montana) and NCI have developed an effective therapy using bacteriophages against multidrug-resistant Klebsiella pneumoniae sequence type 258 (ST258) in mice. The bacterium causes high rates of mortality when left untreated. Although newer antibiotics have shown efficacy against ST258, resistance against these drugs is expected to increase.

The authors found that treating acute sepsis with two phages (phage P1 and phage P2) that target ST258 improved survival: Mice were first injected with ST258 to induce infection. They were then treated at several different times after infection with phage P1, phage P2, or both. Survival outcomes were dramatically improved from 0% in saline-treated control mice to 100% in mice treated with both phages. Early treatment combined with using both phages resulted in the strongest recovery.

The authors noted that although lower bacterial concentrations were seen in the blood and tissues of the phage-treated mice, the recovered ST258 bacterium began to demonstrate phage resistance. Further work on the strategic selection of phages, phage dosing, and engineering may improve the ability to predict therapeutic efficacy of phage treatment in the future. (NIH authors: S. Hesse, N. Malachowa, A.R. Porter, B. Freedman, S.D. Kobayashi, D.J. Gardner, D.P. Scott, S. Adhya, and F.R. DeLeo, mBio 12:e00034-21, 2021)

[BY EMMA ROWLEY, NIAID]

NIEHS: MOSQUITO PROTEIN MAY INHIBIT SOME DANGEROUS VIRUSES
The mosquito protein AEG12 strongly inhibits flaviviruses and weakly inhibits coronaviruses, according to NIEHS scientists and their collaborators. Flaviviruses cause yellow fever, dengue, West Nile, and Zika, among other illnesses. Mosquitoes produce AEG12 when they take a blood meal or become infected with flaviviruses. The researchers found that AEG12 destabilizes the viral envelope, but does not affect viruses without an envelope, such as those that cause pink eye and bladder infections. AEG12 might also be effective against SARS-CoV-2, the coronavirus that causes COVID-19, although it will take years of bioengineering to make AEG12 a viable therapy. (NIH authors: A.C.Y. Foo, P.M. Thompson, S.-H. Chen, B. Lupo, E.F. DeRose, S. Arora, V.D. Placentra, L. Perera, L.C. Pedersen, N. Martin, and G.A. Mueller, Proc Natl Acad Sci USA 118:e2019251118, 2021)

[BY BRANDI CAROFINO, NCI]
COVID-19 Timeline at NIH (March–April 2021)

March 1: An NIH-funded team launches a study to assess an at-home COVID-19 testing system paired with a smartphone app.

March 1: NIH halts two ACTIV-3 clinical trial substudies for hospitalized patients. There were no safety concerns, but the Data and Safety Monitoring Board (DSMB) determined that there was a low likelihood of clinical value.

March 2: NIAID Director Anthony Fauci donates his model of SARS-CoV-2 to the Smithsonian's National Museum of American History. He is awarded the museum’s Great Americans Medal for his leadership during the COVID-19 pandemic and his lifetime work.

March 2: NICHD announces that it will lead a research effort called “Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID)”—to understand how SARS-CoV-2 affects children.

March 2: NIH halts a clinical trial evaluating the safety and effectiveness of COVID-19 convalescent plasma in treating emergency department patients who had mild to moderate symptoms of COVID-19. The treatment was deemed unlikely to benefit these patients.

March 3: NIH Director Francis Collins announces that employees scheduled for qualified urgent medical treatments will be prioritized to receive a COVID-19 vaccine.

March 5: NIH Director Francis Collins updates staff on the improving COVID-19 vaccine supply; NIH received 2,400 Pfizer vaccine second doses from the federal supply chain for Maryland-based employees. Additionally, the Montana Department of Public Health and Human Services supplied 100 Moderna vaccine second doses for staff at NIAID's Rocky Mountain Labs (Hamilton, Montana). NIEHS in North Carolina also received 230 first doses of the Moderna vaccine.

March 8: NIH launches the last of three clinical trials to evaluate the safety and efficacy of the anticoagulant Eliquis to prevent life-threatening blood clots.

March 10: NIH informs staff that HHS has extended authorization for supervisors to approve excused absences for employees caring for dependents at home through September 10, 2021.

March 11: The one-year anniversary of the day that the World Health Organization declared the COVID-19 pandemic.

March 12: In his all-staff email, NIH Director Francis Collins acknowledges that the past year has been a long and difficult one but shares the encouraging news that “nationally, COVID-19 case numbers are gradually dropping [and] more people are being vaccinated every day.”

March 19: Francis Collins announces that all Phase 3-eligible employees have been invited by Occupational Medical Services to schedule their COVID-19 vaccination appointments.

March 22: Results from a large clinical trial, funded in part by NIAID, indicate that AstraZeneca's COVID-19 vaccine, AZD1222, is well-tolerated and protects against symptomatic COVID-19 disease including severe disease or hospitalization.

March 25: NIDCR-led study finds evidence that SARS-CoV-2 infects cells in the mouth. The findings suggest that oral cells and saliva play a bigger role in SARS-CoV-2 infection than previously thought, and may contribute to transmission within and outside the body. (Nat Med, 2021; DOI:10.1038/s41591-021-01296-8)

March 26: NIH Director Francis Collins announces that 2,340 vaccine doses were received to cover all phase 3 employees in Maryland, as well as phase 4 employees who are 75 and older. In addition, NIEHS in North Carolina received 1,170 first and second doses for staff. Collins also reports that NIH has had its first case of a fully immunized staff member test positive for SARS-CoV-2 infection more than 14 days after the second dose.

March 30: NIH announces that a NIAID-led team found a largely intact immune response to three of the newly identified variants in recovered COVID-19 patients and vaccinated individuals. The study concludes that the SARS-CoV-2-specific CD8+ T-cells remain active and offer protection against the emerging variants. (Open Forum Infect Dis, 2021; DOI:10.1093/ofid/ofab413)

March 31: The CDC and NIH launch an initiative called “Say Yes! COVID Test.” The program will provide free, rapid antigen tests to up to 160,000 residents across two communities in North Carolina and Tennessee. The effort aims to determine whether frequent, self-administered COVID-19 testing helps residents reduce community transmission.

March 31: NIAID and Moderna begin phase 1 clinical trials to evaluate the effectiveness of a vaccine designed to protect against the B.1.351 SARS-CoV-2 variant (the South African variant).

April 2: In his email to staff, Francis Collins announces that all NIH employees, including teleworkers, are eligible to be vaccinated in their communities under the classification of essential health workers. He reports that CDC announced results of a new agency study providing strong evidence that mRNA COVID-19 vaccines, both Pfizer and Moderna, are highly effective in preventing SARS-CoV-2 infection among health-care workers, first responders, and other essential workers.

April 7: A new, NIAID-led clinical trial aims to determine whether people who are highly
April 8: NIAID Director Anthony Fauci and colleagues co-author a review article addressing the challenges posed by the COVID-19 and HIV pandemics. The authors conclude that accelerated development and clinical testing of prevention and treatment strategies are urgently needed to mitigate the dual pandemics. (J Infect Dis 2021; DOI:10.1093/infdis/jiab114)

April 8: In his weekly email, NIH Director Francis Collins expresses gratitude to all staff by performing a unique take on Beatles George Harrison’s “Here Comes the Sun.”

April 9: Francis Collins announces that NIH can now offer the COVID-19 vaccine to all employees in phase 4 (staff on maximum telework) of the NIH vaccination plan. He also shares that a research letter (authored by NIAID researchers and others) reported interim results of a phase 3 trial of the Moderna COVID-19 vaccine that found antibody activity remained high in all age groups of a small study population at least 6 months after the second dose. (New Engl J Med 2021; DOI:10.1056/NEJMct2103916)

April 9: President Joseph Biden’s budget proposal includes $51 billion for NIH (a $9 billion increase over the 2021 enacted level).


April 13: A NIAID-funded clinical trial begins testing an investigational monoclonal antibody to treat patients with COVID-19 who are hospitalized with respiratory disease.

April 13: The FDA and CDC initiate a pause on the use of Johnson & Johnson COVID-19 vaccine due to an exceedingly rare blood clotting disorder reported in six cases. The pause is lifted on April 23.

April 14: NIH Director Francis Collins serves as a panelist with colleagues from other medical institutions during a virtual forum titled “Building Vaccine Confidence: Best Practices to Combat Misinformation and Vaccine Hesitancy in COVID-19 Vaccines.”

April 15: A NIAID-sponsored clinical trial closes enrollment. The study was examining the efficacy of two drug combinations to treat hospitalized patients with COVID-19 on supplementary oxygen. The DSMB determined that neither treatment protocol studied is likely significantly better than the other.

April 15: NIH announces that it is awarding up to $33 million over two years to fund nationwide projects that build evidence on safely returning students, teachers, and support staff to in-person school in areas with vulnerable and underserved populations.

April 16: NIH scientists find that the experimental antiviral drug MK-4482 significantly decreases viral particles and disease damage in the lungs of hamsters treated for SARS-CoV-2 infection. MK-4482 is now in phase 2 and 3 human clinical studies. (Emerg Microbes Infect 9:2673–2684, 2020)

April 19: NIH announces it will provide $155 million in funding for a large phase 3 clinical trial to test several existing prescription and over-the-counter medications that treat symptoms of COVID-19. The trial aims to provide self-administered treatment options for adult patients with COVID-19 who have mild-to-moderate symptoms and are not sick enough to be hospitalized.

April 21: A NIAID-sponsored phase 2 and 3 clinical trial launches to evaluate a new antibody used to treat SARS-CoV-2. Called SAB-185, the therapeutic is made from polyclonal human immune cells and will be tested on non-hospitalized people with mild or moderate cases of COVID-19.

April 22: Other trials for therapeutics that treat COVID-19 are underway this week. A phase 3 clinical trial, supported by NIAID and NHLBI, has begun enrollment to test the safety and efficacy of two therapeutics for treating severe COVID-19 in hospitalized patients.

April 23: Participants begin enrolling at the NIH Clinical Center for a new study assessing how people with immune-system deficiencies respond to COVID-19 vaccination.

April 28: NIH Director Francis Collins testifies before the House Energy and Commerce Health Subcommittee on the impact of post-acute sequelae of COVID-19 (PASC), generally known as Long COVID. He highlights NIH’s new research initiative to better understand this condition and find ways to treat or prevent it.

April 29: NIH announces it will fund an additional $29 million in grants for the NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities. The funding will bolster research to help communities disproportionately affected by COVID-19.

April 30: In his email message to staff, NIH Director Francis Collins reports that over 60% of NIH employees have been vaccinated against COVID-19. He calls attention to a new study of the Pfizer and Moderna mRNA vaccines that found fully vaccinated adults 65 years and older, who are among the most vulnerable groups, were 94% less likely to be hospitalized than their unvaccinated counterparts.
and Christopher Wanjek explained in their virtual Demystifying Medicine lecture on February 23rd.

Shelhamer, a professor of otolaryngology at Johns Hopkins School of Medicine (Baltimore) and former chief scientist of the Human Research Program at NASA, is studying sensorimotor physiology, with an emphasis on vestibular and oculomotor systems, and how astronauts adapt to space flight and living in space. In particular he is interested in how weightlessness affects vision and balance.

Wanjek, a health and science journalist who writes regularly about astronomy and previously worked at NASA, described the psychological and physical challenges of traveling in space and settling on another planet.

A major risk of living in space or on another planet is having to survive without relying on Earth. Earth is more than 140 million miles—and seven months of space travel—away from Mars. If an emergency occurred on a mission to Mars or another planet, such as running out of supplies or having a medical crisis, the crew would be out of luck.

To illustrate that point, Shelhamer described a medical emergency that occurred on the International Space Station (ISS) a couple of years ago: An unidentified astronaut had a blood clot in their neck. Although there was no established method for treating them in a microgravity environment, the ISS did have a small supply of blood thinners on board. A doctor on Earth advised NASA how to ration the medication until the next cargo mission could bring more medication to the ISS. The astronaut was treated successfully and survived. What if the same dilemma arose on a trip to Mars, or on Mars itself? Earth wouldn’t be able resupply the mission as easily.

Both Wanjek and Shelhamer described other health issues associated with living in a near-zero-gravity environment including reduced bone density and muscle tone, and a shift of fluids upward that increases volume and pressure in the head. For example, Shelhamer explained, vision is affected as the eyes become slightly flattened and the retina swells. What’s more, our brains use gravity as a constant frame of reference to inform its sense of balance. The brain loses this reference after a person spends a long time in space or on the ISS, so astronauts have a very poor sense of balance when they return to Earth. Both issues are temporary, but could be detrimental when landing in a new environment such as Mars. If you can’t see or move very well, avoiding dangerous situations would be difficult.

Space travel can also affect mental health. Astronauts on the ISS, Shelhamer pointed out, reported increased stress during a six-month study conducted by researchers at the University of Pennsylvania (Philadelphia). Even though some astronauts may “thrive on [stress], it still may be impacting them physiologically,” said Shelhamer. There may be “alternations in immune system function and cardiovascular function.” That stress, along with other perils, such as radiation exposure, can be dangerous.

“The thing that really [keeps] me up at night is the thing we haven’t thought of,” said Shelhamer. “It’s the funny combination of things that happen that we have no way of predicting.”

Shelhamer believes that a broad integrative approach that assesses medical, physiological, and psychological issues is a good way to maintain physiological and psychological fitness for long-duration space flights and life in outer space.

When humans have made it to Mars safely, what other hazards may await? The sun poses far more risk on Mars than on Earth, the speakers said. Earth’s atmosphere is thick enough that sunscreen is sufficient protection against the sun’s harmful rays. With the thinner Martian atmosphere, a little sunbathing would expose humans to life-threatening amounts of radiation. What’s more, the Martian soil contains perchlorates,
chemicals poisonous to humans. You certainly wouldn’t want to grow potatoes in that soil as Matt Damon’s character in the movie The Martian did.

Mars may have a hostile environment, but some workarounds are possible, Wanjek explained. For instance, we could live in caves for radiation protection and use aquaponics with light-emitting diodes to grow plants and raise fish.

Still, we have much to learn about what it would take to be sure people could safely live on another planet. What would be the long-term effects of living in a microgravity environment? Could humans give birth to and raise healthy children in a space colony? Can Mars sustain a natural human settlement?

Wanjek concluded his talk by raising an alternative possibility of living above planets—“in orbiting spheres [with] artificial climate with climate control with perfect gravity”—and visiting planets from there. He displayed a concept image showing modern architecture surrounded by lush trees. “I mean, look at this one; it has patio furniture,” he said, “Wouldn’t you want to live here [rather] than in some ice-fishing hut on Europa?”


Megan Kalomiris, a postbaccalaureate fellow in the Laboratory of Infectious Diseases in the National Institute of Allergy and Infectious Diseases, studies noroviruses. After completing her NIH training in 2021, she will be attending the Science Communications Master’s Program at the University of California at Santa Cruz (Santa Cruz, California). In her spare time, she enjoys taking walks in the woods and playing games (now, virtually) with her friends.

Space colonies: Artist’s rendering of a cutaway view of NASA’s proposed Stanford torus design. This space habitat would be capable of housing 10,000 to 140,000 people; have a comfortable, artificial climate; would rotate to produce artificial gravity; and have a system of mirrors that would provide sunlight and solar energy.
Searching For Answers
NIH’s Undiagnosed Diseases Program Grows Into a Worldwide Model
BY MICHAEL TABASKO, OD

Zarko Stanacev had suffered debilitating symptoms for more than a decade. What started out as episodes of hearing loss and severe headaches escalated to periodic seizures and meningitis. The attacks rendered him nearly comatose, confined him to a wheelchair, and cloaked him in profound fatigue. His medical providers were mystified. Without answers, the prospect of his living a normal life seemed out of reach.

But in 2017, Stanacev was accepted into NIH’s Undiagnosed Diseases Program (UDP), where an interdisciplinary team led by National Human Genome Research Institute (NHGRI) neurologist Camilo Toro set out to discover the source of his puzzling symptoms. They found a mutation in the NLRP3 gene that was causing abnormal inflammation in Stanacev’s body. Hours after being treated with anakinra, a drug used to treat inflammation, he dramatically improved and was up and walking without pain. Finally, he had hope and a path back to a normal life.

For many patients, the UDP represents their last, best hope. The UDP is a trans-NIH initiative hosted by NHGRI. UDP Director William Gahl started the program in 2008 with $280,000 of funding from the Office of Rare Diseases Research (ORDR).

“Steve Groft, director of the ORDR at the time, was getting calls from patients whose diseases had no name,” said Gahl. “Clearly, there was an unmet need.” And the UDP could meet that need.

In the beginning, the UDP had only a staff of four: Gahl, a scheduler, and two nurse practitioners. “I expected we would answer a few people’s questions, do some research in my lab on new diseases, perhaps discover new pathways which might apply to treatments,” he said. Then, two things happened that propelled the UDP beyond Gahl’s expectations.

First, in May 2008, then–NIH Director Elias Zerhouni and other NIH leaders held a press teleconference to announce the UDP. In addition to reporters, representatives from 96 rare-disease organizations were on the phone. “After that, the applications started pouring in,” said Gahl.

Second, next-generation sequencing (NGS) was burgeoning at the time. NGS allowed an entire human genome to be sequenced in a single day instead of years. In addition, whole-exome sequencing (focused on protein-coding regions of DNA) now allowed researchers to selectively search for mutations in a patient’s genetic code that could be causing their symptoms.

NIH’s laboratories are also certified by the Centers for Medicare and Medicaid Services through the Clinical Laboratory Improvement Amendments. The certification was a costly but necessary distinction for a lab’s results to influence a patient’s care. In 2008, however, there was no CLIA certification anywhere for whole-exome sequencing. Therefore, UDP investigators performed the test on a research basis to detect genetic mutations. Then those results were individually certified to confirm each patient’s variant(s).

Three weeks after the press conference, Gahl sat at his desk staring at an eight-inch stack of medical charts. “I remember thinking, what did I just get myself into?” he said. He leaned on the expertise and generosity of his colleagues across NIH. Since then, the growth of the UDP has been nothing short of remarkable. The program has received more than 4,000 medical records; admitted 1,300 patients (43% were children); sequenced 1,900 exomes and 550 genomes; and made more

None of Zarko Stanacev’s physicians could figure out what was causing attacks that rendered him nearly comatose, confined him to a wheelchair, and cloaked him in profound fatigue. NIH’s Undiagnosed Diseases Program, however, found a mutation in the NLRP3 gene that was causing abnormal inflammation in his body. Hours after being given a drug to treat inflammation, he dramatically improved and was up and walking without pain. Pictured: Zarko Stanacev (sitting) and NHGRI neurologist Camilo Toro (standing) who led the team that treated Stanacev.

CREDIT: HTTPS://WWW.YOUTUBE.COM/WATCH?V=MCVWGEHA1FK
than 316 diagnoses. And UDP scientists have produced more than 180 publications.

Young researchers have the opportunity to work alongside seasoned investigators to discover new diseases. In 2011, clinical researchers identified the genetic cause of a rare and debilitating vascular disorder associated with progressive and painful calcification of arteries below the waist (New Engl J Med 364:432–442, 2010). To date, the UDP has discovered 23 new genetic disorders and disease phenotypes.

Today, the UDP’s leadership consists of Camilo Toro, lead neurologist and director of the adult program; Cynthia Tifft, pediatric director; David Adams, attending pediatrician and director of bioinformatics; and May Malicdan, director of translational research. The staff includes internists, neurologists, bioinformatics specialists, and nurse practitioners. All are collaborating with specialists from across NIH.

Medical institutions across the country and all around the world have created programs modeled after the UDP. In 2013, NIH expanded the program to form the Undiagnosed Disease Network, now an extramural network of 12 clinical sites and supporting facilities throughout the United States. By joining the network, the UDP has been able to draw extensive funding from the NIH Common Fund, creating stability and support for the popular program.

Today, nearly half of UDP patients come to NIH with the results of their exome-sequencing in hand. But what the program provides continues to be unique. “We have an unparalleled collection of experts here at NIH that can discuss a case with their colleagues,” Gahl said. “This process would typically take one to two years [but] we can do it in a week.” The treatments are free to the patients. “We can order the tests we think are needed without waiting for insurance to pay.”

The success of the UDP has had a measurable impact. Insurance companies are beginning to cover the cost of genetic sequencing, not only for patients but for their families as well. And, the establishment of UDPs throughout the globe demonstrates how an unmet need is finally being recognized.

Gahl hopes that someday, the UDP will be obsolete. “It’s always been our hope that the program might need to be eliminated,” he said. “If there were no need for a program like this, it would mean that the investigation of rare and new disease had been integrated into our medical-health system.”

The September–October 2010 of the NIH Catalyst includes an article about the UDP’s beginnings: https://irp.nih.gov/sites/default/files/catalyst/catalyst_v18i5.pdf. To learn more about the UDP, go to genome.gov/27544402/the-undiagnosed-diseases-program.

Michael Tabasko is the science writer-editor for the NIH Catalyst.

In April 1986, the Chernobyl nuclear power plant accident in northern Ukraine exposed millions of people in the surrounding region to ionizing radiation, a known carcinogen. The technology to study the genomic and molecular effects on those exposed did not exist at the time.

Scientists from NCI led two international studies that shed new light on how radiation exposure affects human DNA. The first study compared the genomes of 105 mother-father pairs who were exposed to prolonged radiation after the Chernobyl accident and their 130 adult offspring (born 1987–2002). Researchers found no increased incidence of de novo mutations. The findings offer reassurance that ionizing radiation exposure from the accident had a minimal, if any, impact on the health of the subsequent generation.

The second study used samples from the Chernobyl Tissue Bank to document genetic changes in the tumors of 359 people who developed thyroid cancer after being exposed as children or in utero and 81 unexposed individuals born more than nine months after the accident. A particular type of DNA damage known as a double-strand break was strongly associated with radiation dose, particularly for individuals exposed at a younger age. Furthermore, thyroid cancers in children exposed to higher radiation doses were more likely the result of gene fusions, a type of mutation in which the wrong strands of broken DNA are fused back together. (Study 1: Science, eabg2365, 2021; Study 2: Science, eabg2538, 2021)
Lung transplantation is a complicated matter. On the one hand, it offers healthy lungs and a second chance to people with severe cystic fibrosis, chronic obstructive pulmonary disease, pulmonary hypertension, or other diseases that cause severe lung damage. On the other hand, organ rejection—a dangerous form of disease in which the transplant patient’s own immune system attacks their donor organ—is a major risk of a lung transplant. About half of lung transplants fail within five years, the highest failure rate of any transplanted organ.

This dilemma is something Sean Agbor-Enoh knows very well. During his medical training, he became aware that the standard method of detecting organ rejection—a tissue biopsy—was problematic. By the time a biopsy revealed that the organ was being rejected, it was often too late to save the lung. He has dedicated his career to finding better ways to prevent organ-transplant rejection. Today, he is a tenure-track NIH Lasker Clinical Research Scholar and an NIH Distinguished Scholar at the National Heart, Lung, and Blood Institute (NHLBI), where he heads the Lab of Applied Precision Omics (APO). In the APO Lab, his research team is working to develop new ways to detect and treat transplant rejection.

The immune system can’t always differentiate between the good intentions of a lung transplant and the bad intentions of bacteria such as, for example, the life-threatening *Clostridium difficile*. Immune system activation results in a flurry of antibodies streaming through the blood vessels, ultimately latching onto the cells that make up the transplant organ. The resulting tissue damage leads to transplant rejection, and eventually, organ failure. Medicine draws on immunosuppressive drugs to take the strength of the immune system down a notch, easing a transplant into a recipient’s body. Still, 50–75% of patients with transplant rejection die within two years after starting standard treatments using immunosuppressive drugs such as rituximab, which work by binding to and essentially nullifying the effect of the transplant-targeting antibodies.

Agbor-Enoh believes a large reason why patient outcomes are so poor is that the “gold standard” for diagnosis, tissue biopsy, is flawed. For one thing, tissue biopsy is expensive and invasive. It involves a surgical procedure to collect samples of tissue from the transplant organ. But more importantly, tissue biopsy often detects transplant rejection at an advanced stage of the disease when treatment is potentially less effective. “The biopsy that we are using now is enabling us to detect [transplant rejection], but detect it late when [the disease] is very advanced,” said Agbor-Enoh.

With Agbor-Enoh leading the APO Lab, one of its main focuses is donor-derived cell-free DNA (ddcfDNA), small strands of DNA that are released into the bloodstream by the donor organ when it is damaged by the transplant patient’s immune system. The patient has cfDNA as well, but its genetic sequence is different than that of the ddcfDNA, which allows the two to be differentiated from each other and quantified. Agbor-Enoh’s team has found that ddcfDNA can detect transplant rejection two to three months before a tissue biopsy can. “It is very sensitive,” said Agbor-Enoh. “As soon as you start having a few cells in that organ dying, the cell-free DNA test is already positive.”

Currently, his team has found that cfDNA sampled during the early period right after transplantation can predict 80–85% of the patients who will develop chronic rejection and die. In an article published in Circulation, Agbor-Enoh and colleagues sequenced the ddcfDNA of 165 heart-transplant patients (out of 171 participants). They found that cfDNA detects rejection 28 days before heart biopsy. Also, they estimated that by using cfDNA as a biomarker, physicians can safely avoid 81% of invasive heart biopsies. While tissue biopsies cost about $3,000–$3,500, the cfDNA test costs about $150 per sample.

**The Atlantic Coast of Cameroon**

Agbor-Enoh grew up in southwestern Cameroon near Mount Fako, an active volcano on the Atlantic coast. Being “so close to nature...really stimulates a lot of questions in your mind,” he said. He never intended to become a doctor but wanted to study soil, petroleum chemicals in particular. He had even been accepted to a Ph.D. program in England, but his family couldn’t afford the tuition. His father suggested his son attend medical school instead. In Cameroon, medical school was a far less expensive option—at the time it cost about $100 per year, some 1/500 the cost of studying petrochemicals in England. So, Agbor-Enoh went to the University of
Yaoundé (Yaoundé, Cameroon) to pursue a medical degree.

In his fourth year of medical school, he volunteered for a World Health Organization program to help distribute vaccines and medications in remote areas of Cameroon. He wound up in eastern Cameroon, an area without roads or hospitals. Sometimes, he had to walk 8–10 hours to reach the villages where he had to do his job with limited resources. One day, he treated the son of a village chief. The child likely had malaria and was dangerously anemic. “As I was holding the child and trying to figure out ways to get him to breathe, that child died,” said Agbor-Enoh. “It is that experience that made me commit to medicine. It made me go into research to try [to] solve problems, keep people healthy—and alive.”

Thinking in Parallels
As Agbor-Enoh was starting his medical career, he was intrigued by the parallels between the malaria parasite and an organ transplant. Both malaria parasites and transplanted organs have to adapt to living in different environments in order to survive. “If the organ fails to adapt, then the immune system of that host will kill it,” he said. In addition, he noticed the alarming rates at which transplant patients succumb to rejection. He saw transplantation medicine as a field with room for innovation and decided that it would be the area to focus on.

After completing medical school in 2002, Agbor-Enoh came to the United States to pursue a Ph.D. in molecular biology at Georgetown University Medical Center (Washington, D.C.), followed by an internal medicine residency at Johns Hopkins Bayview Medical Center (Baltimore). In 2012, he began a joint clinical fellowship in pulmonary and critical care medicine at the NIH Clinical Center (with Henry Masur) and Johns Hopkins Hospital.

Doctor Valantine is Calling
As Agbor-Enoh was finishing up the fellowships, he received a phone call from Hannah Valantine, who was preparing to move from the Stanford University School of Medicine (Stanford, California) to NIH to start a lab at NHLBI and become NIH’s first chief officer for Scientific Workplace Diversity. At Stanford, Valantine had already been working on repurposing cfDNA to detect heart-transplant rejection. She asked whether he’d like to become a staff scientist in her new transplantation genomics lab. He agreed on the spot and joined NHLBI in 2015.

Under Valantine’s mentorship, Agbor-Enoh developed his own research mission, applied successfully to the Lasker Clinical Research Scholars Program, and soon started the APO Lab.

Planning Ahead
The Agbor-Enoh Lab’s mission is to improve lung-transplant survival by identifying and addressing gaps in lung-transplant care. As a first step, he is developing cfDNA as a tool to detect transplant rejection. His initial studies show that cfDNA only needs a blood draw and detects rejection up to two to three months before biopsy, the invasive method that is currently used. Developing such a tool for clinical use has its challenges and takes a lot of work. Currently, it takes about a week and a half from the time the sample is collected to the time the results are ready. Agbor-Enoh is trying to leverage digital-droplet polymerase chain reaction to reduce the turnaround time of the test. “If you can fix the issue with methods…it will make [the test] more clinically feasible,” said Agbor-Enoh.

Getting the cfDNA test into the hands of clinicians also requires validation by other labs in a large cohort of patients. Agbor-Enoh’s Scientific and Clinical Directors Robert Balaban and Richard Childs (NHLBI) have been great supporters. They share his vision and provide the resources to support the Genomic Alliance for Transplantation, which is a consortium of NHLBI and several heart-lung transplant programs at hospitals in the Washington, D.C., area. The consortium’s goal is to do the necessary studies to get cfDNA ready for use in clinical care as quickly as possible.

Occasionally, Agbor-Enoh invites his lung-transplant patients to his lab meetings to share their stories about lung transplantation and transplant rejection. In doing so, he hopes that the people in his lab “can continue to understand how valuable their work is in improving the lives of these unfortunate patients for whom lung transplantation is the only cure.”

To learn more about Sean Agbor-Enoh and his work, visit the Office of NIH History’s “Behind the Mask Project” interview at https://www.youtube.com/watch?v=PqWryWkboOo. To read a transcript of the interview, go to https://history.nih.gov/display/history/Agbor-Enoh%2CSean%202020.

Ethan Smith is a postbaccalaureate fellow in Jessica Gill’s lab in the National Institute of Nursing Research. His research involves studying biomarkers for traumatic brain injury. After completing his training at NIH, he plans to apply to graduate programs in clinical psychology.
GRÉGOIRE ALTAN-BONNET, PH.D., NCI-CCR  
**Senior Investigator and Head, ImmunoDynamics Group, Laboratory of Integrative Cancer Immunology, Center for Cancer Research, National Cancer Institute**

**Education:** École Normale Supérieure, Paris (B.S. and M.S. in physics); The Rockefeller University, New York (Ph.D. in physics)

**Training:** Postdoctoral fellow, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases (2000–2005)

**Before returning to NIH:** Associate member of Computational Biology and Immunology, Memorial Sloan-Kettering Cancer Center (New York)

**Came to NIH:** In 2000–2005 for postdoctoral training; returned in 2015 as an Earl Stadtman Investigator in NCI

**Outside interests:** Hiking; sailing; cooking; having dinner parties (when pandemic over)

**Website:** https://irp.nih.gov/pi/gregoire-altan-bonnet

**Research Interests:** Thanks to the pioneering work of Steve Rosenberg, colleagues in NCI’s intramural program, and others from all over the world, scientists have been able to harness the power of the immune system to attack tumors. The past 20 years have seen a flurry of novel approaches in cancer immunotherapy to boost leukocyte activation and tumor eradication. Yet we are lacking a systematic and quantitative understanding to propel the personalization, optimization, and generalization of cancer immunotherapies to all cancer patients.

My group is developing experimentally validated quantitative models of the immune response—from signaling responses, to antigens and cytokines, to differentiation and proliferation of leukocytes, to killing of tumors. We engineered a novel robotic cell-culture system to map the combinatorial and dynamic complexity of leukocyte activation. We have also developed new quantitative methods, machine learning, and computational modeling to identify hallmarks of successful immunotherapies (Science 370:1328–1334, 2020).

Our current projects involve the multicellular coordination of immune responses against tumors and pathogenic infections. In collaboration with Nihal Altan-Bonnet’s group at NHLBI, we investigated how beta-coronaviruses—including SARS-CoV2, which causes COVID-19—use lysosomes to leave cells instead of biosynthetic secretory pathways. Such highjacking of lysosomes by beta-coronaviruses explains some of the immune abnormalities observed in COVID-19 patients (Cell 183:1520–1535.e14, 2020). Our continued efforts will help develop tailored immunotherapies against such pathogenic infections and tumors.

BEVIL CONWAY, PH.D., NEI  
**Senior Investigator, Sensation, Cognition, and Action Section, National Eye Institute**

**Education:** McGill University, Montreal (B.Sc. in biology); Harvard Medical School, Boston (M.M.Sc.); Harvard University, Cambridge, Massachusetts (Ph.D. in neurobiology)

**Training:** Postdoctoral training at Harvard Medical School

**Before coming to NIH:** Associate professor in neuroscience, Wellesley College (Wellesley, Massachusetts) and principal research scientist at Massachusetts Institute of Technology (Cambridge, Massachusetts)

**Came to NIH:** In 2016

**Outside interests:** He is a visual artist.

**Website:** https://irp.nih.gov/pi/bevil-conway

**Research Interests:** My group investigates the neural basis for visual perception and uses color as a model system for exploring how the brain processes sensory information. To better understand how the brain enables us to recognize faces, colors, objects, and places, my lab uses functional magnetic-resonance imaging (fMRI) and magnetoencephalography in human participants. These techniques use sensors around the head to noninvasively record blood-flow changes and tiny magnetic fields brought about by brain activity. The lab also does experiments in animal models...
to understand at a cellular and network level how the brain works.

Our work is organized around three broad approaches: 1) using fMRI in humans and nonhuman primates (NHPs) to investigate homologies of brain anatomy and function among these species and to test hypotheses about the fundamental organizational plan of the cerebral cortex in the primate; 2) using microelectrode recording in NHPs to show on a mechanistic level how populations of neurons drive behaviors such as perceptual decisions and categorization; and 3) doing comparative psychophysical studies in humans and NHPs as part of a program of neuroethology to understand the relative computational goals of perception and cognition in different primate species.

In addition to studies of vision, my team conducts experiments using auditory and combined audiovisual stimuli to understand common principles of sensory-cognitive information processing, and to determine how signals across the senses are integrated into a coherent experience. In recent work we discovered a substantial difference in how macaque monkey (*Macaca mulatta*) and human brains process auditory-pitch information (*Nat Neurosci* 22:1057–1060, 2019; DOI:10.1038/s41593-019-0410-7).

Other studies uncovered a universal pattern in how languages across the globe name colors (*Proc Natl Acad Sci U S A* 114:10785–10790, 2017). In a third set of studies, we determined the color information carried by cells in the brain that are responsible for face recognition to test ideas about how the brain detects health and emotions of others. (eNeuro 2021; DOI:10.1523/ENEURO.0395-20.2020 and *Nat Commun* 10:3010, 2019).

And finally, our team recently used brain imaging to decode what colors people see. The study also revealed correlations between neurological signals and patterns in color naming. (*Curr Biol* 31:1–12, 2020)

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**Research interests:** My research focuses on 1) cancer risks in people—medical personnel as well as patients—who are exposed to diagnostic and therapeutic radiation and 2) the etiology of thyroid cancer, which is one of the most radiosensitive tumors.

Within the U.S. Radiologic Technologists Study, the largest cohort of radiologic technologists in the world, I demonstrated that medical staff who perform nuclear medicine procedures and fluoroscopically guided interventional procedures receive doses of radiation that are several times as high as those performing general radiologic procedures. Increased doses are associated with adverse health outcomes. These findings led to efforts to reinforce and improve personal protective equipment and occupational monitoring, and to informed regulatory decisions for occupational dose limits in the United States.

I also investigate risks to patients from nuclear medicine procedures. I led an international effort to extend the follow-up of the largest international cohort of patients with hyperthyroidism. My analysis of those data resulted in a report establishing that radioactive iodine treatment increases cancer risks in these patients (*JAMA Intern Med* 179:1034–1042, 2019). Because of the potential for influencing treatment...
recommendations and patient preferences, my findings have been widely discussed by medical professional societies and clinical guidelines committees.

My descriptive research has shown rising trends in the incidence of advanced thyroid cancer and thyroid cancer–specific mortality, providing support for a true increase in the disease in the United States (JAMA/317:1338–1348, 2017). My etiologic research, which focuses on large cohort studies and international consortia, has helped to establish obesity as a modifiable risk factor for thyroid cancer and as an important contributor to the rising incidence.

EROS LAZZERINI DENCHI, PH.D., NCI-CCR
Senior Investigator and Head, Telomere Biology Unit, Laboratory of Genome Integrity, Center for Cancer Research, National Cancer Institute

Education: University of Milan, Milan, Italy (B.S. and M.S. in biology); European Institute of Oncology, Milan (Ph.D. in molecular oncology)

Training: Postdoctoral fellow at Rockefeller University (New York)

Before coming to NIH: Associate professor, Department of Molecular Medicine, The Scripps Research Institute (La Jolla, California)

Came to NIH: In 2018 as a Stadtman Investigator; became tenured as a senior investigator in March 2021

Outside interests: Sailing and cycling

Website: https://irp.nih.gov/pi/eros-lazzerini-dench

Research interests: Chromosome endcaps, called telomeres, shorten as one ages. I am interested in the mechanisms by which telomeres protect chromosome ends and their deregulation in aging and in pathologies such as cancer. My lab studies telomere-associated proteins to define their role in preventing the activation of the DNA damage–response pathway and suppression of end-to-end chromosomal fusions.

A complementary study in our lab is focused on the in vivo consequences of telomere dysfunction. Telomere length homeostasis plays a critical role in cellular and organism survival. However, in humans, this process is inefficient, and progressive telomere shortening is observed in tissues with a high cellular turnover. In the lab, we probe the role of telomere shortening in aging and tumor onset using mouse models that recapitulate telomere dysfunction in stem cells and other cellular compartments.

Our most recent work revealed that embryonic stem cells could survive and proliferate in the absence of proteins that are usually essential for telomere protection. In this work, we found that embryonic stem cells possess an alternative mechanism of telomere protection triggered by the induction of genes typically used only during the earliest stage of development to stave off unwanted DNA repair. These findings reported on November 25, 2020, in Nature (Nature 589:110–115, 2021) might help explain the survival strategy used by some cancer cells to circumvent growth limits imposed by the natural shortening of telomeres that occurs as we age.

Before coming to NIH: Chair of Microbiology, Sir William Dunn School of Pathology, University of Oxford; Scientific Director, Central Oxford Structural Microscopy and Imaging Centre (Oxford)

Came to NIH: December 2020

Outside interests: Listening to Baroque music; hiking; cooking

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

Research interests: As a structural biologist, I have pioneered the use of mixed structural methods to study host-pathogen interactions and other medically important molecular pathways. My laboratory uses and develops cutting-edge structural methods including cryo-electron microscopy and X-ray crystallography to define molecular mechanisms involved in health and disease.

My lab is focusing on different biological systems ranging from bacterial pathogenesis to human cell division. We are looking at how large, multiprotein complexes, often membrane-crossing, are assembled. In our bacterial pathogenesis studies, we often examine the large membrane-spanning complexes involved in bacterial movement and the secretion of bacterial toxins. In our research on human systems, we examine how serum-resident protein cascades act in immune responses and coagulation; how centrosomes assemble during mitosis; and how a variety of membrane proteins function in protein and membrane maturation, as transporters or cellular receptors. We use multiple biophysical methods to address the questions we pose about these challenging systems, and we often develop software and experimental methods to allow us to obtain the answers we seek.

We have spent many years trying to understand the atomic details of the bacterial flagellum, the long appendage that many bacteria need to move through a fluid environment and cause disease. A
flagellum is a multiprotein motor powered by the movement of ions across the bacterial membrane, an incredibly complex protein nanomachine. Our recent work has illuminated many previously unknown aspects of the machine and has revealed how the bacteria tightly intermesh the protein components with the membrane itself to contain the rapidly rotating motor. Building a clearer picture of these disease-causing machines will open opportunities for novel antibacterial agents in this age of antibiotic resistance. (References for research: 1) Accepted **Nat Microbiol**, bioRxiv 2020.12.05.413195, 2020; 2) **Nat Microbiol** 5:1553–1564, 2020; 3) **Nat Microbiol** 5:966–975, 2020; DOI:10.1038/s41564-020-0703-3)

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**SUNG-YUN PAI, M.D., NCI-CCR**

**Senior Investigator and Chief, Immune Deficiency Cellular Therapy Program, Center for Cancer Research, National Cancer Institute**

**Education:** Harvard College, Cambridge, Massachusetts (B.A. in East Asian languages and civilization); Harvard Medical School, Boston (M.D.)

**Training:** Residency in pediatrics, Boston Children’s Hospital (Boston); clinical fellowship in pediatric hematology/oncology, Boston Children’s Hospital and Dana-Farber Cancer Institute (Boston); research fellowship in rheumatology and allergy immunology, Brigham and Women’s Hospital (Boston)

**Before coming to NIH:** Associate professor in pediatrics, Harvard Medical School; attending physician at Boston Children’s Hospital and Dana-Farber Cancer Institute, and co-director of the Gene Therapy Program, Boston Children’s Hospital and Dana-Farber Cancer Institute

**Came to NIH:** In 2020

**Outside interests:** Spending time with family; cooking; playing flute; reading both fiction and nonfiction

**Website:** https://ccr.cancer.gov/idctp/sung-yun-pai

**Research interests:** I am developing and testing tailored cellular therapies, including allogeneic hematopoietic stem-cell transplantation (for example, bone-marrow transplant) and gene therapy, for children and adults who have genetic diseases of the blood and immune system. One of my goals is to understand how individual genes and the type of chemotherapy given before cellular therapy influences immune reconstitution.

Babies with severe combined immunodeficiency (SCID) are born without T lymphocytes and typically die in infancy without cellular treatment. I led a multi-institutional study with the Primary Immune Deficiency Treatment Consortium showing that giving SCID patients transplants before the onset of infection was critical to survival, that some types of SCID have better immune correction than others, and that using chemotherapy improves correction of the immune system (**N Engl J Med** 371:434–446, 2014). This study and other work underlie the open trial I am leading at more than 40 institutions that involve randomizing patients with SCID to either of two chemotherapy regimens.

Autologous gene therapy uses the patients’ own cells, representing the ultimate personalized treatment. We re-engineered a viral vector that was successful in treating the X-linked form of SCID but caused leukemia. We showed in a clinical trial that the new vector was just as effective and safer, with no leukemias to date after 10 years (**N Engl J Med** 371:1407–1417, 2014). We now have a multi-institutional trial of gene therapy for this disease using low-dose busulfan to further improve immune outcome. My team is also working on developing cellular therapies for Wiskott-Aldrich syndrome and deficiency of dedicator of cytokinesis protein 8.

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**UDO RUDLOFF, M.D., PH.D., NCI-CCR**

**Senior Investigator, Rare Tumor Initiative, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute**

**Education:** Ruprecht Karls University School of Medicine of Heidelberg, Heidelberg, Germany (M.D., Ph.D.)

**Training:** Residency in obstetrics and gynecology at several different teaching hospitals in England; residency in general surgery, New York University School of Medicine and Albert Einstein College of Medicine (New York); fellowship in surgical oncology, Memorial Sloan-Kettering Cancer Center (New York)

**Came to NIH:** In 2009 as tenure-track investigator in NCI-CCR, first in the Surgery Branch (2009–2013), then in the Thoracic and GI Oncology Branch (2013–2018) and Rare Tumor Initiative, Pediatric Oncology Branch (2018–present)

**Outside interests:** Spending time with his nine-year-old daughter; reading; volunteering for the German-American Heritage Foundation; hiking

**Website:** https://irp.nih.gov/pi/udo-rudloff

**Research interests:** My laboratory concentrates on the discovery, translation, and early-phase clinical testing of novel therapies for patients with pancreatic or other solid-organ cancers. We have built a program that integrates phenotype-directed drug screening with target deconvolution (the process of identifying the molecular targets of active hits) and translational science to arrive at drug candidates that target novel essential mechanisms of cancer and yield...
candidates with favorable pharmacokinetic and toxicokinetic properties.

I led efforts for the preclinical and clinical development of the first-in-class, small-molecule metarrestin, which suppresses metastasis in pancreatic cancer and other solid-organ cancers. Metarrestin targets the perinucleolar compartment, which is associated with the ability of cancer cells to metastasize. Orally administered metarrestin has favorable bioavailability and biodistribution across different species, achieves high intratumoral exposure concentrations, and has a predictable toxicity profile. We are enrolling patients in a first-in-human phase 1 study of metarrestin (Sci Transl Med 10:441–455, 2018).

A second drug-discovery program focuses on tumor-associated macrophages, a major pro-tumor immune-cell population in many solid-organ cancers. Tumors typically co-opt macrophages to promote tumor growth and evasion from immune surveillance. In pancreatic cancer models, we found that the first-in-class synthetic host-defense peptide design RP-182 improved responses to chemotherapy and checkpoint blockades by binding to the innate immune checkpoint CD206 and targeting CD206-positive matrix-2 (M2)-like tumor-associated macrophages. (Sci Transl Med 12(530):eax6337, 2019). RP-182 reprograms tumor-associated macrophages and increases cancer-cell phagocytosis and antitumor immune responses in various cancer models. Through several in silico (computer simulation), medicinal-chemistry, and structural-biology approaches we have recently replaced RP-182 with another small-molecule design that has improved pharmacokinetic features and is yielding a drug candidate for advanced preclinical studies.

We have been issued a patent for “Peptide-Based Methods for Treating Pancreatic Cancer” and a provisional patent for “Small Molecules with Selective Activity Against the M2 Phenotype of Macrophages.”

We have also found that pancreatic tumors with KRAS G12R mutations (present in 15–18% of pancreatic cancers) show increased response to the MEK inhibitor selumetinib in preclinical models. (Cancer Discov 10:104–123, 2020). A phase 2 clinical trial, however, did not show tumor regressions in patients with advanced pancreatic cancer who were treated with a single-agent MEK inhibitor. We are currently evaluating, preclinically, the best possible MEK combination therapy for this patient subpopulation.

Research interests: I am exploring the nature and causes of fatigue in relation to cancer and its treatments. Fatigue is a common and debilitating condition that affects most cancer patients, impairing their health-related quality of life. To date, fatigue remains poorly characterized with no diagnostic test to objectively measure the severity of this condition. In addition, evidence has shown that the biology of cancer-related fatigue (CRF) is complex, and the condition may be caused by a cascade of biologic events in response to cancer and its treatments.

Acknowledging the individual variabilities in CRF, even among patients receiving similar treatments and having the same disease condition, my team observed that only a subpopulation of patients experience chronic fatigue after completing primary cancer treatment. The individual susceptibility to activate specific glutamate receptors seems to have a role in the chronic fatigue of a specific group of cancer patients months after completing their primary treatment. (Transl Psychiatry 8:article number 110, 2018). We used this discovery to conduct a proof-of-concept clinical trial to investigate the antifatigue effects of inhibiting glutamate receptors using low-dose ketamine. This study is actively enrolling participants.

Recently, my group also found that cancer survivors carrying a specific polymorphism (Val166Met) of their brain-derived neurotrophic factor (BDNF) gene experienced less fatigue. Although Val166Met has been shown to greatly increase the risk for depression in healthy individuals, it did not affect depression symptoms in these cancer survivors (Transl Psychiatry 10:article number 302, 2020). This is an interesting discovery, considering that fatigue has always been associated with depressed mood. Using a mouse
model, my team is exploring the unique brain networks associated with this specific BDNF polymorphism to help us understand how fatigue is perceived and experienced.

LEI SHI, PH.D., NIDA
Senior Investigator and Chief, Computational Chemistry and Molecular Biophysics Section, Molecular Targets and Medications Discovery Branch, National Institute on Drug Abuse

Education: Beijing University, Beijing (B.S. in biochemistry and molecular biology); Columbia University Medical Center, New York (M.A., M.Phil., and Ph.D. in pharmacology)

Training: Postdoctoral training in molecular recognition at Columbia University College of Physicians and Surgeons (New York) and in physiology, biophysics, and computational biomedicine at Weill Medical College of Cornell University (New York)

Before coming to NIH: Assistant professor, Department of Physiology and Biophysics, Weill Medical College of Cornell University

Came to NIH: In 2015

Outside interests: Playing and watching sports; enjoying wine; watching movies

Website: https://irp.nih.gov/pi/lei-shi

Research interests: Membrane proteins (MP) initiate intracellular signaling pathways, control the flow of energy and materials in and out of the cell, and thereby account for more than 30% of the human proteome and 40% of drug targets. My lab is investigating the structural basis of MP functions to advance the mechanistic understanding of key cellular processes. Using a combined computational and experimental approach, we identify and characterize the elements that determine the recognitions between MPs and their corresponding ligands, between MPs and their coupled proteins, and between MPs and the lipid environment. The integrated findings allow us to rationally develop small-molecule compounds for novel drug discovery.

Specifically, for G-protein-coupled receptors, our findings delineate the structural determinants of ligand selectivity and efficacy for dopamine receptors from both protein and small-compound perspectives. Our findings also describe the structural basis of allosteric mechanisms at these receptors. (Allosteric regulation is when a ligand, called an effector, binds to a protein site that is topographically distinct from a protein’s active site in which the activity characterizing the protein is carried out.) These mechanistic findings are being leveraged to identify novel lead compounds for both research and therapeutic purposes. For neurotransmitter transporters, we defined a novel allosteric mechanism of transport. Based on these findings, we and our collaborators discovered and optimized high-affinity allosteric inhibitors bound to serotonin transporters. Thus we have opened the door for clinical translation of allosteric inhibitors to reduce the side effects of current antidepressants.

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
FeICom: Fellows Committee
FDA: Food and Drug Administration
FNII: Foundation for the NIH
FNLI: 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
NCI: National Center for Complementary and Integrative Health
NCII: 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
NIHHS: 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
ORI: Office of Intramural Research
ORS: Office of Research Services
ORWH: Office of Research on Women’s Health
OTT: Office of Technology Transfer
PHOTOGRAPHIC MOMENT

Cherry Blossoms at NIH

Cheery cherry blossoms help to chase away the COVID blues. These blossoms are outside the NIH entrance near the Metro.