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National Institutes of Health

'ETHICAL PRESSURE' A FACTOR

Ethicists Discuss Covid Vaccine Issues

BY RICH MCMANUS

The bioethicist and the auto mechanic share at least one thing in common. When you go to see one, you have a problem.

On Oct. 7, at the first of four Ethics Grand Rounds sessions held this academic year, a panel of three experts considered the question, "In vaccine trials for Covid-19, is there an obligation to offer the first vaccine shown to be effective to all participants?"

It is estimated that there are more than 200 covid vaccines in development worldwide, said Dr. Emily Erbelding, director of NIAID's Division of Microbiology and Infectious Diseases. Five candidates are either planning or conducting phase 3 trials, 3 of which are underway in the United States already.

Dr. Emily Erbelding of NIAID presents the case.

The stakes are high. As of Oct. 7, there were 7.4 million cases of Covid-19 in the U.S. and more than 210,000 deaths; 40,000 to 50,000 new cases were being diagnosed daily. (As of Nov. 5, new cases had topped 100,000 in a day for the first time and nearly 234,000 people in the U.S. had died of Covid-19.)

"The U.S. is leading the world in this set of grim statistics," Erbelding noted.

Vaccines are undeniably effective, she added. Worldwide, they prevent some 3 million deaths each year, from a variety of diseases.

More than $10 billion funds Operation Warp Speed, a U.S. effort to develop covid vaccines and therapeutics, Erbelding reported. Independent of that effort, Pfizer has a phase 3 vaccine in trials; the product may eventually be purchased by OWS. And Merck has a vaccine in early stages of development.

The challenge for ethicists: What should investigators do if an efficacy signal is identified in one of the trials? Should they offer the vaccine to those in the placebo arm of that trial? Should they offer the vaccine to individuals participating in trials of other

SEE **ETHICS**, PAGE 4

THAT OTHER DEADLY EPIDEMIC

In Pursuit of Vaccines Against Opioids

BY CARLA GARNETT

Dr. Thomas Kosten

Decades before the worldwide quest for a Covid-19 vaccine, longtime NIH grantee Dr. Thomas Kosten and collaborators were pursuing effective inoculation against another growing epidemic—opioid addiction. In a recent virtual lecture at Clinical Center Grand Rounds, he discussed the effects one widespread crisis is having on another and his quarter century of research on "Treating the Hidden Epidemic: Anti-Opioid Vaccines."

SEE **KOSTEN**, PAGE 8

WACHTEL WINNER

Gilbert's Research Paves Way for New Cancer Drugs

BY DANA TALESNIK

Dr. Luke Gilbert

The potential to develop new, more effective cancer drugs may be bolstered by a process akin to flipping a switch, or perhaps many switches. One young biologist's pioneering work in gene regulation—turning genes on and off—is paving the way for advances in cancer research.

Dr. Luke Gilbert, assistant professor at the University of California, San Francisco,

SEE **GILBERT**, PAGE 6

Bee Seen, and other natural sights on p. 12.

ALSO THIS ISSUE

Marcus To Give ODP Early-Stage Investigator Talk, Nov. 17

NIH's Office of Disease Prevention will host the 2020 ODP Early-Stage Investigator Lecture "Scaling Up HIV Pre-Exposure Prophylaxis to End the HIV Epidemic," by Dr. Julia Marcus. This virtual lecture will take place on Tuesday, Nov. 17 at 11 a.m. The event is open to the public and there will be an opportunity to ask questions at the end of the presentation.

Dr. Julia Marcus

Daily oral HIV pre-exposure prophylaxis, or PrEP, is up to 99 percent effective in preventing HIV transmission and has been FDA-approved since 2012. However, of the 1.2 million Americans who could benefit from PrEP, less than 20 percent have used it, and there are substantial racial and ethnic disparities in uptake.

Scale-up of PrEP is a critical component of the federal initiative to end the HIV epidemic, but achieving this goal will require effective strategies to improve PrEP implementation.

In this ODP presentation, Marcus will discuss her research on strategies to improve PrEP uptake, including the use of electronic health records to help health care providers identify patients who may benefit from PrEP.

Marcus is an infectious disease epidemiologist and associate professor in the department of population medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute, as well as adjunct faculty at the Fenway Institute. Her research focuses on HIV, hepatitis C and other sexually transmitted infections, with a primary interest in the implementation of PrEP for HIV prevention.

Her studies have leveraged data from electronic health records to identify patients who may benefit from PrEP, to characterize PrEP uptake and continuation and to document clinical outcomes among PrEP users in real-world health care settings.

Marcus's work has been funded by several institutes, including NIAID, NIMH and NIMHD.

To register, visit https://prevention.nih.gov/news-events/early-stage-investigator-lecture/2020-awardee. The lecture will be recorded and available on the ODP website within a week.

Rural Health Seminar Focuses on Covid

The 2020 NIH Rural Health Seminar: Challenges in the Era of Covid-19 will be held virtually on Thursday, Nov. 19 from 1 to 5 p.m. at https://videocast.nih.gov/watch=38788.

It will bring together researchers, medical practitioners and others to explore topics in rural health. Learn about and explore the impact of Covid-19 on rural populations, systems and workforce issues, and community engagement to respond to the pandemic. The seminar is coordinated by the NIH rural health interest group and co-sponsored by NIMHD and NCATS.

The seminar will provide an opportunity to engage and explore important issues of rural health. Sessions include: Rural Population Impact and Response in the Time of Covid-19 and Researchers and Community Partners Respond to the Challenges of Covid-19.

Today, approximately 20 percent of the U.S. population—about 60 million people—live in rural areas, which make up 97 percent of the land area in the United States. People living in rural America have less access to health care and are more likely than residents of urban areas to die from chronic conditions such as heart disease, cancer, stroke and chronic lower respiratory disease.

Moreover, long-standing systemic health and social inequities have put many rural residents at increased risk of getting Covid-19. The rural/urban inequities in health and health care warrant more rigorous and innovative scientific research to improve testing, contact tracing and future vaccination for rural Americans.

For details on how to register, visit https://nimhd.nih.gov/news-events/conferences-events/rural-health.html. The seminar will be archived for those unable to view it live.

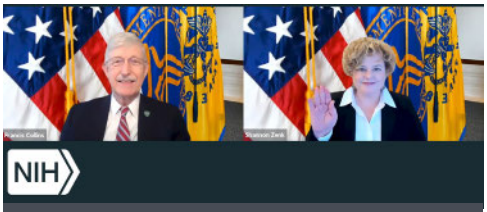
What I Learned from Being on TV

Whether you are a Zoom, Skype or WebEx presenter or participant, what have you learned—during the course of enforced distance from your regular workplace—about these modalities?

Are you a natural host, the next Alex Trebek? Or are you the first to hit mute and black out the video? What effect does seeing yourself on a video screen have? Is there an optimum duration to any kind of video interaction? What changes have you made at home to better accommodate video participation?

Do you ever get or give feedback, based on your involvement with video? Are there things you just can't stand about a video chat?

Send us your observations, in just a few sentences, and we will publish the ones that best capsulize your reactions. You can submit anonymously or include your name. Email the *Record* at rm26q@nih.gov or cg9s@nih.gov.

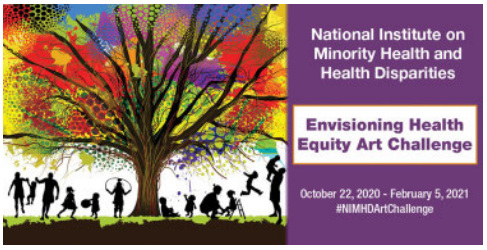


NINR Director Sworn In

Dr. Shannon Zenk has officially joined the NIH community as director of the National Institute of Nursing Research. Out of an abundance of caution during the pandemic, her swearing-in ceremony was held virtually on Oct. 14. She is shown above with NIH director Dr. Francis Collins, who made the appointment.

NIMHD Hosts National Art Competition

As part of its 10th anniversary celebration, the National Institute on Minority Health and Health Disparities is hosting a national art competition inviting teens and adults to create images (paintings, drawings, photos, digital art, etc.) that express NIMHD's vision: an America in which all populations will have an equal opportunity to live long, healthy and productive lives.



The goal of the competition is to raise national public awareness about the prevalence and impact of health disparities and inspire further research on minority health and health disparities.

Submit art until Feb. 5, 2021. First, second and third place prizes will be awarded in two age categories: teen (16 to 18 years old at time of submission) and adult (19 years or older).

Entries may be submitted by an individual or a group of individuals. For details, visit https://nimhd.nih.gov/programs/edu-training/art-challenge/.

'COPING WITH COVID'

How Can We Sleep Well During the Pandemic?

BY MARLA BROADFOOT

Getting a good night's sleep can be difficult under normal circumstances. But it can be even more challenging during a global pandemic, said Dr. Chandra Jackson, who studies the environment and sleep at NIEHS.

Even before the pandemic, millions of Americans suffered from sleep disorders.

Jackson discussed the connection between sleep and health with Dr. Marishka Brown, program director for sleep disorders medicine research at NHLBI, as part of the #CopingWithCOVID19 livestream series. Approximately 5,600 people from as far away as Bangladesh, Kenya and Brazil tuned in live on NIH Facebook and Twitter feeds.

"We are all undoubtedly affected by the pandemic and in different ways," said Jackson, who holds a joint appointment at NIMHD. "Many people are either sleeping less or more than they should. Some are sleeping at different times or getting a lower quality of sleep. Either way, we know that optimizing your sleep helps with energy levels, emotional wellness and mental health, the immune system and brain function."

Dr. Chandra Jackson studies how physical and social environments affect health and contribute to health disparities.

PHOTO: STEVE MCCAW

Even before the emergence of Covid-19, an estimated 1 in 3 adults did not regularly get the recommended amount of at least 7 hours of uninterrupted, quality sleep needed to protect their health. Jackson said it is likely that the stress that keeps many people up at night has increased in recent months. They may face feelings of isolation or depression, as well as financial strain and job or housing insecurity.

"Our routines have also been disrupted, and it can be difficult to adjust to this new way of living," she said. For example, keeping track of time can be difficult without the typical cues such as dropping kids off at school in the morning or leaving the office in the afternoon.

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"No matter how good a sleeper you think you are, there is usually room for improvement."

–DR. CHANDRA JACKSON

• • •

Simply staying home rather than going outside can greatly lower one's exposure to natural light, throwing off the circadian rhythms that tell the body when to sleep and when to remain alert.

Jackson said people should rest assured that everyone has trouble sleeping from time to time.

"No matter how good a sleeper you think you are, there is usually room for improvement," she noted.

Below are some tips Jackson gave for catching the most Zs.

• **Pay attention to light.** Get bright light early in the morning and avoid bright or blue light at night, which can suppress the production of the sleep hormone melatonin.

• **Practice a relaxing bedtime ritual.** Help yourself wind down from the day by meditating, taking a bath or shower, listening to gentle music or reading a book.

• **Create an inviting space.** Keep your bedroom cool, invest in a good mattress and pillows and try blackout curtains, earplugs or soft white noise.

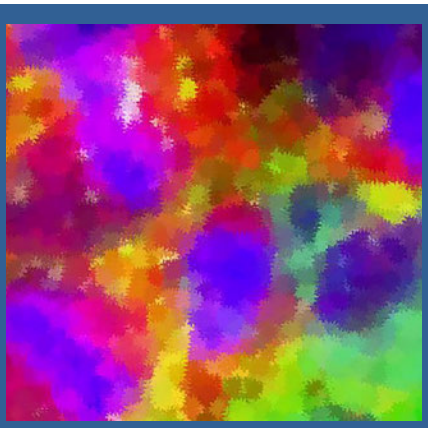
• **Be aware of hidden sleep stealers.** In the hours before bed, turn off electronics and avoid excessive or heavy food or liquid intake, caffeine, nicotine and alcohol.

• **Clear your mind.** If you cannot sleep because your mind is racing, write down your thoughts or a to-do list for the next day before going to bed.

• **Take short naps.** Avoid long naps or naps later in the day, which could hinder your nighttime sleep.

• **See your physician.** Talk to your doctor if you are concerned about your sleep, have difficulty falling asleep or sleeping through the night, or have been told you snore loudly.

The #CopingWithCOVID19 livestream series includes nine wellness videos. A recording of the conversation between Jackson and Brown is available at https://bit.ly/3ihpmpV.



ON THE COVER: *Stem Cells. NIH scientists showed how ancient retroviral genes, or "junk DNA," may play a role in helping stem cells decide to become neurons. The image shows stem cells in a petri dish. The blue dots represent cell nuclei. Green dots represent HERV-K, HML-2 viral envelope proteins encoded by junk DNA, while red dots represent the immune cell protein CD98HC. Interactions between the two proteins produced a yellow color. The study suggests that these interactions restrain stem cells from becoming neurons and that turning off HERV-K, HML-2 activity frees them.*

IMAGE: NATH LAB, NINDS

The NIH Record

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National Institutes of Health
Turning Discovery Into Health

vaccine candidates?

The FDA has established an efficacy benchmark—a vaccine would have to demonstrate at least 50 percent protection vs. placebo. Assuming that a candidate achieves that standard, two concerns arise, said Erbelding: Breaking the blind might undermine longer-term data that a continued study might uncover. And, an interruption to declare success complicates other trials—should the people in the placebo arms of those trials be offered the vaccine that showed early success?

Addressing that tension was Dr. Joseph Millum of the Clinical Center's department of bioethics and the Fogarty International Center.

Assuming the vaccine was not available outside of clinical trials, a dilemma arises, he said. Participants in the placebo arm are at greater risk of infection, "but there may be important scientific questions that can only be answered by continuing the study," including what the duration of the vaccine's efficacy might be.

Millum underscored the fundamental ethical challenge of all clinical research: It exposes participants to risks for the benefit of others, not necessarily for the benefit of the participants themselves.

A philosopher, Millum added other concerns: Is withholding the vaccine imposing a risk? If it is, a risk/benefit analysis is needed, as "social value can justify asking folks to take on this risk. Comparative judgments are always required in risk/benefit analysis."

Does the added social value justify the added risk? It depends, Millum said. "What are [participants'] chances of infection? What underlying risk factors do they have? How confident are we in the estimate of efficacy?"

He concluded that risks could be justified if they were low and were necessary to gain socially valuable information.

Discussant Dr. Steven Goodman, associate dean of clinical and translational research and professor of epidemiology and population health and of medicine at Stanford University, said the terms of the argument reminded him of an old joke.

★★★

"Letting [trials] go to their planned end is the way to earn trust. It would be the death knell for vaccine trials to start cutting them off early for non-scientific reasons."

–DR. STEVEN GOODMAN

★★★

"How do you pronounce the capital of Kentucky—is it Louis-ville, or Louie-ville? Neither. It's Frankfort.

"It's a lame joke, but it is relevant to a serious question," he said, suggesting that the way the question was framed led panelists down too limited an analytic path. He suggested an augmented, expanded analysis.

First off, a vaccine clinical trial is not therapeutic; it won't cure a disease, but it may prevent one. And should herd immunity occur, "If everyone else is immune, you don't need to be." So some of our ethical intuitions derived from therapeutic trials need to be modified.

The key unit of analysis, Goodman argues, should be at the population level, and framed in terms of treating risk, not disease.

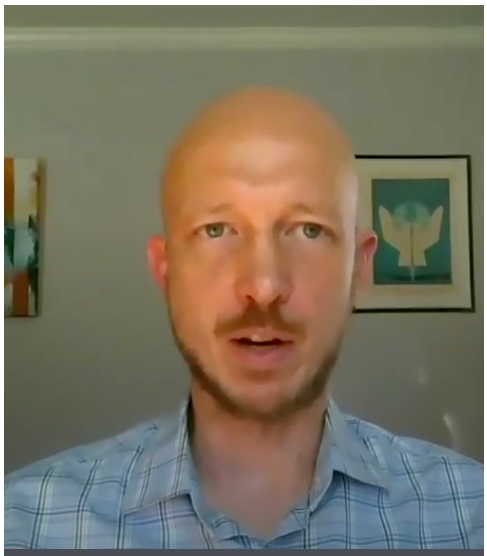
Unlike a therapeutic trial, people can take their own measures to reduce their risk. "People can avoid [Covid-19] risk by the usual techniques—distancing, mask-wearing, hand-washing," he said. "Preventive options abound, in the absence of a vaccine...Self-protection is as, or more effective, than a vaccine." So if they find out they were in the placebo arm, they don't need the vaccine to protect them going forward.

And as to risk, Goodman noted that, in the U.S., there would be about a 1 percent chance of getting infected during the trial and 1 percent risk of dying from Covid-19 if you get infected. So an individual's net chances of dying from Covid-19 in the trial are about 1 percent of 1 percent, or 1 in 10,000. "If the vaccine is 50 percent effective, then your risk of dying is reduced by 1 in 20,000."

Not only is that absolute benefit very small, but "the folks in the placebo arm have also avoided the risk of the vaccine itself," said Goodman. Therefore, there is little "ethical pressure" after the trial to offer the vaccine first to average-risk placebo group members over those at higher risk for Covid-19 death either outside or inside the trial.

All discussants acknowledged other important social factors influencing their opinions, including the possibility of "compounding injustice" to certain

Stanford's Dr. Steven Goodman noted, "I am not a card-carrying ethicist, though I do count some as friends and colleagues."



Dr. Joseph Millum of the Clinical Center's department of bioethics and the Fogarty International Center underscored the fundamental ethical challenge of all clinical research: It exposes participants to risks for the benefit of others, not necessarily for the benefit of the participants themselves.

minority populations most heavily affected by Covid-19 if the trial population was not representative.

During a brief Q&A, someone asked if there is an obligation to tell everybody, in any trial, if there's been an efficacy finding. Goodman said yes, and Erbelding added, "Unless you are living in a cave, you will find out anyway."

Added Millum, "This underscores the importance of communicating with participants in any trial. We need to be clear, given the importance of their involvement."

Said Goodman, "[A Covid-19 vaccine trial] is not like [a trial offering treatment for] cancer or serious cardiovascular disease, where there is much more ethical pressure" for treating those in the placebo arm.

The final question touched on public skepticism about vaccines in general. Would continuation of a trial, once efficacy had been shown, fuel even more distrust?

Answered Goodman, "Letting [trials] go to their planned end is the way to earn trust. It would be the death knell for vaccine trials to start cutting them off early for non-scientific reasons."

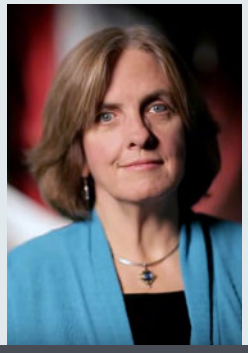
The full discussion is archived at https://videocast.nih.gov/watch=38781.

KUDOS

NAM Honors Six NIH Scientists

Six NIH scientists are among 90 new members and 10 international members elected to the National Academy of Medicine during its annual meeting Oct. 19. They are:

Dr. Peter L. Choyke, senior investigator, Molecular Imaging Program, National Cancer Institute, "For pioneering advances in the imaging of prostate cancer that have enabled accurate localization of clinically significant tumors. His work has allowed more accurate and efficient biopsies as well as focal therapies that cause fewer side effects than conventional therapies."



Above are (from l) Dr. Peter Choyke, Dr. Cynthia Dunbar and Dr. Heinz Feldmann. Below are (from l) Dr. Louis Staudt, Dr. Hannah Valantine and Dr. Carlos Zarate.

Dr. Cynthia E. Dunbar, NIH distinguished investigator and branch chief, National Heart, Lung and Blood Institute, "For leading pioneering genetic marking and therapy trials targeting hematopoietic stem cells and developing uniquely predictive non-human primate models to successfully improve the safety and efficiency of various gene therapies as well as gain insights into hematopoiesis and immunology."

Dr. Heinz Feldmann, chief, Laboratory of Virology, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, "For leading the development of the vesicular stomatitis virus-based vaccine platform that resulted in the first Ebola vaccine. His mobile diagnostic laboratory for public health and biodefense emergencies is now used by the World Health Organization."

Dr. Louis M. Staudt, chief, Lymphoid Malignancies Branch, and director, Center for Cancer Genomics, National Cancer Institute, "For demonstrating that genetic profiling can distinguish lymphoma subtypes, predict patient survival and individualize therapy, thus playing a key role in launching the era of cancer precision medicine. He devised loss-of-function genetic screens for essential cancer genes, thereby enabling effective targeted therapies for molecular subtypes of lymphoma."

Dr. Hannah A. Valantine, professor of medicine, Stanford University; former NIH chief officer for scientific workforce diversity and senior investigator, National Heart, Lung and Blood Institute, "For her national leadership in both scientific workforce diversity and cardiac transplantation research. Her data-driven approach in these two important areas has led to game-changing policies and new programs that enriched the nation's biomedical talent pool and have generated paradigm-shifting innovations in patient care."

Dr. Carlos Alberto Zarate Jr., NIH distinguished investigator and chief, Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, "For demonstrating that a single ketamine infusion has rapid, robust and relatively sustained antidepressant effects in individuals with treatment-resistant depression and bipolar depression, in addition to significant anti-suicidal and anti-anhedonic effects. Identifying ketamine as a rapid-acting antidepressant and anti-suicidal ideation agent was a paradigm shift in psychiatry."

Gilbert

CONTINUED FROM PAGE 1

heads a lab that models and maps how genes function and interact in health and disease. Their experiments aim to reveal which genes and genetic interactions drive cancer progression and response to treatment.

"It's really the early-career investigators who make some of the most important contributions in the field," said Dr. Tom Misteli, director of NCI's Center for Cancer Research, at a recent CCR Grand Rounds held virtually via WebEx. This year, he added, it's especially important to recognize and support promising young researchers, many of whom continue to face tough research challenges during the pandemic. "We have to make sure...they can build their careers despite all the difficulties and the slowdown at the moment."

Gilbert delivered the 8th annual AAAS-sponsored Wachtel Lecture, co-hosted by NCI, during which he was honored with the Martin & Rose Wachtel Cancer Research Award, which comes with a $25,000 prize from the Wachtel endowment. The award recognizes the outstanding contributions of early-career cancer investigators.

Gilbert's contributions are enabling previously impossible experiments. His lab at UCSF developed CRISPR-based genetic screens for manipulating genes within human cells.

"These tools represent a new ability to turn endogenous human genes off and on, or up and down, flexibly and in a quiet way where, in one cell, we can turn one gene off and another gene on," said Gilbert. "What's perhaps more useful is to be able to, in a single experiment, turn every gene off or every gene on, and we've shown that we can do this."

Gilbert's lab chose a chronic myeloid leukemia cell line for its first-ever CRISPRi/a—a combination genome scale screen he designed to analyze large groups of gene pairs. By turning genes off, Gilbert's team could see the genes required for cell proliferation and cell survival. Then, by zooming in, they found that a third were tumor suppressor genes. The deeper they probed, the more they learned about gene function and cell health, prompting further experiments.

The approach is shedding light on how oncogenes and tumor variations affect a patient's response to cancer therapies. For example, Gilbert's lab began studying a new class of cancer drugs that can inhibit the oncogene $KRAS^{G12C}$.

"These tools represent a new ability to turn endogenous human genes off and on," Gilbert said.

"Mutant KRAS is a major driver of tumorigenesis and drug resistance," Gilbert explained in his AAAS Wachtel Prize essay, published in *Science Translational Medicine*. "However, until recently, this oncogene was considered undruggable."

New KRAS inhibitor drugs are now in phase 1 and 2 clinical trials to treat non-small cell lung cancer (NSCLC), colon cancer and pancreatic cancer, said Gilbert. But responses have varied. Some patients have acquired drug resistance, leading Gilbert to further explore which genes are controlling reactions to these drugs and how to improve response.

"The key here is that these drugs...are nontoxic, meaning we can leverage them into combination therapies," he said. And that was their next step. When they combined the KRAS inhibitor with another FDA-approved drug—a CDK4 inhibitor that had already gone through phase 3 trials for NSCLC—this induced a nearly complete tumor regression in a mouse model.

"We're really excited. There's a clinical trial testing this hypothesis right now," Gilbert said, "and it really would be a huge win, I think, for functional genomics if this was a useful combination therapy."

The work Gilbert described thus far illustrates genetic interactions that perturb a single gene. "By analogy, that's like me as a 5-year-old just coming up to a piano and banging one key again and again, at an annoying, really loud intensity," said Gilbert, intent on moving beyond single-gene perturbations toward something closer to a genetic concerto.

Gilbert found inspiration in yeast genetics. "The key insight, I think, from the yeast field was that studying the relationship between pairs of genes is useful, but studying hundreds to thousands of pairs of genes is even more useful, and not just in a sense that you get more data," he said, " but there [are] actually emergent properties from large datasets that are useful for annotating gene function."

Perturbing large sets of genes and clustering them by function in yeast yielded new information about previously uncharacterized genes, giving rise to the idea to run such experiments in human cells. Gilbert has since designed genetic interaction maps using CRISPRi/a that can measure hundreds of thousands of interactions in a single

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"The key insight, I think, from the yeast field was that studying the relationship between pairs of genes is useful, but studying hundreds to thousands of pairs of genes is even more useful...There [are] actually emergent properties from large datasets that are useful for annotating gene function."

~DR. LUKE GILBERT

• • •

Gilbert displays the plaque he earned as winner of the Martin & Rose Wachtel Cancer Research Award, which comes with a $25,000 prize from the Wachtel endowment.

experiment. The maps cluster genes into known protein complexes and pathways, he said, helping researchers classify individual genes and identify rare synthetic lethal gene pairs.

Gilbert harkened back to the beginnings of genetics, when Gregor Mendel studied how gene pairs influenced complex phenotypes such as flower color or pea shape.

"Human cells obviously don't have flowers and peas, but can use the transcriptome as a complex readout of cell state," said Gilbert. Some of his latest experiments involve pooling CRISPR screens and perturbing pairs of genes, using a single-cell RNA-sequencing platform called Perturb-SEQ, to measure stasis relationships at the level of the transcriptome—that is, all gene readouts present in a cell.

"Where I think we should be going as a group of biologists is towards trying to perturb pairs of genes and sets of genes, and turn them on and off in different combinations," said Gilbert. "Essentially, if we do this at a very large scale, we'll let biology speak to what's important in creating cell function." This research could have a range of therapeutic applications, not only in cancer but also across all of biology.

Corwin Describes a Nurse Scientist's Path

Dr. Elizabeth Corwin recently presented "Symptom Science Across the Lifespan: Metabolites, Microbes and Maternal Health." While this was the third NINR Director's Lecture of 2020, it was the inaugural lecture for new NINR director Dr. Shannon Zenk, who provided opening remarks. Zenk said that Corwin's "influential research has given us new insights into how the microbiome influences pregnancy outcomes and how fatigue may be related to postpartum depression."

Dr. Elizabeth Corwin

PHOTO: COLUMBIA SCHOOL OF NURSING

Corwin's journey to becoming a nurse scientist highlights how varied that path can be. She received a bachelor of science in zoology followed by a Ph.D. in physiology. During her postdoctoral fellowship, she was introduced to clinical research, which inspired her to step out of her faculty position to return to school for a bachelor's degree in nursing and become a family nurse practitioner. "I always say it and I mean it," she said. "Going back to school and becoming a nurse practitioner was the best professional decision of my life."

Corwin currently leads interdisciplinary research focusing on the biological, behavioral and environmental impacts on maternal health in underserved and socially disadvantaged populations. Throughout her research career, she has combined her expertise as a basic scientist with her experience caring for women and families across the lifespan.

The video of her talk is available at www.ninr.nih.gov/newsandinformation/newsandnotes/corwin-video.

NIDA/NIAAA's Leggio Receives SfN Award

Dr. Lorenzo Leggio recently received the Jacob P. Waletzky Award from the Society for Neuroscience (SfN). Leggio is a senior investigator (clinical) in the intramural research programs of both the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. He is also chief of the NIDA Translational Addiction Medicine Branch and chief of the joint NIDA/NIAAA clinical psychoneuroendocrinology and neuropsychopharmacology section.

Dr. Lorenzo Leggio

An internationally renowned physician-scientist, Leggio is recognized for his innovative research on novel neuropharmacological targets and pharmacotherapies for alcohol and substance use disorders. The award, supported by the Waletzky Award Prize Fund and the Waletzky family, is given to a young scientist whose independent research has led to significant conceptual and empirical contributions to the understanding of drug addiction. Leggio will deliver the 2020 Jacob P. Waletzky Memorial Award Lecture at the 2020 NIDA-NIAAA Mini-Convention, Frontiers in Addiction Research, on Jan. 7, 2021. Read more at https://irp.drugabuse.gov/leggio-waletzky-award/.

Kosten

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Kosten began by acknowledging the impact of the coronavirus pandemic on fentanyl overdoses and abuse in the U.S. He said one might guess that during covid, substance abuse would decrease. After all, with a great many folks on lockdown, largely confined to home and operating under so many restrictions, the drug overdose rate should decline, right?

"But in fact," Kosten said, "there's been a marked increase in the percentage of overdoses, when you compare 2020 during covid with 2019." There has been a steady rise in ODs every month since February. May 2020 saw a 42 percent increase in overdoses compared to May 2019.

"The covid epidemic has not cut back on overdoses," he said. "Covid has accelerated the escalation of this overdose epidemic."

The Waggoner professor in psychiatry, pharmacology, neuroscience, immunology and epidemiology at Baylor College of Medicine and MD Anderson Cancer Center, Kosten has a long history of support from and collaboration with NIH. He also closely collaborates with his wife, Dr. Therese Kosten, who works at the University of Houston and has NIDA support, and most recently with Dr. Elizabeth Norton of Tulane University, who has NIAID support.

Kosten gave the recent Contemporary Clinical Medicine: Great Teachers Lecture, sharing lessons his group has learned from 25 years of clinical trials of stimulant vaccine efficacy.

"Beginning in 2014, the [fentanyl] epidemic really took off in a very profound way," he said, tracing the most recent—and deadliest—surge in opioid addiction history.

Why have we seen so many opioid deaths?

"Fentanyl is substantially more potent than natural opioids or semi-synthetics," Kosten explained, describing how drug products and their ill-advised cocktails have grown deadlier in just the last decade. "It's about 50 to 100 times more potent than morphine. It's very rapidly acting, and carfentanil [an opioid prescribed by veterinarians and not approved for humans, but now being mixed with other illicit opioids and stimulants] is about 10,000 times more potent than morphine and 100 times more potent than fentanyl. Carfentanil causes almost instant death in people."

Adding to reasons for increased mortality rates, the anti-OD medication naloxone provides only a short-term reversal of opioid overdose with fentanyl. Even then, the usual amount of naloxone is insufficient and OD reversal requires multiple doses at naloxone's usual strength.

In addition, there seems to be low community awareness in the marketplace. Kosten said that "drug users seeking heroin seem largely unaware that they are using fentanyl," and street dealers seem not to realize that their products contain fentanyl.

"We need to educate users on harm-reduction measures," he said. Such measures include using less of the drug, not using alone and taking turns when using, avoiding mixing drugs and having the overdose-reversing naloxone on hand. "We've made some progress in our educational efforts in all those areas, but not enough."

Kosten said, "Covid has accelerated the escalation of this overdose epidemic."

In the covid era, Kosten said, overdose clusters have shifted from centralized urban sites to nearby suburban and rural areas where there are many more people to affect who are less educated about drug abuse. The stress and isolation of social distancing also reduces community support. Finally, there are the physiological aspects: Drug abuse damages the lungs, cardiovascular system and metabolic system, which makes individuals more vulnerable to Covid-19.

"Those are some of the many reasons we think overdoses are going up with covid," he said.

Could the pandemic help reduce substance abuse in any way?

While there has been a disruption of sorts to opioid markets, Kosten observed, the illicit drug trade is "a lot like the stock market—largely resilient." The coronavirus crisis has made it harder for users to get illicit drugs. The covid pandemic also offers users better access to care with telemedicine outreach into abusers' homes. And virtual support meetings have proliferated with more hotlines emerging for immediate help.

Kosten described how opioid vaccines coax production of antibodies to the drug and how these antibodies work like a sponge in an overdose victim's blood, absorbing and reducing brain concentrations of the drug and preventing activation of the brain's mu opioid target receptors.

"This first prevents the drug from getting into the brain," he explained, "and because the affinity of these antibodies is much higher than the affinity of the opiate receptor for fentanyl, the antibodies will—in effect—pull the fentanyl out of the brain."

Slowed brain entry also is a very important aspect of vaccine effectiveness, Kosten emphasized, because "abuse potential depends upon speed of brain entry."

Kosten then shared data from studies of vaccines for oxycodone and smoked cocaine. One trial, conducted in collaboration with Columbia University, showed an "almost 80 percent reduction in the high from smoking 25 milligrams of cocaine—which is a quite reinforcing dose—so that was a pretty nice blockade...This study was a very nice proof-of-concept that these antibodies were doing what we hoped they would."

He described a candidate fentanyl vaccine that works in a similar way and with comparable results in animal trials. His group hopes to move that vaccine into human studies soon.

Looking at the amount of antibody that vaccinated individuals produced in a multisite cocaine study, titers ranged from 250-plus (terrific) to under 40 (disappointing). Kosten acknowledged, "That is the problem with this vaccine approach—how much variation in antibody levels you get across individuals to these vaccines." The more antibody produced, the greater an individual's blockade of the drug will be and the more likely that he or she will attain sustained abstinence.

Still, Kosten concluded, arguments in favor of anti-opioid vaccines are strong: Medical risks are minimal because vaccines employ safe carrier proteins and only tiny quantities of the abused drug. Vaccines also provide a sustained but reversible drug blockade, introduce no direct brain effects or side effects and require minimal compliance after the patient is vaccinated.

Research on opioid vaccine development is as fast and furious as efforts toward a covid vaccine, Kosten said. See his full presentation at https://videocast.nih.gov/watch=38348.

An NIH study of 5,000 women has found that approximately 1 in 4 experienced high levels of depressive symptoms at some point in the 3 years after giving birth.

Postpartum Depression May Persist 3 Years After Giving Birth

An NIH study of 5,000 women has found that approximately 1 in 4 experienced high levels of depressive symptoms at some point in the 3 years after giving birth. The rest of the women experienced low levels of depression throughout the 3-year span. The study was conducted by researchers at NICHD. It appears in the journal *Pediatrics*.

The American Academy of Pediatrics recommends that pediatricians screen mothers for postpartum depression at well-child visits at 1, 2, 4 and 6 months after childbirth. Researchers identified four trajectories of postpartum depressive symptoms and the factors that may increase a woman's risk for elevated symptoms. The findings suggest that extending screening for postpartum depressive symptoms for at least 2 years after childbirth may be beneficial, the authors write.

"Our study indicates that 6 months may not be long enough to gauge depressive symptoms," said Dr. Diane Putnick, the primary author and a staff scientist in NICHD's Epidemiology Branch. "These long-term data are key to improving our understanding of mom's mental health, which we know is critical to her child's well-being and development."

The researchers analyzed data from the Upstate KIDS study, which included babies born between 2008 and 2010 from 57 counties in New York State. The study followed 5,000 women for 3 years after their children were born.

Scientists Use Clues in Human Genome to Discover New Inflammatory Syndrome

Researchers from NIH have discovered a new inflammatory disorder called vacuoles, E1 enzyme, X-linked, autoinflammatory and somatic syndrome (VEXAS), which is caused by mutations in the *UBA1* gene. VEXAS causes symptoms that included blood clots in veins, recurrent fevers, pulmonary abnormalities and vacuoles (unusual cavity-like structures) in myeloid cells. The scientists reported their findings in the *New England Journal of Medicine*.

Nearly 125 million people in the U.S. live with some form of a chronic inflammatory disease. Many of these diseases have overlapping symptoms, which often make it difficult for researchers to diagnose the specific inflammatory disease in a given patient.

Researchers at NHGRI and collaborators from other NIH institutes took a unique approach to address this challenge. They studied the genome sequences from more than 2,500 individuals with undiagnosed inflammatory diseases, paying particular attention to a set of more than 800 genes related to the process of ubiquitylation, which helps regulate both various protein functions inside a cell and the immune system overall. By doing so, they found a gene that is intricately linked to VEXAS, a disease which can be life-threatening. So far, 40 percent of VEXAS patients who the team studied have died, revealing the devastating consequences of the severe condition.

"We had many patients with undiagnosed inflammatory conditions who were coming to the Clinical Center, and we were just unable to diagnose them," said Dr. David B. Beck, clinical fellow at NHGRI and lead author of the paper. "That's when we had the idea of doing it the opposite way. Instead of starting with symptoms, start with a list of genes. Then, study the genomes of undiagnosed individuals and see where it takes us."

NIH Scientists Discover Key Pathway in Lysosomes that Coronaviruses Use to Exit Cells

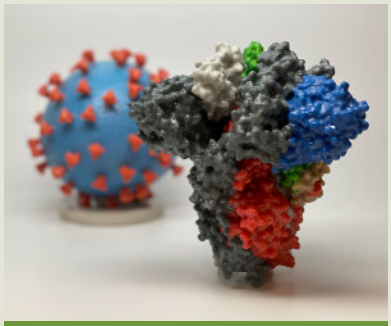
Researchers at NIH have discovered a biological pathway that the novel coronavirus appears to use to hijack and exit cells as it spreads through the body. A better understanding of this important pathway may provide vital insight in stopping the transmission of the virus—SARS-CoV-2—that causes Covid-19 disease.

In cell studies, the researchers showed for the first time that the coronavirus can exit infected cells through the lysosome, an organelle known as the cells' "trash compactor." Normally, the lysosome destroys viruses and other pathogens before they leave the cells. However, the researchers found that the coronavirus deactivates the lysosome's disease-fighting machinery, allowing it to freely spread throughout the body.

Targeting this lysosomal pathway could lead to the development of new, more effective antiviral therapies to fight Covid-19. The findings, published Oct. 28 in the journal *Cell*, come at a time when new coronavirus cases are surging worldwide, with related U.S. deaths nearing 225,000.

Scientists have known for some time that viruses enter and infect cells and then use the cell's protein-making machinery to make multiple copies of themselves before escaping the cell. However, researchers have only a limited understanding of exactly how viruses exit cells.

Conventional wisdom has long held that most viruses—including influenza, hepatitis C and West Nile—exit through the so-called biosynthetic secretory pathway. That's a central pathway that cells use to transport hormones, growth factors and other materials to their surrounding environment. Researchers have assumed that coronaviruses also use this pathway.



3-D print of a spike protein of SARS-CoV-2—also known as 2019-nCoV, the virus that causes Covid-19—in front of a 3-D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. Researchers at NIH have discovered a biological pathway that the virus appears to use to hijack and exit cells as it spreads through the body.

IMAGE: 3DPRINT.NIH.GOV

Dr. Mary Kay Floeter

NINDS's Floeter Retires After 30 Years of Government Service

BY SHANNON E. GARNETT

Dr. Mary Kay Floeter, a senior clinician in the motor neuron disorders unit in the Neurogenetics Branch of NINDS's Division of Intramural Research, retired Sept. 30 after 30 years of federal service—all with NINDS.

"I will miss the people I've worked with for many years who have been incredibly supportive and collaborative, and the trainees whose excitement and curiosity always pushed the research further in new directions," said Floeter. "I'm proud and humbled by their accomplishments in their post-NIH careers."

Floeter's research focused on motor neurons and spinal motor circuits in neurodegenerative disorders that affect the corticospinal tract. She earned her M.D. and Ph.D. from Washington University in St. Louis and completed a residency in neurology at the University of California, San Francisco. After postdoctoral work at UCSF, she came to NIH as a senior staff fellow in the Laboratory of Neural Control (LNC) to study movement control in mammalian spinal cord circuits.

"During my residency I observed a number of patients with movement disorders whose involuntary movements resembled fragments of coordinated voluntary movements," she said. "I became interested in finding ways to use circuits that produce fragments of coordinated movement to help return movement to patients who had become paralyzed from a neurological injury."

In 1993, as LNC relocated from Bldg. 36 to the then-new Bldg. 49, Floeter moved from NINDS's basic research program to its clinical research program in Bldg. 10 to train in clinical neurophysiology and conduct research with Dr. Mark Hallett who was serving as NINDS clinical director at the time.

"The first patients we studied had hereditary hyperekplexia, also called hereditary startle disease, which had only recently been found to be caused by a mutation in one of the subunits of the glycine receptor," recalled Floeter. "Glycine is the inhibitory transmitter used by certain interneurons of the spinal cord. When repeatedly exposed to a loud sound, such as a handclap, the startle response fails to habituate in patients with hereditary hyperekplexia, and muscle activation spreads to their limbs—well beyond the eyeblink that normally occurs. In these patients, we found that certain reflexes mediated by glycinergic interneurons were reduced."

Later she joined the electromyography (EMG) section of the Clinical Neurophysiology Branch as a clinical associate. And in 1996, she was selected to serve as section chief—overseeing the diagnostic EMG laboratory with a small budget for continuing research studies.

"Over the next decade, I trained clinical fellows in diagnostic EMG, always seeking to explain normal and abnormal findings using basic principles of physiology," she said.

Floeter was tapped to become NINDS deputy clinical director in 2006—a position she held until 2012–serving as acting clinical director for 4 of those years. She then took a partial break from the intramural program to serve on detail to the Office of Clinical Research in the NINDS Division of Extramural Research, where she helped to develop a vision for sharing clinical data and worked on the newly formed NeuroNext effort.

In 2013, Floeter returned to the intramural side to conduct a natural history and biomarkers study of C9orf72 in people with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The purposes of the study were to describe the natural history of disease in people who carry a repeat expansion mutation in the C9orf72 gene and to find biomarkers that relate to how the disease progresses.

"I teamed up with NIA's Dr. Bryan Traynor to carry out this study of persons carrying a hexanucleotide repeat mutation in the gene C9orf72—a mutation that Bryan and his colleagues had recently discovered as the most frequent familial cause of ALS and FTD in the U.S. and northern Europe," Floeter explained. The study, which is still active, has completed recruitment.

Throughout her career, Floeter has authored numerous scientific articles. She is a fellow of the American Association of Neuromuscular and Electrodiagnostic Medicine and is a member of the American Academy of Neurology and the American Neurological Association.

"I will stay involved in clinical research to an extent, serving on certain advisory committees and as a volunteer in the NINDS EMG section," she said. "I also plan to travel and visit distant family once the pandemic ends."

Dr. Neil Caporaso

Caporaso Retires from NCI

Dr. Neil Caporaso, an internationally recognized expert in genetic and environmental factors influencing lung cancer, chronic lymphocytic leukemia (CLL) and related familial hematologic disorders, retired from the National Cancer Institute's Division of Cancer Epidemiology and Genetics in October. He served as chief of the Genetic

Epidemiology Branch from 2011 to 2016 and was most recently a senior investigator in the Occupational and Environmental Epidemiology Branch.

Caporaso's earliest work focused on the then-controversial idea that genes could influence cancers with known strong environmental determinants. He advocated for and performed studies using pharmaco-genetic tools and biomarkers to demonstrate the importance of genetic variation in risk for lung and bladder cancer, malignancies with strong environmental influences. This and other work on genes involved in metabolism of carcinogens and other substances provided early prototypes for future large-scale biomarker studies of cancer.

Based on these principles, Caporaso and colleagues launched a landmark case-control study of lung cancer known as the EAGLE (Environment and Genetics in Lung Cancer Etiology) study. One of the many novel findings from EAGLE identified short time to first cigarette as an independent risk factor for lung cancer and chronic obstructive pulmonary disease. Recently, Caporaso described the unique characteristics of light and intermittent smokers in a comprehensive analysis of data pooled from three nationally representative surveys.

He utilized the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Cohort Study and other cohorts to evaluate and validate new technologies for biomarker studies, laying the groundwork for the study of cytokines, metabolomics and the microbiome, which have accelerated the science broadly on these important aspects of human health.

In the study of lymphoproliferative malignancies, Caporaso made seminal contributions to research on CLL, Hodgkin lymphoma, non-Hodgkin lymphoma and Waldenström macroglobulinemia, including numerous clinically significant findings.

While most of his work focused on observations from large study populations, Caporaso did not overlook the importance of individual participants. A unique single-cell integrative study on a CLL patient identified chromosomal alterations in early cell clones, elimination of clonal populations following therapy and subsequent appearance of new alterations that present in a major clonal population dominant at the patient's death. The study demonstrated that CLL can evolve gradually during indolent phases and undergo rapid changes following therapy.

Recently, Caporaso has been engaged in novel research investigating the possible role of sleep, circadian rhythms and chronotype in relation to cancer. He conducted early studies investigating the role of biomarkers in sleep and circadian disruption and has postulated that insulin resistance, which plays an important role in obesity, may be a common link in circadian and sleep disorders.

Dr. Leonard Laster

NIH Alumnus Laster Mourned

Dr. Leonard Laster, a former NIH scientist who went on to become vice president and dean of the State University of New York, Brooklyn, Downstate Medical Center, president of Oregon Health Sciences University and chancellor of the University of Massachusetts, Worcester, died recently at age 92.

He was born in the Bronx and graduated from Harvard College, 2 years after entering at age 15. He graduated from Harvard Medical school in 1950.

Laster served at NIH from 1954 to 1973. During that time, he was chief of the section on gastroenterology at the National Institute of Arthritis and Metabolic Diseases, where he made significant contributions to the field of gastrointestinal and metabolic disease, including his research on celiac disease and his discovery of the biochemical pathway for the inborn disease of alkaptonuria.

During his NIH years, he strove to have an impact nationally and was asked by the White House and NIH to represent the medical viewpoint in the President's Office of Science and Technology, where he worked to shape national health science policy from 1969 to 1973.

He is survived by his wife of 64 years, Ruth Ann (Leventhal) Laster, two daughters, a son, and several grandchildren. R

VOLUNTEERS

Ocular Symptoms in Patients with Confirmed Covid-19 Infection: A Survey Study

Reports have shown that Covid-19 infection can be associated with eye symptoms. Through an online survey, researchers at the National Eye Institute want to learn more about eye symptoms associated with Covid-19 infection. With this survey, investigators hope to discover how common eye symptoms are in Covid-19 infection and how they relate to other Covid-19 associated symptoms. The survey is expected to take 10 to 20 minutes. You do not need to have had any eye symptoms in order to participate. You may participate if you are at least 18 years of age with a history of a confirmed positive Covid-19 test. Join by visiting https://go.usa.gov/x7Tjh or email eyecovid-19@nih.gov.

Patients with Sickle Cell Disease Sought

Researchers at NHLBI are now recruiting patients with sickle cell disease to participate in a new clinical trial. This study will evaluate the effects of a natural supplement (Isoquercetin) on the markers reflecting blood-clotting risks in patients with sickle cell disease. To learn more, contact the Clinical Center Office of Patient Recruitment at 866-444-2214 (TTY 800-877-8339) or prpl@cc.nih.gov. Refer to study 20-H-0137. Read more at https://go.usa.gov/x7TDY.

Healthy Volunteers Needed

NIDDK researchers seek healthy volunteers (18-45 years old) to participate in a study investigating how dopamine affects body weight and eating behavior. Participants must be able to visit the Clinical Center for 5 consecutive days to pick up food and then have a 5-day inpatient stay. For more information, call the Clinical Center Office of Patient Recruitment, 1-866-444-2214 (TTY for the deaf or hard of hearing: 1-866-411-1010) or email prpl@cc.nih.gov. Read more at https://go.usa.gov/xPTBn. Refer to study 18-DK-0132.

Nature Soothes

Enjoy here the latest contributions seen in nature from NIH'ers.

This column of images comes to us courtesy of Dr. Deborah Henken, a program officer at NICHD who takes pictures on walks to and from work, and at lunchtime. Above, a precious pollinator in action, captured by Henken on an afternoon walk home from work.

Below, see if you can pick out the heron Henken spotted on her morning walk to work in Gaithersburg.

At bottom, a Monarch butterfly caterpillar, eating its way through a milkweed plant, seen by Henken on her lunch walk.

Dr. Lanyn Taliaferro of NIAID's Radiation and Nuclear Countermeasures Program enjoyed this view over the summer while visiting Tygart Lake State Park in West Virginia. She took the photo below while hiking in White Oak Canyon in Shenandoah National Park in Virginia.

PHOTOS: LANYN TALIAFERRO