

NOT A FAIR FIGHT

‘Viruses Don’t Play By Our Rules,’ Says MacPhail

BY CARLA GARNETT

Those who don’t learn from history are doomed to repeat it, or so the saying goes. So what can past worldwide pandemics teach us about future deadly outbreaks and the systems we’ve developed to combat them? Dr. Theresa MacPhail, a medical anthropologist who lived in China just after a deadly virus struck there, visited NIH recently to share her insights into the “Evolution of Viral Networks: H1N1, Ebola and Zika.”

“Outbreaks are about more than just biology and epidemiology,” she said. “Our responses to outbreaks are conditioned by



At NLM, Dr. Theresa MacPhail lectures on viral outbreaks.

what we know about past outbreaks. They rely upon institutions and structures put in place as a result of prior outbreaks and are often as much about politics and economic constraints as they are about science.”

MacPhail moved to Hong Kong in 2003, just as 37 countries around the world were recovering from severe acute respiratory

syndrome, or SARS, which originally broke out in south China and killed nearly 800 people. Before the pandemic was contained, more than 8,000 cases had been reported globally. Two years later, when bird flu erupted, “the government’s response was swift and unforgiving,” MacPhail said. “SARS was a dramatic event in China and colored the public health response to everything that followed it.”

MacPhail’s lecture was the keynote of “Viral Networks: An Advanced Workshop in Digital Humanities and Medical History,” sponsored jointly by the National Library of Medicine and the National Endowment for the Humanities (NEH). NEH and NIH recently extended their 6-year-old collaboration with a new memo of understanding through 2021.

“I’ve recognized through time that humanities have much to offer us as we

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First lady visits inn on Valentine’s Day; see p. 2.

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Kaelin Advocates Robust Approach to Cancer Research

BY DANA TALESNIK

Dr. William Kaelin, Jr. has a message for young investigators entering medical research: “The most dangerous result in science is the one you were hoping for, because you declare victory and get lazy.”

For example, some investigators rush to link their favorite gene to a prognosis so as to proclaim clinical relevance, said Kaelin, a clinician who is a Harvard Medical School professor and Howard



Dr. William Kaelin, Jr.

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SMARTPHONE DASHBOARDS

Big Data May Help Patients Manage Their Health

BY ERIC BOCK

Wearable biosensors may soon be able to detect when a person is getting sick before he or she realizes it, said Dr. Michael Snyder at a recent NIMH Director’s Innovation Speaker Series lecture at the Neuroscience Center.

“Big data will have value. Now, it’s a question of which data forms will have more value,” said Snyder, Stanford W. Ascherman professor and



Dr. Michael Snyder

SEE **BIOSENSORS**, PAGE 4

Bor To Speak on HIV Prevention, Mar. 19

Dr. Jacob Bor, winner of the Office of Disease Prevention's 2018 Early-Stage Investigator Lecture, will present "The Promise and Pitfalls of HIV Treatment-as-Prevention: Quasi-Experimental Evidence from South Africa" on Monday, Mar. 19 from 3 to 4 p.m. at the Neuroscience Center Bldg., Rm. A1/A2.

Bor is an assistant professor and Peter T. Paul career development professor in the departments of global health and epidemiology at Boston University School of Public Health. His research applies the analytical tools of economics and data science to the study of population health, with a focus on HIV treatment and prevention in southern Africa. Current research interests include chronic disease management in low-resource settings; economic spillover effects of HIV treatment; decision-making in HIV-endemic risk environments; population health impacts of social policy; and causal inference in public health research. His work has been published in *Science*, *The Lancet*, *PLOS Medicine*, *Epidemiology* and *Health Affairs*.



The ODP Early-Stage Investigator Lecture recognizes early-career prevention scientists who have not yet competed successfully for a substantial NIH-supported research project, but who have already made outstanding research contributions to their respective fields and are poised to become future leaders in prevention research.

The lecture is free and open to the public; attendees can join either in person or via <https://videocast.nih.gov>. Registration is not required. For more information, contact Dr. Stephanie George, stephanie.george@nih.gov.

NIMH Launches Twitter Account for Director

The National Institute of Mental Health has launched an official Twitter account—@NIMHDirector—for its director, Dr. Joshua Gordon. As the lead federal agency for research on mental disorders, NIMH established its enterprise Twitter account, @NIMHgov, in May 2009. It surpassed more than a million followers earlier this year.

"I'm hoping to make the most of this opportunity to share exciting new developments in mental health research," said Gordon. "I understand the impact of social media and I'm eager to join the conversation on Twitter."

Gordon joined NIMH in September 2016. Through Twitter, he plans to share his vision and priorities.



First lady Melania Trump chats with Caitlyn Ribas, 12, sister of NICHD patient Annie Ribas of Silver Spring, as she visits with kids at the Children's Inn at NIH on Valentine's Day. At left is inn CEO Jennie Lucca and looking on is NIH director Dr. Francis Collins.

PHOTOS: ERNIE BRANSON

First Lady Sweetens Valentine's Day at Inn

First Lady Melania Trump visited youngsters at the Children's Inn at NIH on Feb. 14, decorating cookies and exchanging Valentine's Day cards with them and encouraging them in their fight against rare or critical illnesses.

Inn CEO Jennie Lucca and NIH director Dr. Francis Collins provided Trump with a tour of the inn and participated in activities alongside her.

"It was fun making cookies and meeting and talking to the first lady," said Amber Negrete, 8, of California, who is staying at the inn while receiving gene therapy at the National Institute of Neurological Disorders and Stroke for giant axonal neuropathy, a rare genetic disorder that progressively affects nerve functioning, much like ALS. "I was excited because she said to me, 'You're gorgeous,' and I asked her how it feels to be first lady, and she said 'good.'"

"This was very fun," added Saffron Wolley, 16, of London, England, who is being treated for a rare disorder at the National Institute of Child Health and Human Development. "The first lady was so positive. She is very tall and glamorous. I gave her my valentine. She said it's very lovely."

At the end of the first lady's visit, inn resident Lucy Wiese, 9, of Midlothian, Va., and Lucca presented Trump with a special gift created by the children for the Trump family, including a finger-painted heart with a Valentine's Day message, a FLOTUS apron with the inn logo, Valentine's Day T-shirts for the first family and inn mugs labeled FLOTUS and POTUS.

"I made a couple of Valentine's Day cards for her, and she asked me where I live and how old I am," said Wiese, who underwent a successful bone marrow transplant for a rare immunodeficiency.

"She was really nice," said Annie Ribas, 9, of Maryland, who was successfully treated for Cushing syndrome at NICHD. "She would ask questions about why people were staying here, and we wished each other a happy Valentine's Day."



The first lady embraces Alexis "Lexi" Bingham, 8, of Montrose, Calif. She is an NINDS patient being treated for myopathy.

Cashion Named NINR Acting Deputy Director

Dr. Ann Cashion was recently appointed acting deputy director of the National Institute of Nursing Research.

She has been at NINR for more than 6 years, first as a senior advisor to the director, followed by acting scientific director and, since 2013, as scientific director.

Prior to her appointment at NINR, Cashion was professor and chair of the department of acute and chronic care in the College of Nursing, University of Tennessee Health Science Center in Memphis. She joined the faculty in 2000, shortly after earning her doctorate at UTHSC.

During her tenure there, Cashion conducted research focused on clinical outcomes following solid organ transplantation, including early biomarkers of acute rejection in recipients of pancreas transplantations and genomic and environmental predictors of weight gain in recipients of kidney transplantations.

She also shared her expertise, mentoring numerous doctoral students on how to



Dr. Ann Cashion

PHOTO: ERNIE BRANSON

incorporate genomics into their programs of research and chairing an NIH integrated review group study section for training applications.

“Dr. Cashion has been instrumental in leading NINR’s Division of Intramural Research over the past 5 years,” said NINR director Dr. Patricia Grady. “I look forward to the vision and leadership she will bring to the institute in her expanded role as acting deputy director of NINR.”

Cashion will also maintain her responsibilities as scientific director. Her profile is available at <https://www.ninr.nih.gov/researchandfunding/dir/ann-cashion>.—

Diana Finegold 

C.A.R.E. Channel Provides Relaxing Imagery, Music

The Clinical Center now offers access to the C.A.R.E. Channel, which provides a healing environment to patients and their care providers. Images can be seen on hospital TVs or downloaded from www.healinghealth.com.

The channel’s name is an acronym for “Continuous Ambient Relaxation Environment.” View it for free on channel 08 anyplace the Clinical Center cable system is operable.

Running 24/7, it features nature imagery during the day and transitions to a moving star-filled sky during the night, accompanied by original instrumental music designed to be soothing and relaxing.

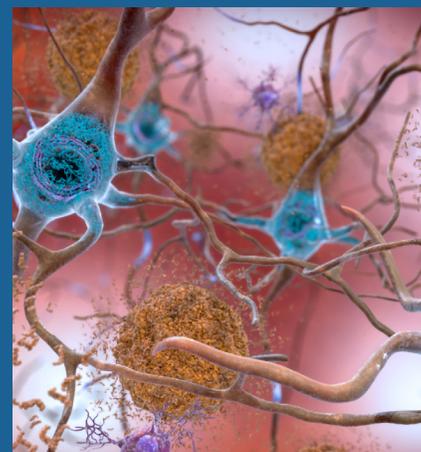
“When a project involves improving our patients’ experience, it’s never a hard sell to get Clinical Center staff excited to team up and make it happen,” said John Pollack, chief of the department of spiritual care.

The C.A.R.E. Channel is brought to the CC through a collaboration between the departments of spiritual care and nursing. The programming runs 84 hours before repeating itself, which is fitting for extended stays common to the hospital.

The channel is a tool that for some patients may help reduce anxiety, assist with restfulness and offer a positive focal point when in discomfort.

The relaxing images may help calm nerves in clinics and waiting rooms. Outpatients and caregivers may wish to tune in as they wind down in the Safra Lodge from a hectic appointment slate. Or inpatients may find it a welcome alternative if they don’t wish to or are unable to follow news and plot-driven shows. The possibilities are many—whether to add serenity or just drown out hospital noise.

Questions about the channel? Email Pollack at john.pollack@nih.gov.



ON THE COVER: In the Alzheimer’s-affected brain, abnormal levels of the beta-amyloid protein clump together to form plaques (brown). Abnormal collections of the tau protein accumulate and form tangles (blue).

IMAGE: NATIONAL INSTITUTE ON AGING

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At left, Snyder presents at a recent NIMH Director's Innovation Speaker Series lecture. Above, NIMH director Dr. Josh Gordon asks a question following Snyder's talk.

PHOTOS: CHIA-CHI CHARLIE CHANG

Biosensors

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chair, department of genetics and director, Center for Genomics and Personalized Medicine at Stanford University.

To answer that question, Snyder began enrolling patients 8 years ago in a longitudinal study at Stanford to characterize an individual's healthy state and observe what happens when he or she gets sick.

All enrolled patients have their genomes sequenced and give blood samples so Snyder can build a "personal omics profile." This includes information on how a genome is expressed, microbes found on the skin and in the stomach, a person's metabolic profile and even substances a person is exposed to in the environment.

When participants are healthy, his lab takes samples from them every 2 or 3 months. The lab also takes samples whenever someone gets sick.

"We're making billions of measurements every time we sample folks," he noted.

Snyder was the first to enroll in the study. Since then, he's been through 11 viral infections, a Lyme disease diagnosis and a bike accident. "I don't look for these things, but when they happen I might as well get good data," he said.

Sequencing his DNA was valuable. His genome suggests he's at increased risk for high cholesterol, a type of skin cancer called

basal cell carcinoma and type 2 diabetes. Of the patients enrolled in the study, "17 percent of people had clinically actionable information in their genome," he said. This includes individuals who are at high risk for cancer, one person who was misdiagnosed with type 2 diabetes (but was really

★ ★ ★

Of the patients enrolled in the study, 17 percent of people had clinically actionable information in their genome.

★ ★ ★

a different form of diabetes called MODY) and another person who was at high risk for a heart defect and was later found to have that defect.

Besides genome sequencing, other types of data were also valuable. For example, some were pre-diabetic and had no idea they had the condition. Another patient had a serious heart condition. And one patient had undiagnosed lymphoma. Because it was caught early, it was treatable.

A few years ago, Snyder incorporated data from wearable sensors into the study. He can now measure heart rate, skin temperature, blood oxygen levels and activity and sleep patterns. He wears eight of them daily.

"Nearly all of these wearables will

transfer information back into your iPhone," he explained.

Because of a wearable, he discovered that blood oxygen levels decrease on flights. He believes the drop in blood oxygen causes fatigue. Usually, the levels will go back to normal on long flights.

On one flight to Norway, he saw his oxygen level decrease more than normal. It stayed low until he got off the plane. He later learned that his heart rate and skin temperature increased. He warned a doctor in Norway that he might have Lyme disease because he remembered helping his brother put up a fence in rural Massachusetts a few weeks earlier.

The doctor prescribed doxycycline, an antibiotic used to treat early Lyme disease. Later tests confirmed he had the disease.

"The first I detected the disease was with my wearables," he said.

He believes a person's heart rate will predict when someone is starting to get sick. His team is writing an algorithm that will alert people when they should see a doctor if their heart rate goes up higher than expected based on their activity. He hopes that smartphones will become personal health dashboards that interpret data for patients.

"This information can be shared with your physician so that your physician can get better measurements," Snyder concluded. "That's very powerful." **R**

'GO RED' 2018

Annual Red Dress Collection Gathers Celebrities, Heart Disease Survivors

Stars took to a New York City runway on Feb. 8 for the American Heart Association's annual "Go Red for Women" Red Dress Collection, presented by Macy's at the Hammerstein Ballroom in Manhattan. Go Red is an event in which celebrities and top designers show their commitment to women's heart health during New York Fashion Week and American Heart Month. Founded in 2004 by the National Heart, Lung and Blood Institute's The Heart Truth campaign in partnership with AHA, the event reminds women of the need to protect their heart health and take action in the fight against heart disease and stroke in women.

Alongside celebrities from the stage, screen, fashion and music realms, walking in this year's show were two heart disease survivors—Macy's employee Karen A. Hill from Washington D.C., who is living with cardiomyopathy, as well as an AHA national spokeswoman and Go Red For Women "Real Woman" Lilly Rocha from Pasadena, Calif., who survived a heart attack at age 37. This year's show was hosted by actress Marisa Tomei.



Actress Marisa Tomei hosts 2018 event.



Above, Go Red for Women "Real Woman" Lilly Rocha (r) walks the runway with D.C.'s Karen A. Hill, who is living with cardiomyopathy; below, Surgeon General Jerome Adams and daughter Millie pause for a pic on the event's red carpet.



ABC News chief meteorologist Ginger Zee walked the runway on Feb. 8 and gave birth to her second son on Feb. 9.



Actress Marion Ross walks the runway in memory of her parents who both died of heart disease.



Star studded. Celebrities take to a New York City runway on Feb. 8 for the American Heart Association's annual "Go Red for Women" Red Dress Collection.

PHOTOS: NICHELLE LEWIS/NHLBI; GETTY IMAGES/AHA



Outbreaks of old. At left, St. Louis Red Cross Motor Corps is on duty during October 1918 influenza epidemic. At center, precautions taken in Seattle, Wash., during the Spanish influenza epidemic would not permit anyone to ride on the street cars without wearing a mask. (IMAGES COURTESY LIBRARY OF CONGRESS) At right, in her lecture, keynote MacPhail examined how global viral networks have operated during more recent infectious disease crises.

Viruses

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bring a scientific and engineering approach to thinking about that which can only be experienced by humans,” noted NLM director Dr. Patricia Flatley Brennan, in opening remarks.

Delivering her lecture, coincidentally 100 years to the day of the start of the killer 1918 influenza pandemic, MacPhail, assistant professor of science and technology studies at Stevens Institute of Technology, said, “SARS had proven we needed a more robust international response system... What bird flu proved was that we needed a more robust surveillance system. The

“Viruses do not play by our rules. They confound our expectations and force us to become like them in order to effectively battle them. The global viral network needs to keep evolving but clearly we need to start rethinking about how we do that.”

—DR. THERESA MACPHAIL

global community couldn’t afford to be taken by surprise if another highly infectious pathogen were to emerge.”

By 2009, when a novel strain of H1N1 influenza broke out in Mexico, an international public health response system—a so-called “viral network”—was experience-informed and ready for the world stage, MacPhail said. Given lessons from SARS and bird flu, would the system master the challenges presented by a fast-moving, mostly unpredictable infection?

MacPhail defines a viral network as “any group of people, institutions, technologies and other living and non-living things—like viruses—that are interconnected in order to produce information or knowledge. The network exists to create, revise and transmit information to get everyone on the same page. That’s its whole function. And that function is critical to us being able to act... The viral network is a super-organism that relies upon its individual parts and yet is able to transcend them.”

MacPhail’s lecture pitted the viral network’s 2009 performance—she wrote a widely regarded book, *The Viral Network: A Pathography of the H1N1 Pandemic*, about it—against two more recent pandemics: the 2014–2015 Ebola crisis and the 2015 Zika outbreak.

She focused on three aspects of the viral network—lab work, surveillance and information-sharing/coordination systems.

“We have to think about outbreaks, epidemics and pandemics holistically,” she said. “We have to look at everything—history, politics, economics, biology, culture—all at once in order to understand not only what



NLM director Dr. Patricia Flatley Brennan (l) welcomes MacPhail and NEH Chair John Parrish Peede. Remarking on the newly extended partnership between NLM and NEH, he said funding studies on the history of medicine reveals “not only profound ways medical science has shaped our history and our culture, but also how much rigorous humanities research has to contribute to our understanding of sickness and health.”

LECTURE PHOTOS: CHIA-CHI CHARLIE CHANG

happened, but also what is happening and what is likely to happen in the future.”

Had 2009 lessons produced any changes in the network? MacPhail asked. “Had the virus that is global health adapted, mutated or evolved to be better able to respond to large-scale highly transmissible infectious diseases?”

The reviews were somewhat mixed.

“Lab science forms the core of the entire super-organism that is global health,” argued MacPhail, who in 2009 worked in the global disease detection unit of the Centers for Disease Control and Prevention in Atlanta and witnessed the culture of pathologists and epidemiologists first-hand in real time as H1N1 occurred.

The genetic sequencing of H1N1 “was a watershed event,” she reported. “It was to date the fastest, most transparent production of phylogenetic information on any new virus that has ever taken place. Laboratories around the globe worked together pretty seamlessly to produce quality information—the viral network at its best.”

Labs remain the most adaptable segment of the global health system, she said. But, “lab capacity is always a problem during any outbreak of infectious disease, no matter where you are. Because of this, strengthening lab capacity has been a key focus of pandemic planning.”

Unlike the big-city emergence of H1N1 in Mexico, the first cases of Ebola occurred, in late 2013, in impoverished rural areas and initially were missed by the network. It wasn’t until May 2014 that a sentinel lab in Kinshasa, central Africa, sounded an alarm. A case reported in Sierra Leone in March had been ignored.

“Sporadic cases of Ebola are normal for certain locations,” so no red flags were triggered by the first cases, MacPhail explained. “That’s the real issue here—the viral network doesn’t reach everywhere...Clearly there are many gaps in our surveillance and lab capabilities.”

Ebola, capitalizing on these system vulnerabilities, was able to get a foothold, she pointed out. For Zika, labs were deemed generally successful; however, political realities—the virus affected pregnant women and infants—intruded on surveillance and coordination efforts. Again, the infection largely won.

“Public health in all its forms is constantly

focused on its past,” MacPhail said. “It tries to learn from its history but in doing so it often repeats the same mistakes.”

Having data and circulating it widely is not the same as having knowledge, she explained. Context is crucial, and that comes only from seasoned, expert analysts, who often are in short supply.

MacPhail said the narrative is the same for H1N1, Ebola, Zika—and in many ways for today’s H3N2 flu outbreak, which is swiftly showing itself to be the worst influenza epidemic in recent history.

“We’re bad at predicting because pathogens are great at surprises,” she said. “They pop up in weird places, at weird times and seem harmless...and we can’t care about everything. Our resources are limited. Global health makes choices about what to prioritize.”

Without more resources, surveillance capacity and expertise, MacPhail said, “we won’t see the next thing coming either.”

Reviewing how each pandemic played out, she made valuable observations: Chiefly, the network is not flexible enough to adapt

quickly to ever-changing pathogens and conditions, and past information often can hinder as well as help in real-time crises.

“Viruses do not play by our rules,” she concluded. “They confound our expectations and force us to become like them in order to effectively battle them. The global viral network needs to keep evolving but clearly we need to start rethinking about how we do that.”

MacPhail’s lecture is archived online at <https://videocast.nih.gov/summary.asp?Live=26977&bhcp=1>. 



MacPhail and Brennan share a light moment at the lecture.

New Text Campaign from NINR, MedlinePlus

The National Institute of Nursing Research and the National Library of Medicine’s MedlinePlus have teamed up to offer a text message service for those living with serious illnesses and their families. The campaign launched on Feb. 5 and offers weekly text messages about palliative care in English and Spanish.

Palliative care’s primary purpose is to relieve the pain and other symptoms associated with serious illnesses and improve quality of life. The text messages provide information about what palliative care is, the benefits of palliative care and resources on how to manage the symptoms of a serious illness. Messages address both adult and pediatric patients and their families.

To sign up for the text messages, text MP CARE to 468311 for English messages or MP CUIDAR to 468311 for Spanish messages.

Visit <https://medlineplus.gov/palliativecaretexts.html> for more details.

Living with a serious illness?

Find out how palliative care can help you and your family.

Get palliative care texts.
Text MP CARE to 468311.



Kaelin

CONTINUED FROM PAGE 1

Hughes Medical Institute investigator. He tells his students to do better: think logically, speak clearly with words that have precise meanings and don't assume correlation together with plausibility proves causation.

"You have to be careful with inferring causality," said Kaelin, speaking at a recent Wednesday Afternoon Lecture in Masur Auditorium. "Showing that a protein is associated with a bad prognosis in a given cancer is not sufficient to claim it is a good cancer target."

A focus of Kaelin's research is hypoxia, or oxygen deficiency. Within a tumor, hypoxia is usually associated with a bad prognosis, he said. Many therefore argue hypoxia causes aggressive tumor growth. But Kaelin cautioned that aggressive tumors can become hypoxic when they outgrow their blood supply. "So one can't always be sure whether hypoxia is the cause or the result of aggressive tumor growth."

A central thrust of Kaelin's talk was robustness. "If a result is true, but only true in your favorite cell line, and it had to be Friday, and the Red Sox had to have won the night before, the result might be true but not robust, and we need [results] that are highly robust," Kaelin said, illustrating a persistent

problem in medicine that he's written and spoken about extensively—reproducibility.

Many experiments have outcomes that hold true only under narrow conditions, Kaelin warned, making it difficult for other researchers to replicate those results. Experiments that are robust—able to withstand a variety of conditions—are more likely to have practical implications, he said, such as in human clinical trials.

Kaelin's lab studies tumor-suppressor genes. When these genes mutate, they remove brakes that help prevent cancer.



"A good scientist lives for the unexpected result," Kaelin said. "Sometimes the surprises are the first step toward meaningful discovery."

PHOTOS: CHIA-CHI CHARLIE CHANG

His experiments on certain proteins encoded by these genes hold the potential for new drugs against cancer and other diseases. Yet in recent years, Kaelin noted, a staggering number of papers nominating new cancer drug targets contain

translational, even if rooted in basic science observations that in years past would have been more fully developed and explored, he said. "And honestly describing unexpected findings can be a death knell for publication."

Kaelin recalled submitting a paper



"...People who tell you how truly transformative science gets done would tell you—especially in the early days—you'd be better off having 10 people going in different directions, looking under rocks, and hoping 1 or 2 of them actually discover something."

-DR. WILLIAM KAELIN, JR.



irreproducible results, which impedes the development of new drugs.

When it comes to validating preclinical cancer targets, Kaelin said, corroborating lines of evidence are a scientist's best friend. As a postdoc in the 1980s, he would write a paper using multiple arguments to prove a concept; today, he said, papers often cite a variety of concepts, each proven only one way.

In today's funding environment, many investigators feel compelled to have their papers culminate in experiments that feel

in which he treated eight different renal carcinoma cell lines with a new anticancer drug. The editor initially wanted to reject the paper because several cell lines didn't react to the inhibitor as Kaelin expected and he couldn't yet explain why. Demanding that papers have no unanswered questions can delay progress and contribute to the robustness problem, he argues.

"Many people would have cherry-picked the data from the responding cell line models and buried the data from the non-responder models," said Kaelin. "Then

someone comes along and doesn't see the expected result when they study one of the non-responder models."

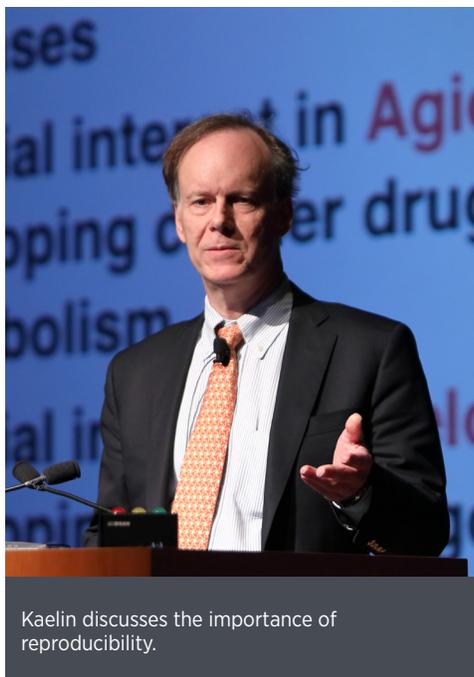
One scientist's unexplained results or unexpected findings can lead to another researcher's new discovery. Subsequently, the kidney cancer drug in question went into trial with some encouraging results. But just as predicted by the laboratory experiments, some patients seemed to respond and others did not. And heterogeneous responses are the rule rather than the exception in the clinic.

For example, Kaelin described his work on leukemias caused by IDH mutations. IDH mutations cause the production of 2-HG, an oncometabolite that causes certain cancer cells to proliferate. His group showed that blocking 2-HG production inhibited leukemic cells in the laboratory. A drug that blocked 2-HG production indeed worked remarkably well in clinical trials, but only for about 30 percent of patients.

Kaelin also implored his fellow scientists to work harder to show that the chemical and genetic tools they use in the laboratory are having their cellular effects by inhibiting their intended targets rather than by unintended actions on unsuspected targets. A drug may seem to be the next miracle in the lab—until further study. "The rosier interpretation is everything is on-target and the model is correct," said Kaelin. "A good scientist also considers the least interesting interpretation to their data."

Even with a good drug, responses to targeted agents are often short-lived, said Kaelin, so there's not much chance of a cure with a single agent. That's why combining drugs remains so critical. "The classical way to avoid resistance is to combine drugs that have distinct mechanisms of action, are not cross-resistant with one another and have toxicities that don't overlap in a prohibitive way."

Sometimes, a drug all but discarded can lead to new paths in drug development. Thalidomide—given to pregnant women in the 1950s until it was found to cause severe birth defects—and related drugs such as lenalidomide have turned out to be useful drugs for certain malignancies, notably multiple myeloma. Kaelin and Ben Ebert at Harvard, working in parallel, showed that thalidomide-like drugs bind to a protein called cereblon and reprogram



Kaelin discusses the importance of reproducibility.

it to destroy a protein needed by multiple myeloma cells.

Kaelin also commented on the role academic investigators play in the biomedical ecosystem. He noted that scientists learn the rules of a system and engineers apply that knowledge to do useful things. "Historically," said Kaelin, "the secret sauce in biomedical research in this country has been the symbiotic relationship...between pharma companies on the engineering side and investigators doing the science."

Kaelin's motivation for sharing his observations goes beyond professional interest. It comes as a personal plea in memory of his late wife, Carolyn, a renowned breast cancer surgeon who lost her 4-year battle with glioblastoma in 2015.

"One of many frustrations in treating my wife was that everything I had available to treat her was really based on science that was done 10 or 20 years ago," said Kaelin.

In the coming years, cancer patients will rely on the science being done now. "The first questions should be: Is this [research] true and robust? Is someone likely going to be able to build on this?"

Kaelin lauded NCI's Cancer Moonshot but said it was the "right mission, wrong metaphor." Putting a man on the moon was an engineering feat limited by resources; curing cancer is a scientific effort limited by lack of knowledge; much remains unknown, including the time lines for cures.

"If you're going to put a man on the moon, you want everyone going in the same direction," he said. "But people who tell you how truly transformative science gets done would tell you—especially in the early days—you'd be better off having 10 people going in different directions, looking under rocks, and hoping 1 or 2 of them actually discover something."

Kaelin concluded with a message: "My wife never gave up. To the young people—please don't give up." **R**



Corbie-Smith To Give NIMHD Director's Lecture, Mar. 13

Dr. Giselle Corbie-Smith will give the next lecture in the NIMHD Director's Seminar Series on Tuesday, Mar. 13 at 2 p.m. in the Porter Neuroscience Research Center Bldg., Rm. 610. She will discuss "Valuing Their Voice: Creating an Infrastructure to Support Patient-Centered and Community-Engaged Research."

Corbie-Smith is the Kenan distinguished professor of social medicine and medicine at the University of North Carolina School of Medicine and director of the Center for Health Equity Research. She also directs the Program on Health Disparities at the Cecil G. Sheps Center for Health Services Research at UNC-Chapel Hill.

Corbie-Smith has been a member of several national and regional committees including Institute of Medicine groups examining the ethical issues of involving minority and underserved communities in housing-related research and on standards for systematic reviews in comparative effectiveness research.

Nationally recognized for her work on practical and ethical issues regarding involvement of minorities in research, Corbie-Smith received an M.D. from Albert Einstein College of Medicine and a master's degree in clinical research from Emory University.

For reasonable accommodation, call (301) 402-1366 or the Federal Relay, (1-800-877-8339).

Epilepsy Study Links Mossy Brain Cells to Seizures and Memory Loss

A small group of cells in the brain can have a big effect on seizures and memory in a mouse model of epilepsy. According to a new study in *Science*, loss of mossy cells may contribute to convulsive seizures in temporal lobe epilepsy (TLE) as well as memory problems often experienced by people with the disease. The study was funded by NINDS.

“The role of mossy cells in epilepsy has been debated for decades,” said Dr. Vicky Whittemore of NINDS. “This study reveals how critical these cells are in the disease, and the findings suggest that preventing loss of mossy cells or finding ways to activate them may be potential therapeutic targets.”

Mossy cells, named for the dense moss-like protrusions that cover their surface, are located in the hippocampus, a brain area that is known to play key roles in memory. Loss of mossy cells is associated with TLE, but it is unknown what role that plays in the disease. Using state-of-the-art tools, Dr. Ivan Soltesz and his team at Stanford University were able to turn mossy cells on and off to track their effects in a mouse model of epilepsy.

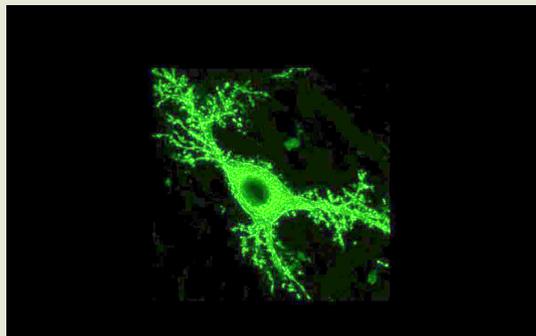
“This study would not have been possible without the rapid advancement of technology, thanks in part to the BRAIN Initiative, which has encouraged scientists to develop innovative instruments and new ways to look at the brain,” said Soltesz. “It’s remarkable that we can manipulate specific brain cells in the hippocampus of a mouse. Using 21st century tools brings us closer than ever to unlocking the mysteries behind this debilitating disease.”

In TLE, many seizures, known as focal seizures, originate in one part of the brain and are evident on electroencephalography scans that show the brain’s electrical activity. These seizures can result in symptoms such as twitching or a strange taste or smell, and many people with TLE might not be aware that these symptoms are seizures. Sometimes, focal seizures can spread throughout the entire brain becoming generalized, resulting in involuntary muscle spasms, or convulsions, that affect the limbs and other parts of the body as well as loss of consciousness.

Researchers Identify Risk Factors for Sleep Apnea During Pregnancy

Snoring, older age and obesity may increase a pregnant woman’s risk for sleep apnea—or interrupted breathing during sleep—according to researchers funded by NICHD and NHLBI. The study appears in the *American Journal of Obstetrics and Gynecology*.

“Our study found an easy, inexpensive way to screen large numbers of women at higher risk of sleep apnea during pregnancy,” said study co-author Dr. Uma Reddy of NICHD’s Pregnancy and Perinatology Branch. “Right now, this means we’ll be able to rapidly identify women who may benefit from further testing. Depending on what we learn from future studies, our findings could also lead to improvements in pregnancy outcomes.”



New findings in a study of mice suggest that a loss of mossy cells may contribute to seizures and memory problems in a form of epilepsy.

IMAGE: IVAN SOLTESZ, STANFORD UNIVERSITY

In an earlier study of first-time pregnancies, the researchers found that sleep apnea increases a woman’s risk for hypertensive disorders and gestational diabetes. Currently, there are no medical guidelines or treatment recommendations for sleep apnea during pregnancy. NIH currently supports a study of potential treatments for pregnancy-related sleep apnea and is planning a larger one to be conducted by the NICHD-funded Maternal-Fetal Medicine Units Network.

In the current study, participants responded to questionnaires about their sleep habits, snoring and daytime sleepiness in early pregnancy (6 to 15 weeks) and mid-pregnancy (22 to 29 weeks). The women also underwent sleep apnea testing using an at-home monitoring device.

Researchers found that 3.6 percent of 3,264 women in early pregnancy and 8.3 percent of 2,512 women in mid-pregnancy had sleep apnea. Risk factors for having the condition included frequent snoring (3 or more nights

per week), older maternal age and being overweight or obese as determined by body mass index.

Study To Assess Biomarker as Indicator of Whether LRTIs Improve with Antibacterial Treatment

A new clinical trial sponsored by NIAID aims to determine whether low blood levels of the protein procalcitonin can reliably indicate whether a person’s lower respiratory tract infection will improve with antibiotic treatment.

Lower respiratory tract infections (LRTIs) can cause a variety of symptoms, including persistent coughing, wheezing, chest pain, fever and rapid or difficult breathing. Health care providers often prescribe a course of antibiotics as standard treatment without knowing for certain whether an infection is bacterial or viral. Taking antibiotics for viral infections is not only ineffective but can also introduce potential side effects and promote antimicrobial resistance.

Procalcitonin (PCT) is normally produced by the healthy human body in minute quantities and serves as a precursor to calcitonin, a hormone that helps regulate calcium levels. Currently, medical professionals are able to test patients’ blood for high PCT levels, which are an indicator of bacterial sepsis, a life-threatening complication of infection that triggers inflammation throughout the body. The researchers leading the new clinical trial theorize that low PCT levels in patients with LRTIs may indicate that the infection is viral, not bacterial.

“Health care providers and patients benefit from precise diagnostic tests to guide treatment decisions,” said NIAID director Dr. Anthony Fauci. “An effective biomarker for confirming that a lower respiratory tract infection is viral and thus not treatable with antibiotics would be a significant development in our collective efforts to reduce inappropriate use of antibiotics and combat antimicrobial resistance.”



Snoring, older age and obesity may increase a pregnant woman’s risk for sleep apnea, according to research funded by NIH.

IMAGE: PERBOGE/THINKSTOCK

The study is being led by principal investigator Dr. Ephraim Tsaliq of Duke University and the Durham VA Health Care System in Durham, N.C.

Longtime Scientist, Administrator Mathieson Mourned

BY L. JEAN PATTERSON

Dr. Bonnie Mathieson, who had a long and distinguished career at NIH spanning 43 years, passed away unexpectedly on Jan. 8. Mathieson, who retired from NIH on Dec. 29, 2017, was snorkeling in Aruba when she had a massive heart attack. She had been recognized for 40 years of service at the NIH Office of the Director 2017 Honor Awards Ceremony in November.

Mathieson most recently served as a health scientist administrator in the NIH Office of AIDS Research. During her tenure as the lead for HIV/AIDS vaccines at OAR, she was instrumental in advancing the NIH AIDS vaccine program in countless ways. She lent her expertise, wisdom, advice and support to numerous vaccine trials and helped develop a vaccine scholars program to train the next generation of scientists.



Dr. Bonnie Mathieson

in medical microbiology from Stanford University.

Mathieson was a tireless advocate for young people, women and early-career investigators. Her colleagues knew her as an international leader in the HIV vaccine field and a devout supporter of research to prevent HIV and improve the health

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“Bonnie possessed a genuine passion for bench science and dedicated the later part of her career to guiding HIV vaccine research at NIH.”

-DR. MAUREEN GOODENOW

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Prior to joining OAR, Mathieson was a program officer in the Vaccine Branch of NIAID's Division of AIDS, where her immunology expertise was vital to NIH's mission of developing and testing an HIV vaccine.

Before joining NIAID, she made seminal contributions to the field of basic T cell immunology as an investigator at NCI. Mathieson also served on review boards for the World Health Organization, European Commission, Canada and the Gates Foundation. She published more than 125 articles and chapters and routinely received performance awards during her tenure at NIH. Mathieson also won an Alumnus Award from Weill Cornell Medical College, where she received a Ph.D. in biological sciences. She earned her bachelor's degree in botany from the University of Illinois and a master's degree

and outcomes of people living with HIV. According to coworkers, those fortunate enough to know Mathieson lost a dear friend.

“Bonnie possessed a genuine passion for bench science and dedicated the later part of her career to guiding HIV vaccine research at NIH,” noted Dr. Maureen Goodenow, OAR director. “She was a well-respected member of the NIH community who enthusiastically supported, advised and questioned her colleagues in equal parts. The keen perceptions and insights Bonnie contributed to the field of HIV science cannot be overstated and her passing is a deep loss to the field.”

Mathieson is survived by her husband Donald, their daughter Cynthia, their son Daniel and his wife Jessica, 2 grandchildren, Cash and Nathaniel, and 5 sisters and brothers. She was preceded in death by one sister. **R**

HIV Vaccine Study Needs Subjects

Vaccine Research Center researchers seek persons 18-60 years old who are living with HIV for a research study. The study evaluates an investigational product targeting the HIV virus to determine if it is safe and can generate an immune response. Compensation is provided. For more information, call 1-866-444-1132 (TTY 1-866-411-1010) or email vaccines@nih.gov. Se habla español.

Healthy Volunteers Needed

NIAID researchers seek healthy volunteers, 18-50 years old, for an investigational vaccine study targeting respiratory syncytial virus (RSV). Compensation is provided. For more information, call 1-866-833-5433 (TTY 1-866-411-1010). Email vaccines@nih.gov or visit <http://bit.ly/2nOkOvY>.

Study in Search of Overweight Men

NIDDK researchers are seeking overweight/obese men, 18-50 years old, to participate in a study looking at a potential link between consumption of processed foods and the development of metabolic syndrome. Participants will be required to remain in the hospital for 1 month on 2 separate occasions and eat only the meals provided by NIH during that time. Compensation is provided. To learn more, call the Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010). Read more at <https://go.usa.gov/xRRE7>.

Flu Vaccine Study Recruits Healthy Volunteers

Vaccine Research Center researchers seek healthy volunteers, 18-70 years old, for an investigational influenza vaccine study. Scientists are testing new vaccines to determine whether they are safe and effective in preventing the flu. Compensation is provided. For more information, call 1-866-833-5433 or email vaccines@nih.gov. Read more at <https://go.usa.gov/xNH7U>. Refer to study VRC316.

NHLBI Study Needs Patients

NHLBI researchers are testing two low doses of danazol on individuals with short telomere disease and bone marrow disease, lung or liver disease. For more information, call the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Read more at <https://go.usa.gov/xnPYm>. Refer to study 18-H-0004.



ABOVE: Sen. Maggie Hassan (D-NH, l) meets with (from l) NCI director Dr. Ned Sharpless, NIH principal deputy director Dr. Lawrence Tabak, NIH director Dr. Francis Collins, NIAID director Dr. Anthony Fauci and NICHD director Dr. Diana Bianchi.



Above, Collins greets Hassan at the outset of the visit. Below, Hassan chats with Sharpless during hospital tour.



Hassan (r) enjoys a laugh with Fauci, Bianchi and Collins.

New Hampshire Senator Visits NIH

U.S. Sen. Maggie Hassan (D-NH) visited NIH on Feb. 16, meeting first in the Clinical Research Center's medical board room with NIH leadership before proceeding to briefings by scientists—and a patient encounter—at NCI, NINDS and NEI.

The morning visit was capped by a stop at the Children's Inn at NIH.

PHOTOS: CHIA-CHI CHARLIE CHANG, SONJA LUECKE



Dr. Dorian McGavern, senior Investigator in NINDS's viral immunology and intravital imaging section, shares his work with Hassan.



At left at the inn, Hassan greets (from l) Cathy Morales, the inn's chief program and services officer; Amanda Harrison of Riverview, Fla., and her daughter Macy, 5, an NINDS patient; and Collins. In photo at right, Hassan talks with a patient in NCI's Pediatric Oncology Branch.

