

## THE SKINNY ON HIGH-FAT DIET Does Keto Boost Sports Performance?

BY CARLA GARNETT

An athlete's ultimate goal is to reach peak performance during competition. To boost the odds of success, elite contenders try to optimize each part of the formula—conditioning, practice and diet.

Sports prep used to include carb-loading—eating, for example, a big bowl of pasta to maximize energy in the form of glycogen stored in the muscles. Then along came reports of possible advantages for athletes eating a low-carb high-fat (LCHF), or ketogenic, diet. Keto trains the body to convert fat to energy.

Could carb-unloading help athletes reach the peak they're pursuing?

To explore the state of the science on the topic, Dr. Louise Burke, chief of nutrition strategy at the Australian Institute of Sport and director since 2005 of the International Olympic Committee Diploma in Sports Nutrition, presented "Effects of a Ketogenic Diet on Exercise, Metabolism and Endurance Performance" at a recent seminar sponsored by NIDDK.

"My whole life is [centered] around helping athletes go faster, higher and stronger," she said. "Looking at different diets and their ability to provide fuel for their event is part of my practice. And although the story around eating to provide high carbohydrate availability for the muscle is clear in showing performance benefits for endurance sport, it is still tantalizing to look at the body's high larger fat reserves as untapped gold."



Dr. Louise Burke discusses best eating plans for athletes at a recent NIDDK seminar.

SEE **KETO DIET**, PAGE 4

## Good Science Accounts for Bias, Prejudice, Saini Says

BY ERIC BOCK

The best science challenges lazy thinking and looks beyond stereotypes, said Angela Saini, a British science journalist and broadcaster, in a recent lecture on "Gender, Race and Power in Science," at Lister Hill Auditorium, Bldg. 38A.



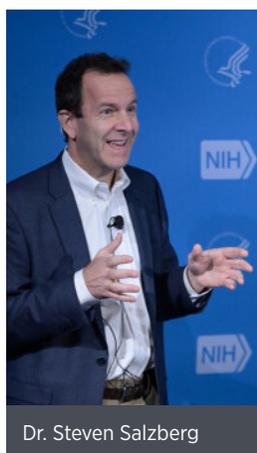
Angela Saini

"When we bring our stereotypes and our assumptions into our work and look at the scientific evidence through those lenses, then we make mistakes," she warned. "When we see

SEE **SAINI**, PAGE 6

## TUXEDO JUNCTION Salzberg Uses Latest Tech Tools to Find, Analyze Novel Genes

BY DANA TALESNIK



Dr. Steven Salzberg

The global scientific community rejoiced when the first human genome was sequenced in the early 2000s. If we could find every gene in the human body and eventually identify what each one did, we could decode the many mysteries of disease. Now, as we continue to build upon that groundbreaking international research collaboration, is it

SEE **SALZBERG**, PAGE 8



Their hearts will go on? CFC karaoke draws out the love and hidden talents. See p. 12.

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**Donate Use-or-Lose Hours to NIH Leave Bank by Jan. 4, 2020**

In 2018, NIH employees lost an estimated \$4 million in annual leave. Don't lose yours. The Leave Bank offers you the opportunity to put that leave to use by donating your Use-or-Lose leave to the bank by Jan. 4, 2020, via ITAS. When you donate to the Leave Bank, you help a co-worker in need, like this recipient:

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To donate, log in at <https://itas.nih.gov>. On the tool bar, select "Donate to Leave Bank." Enter the type of leave (annual or restored annual), then the number of hours you wish to donate, and select "OK."

More information on the program can be found at <http://hr.nih.gov/leavebank>. For questions, call (301) 443-8393 or email [LeaveBank@od.nih.gov](mailto:LeaveBank@od.nih.gov).

**Lecture on Origins of INSERM, Dec. 17**

The Office of NIH History and Museum will host a special lecture about the history of INSERM, the French biomedical research funding agency similar to NIH. The speaker is Pascal Griset, professor of modern history organization at Sorbonne Université and Comité pour l'histoire de l'INSERM. His talk is titled "Biomedical Research in France and Its Institutionalization, 1940-1970: At the origins of INSERM."

It will be held on Tuesday, Dec. 17 from 4 to 5 p.m. in Bldg. 10, Rm. 2C116, followed by a reception.

Griset is the co-author of a book on INSERM history, *Au coeur du vivant: 50 ans de l'INSERM (At the Heart of Life: 50 Years of INSERM)*. He will discuss the pre-origins of INSERM in the creation of the Centre National de la Recherche Scientifique in 1939 and then the creation of INSERM itself in 1964. Griset will describe the sociopolitical construction of French research funding and the role played by the United States and, in particular, the Rockefeller Foundation.

Beyond an institutional history, Griset will highlight how the French scientific community has become part of the more global dynamics of the construction of biomedical sciences.



At the award ceremony were (from l) Dr. Geraldina Dominguez, director, AIDS Malignancy Program, NCI; Dr. Robert Yarchoan, director, Office of HIV and AIDS Malignancy, NCI; Dr. Patrick Moore; then-NCI acting director Dr. Douglas Lowy; and Dr. Yuan Chang.

**NCI Marks 25th Anniversary of KSHV Discovery**

The National Cancer Institute's Office of HIV and AIDS Malignancy recently hosted the 17th International Conference on Malignancies in HIV/AIDS. This year marks the 25th anniversary of the discovery of the Kaposi sarcoma-associated herpesvirus (KSHV) by the husband-and-wife team of Drs. Patrick Moore and Yuan Chang, both of whom are professors at the University of Pittsburgh's Hillman Cancer Center.

At the meeting, Dr. Douglas Lowy, then acting director of NCI, presented them with the NCI Director's Career Achievement Award, highlighting the scientific advances made by these two researchers. In particular, the award was given for their discovery of 2 of the 8 known oncogenic viruses (KSHV and Merkel cell polyomavirus), the biology of these viruses and the means by which they cause cancers.

It had been recognized for some time that Kaposi sarcoma (KS) occurs more frequently in some AIDS risk groups than others, suggesting that a second transmissible agent causes KS. The identity of this agent remained elusive until 1994, when Chang and Moore co-discovered KSHV, also called human herpesvirus 8, and showed that it is the cause of KS and certain other cancers. This finding has since led to a goldmine of research, understanding and clinical advances.



**'Future Star' Leadership Program Begins**

The Federal Asian Pacific American Council recently launched a new Future Star Program (FSP) to offer individual mentoring and professional development for high school students. FSP is open to all and aims to help the next generation to identify federal, state and local government youth internship opportunities, training or volunteer opportunities, improve youngsters' communication/interview skills and develop leadership experience. Involved in the effort are (front, from l) Paul Li, Jassé Dickens, Lily Qi, Dr. Richard Nakamura and Dar-Ning Kung. At rear are (from l) Ye Yan, Huaying Zhao, Xinzhi Zhang, Kelvin Xu, Chao Wu, Daniel T. Lee, Rebecca Wong, Nancy Tian and Perry Chan.

## NCI's Kochenderfer Wins Trailblazer Prize

BY DANA TALESNIK

Advances in cancer immunotherapy—a treatment that harnesses the body's immune system to destroy malignancies—are showing great potential against certain types of cancer. NIH recently celebrated one of its own, Dr. James Kochenderfer, an investigator in NCI's Surgery Branch, for his pioneering work developing T-cell transfer therapies for blood cancers.

In October, the Foundation for the NIH (FNIH) awarded Kochenderfer the second annual Trailblazer Prize for Clinician-Scientists, recognizing his outstanding research contributions that have led to innovations in patient care.

Kochenderfer's research focuses on treating leukemia, lymphoma and multiple myeloma, the three major types of blood cancer, all of which usually are fatal. To date, his team has had the greatest success treating lymphoma.

"With lymphoma, we have patients who would have a life expectancy of 6 months or less who have been in remission now for more than 5 years," said Kochenderfer. "It's exciting because it's a totally new type of treatment, using the patient's own T cells to fight and eliminate cancer."

T cells are a type of white blood cell involved in the body's immune response. In CAR-T cell therapy, some of the patient's T cells are removed and genetically engineered to proliferate and produce new surface proteins called chimeric antigen receptors (CARs). The modified immune cells are then infused back into the body where they identify and attack cancer cells. The novel treatment has proven effective for some hematologic malignancies.

"My whole career has been focused on CAR-T cell therapies," said Kochenderfer, who arrived at NCI in 2002. He was the first to demonstrate the effectiveness of anti-CD19 CAR-T cells in humans, leading to the first FDA-approved CAR-T cell therapy for lymphoma.

In 2009, a patient arrived at NIH with a high disease burden of lymphoma. After treatment, the lymphoma shrank.

"He was the first patient ever to show that anti-CD19 CAR-T cells were actually



Dr. James Kochenderfer (r) accepts the 2019 Trailblazer Award from Dr. John Gallin, who along with his wife Dr. Elaine Gallin, funds the annual award.

effective in humans," said Kochenderfer.

The patient had a recurrence the following year. After another round of CAR-T cell treatment, the patient remains in complete remission nearly 10 years later.

CAR-T cells are very specific and require a good target, Kochenderfer explained. Currently, the treatment is effective only for blood cancers, though other NCI investigators are working to find viable targets for solid tumors.

For patients with chemotherapy-resistant diffuse B-cell lymphoma, the most aggressive type of lymphoma, the protein CD19 from the cell's surface is the target.

"It's not a guess as to what might happen," said Kochenderfer. "We specifically put a gene into the T cell and it binds to a specific target on the malignancy."

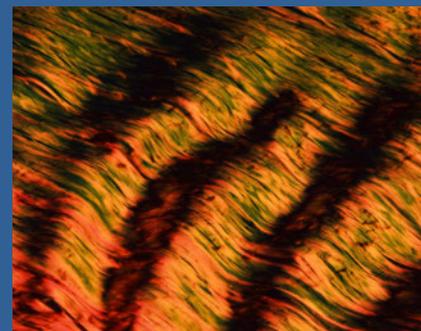
Kochenderfer recently began going after another blood cancer target. He invented and recently led the first clinical trials to test anti-B-cell maturation antigen (BCMA) CAR for the treatment of multiple myeloma. His team has had some success, he said, though so far the remissions have not lasted as long as they do for his lymphoma patients.

The Trailblazer Prize, made possible by a donation from Drs. John and Elaine Gallin, honors early-career clinician-scientists and bestows a \$10,000 honorarium for their critical role in biomedical research and

clinical care. FNIH's Charles A. Sanders Legacy Fund also awarded Kochenderfer and three prize finalists—extramural investigators working on drug delivery, neurology and genomics—\$5,000 in support of their laboratories.

Kochenderfer and his lab continue to design new CARs, hone them in preclinical experiments and test the most promising ones in phase 1 clinical trials. He currently has a lymphoma protocol as well as two clinical trials for multiple myeloma, targeting different antigens.

"It's a great honor to be recognized for all the hard work that's gone into [developing these treatments]," said Kochenderfer, "and it's greatly appreciated that FNIH supports translational research." 



ON THE COVER: *The crimp pattern (waviness) of collagen fibers in a medial collateral ligament, which is the ligament on the inner part of the knee.*

IMAGE: DR. RAY VANDERBY, UNIV. OF WISCONSIN

### The NIH Record

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## Keto Diet

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First, Burke defined terms. She explained that at the lay level, endurance sports are “typified as submaximal events that involve exercise intensities of approximately 60 percent to 80 percent of the athlete’s maximum volume of oxygen inhaled and absorbed by the body—their ‘VO<sub>2max</sub>’”

However, she continued, this fails to capture the concept that high-performance athletes strive to compete at the highest possible proportion of their maximal aerobic energy production over the duration of their events—lasting at least 30 minutes of sustained or intermittent periods, and even more so at critical times.

“It’s about being able to produce energy on demand as economically as possible, according to the demands of the sport,” Burke said. “This requires both the muscle substrate—fuel—and the oxygen to support its oxidation.”

A distance runner herself, Burke visited NIH just days before she was set to compete in the New York City Marathon. Addressing the hype surrounding keto, fitness and conditioning, she traced the popularity of the diet.

Burke recalled being a first-year dietitian in 1983 when physician-scientist Dr. Stephen Phinney and colleagues wrote about “this incredibly innovative idea that we could train the muscle to be better able to use fat as an energy source.”

Phinney’s study compared performance results from five subjects who followed first a traditional carb-loading eating plan and then an LCHF diet. Both regimens produced similar performance if you considered the group average. However, Burke pointed out, the mean response to the LCHF diet was largely explained by the response of one cyclist who performed significantly better on the keto plan.

“The individual variability in response to the ketogenic diet is really quite profound,” she said, reviewing highlights of the original protocol.

“Now that I look back at the study with 35 years of experience with elite athletes,” Burke continued, “I also realize that if there was any study set up to show the benefits of keto, it would have been that study. It had well-trained cyclists who had time for keto adaptation to occur and the residual fatigue



Burke discusses sports-training diets at NIH lecture.

PHOTOS: MARLEEN VAN DEN NESTE

to abate. It allowed them to exercise at very moderate intensities at steady state—no need to power up a hill, break away from the pack or sprint to the line. And the carbohydrate trial was done without allowing the riders to gain the benefits of a pre-race carbohydrate-rich meal or further carb intake during the exercise protocol. It wasn’t a totally fair comparison between dietary approaches—and even then, the LCHF diet didn’t achieve a benefit. It just didn’t impair performance, on average.”

For many, that one outlier in that one study was plenty. Over the next few decades, articles and books touting keto spread rampantly across the sports world. And despite there being no additional scientific studies reproducing those initial findings, “anecdotal”—personal testimony by elite athletes—professing the power of keto grew.

Burke and colleagues wanted hard evidence. They have been working for the past 4 years to understand the effects of LCHF on athletic performance.

At NIH in a packed FAES classroom, she discussed results from Project Supernova, a unique study concept that teamed clinical research with an elite athlete training camp atmosphere in which nutrition and exercise would be carefully controlled, monitored and overseen by sports nutritionists.

Supernova has tested dozens of elite athletes—world-class speed walkers—in separate groups.

One group followed a high-carb availability eating plan that matched fuel costs to carbohydrates going in.

“Every session of exercise they did was surrounded by carbs—before, during and after,” Burke explained. “That’s not what the

guidelines of sports nutrition are any more, by the way. We now recommend a periodized-carbohydrate approach, matching the goal of the session to the nutritional strategy. So we also included a diet providing that type of support—overall, it contained the same amount of carbs as the high-carb availability approach. But it manipulated how it was spread over the week, so that some training sessions enjoyed full carb support while others included the additional training stimulus of low-glycogen exercise.”

Another group of speed walkers followed a keto diet. Supernova allocated the participants to these groups according to their beliefs about what would work best for them.

“It’s really important if you’re doing a performance study that your athletes believe in what they’re doing,” Burke said.

“So, what happens when you put world-class athletes at the beginning of a season together for 3½ weeks?” she asked. “Well, they all improved their aerobic capacity... all improved by the same amount. But then we looked at performance. Despite all improving fitness, [only] the carbohydrate-supported group improved their race times; we didn’t see any [speed] improvement in the keto group. There was about a 7 percent to 8 percent difference in performance between the carb-supported groups and the keto group.”

“Something was happening with metabolism to change the economy of the oxygen utilization,” Burke noted. “There’s something about the keto diet that’s requiring more oxygen utilization to produce the same power or speed. Of course, we can explain that by examining the pathways of carbohydrate and fat oxidation. Although fat oxidation provides more energy per gram of substrate, it also requires more oxygen to produce the same amount of energy. That becomes important when an athlete is trying to work at very high proportions of the maximal aerobic capacity, because the limiting factor shifts to the oxygen supply rather than the available substrate.”

Burke and colleagues found that although elite athletes adapt quickly to converting stored fat to energy, this advantage becomes a liability when the event requires high-intensity aerobic performance.

“You absolutely can use fat as fuel,” she said. “You just need more oxygen to do it, and you may not be able to deliver that to the mitochondria to keep pace. That is why having a supply of carbohydrate, and muscle pathways primed to use it, provides ‘the top gear’ that wins so many endurance events.”

In subsequent versions of Supernova, researchers explored keto from other angles, including whether the diet improves oral microbiome health.

“It may cause an unexpected problem of knocking out the bacteria in our mouths that help us to convert the nitrate in vegetables to nitrate to feed our nitric oxide production,” Burke said.

Supernova also looked at whether LCHF could be used periodically, in combination with carb-loading diet models, to get the advantages of both eating plans. Turns out, “keto benefits interfere with our ability to use carbohydrate effectively, even when we have the stores,” she noted.

The bottom line is that the keto diet seems suited to a small subset of endurance sports—ultra-endurance events undertaken at modest intensities, especially where the athlete is unable or unwilling to continue to take in extra carbohydrate supplies.

In this day and age of social media, where a fervent post by even one LCHF advocate with thousands of followers can seem to outweigh scientific evidence from several clinical trials, Burke has been painted by some as anti-keto. Nothing could be further from the truth, she said.

She and the Olympic-caliber athletes and trainers she works with want whichever nutrition plan will provide optimum performance at the precise times that competitors need it. And everyone ought to want proof of what works, not hearsay.

“There is room in sport for keto,” Burke concluded. But it shouldn’t be seen as a miracle diet for all athletes. “Furthermore, even with a carb-supported approach for the majority of endurance events, athletes need a targeted and personalized approach to determine the best nutrition strategy for training and racing.

“All diets exist in both ‘good’ and ‘bad’ forms,” she concluded, pointing out that consuming “fat bombs” or “dirty keto”—overeating or otherwise abusing the tenets of LCHF—is not healthy and obviously will not boost any athlete’s performance. “I say, whatever diet you’re on, keep it real.” **R**

## KUDOS

## AAAS Honors Five from NIH

Five NIH scientists have been named fellows of the American Association for the Advancement of Science. Election is an honor bestowed upon AAAS members by their peers. This year, 443 members have been awarded this honor by AAAS because of their scientifically or socially distinguished efforts to advance science or its applications.

The honorees, and their sections, are:



Dr. Francesco DeMayo



Dr. Kelly Ten Hagen



Dr. Piotr Grodzinski



Dr. R. Douglas Fields



Dr. John Beutler

From the section on biological sciences—Dr. Francesco DeMayo, senior investigator and chief of the Reproductive and Developmental Biology Laboratory, NIEHS.

From the section on dentistry and oral health sciences—Dr. Kelly Ten Hagen, senior investigator and chief, developmental glycobiology section, NIDCR.

From the section on engineering—Dr. Piotr Grodzinski, chief, Nanodelivery Systems and Devices Branch, Cancer Imaging Program, NCI.

From the section on neuroscience—Dr. R. Douglas Fields, chief of the section on nervous system development and plasticity, NICHD.

From the section on pharmaceutical sciences—Dr. John

Beutler, head of the chemical diversity and development section of the Molecular Targets Program, NCI.

New fellows will be presented with an official certificate and a gold and blue (representing science and engineering, respectively) rosette pin on Feb. 15, 2020.

The tradition of AAAS fellows began in 1874, but AAAS was founded in 1848 and includes more than 250 affiliated societies and academies of science. It is the world’s largest general scientific society and publisher of the journal *Science*, as well as *Science Translational Medicine*; *Science Signaling*; a digital, open-access journal, *Science Advances*; *Science Immunology*; and *Science Robotics*.



"It wasn't biology holding women back. It was men, institutions, establishments and ideologies holding women back," said Saini.

PHOTOS: MARLEEN VAN DEN NESTE

## Saini

CONTINUED FROM PAGE 1

everything through those assumptions, we start to assume the world is the way we've always imagined."

Bias, discrimination and prejudice have been present since the birth of modern science during the Enlightenment, the 18th century period heralded for rationality. Influential scientists such as naturalist Charles Darwin assumed that biological differences between men and women explained gender gaps.

"Darwin ignored the possibility that society looked the way it did because of historic oppression and the denial of opportunities to women," said Saini.

Girls didn't have the same educational opportunities as boys, she added. The few who received an education couldn't go to college. Until the middle of the 20th century, they were prevented from joining scientific academies. In 1911, for example, the French Academy of Sciences rejected the membership application of Nobel Prize winner Marie Curie.

"It wasn't biology holding women back," she said. "It was men, institutions, establishments and ideologies holding women back."

Men, she said, have also used evolution to suggest male dominance is "hard-wired into our species." Chimpanzees, for example, are one of humans' closest relatives. Male chimps are violent and dominant over females.

"We forget this isn't the full story," cautioned Saini.

Another species closely related to humans is the pygmy chimpanzee. They weren't studied because it was thought they behaved like their bigger relatives. Research has shown pygmy chimpanzees are female-dominated.

Scientific racism also emerged during the Enlightenment. Even Darwin—an

• • •  
*"Darwin ignored the possibility that society looked the way it did because of historic oppression and the denial of opportunities to women."*

-ANGELA SAINI

abolitionist—believed "there were substantial differences between groups of people, and some were more evolved than others." Saini said science was used to justify some of the worst atrocities over the past few centuries, including genocide, slavery, colonialism and apartheid.

After World War II, the United Nations Educational, Scientific and Cultural Organization, or UNESCO for short, released statements saying "racism is wrong, it has no place in science, the idea of race is a fallacy. It has no biological basis, it only has a social basis," Saini noted.

Things didn't change overnight. Today, well-intentioned scientists still use the language of the past. Saini interviewed one respected researcher who called mixed-race people "hybrids," an inappropriate term that isn't even scientifically accurate.

It is now understood that race is a social construct that has no basis in biology. Proximity, Saini said, explains the genetic commonality between people. A child, for example, most closely resembles his or her parents. There's a weaker genetic connection between that same child and his or her cousins. That commonality gets weaker as a geographical area gets larger. At the continental level, statistical commonalities are very vague.

Routinely, Saini sees scientists who look for differences between socioeconomic groups that are defined using race. In the United States, for instance, more African Americans die from diseases resulting from high blood pressure. If hypertension was rooted in skin color, she'd expect to see the highest rates of hypertension to be found in African countries.

Yet that's not the case. Germany and Finland—two countries whose diets are high in salty meat and cheese—had the highest hypertension rates when age-adjusted.

"If you're poor anywhere in the world, but particularly in the U.S., your diet is likely to

• • •  
contain more processed foods, so it's more likely to have fattier or saltier foods," she said.

Even though there is a clear environmental explanation, scientists routinely look for a genetic cause. She added, "What is [actually] a socioeconomic gap is treated as a racial gap."

She challenged scientists to keep pushing beyond bias and stereotypes.

"If we're not, then we're feeding the very prejudice and lazy thinking the public at large wants science to combat," Saini concluded. **R**

## Conference Focuses on HIV Care and Treatment

The National Institute of Nursing Research recently hosted “Strengthening the Impact of Community Health Workers on HIV Care and Viral Suppression in the U.S.,” a conference in support of the HHS initiative to reduce new HIV infections in the United States by 75 percent in 5 years and by 90 percent by 2030 as proposed in *Ending the HIV Epidemic: A Plan for America*.

The 2-day conference launched an NIH Office of AIDS Research-funded initiative to establish evidence for engaging community health workers to close the gap between antiretroviral therapy prescription and viral suppression, a crucial step in preventing the transmission of HIV, improving lives and ending the HIV epidemic. Community health workers can be a bridge between communities and the health care system and are associated with improved health outcomes, enhanced disease management and reductions in health care delivery costs.

The trans-NIH event brought together representatives from CDC, HRSA and OASH, researchers, health professionals, nurse scientists and community health workers to identify research gaps, share best practices and learn from each other and explore collaborations.

Keynote addresses were delivered by Rear Admiral Sylvia Trent-Adams, principal deputy assistant secretary of health; Dr. Joia Mukherjee of Harvard Medical School and chief medical officer of Partners in Health; and Dr. Michael Mugavero, professor of medicine and senior scientist, Center for AIDS Research, University of Alabama, Birmingham.

Conference cosponsors included the NIH Office of AIDS Research, NIDA, NIMH, NIMHD and the Tribal Health Research Office.—**Adrienne Burroughs**



Rear Admiral Sylvia Trent-Adams discusses the role of community health workers in HIV care and research.

PHOTO: LESLIE KOSSOFF



## ORWH Advisory Committee Meets

Dr. Janine Clayton (above, l), director of the Office of Research on Women’s Health, welcomes NIBIB director Dr. Bruce Tromberg to the 49th meeting of the advisory committee on research on women’s health. He discussed “Engineering and the Future of Women’s Health,” including advances in imaging to detect breast cancer. At right, Elizabeth Spencer, ORWH deputy director, addresses the Oct. 23 meeting, which included presentations on maternal morbidity and mortality, a legislative update and an overview of ORWH’s strategic plan. More information is available at <https://orwh.od.nih.gov/about/advisory-committees/advisory-committee-research-womens-health>.



## Canadian Counterparts Visit NIH

NIH leaders and scientific staff met with a delegation of their counterparts (above, l) from the Canadian Institutes of Health Research (CIHR) on Nov. 22 for a day-long symposium organized by the Fogarty International Center. The event, opened by NIH director Dr. Francis Collins, included two cross-cutting plenary panels and 18 technical break-out groups. The symposium was intended to explore new ways to collaborate on building the research workforce, advancing game-changing emerging technologies and discovering treatments and cures for diseases. At right, as a sign of goodwill, CIHR president Dr. Michael Strong (r) presented Fogarty director Dr. Roger Glass with maple syrup cookies from Canada.

PHOTOS: CHIA-CHI CHARLIE CHANG



possible there are more genes we haven't yet discovered?

"We in the scientific community have been trying to figure out for a very long time how many genes the human genome has," said Dr. Steven Salzberg, Bloomberg distinguished professor and director, Center for Computational Biology at Johns Hopkins University. He spoke at a recent seminar in Lipsett Amphitheater.

While we still don't know our exact number of genes—intervals on the genome that get transcribed and provide function to an organism—researchers wildly overestimated that we had millions of them when the genetic code was first cracked in 1964. Ongoing research has shrunk that estimate to about 20,000 protein-coding genes, and that number continues to evolve.

Even the two major gene databases—NCBI's RefSeq and the NHGRI-European Molecular Biology Laboratory consortium GENCODE—disagree on the total number of human genes. Salzberg, whose lab develops computational tools to analyze DNA and RNA sequences, wanted to help settle this discrepancy. Three years ago, his lab embarked on a project to rebuild the human genome catalog.

"RNA sequencing data has really transformed our ability to figure out what genes are present in the genome," and which are functional, Salzberg said.

As he began deep sequencing tissues, his lab got overloaded with massive reads in the many millions per sample. It would take nearly a day to map and assemble the transcripts of each expressed gene.

"You don't do just one experiment when doing RNA sequencing," he said. "Typically, you do many experiments and compare the different conditions to one another to see what genes are differentially expressed between healthy and diseased tissues."

The need for speed led Salzberg's team to update their "Tuxedo Suite" of computational tools, software that includes Bowtie and TopHat to do RNA sequence alignments and Cufflinks to assemble the RNA reads and quantify the levels of gene expression. Their newer HISAT2 is as accurate and 50 times faster than TopHat, he said. And the new,



Salzberg hopes to help rectify the lack of diversity from the first human genome reference consortium.

PHOTOS: MARLEEN VAN DEN NESTE

faster StringTie, which replaced Cufflinks, enabled Salzberg to build a genome catalog.

Last year, Salzberg's group published a catalog called CHES (Comprehensive Human Expressed SequenceS). They started with a massive RNA sequence dataset of 900 billion reads, he said, and found 30 million transcript variants across 700,000 locations on the genome.

"Our strategy was to run everything through this new Tuxedo pipeline, align everything with HISAT2 and assemble it with StringTie," he said. "Then we compared all the assemblies to each other."

Most of the 30 million transcript variants were not genes, said Salzberg, but transcription noise, that of extraneous RNAs. After comparing their data to what's in RefSeq and GENCODE, they filtered out all but 1 percent of found transcripts.

"In case you're disturbed by this, thinking: 'It can't be that 99 percent of transcription is a waste,' you're correct. It's not a waste," said Salzberg. In a subsequent calculation, they found that all the transcripts they discarded collectively added up to one-third noise "and two-thirds were parts of the 43,000 that we think are real genes."

The CHES catalog includes 224 new protein-coding genes and 2,600 novel non-coding RNAs. Salzberg also found more than 100,000 novel transcripts from known protein-coding genes.

"Something's happening," he said.

"Something's getting transcribed, whether or not it gets turned into a protein."

Meanwhile, Salzberg's lab is also involved in a project that may have uncovered previously unfound genetic base pairs. We've known for decades that every person has 3 billion base pairs of genetic letters, representing the complete set of DNA in the human body. Is it possible we each might have millions more?

Working with CAAPA, the Consortium on Asthma among African Ancestry Populations in the Americas, Salzberg's lab sequenced the genomes of 910 Africans from across the Americas and the Caribbean, looking for genetic markers for asthma and allergy. For 2 years, they worked to assemble genetic pieces not found in GRCh38, the first fully sequenced genome from the NIH-led effort.

"We know from genetics that Africans are a pretty diverse population, more diverse than Europeans," said Salzberg, "and we thought we might find a lot of interesting chunks of DNA that are just missing from GRCh38."

With this project, Salzberg hopes to help rectify the lack of diversity from that first human genome reference consortium. When the draft of the first sequenced human genome was published in 2001, the original plan was to compile samples from dozens of people. But due to time constraints, 65 percent was based on one person, a man from upstate New York, and the rest was a mosaic from other people sampled.

For the CAAPA project, Salzberg's team took all the genetic pieces that didn't map to GRCh38, assembled them and, after removing redundancies, wound up with 296 mega-bases and genes not annotated in GRCh38, some of which turned up in hundreds of the 910 people.

"This is the African Pan Genome," Salzberg said, "the regular genome plus at least another 300 million bases."

The sequence Salzberg is calling the Pan Genome has many insertions that might also be present in the general population.

"They're probably not African-specific," he said. "They are just human sequences that are missing from GRCh38, again pointing to the need for more reference genomes than we have right now." 



IMAGE: MONKEYBUSINESSIMAGES/ISTOCK

## High Amounts of Screen Time Begin as Early as Infancy, Study Suggests

Children's average daily time spent watching television or using a computer or mobile device increased from 53 minutes at age 12 months to more than 150 minutes at 3 years, according to an analysis by researchers at NIH, the University at Albany and New York University Langone Medical Center.

By age 8, children were more likely to log the highest amount of screen time if they had been in home-based childcare or were born to first-time mothers. The study appears in *JAMA Pediatrics*.

"Our results indicate that screen habits begin early," said Dr. Edwina Yeung, the study's senior author and an investigator in NICHD's Epidemiology Branch. "This finding suggests that interventions to reduce screen time could have a better chance of success if introduced early."

The American Academy of Pediatrics recommends avoiding digital media exposure for children under 18 months of age, introducing children 18 to 24 months of age to screen media slowly and limiting screen time to an hour a day for children from 2 to 5 years of age.

In the current study, researchers found that 87 percent of the children had screen time exceeding these recommendations. However, while screen time increased throughout toddlerhood, by age 7 and 8, screen time fell to under 1.5 hours per day. The researchers believe this decrease relates to time consumed by school-related activities.

## Eastern Equine Encephalitis Virus Poses Emergent Threat

Although eastern equine encephalitis (EEE), a mosquito-borne illness, has existed for centuries, 2019 has been a particularly deadly year for

the disease in the United States. As of Nov. 12, 36 confirmed cases of EEE had been reported by 8 states; 13 of these cases were fatal.

In a new commentary in *The New England Journal of Medicine*, officials from NIAID describe the eastern equine encephalitis virus (EEEV) that causes EEE, current research efforts to address EEE and the need for a national strategy to address the growing threat of EEEV and other emerging and re-emerging viruses spread by mosquitoes and ticks (known as arboviruses).

There were 12 documented U.S.-based EEE epidemics between 1831 and 1959. The virus is spread between *Culiseta melanura* mosquitoes and various tree-perching birds found in forested wetlands. Occasionally, other mosquito species transmit the virus to people and other mammals.

In people, EEEV takes roughly 3 to 10 days to cause symptoms. The virus initially causes fever, malaise, intense headache, muscle aches, nausea and vomiting; specific diagnostic



IMAGE: HENRIK\_L/ISTOCK

testing may not reveal anything as EEEV is difficult to isolate from clinical samples and testing for EEEV antibodies may be negative.

Neurologic signs of EEE, which may appear within 5 days of infection, initially are nonspecific but rapidly progress. Most people (96 percent) infected with EEEV do not develop symptoms; however, of those who do, one-third or more die, and the others frequently suffer permanent and severe neurologic damage.

Several EEE vaccine candidates are in development but may have trouble reaching advanced development and licensure, according to the authors.

## Side Effects Mild, Brief with Single Dose of Ketamine

One of the most exciting recent breakthroughs from research funded by NIMH is the development of a fast-acting medication for treatment-resistant depression based on ketamine. This treatment is bringing new



IMAGE: STEVANOVICIGOR/ISTOCK

hope to people and families affected by major depression.

NIH researchers found that a single, low-dose ketamine infusion was relatively free of side effects for patients with treatment-resistant depression. Dr. Elia Acevedo-Diaz, Dr. Carlos Zarate and colleagues at NIMH report their findings in the *Journal of Affective Disorders*.

Studies have shown that a single, subanesthetic-dose (a lower dose than would cause anesthesia) ketamine infusion can often rapidly relieve depressive symptoms within hours in people who have not responded to conventional antidepressants, which typically take weeks or months to work. However, widespread off-label use of intravenous subanesthetic-dose ketamine for treatment-resistant depression has raised concerns about side effects, especially given its history as a drug of abuse.

"The most common short-term side effect was feeling strange or loopy," said Acevedo-Diaz. "Most side effects peaked within an hour of ketamine administration and were gone within 2 hours. We did not see any serious, drug-related adverse events or increased ketamine cravings with a single administration."

To overcome the limitations associated with side effects and intravenous delivery, ongoing research efforts seek to develop a more practical rapid-acting antidepressant that works in the brain similarly to ketamine.

## Fond Farewells for NIEHS's Birnbaum

BY KELLY LENOX

Family, friends and colleagues packed the room Oct. 3 to celebrate the career and leadership of Dr. Linda Birnbaum as she retired after 40 years as a federal scientist, including 10 years as director of NIEHS and the National Toxicology Program (NTP).

The celebration followed one in Bethesda on Sept. 12, hosted by NIH director Dr. Francis Collins. Although he was not able to attend the North Carolina event in person, a group of musicians from the institute performed “Linda B” (to the tune of “Lemon Tree,” made popular by Peter, Paul and Mary, among others) by Collins.



On hand at the retirement celebration were (from l) acting NIEHS director Dr. Rick Woychik, acting chief of staff Dr. Richard Kwok, scientific director Dr. Darryl Zeldin, Dr. Linda Birnbaum, associate NTP director Dr. Brian Berridge, acting deputy director Dr. Gwen Collman, NIEHS Executive Officer Chris Long and Birnbaum's chief of staff Dr. Mark Miller.

PHOTO: STEVE MCCAWE

drew not only from across her institute, but also from across NIH. Such efforts included developing the GuLF Study and the NIH Disaster Research Response program, which grew out of the oil spill experience; responding to West Virginia's Elk River chemical

for public health and support of clinical research. Speakers voiced many wishes for a great retirement.

“I have gotten so many beautiful emails, cards and notes,” said Birnbaum. “When you've had a job that you absolutely love, you really don't need any thanks.”

Woychik announced that the NIH board of scientific directors voted unanimously to name Birnbaum an NIH scientist emeritus. She will serve as lead researcher of the NTP Laboratory of Toxicokinetics and Toxicology.

## Kramer To Direct CSR Communications Office

Dr. Kristin Kramer has been named director of the Center for Scientific Review's newly established Office of Communications and Outreach.

She previously served as CSR's knowledge management coordinator, a position that involved communications primarily related to designing and managing web content.

In that capacity, she led the redesign of CSR's website based on a broad range of stakeholder input. Kramer also served as a scientific review officer within CSR's emerging technologies and training in neurosciences integrated review group and within the brain disorders and clinical neuroscience IRG.

Since June 2019, she has been on a full-time detail in the CSR Office of the Director, where she launched CSR's new social media presence. In addition, she has been overseeing other new initiatives such as the development of a web interface to allow scientific societies and NIH program staff to suggest potential reviewers and the revitalization of CSR's Early-Career Reviewer Program.

In her new post, Kramer will lead efforts to develop and implement a comprehensive communication and outreach strategy that



Dr. Kristin Kramer

“She energizes and inspires us to seek that passion that brought us to science to begin with.”

-NIH PRINCIPAL DEPUTY DIRECTOR DR. LAWRENCE TABAK

NIH principal deputy director Dr. Lawrence Tabak joined the celebration, where he described Birnbaum as prolific, creative, flexible, a good mentor and tenacious.

“She energizes and inspires us to seek that passion that brought us to science to begin with,” he said. Tabak shared figures on publications, citations and other data that illustrated the importance of Birnbaum's research.

The presence of family members brought her life outside the institute to the forefront. Birnbaum's sister Sue Silber described the camaraderie and strong connections among members of their extended family. She noted that Birnbaum is mother, grandmother, wife, sister, aunt and great-aunt. “She has quite miraculously balanced these roles with that of institute director,” Silber noted.

Tabak spoke of Birnbaum's creativity in leading important projects in ways that

spill; and opening the NIEHS clinical research unit in North Carolina.

Acting NIEHS director Dr. Rick Woychik highlighted achievements such as diversifying the ranks of tenure-track researchers and keeping the institute at the forefront of emerging contaminant research so that it is a trusted source of information. He also noted Birnbaum's support for bringing cutting-edge technologies such as cryo-EM and predictive toxicology to the institute.

Veronica Robinson, from NTP and the local chapter of Blacks in Government, spoke of Birnbaum's impact around the halls of the institute. “I have watched the way you do what you do, and you have been an inspiration,” she said.

In a montage of video clips made by NIEHS staff, the theme of inspiration was repeated, along with seeing Birnbaum as a role model through her leadership, passion

focuses on engagement with the broader external scientific community, scientific societies, NIH institute/center programs and other agencies. Through communications and targeted outreach, CSR aims to enhance the transparency of the peer review process and capitalize on the diversity that comes with a large audience to improve communication strategies as well as the peer review process.

Kramer earned a Ph.D. at the University of Minnesota, Twin Cities, and was an assistant professor at the University of Memphis, where she established a research program in behavioral neuroscience prior to joining CSR.

## Tabak Honored in England

On Oct. 16, NIH principal deputy director Dr. Lawrence Tabak was one of seven “honorary graduands” recognized at King’s College London’s honorary degree ceremony. He was cited for being “a world leading clinical academic in oral and dental research whose major research has been on the structure, biosynthesis and function of glycoproteins.”

The event was held on the college’s Strand Campus, along the River Thames in the heart of London.

## NIA Alumnus Warner Mourned

Dr. Huber Warner, a biochemist who led the National Institute on Aging’s Biology of Aging Program, died on Sept. 12 in St. Paul, Minn. He was 83.



Dr. Huber Warner

He joined NIA in 1984, managing the Molecular Biology Program while also serving as chief, Biochemistry and Metabolism Branch. In January 2000, he was named associate director of NIA’s Biology of Aging Program. Warner played a large part in expanding the scope and scale of aging research at NIA while helping to mentor a new generation of scientists. His research

interests included oxidative stress, molecular mechanisms of apoptosis, functional genomics and stem cells.

“Huber was not only a well-respected scientist and leader in our field, but also his gentle nature made him beloved by both the community and his colleagues,” said Dr. Felipe Sierra, director of NIA’s Division of Aging Biology (DAB).

Dr. Dick Sprott, Warner’s predecessor at DAB, said, “Dr. Warner served with diligence and great scientific acumen. While his insights were important for the biology of aging field, we will remember him for leadership and common sense. I, like many others, will always treasure his sound advice and friendship.”

NIA director Dr. Richard Hodes said, “The entire NIA family is saddened by the loss of Dr. Warner. He helped guide and grow the study of aging biology at the NIH and NIA with a steady hand and curious mind. He will be deeply missed.”

Warner was born in 1936 in Glendale, Ohio. He received a doctorate in biochemistry from the University of Michigan in 1962, and following postdoctoral work at M.I.T., he joined the faculty of the department of biochemistry at the University of Minnesota in 1964. He was a member of the American Society for Biochemistry and Molecular Biology and a fellow of the Gerontological Society of America.

After leaving NIA in 2004, he returned to the University of Minnesota, where he served as associate dean of research until his retirement in 2010. He spent his later years at the university’s independent living community and returned often with family to his beloved Cawaja Beach in Ontario, Canada.

Warner was known for his many athletic interests and as an enthusiastic volunteer coach for youth sports. He played hockey growing up and tennis in his later years and was a member of the NIH tennis and sailing clubs.

He is survived by sons Geoffrey and Peter; daughter-in-law Dawn; and 3 granddaughters: Chloe, Laurel and Alexandra.

Donations in his memory can be made to the Huber Warner Fellowship in Molecular Biology, University of Minnesota Foundation, 200 Oak Street, SE, Suite 500, Minneapolis, MN 55455-2010. 

## Patients with CLL Sought

Chronic lymphocytic leukemia (CLL) patients, team up in your fight against leukemia. NCI scientists are conducting a study using IL-15 in combination with obinutuzumab with hopes of discovering effective treatments. There is no cost for treatments and travel assistance is available within the U.S. Specialists at the Clinical Center Office of Patient Recruitment are standing by to help you: 1-866-444-2214 or [prpl@cc.nih.gov](mailto:prpl@cc.nih.gov). Refer to study 19-C-0024. Read more at <https://go.usa.gov/xmye4>.

## Menopause & Mood Study

A 7-week outpatient study is accepting post-menopausal women ages 45 to 65 who struggled with irritability, anxiety, sadness or depression during perimenopause and had symptoms that improved with the use of hormones. There is no cost to participate. Compensation is provided. To learn more about the study call (301) 496-9576 (TTY 1-866-411-1010) or visit <https://go.usa.gov/xPkKB>. Refer to study 18-M-0144.

## How Does Puberty Affect Brain Development?

Your 8-year-old healthy child is invited to participate in an NIH outpatient research study that examines how puberty affects brain development. Participation includes 1-3 day outpatient visits to the Clinical Center every 8-10 months until age 17, for a physical examination, body measurements, questionnaires, MRI scans, blood draws, urine collection and x-rays. Participants must not have any chronic medical or psychiatric illnesses, nor be on any long-term medication. Parents must agree to their child’s participation. Evaluations and research procedures are free of cost. Compensation is provided. Call for information and eligibility criteria: (301) 496-9576 (TTY 1-866-411-1010). For a detailed protocol description, visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and refer to study 11-M-0251.

## Study Needs Infants, Children

The Clinical Center seeks infants 3-12 months and young children 1-5 years of age who are developing typically. The study aims to learn more about the motor skill and brain development of young children who are at high risk for or diagnosed with cerebral palsy (CP) and autism spectrum disorder (ASD) compared to young children with typical development. The results of this study may assist with better methods for early diagnosis as well as improved treatment for children with CP and ASD. This is an outpatient visit and all minor participants require parents’ permission to participate. To learn more, contact the Clinical Center Office of Patient Recruitment at 1-800-411-1222 or [prpl@cc.nih.gov](mailto:prpl@cc.nih.gov). Refer to study 18-CC-0052. Read more at <https://go.usa.gov/xpBJD>.



At left, Team NIDA Notes, led by director Dr. Nora Volkow (c), performs “Baby Shark,” the anthem that propelled the Washington Nationals to a World Series title. At right, the Building Wonderfals, led by NIH director Dr. Francis Collins (l), sings “With a Little Help from My Friends.”

PHOTOS: CHIA-CHI CHARLIE CHANG

## ICs Sing for CFC at Karaoke Contest

It may not have been famed nightclub the Birchmere, but there was formidable talent and an enthusiastic crowd at NIH’s first-ever karaoke competition on Nov. 14. The event was this year’s Directors’ Challenge in support of the Combined Federal Campaign.

First up were the Building Wonderfals, led by NIH director Dr. Francis Collins, singing the Beatles’ “With a Little Help from My Friends.” Among other notable performances were NHLBI senior investigator Dr. Cynthia Dunbar singing “My Heart Will Go On” from the *Titanic* soundtrack, with NHLBI director Dr. Gary Gibbons re-enacting key scenes from the popular motion picture.



Celebrity judges listen to emcee John Burklow (r). They are (from l) NIH principal deputy director Dr. Lawrence Tabak, ORS Director Colleen McGowan and NIH deputy director for management Dr. Alfred Johnson.



**The Titanic captain spots an iceberg!** NHLBI Heartthrobs (a.k.a. NHLBI director Dr. Gary Gibbons and senior investigator Dr. Cynthia Dunbar) won the hearts of the audience and judges with their comic timing and karaoke performance.



CIT’s Tyrone Steele poses with his trophy for winning the 2019 CFC Directors’ Challenge.

CIT’s Tyrone Steele brought down the house singing Chris Stapleton’s “Tennessee Whiskey,” drawing perfect 10s from a panel of “celebrity judges” to clinch first place.

“Someone needs to give up his day job!” said Colleen McGowan, director of the Office of Research Services. She served as one of the judges, along with Dr. Lawrence Tabak, NIH principal deputy director, and Dr. Alfred Johnson, NIH deputy director for management.

Runner-up was NEI, with Frankie Valli’s “Can’t Take My Eyes Off of You,” while NCI took third place singing Stevie Wonder’s “Signed, Sealed, Delivered.”

The event was emceed with grace and humor by John Burklow, NIH associate director for communications and public liaison.

The Directors’ Challenge is held each year in support of the CFC, the federal government’s workplace giving drive that helps staff donate to their favorite causes from among more than 6,000 participating not-for-profit organizations. More information and the donation portal are at <https://cfc.nih.gov/>. —Amishi Shah



The Ocular Dominance team from NEI was led by acting director Dr. Santa Tumminia (l) in a rendition of “Can’t Take My Eyes Off of You.”



The Paper Pushers from NCI perform “Signed, Sealed, Delivered.”