

## CLINICAL PROMISE SHOWN

### Nicolelis Outlines Progress in Brain-Machine Interfaces

BY RICH MCMANUS

There is probably no other scientist in the world for whom peer review meant having his experiment succeed in front of a stadium full of 75,000 screaming Brazilians, with another 1.2 billion people watching on live television.

But at the start of the 2014 World Cup at Corinthians Arena in Sao Paulo, Dr. Miguel Nicolelis witnessed his patient Juliano Pinto, a paraplegic, not only kick a soccer ball to start the tournament, but also “feel” his foot striking the ball.

The patient, a former athlete outfitted

with a brain-controlled robotic exoskeleton who had been paralyzed for 9 years, “didn’t say, ‘I kicked the ball!’” said Nicolelis. More importantly, he said, “I *felt* the ball!”

It took a team of 156 scientists from 25 countries on 5 continents to reach this moment for which neuroscientist Nicolelis had been preparing for 20 years. He recruited the team by dangling field tickets to the World Cup in front of potential recruits.

“It was a hard way to win a free ticket to the game, but that is the Brazilian way,” quipped Nicolelis, a native of that country.

Now a professor of neuroscience at Duke University School of Medicine, Nicolelis, who won an NIH Pioneer Award in 2010 for work he said couldn’t earn a penny of funding a decade earlier, spoke Oct. 16 at an NIH Director’s Lecture in Masur Auditorium.

In the late 1980s, Nicolelis, who has been



Duke’s Dr. Miguel Nicolelis discusses his research on brain-machine interfaces.

SEE NICOLELIS, PAGE 4



NIH director, public radio host team up for CFC launch. See story, p. 12.

#### ALSO THIS ISSUE

Adaptive Immune System Is Millions of Years Old, Cooper Finds.....	3
Flu Vaccination During Pregnancy Saves Lives, Says NIEHS’s Wilcox.....	5
Former IRTA Fearce Pursues Career Goals with Perseverance.....	7
Milestones.....	11
Seen.....	12

## ZOOM OUT FOR CLARITY

### Bologna Advises ‘Stepping Back’ to Aid Diagnosis

BY CARLA GARNETT



Dr. Jean Bologna

A lecture that evokes fried eggs, kale and fried chicken might seem like the perfect noon-hour assignment. Unless, of course, the talk likens such food to skin lesions, complete with life-size four-color illustrations. Then the

plum job could easily become a lunchtime chore only dermatologists (and their closest medical friends and scientific relations) would love.

SEE BOLOGNIA, PAGE 6

## ‘AI CENTAURS?’

### Feigenbaum Searches for Signs of Computer Creativity

BY DANA TALESNIK



Dr. Edward Feigenbaum

As a child, Dr. Edward Feigenbaum had watched his father, an accountant, feverishly tapping the buttons on his calculator to do his math. The idea that machines could speedily replicate human computations fascinated the younger Feigenbaum. In college at Carnegie Tech (later Carnegie Mellon University), under the mentorship of future Nobel laureate Herbert Simon, he

SEE FEIGENBAUM, PAGE 8



## ORWH Publishes Biennial Report

The Office of Research on Women's Health recently published the *Report of the Advisory Committee on Research on Women's Health, Fiscal Years 2017-2018*. This publication, often referred to as the "biennial report," details the NIH-wide programs and accomplishments carried out in fulfillment of ORWH's core mission.



4 Report of the NIH Advisory Committee on Research on Women's Health | Fiscal Years 2017-2018

The report highlights background information on ORWH, its research initiatives, its support of biomedical career development and its monitoring of adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research. The biennial report also provides highlights from research on women's health and on the influence of sex and gender on health and disease supported by the institutes and centers and the Office of the Director.

Finally, the report presents information on NIH budget allocations for women's health research during fiscal years 2017 and 2018. You can read the full report at [https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH\\_BR\\_MAIN\\_final\\_508.pdf](https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_BR_MAIN_final_508.pdf).

## NIH Community College Day, Nov. 26

The Office of Intramural Training & Education will hold NIH Community College Day on Tuesday, Nov. 26 from 8 a.m. to 4 p.m. at Natcher Conference Center. The event will provide community college students and faculty an opportunity to visit the campus and learn about careers and training opportunities in biomedical and health care fields. To register and for more information visit [www.training.nih.gov/communitycollegeday](http://www.training.nih.gov/communitycollegeday).

## White House Honors NIH HBCU Program

In 2017, Diane Frasier, director of the Office of Acquisition and Logistics Management, established the Path to Excellence and Innovation (PEI) Program in accordance with a White House initiative to promote excellence and innovation at historically black colleges and universities (HBCUs). PEI's mission is to empower HBCUs with the knowledge, resources and skills they need to compete for and win partnership opportunities within NIH.

On Sept. 9, the PEI program received the Chairman's Award from the White House Initiative on HBCUs at the 2019 National HBCU Week Conference.

The award recognizes NIH's efforts to strengthen HBCUs' ability to participate equitably in federal programs, explore new ways to improve the relationship between the federal government and HBCUs and establish how each agency intends



## NIH, Gates Foundation Launch Global Initiative

On Oct. 23, NIH announced plans to invest at least \$100 million over the next 4 years toward the goal of developing affordable, gene-based cures for sickle cell disease (SCD) and HIV. The Bill & Melinda Gates Foundation will also invest \$100 million toward this goal. The intention is for these cures to be made globally available, including in low-resource settings. On hand for the announcement were (above, from l) NHLBI director Dr. Gary Gibbons, Dr. Trevor Mundel, president of the Global Health Program at the Bill & Melinda Gates Foundation, and NIH director Dr. Francis Collins (NIAID director Dr. Anthony Fauci participated by phone). At right, Collins and Mundel share a light moment. They hope to see clinical trials in the United States and relevant countries in sub-Saharan Africa within the next 7 to 10 years. For more details, visit <https://www.nih.gov/news-events/news-releases/nih-launches-new-collaboration-develop-gene-based-cures-sickle-cell-disease-hiv-global-scale>.

PHOTOS: LESLIE KOSSOFF



NIH's Diane Frasier accepts the Chairman's Award from Johnathan Holifield.

to increase the capacity of HBCUs to compete effectively for grants, contracts and cooperative agreements.

The White House acknowledged NIH's implementation of the first NIH HBCU Industry Day on Mar. 12. The event brought HBCUs, industry and NIH acquisition, grant and program officials together to collaborate on best practices and form partnerships.

Currently, there are six HBCUs in NIH's pilot program—Jackson State University, Howard University, Hampton University, Meharry School of Medicine, Morehouse School of Medicine and the University of the Virgin Islands.

If your institute or center has programs concerning the infrastructure and/or training of HBCU administrators, email [NIHSmallBusiness@nih.gov](mailto:NIHSmallBusiness@nih.gov).

## LAMPREY ANTIBODIES USEFUL?

**Adaptive Immune System Is Millions of Years Old, Cooper Finds**

BY ERIC BOCK

Our adaptive immune system's ability to remember pathogens it previously encountered depends upon 2 types of lymphocytes called T and B cells, which may have arisen 500 million years ago, said Dr. Max Cooper at the William E. Paul Lecture, Cooper's first major talk since winning the 2019 Albert Lasker Basic Medical Research Award.



Dr. Max Cooper gives the 2019 William E. Paul Lecture.

PHOTOS: LISA HELFERT

“What these cell types were using for antigen recognition before then is one of many unanswered questions,” said Cooper, a professor of pathology and laboratory medicine at Emory University School of Medicine and a Georgia Research Alliance eminent scholar. He spoke in Masur Auditorium on Oct. 2.

To find answers, his lab studies sea lampreys, an ancient jawless predator that has proven to have a sophisticated immune system. Sea lampreys have rasp-like tongues and rings of sharp teeth they use to latch onto their prey. The animal is famous for being an invasive inhabitant of the Great Lakes. Each adult sea lamprey can kill roughly 35 kilograms of fish in a year. The jawless vertebrates—lampreys and hagfish—are thought to have diverged from the jawed vertebrates more than 500 million years ago.



“We couldn't go back and look at the earliest jawed vertebrate representatives. Because they had all died out by around 360 million years ago, we know about them only through their fossilized remains,” Cooper said.

The two types of white blood cells called B and T lymphocytes are the major components of the jawed vertebrates' adaptive immune system. Both types of lymphocytes are derived from stem cells located in the bone marrow. Once B cells develop from their bone marrow precursors, they circulate throughout the body. Mature B cells have surface antigen-specific receptors, allowing the cell to recognize and bind to invasive pathogens. T cells are also derived from their bone marrow precursors but they mature in a lymphatic organ called the thymus, where they develop a diverse repertoire of receptors, each of which can recognize specific antigens.

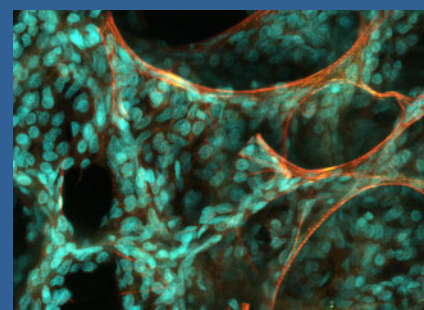
Lampreys lack the cardinal features of the antigen receptor system found in all of the jawed vertebrates' adaptive immune system, Cooper said. Lampreys instead produce variable lymphocyte receptors (VLRs) by assembling different combinations of leucine-rich repeat proteins to create a vast repertoire of receptors to recognize and fight against specific pathogens.

“When we first saw this unexpected VLR diversity, the light came on for us. Although this was not what we started out looking for, we realized that this remarkable variability could be the basis for a recognition system that could discriminate between different antigens,” he said.

At one time, jawed and jawless vertebrates shared a common ancestor, but Cooper believes that due to subsequent convergent evolution—the process where

organisms independently evolve different solutions to achieve the same function—the two types of vertebrates evolved different types of antigen receptors. Since lamprey VLRs have unique antigen specificities, Cooper hopes to use the lamprey VLR antibodies for diagnosis and potential treatments for cancer.

The Paul lecture honors the legacy of Dr. William E. Paul, who was the leader of the NIH immunology community. The lecture recognizes outstanding contributions in immunology. **R**



ON THE COVER: *Human pediatric lung alveolar walls (green-stained nuclei) draped over elastin fibers (red), as seen through a multi-photon microscope. An individual alveolus, the gas-exchanging structure of the lung, is about the thickness of a sheet of paper. The image is part of NHLBI's LungMAP project, a historic effort to understand the molecular and cellular architecture of the human lung. This year marks the 50<sup>th</sup> anniversary of the founding of NHLBI's Division of Lung Diseases. November is National COPD Awareness Month.*

IMAGE: GLORIA PRYHUBER, CORY POOLE, UNIVERSITY OF ROCHESTER MEDICAL CENTER, SUPPORTED BY NHLBI

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## Nicolelis

CONTINUED FROM PAGE 1

NIH-funded for 31 years, first recorded extracellular signaling from the brain of a rhesus monkey. Since then, he and colleagues have established a set of 10 principles governing neurocircuit plasticity and dynamics that appear to hold true across mammalian species.

Their most important basic science findings, he said, include “principles of neural ensemble physiology,” which involve “distributed coding, plasticity and multitasking—a single neuron is informative of several behavioral parameters.”

Nicolelis and his team at Duke set out to record brain-firing in animals “completely free to behave” any way they want, which is a courtesy, minus electrode-implantation, he proudly extends to his graduate students.

They began with rats, using chronic implants capable of recording hundreds of cells at once, for long periods of time. Nowadays, they use 3-D-printed recording cubes that can be implanted 10 at a time, 5 in each monkey brain hemisphere.

“These are flexible filaments, not rigid electrodes,” Nicolelis explained. “They move and flow with the tissues. They work months and years after implantation.” The researchers can link a single neuron per wire and are now up to 800-900 wires per animal.

“Monkeys can live for a decade after the implant,” Nicolelis said. His current record is 7.5 years in 2 monkeys.

Microchips within the cubes send information wirelessly to nearby computers that record which neurons in the brain encode specific movements. It turns out that the primary motor cortex is the seat of movement in mammals.

By mapping the neurocircuitry from thought to action, Nicolelis’s team could train monkeys to graduate from using a low-friction joystick to complete a visual task resulting in the reward of orange juice or grapes (“As you know, monkeys will do anything for orange juice,” Nicolelis explained, “and they like grapes even more than they like juice.”) to using their eyes alone to guide cursor movement toward the reward.

“To our shock, we learned that monkeys could move the cursors with their eyes, not the stick,” said Nicolelis.

In only a week of conditioning trials, monkeys could learn to guide an electronic wheelchair toward a plate of grapes—using the brain alone—as easily as they could by hand. This proved the concept of brain-machine interfaces (BMI): Animals can neurally control tools as if they are natural extensions of their own body.

It was a short leap from there to the design of novel neuroprosthetic devices such as the one that helped Pinto kick his soccer ball.

That very public success had been preceded by a search, among the 65,000 patients suffering paralysis in Brazil, to a group of 8 finalists. Unlike animal experiments, in which electrodes are implanted, noninvasive EEG is the mode of BMI in humans.

Patients with paralysis typically have no sensation below the level of the spinal lesion. But some tactile sensation can remain in the forearm; this is where Pinto “felt” the sensation of kicking the ball, via a haptic display on his arm.

“Some of our patients develop a vivid phantom sensation of their legs,” said Nicolelis. “They have literally used their brains to adjust the parameters of their feedback.”

In 3 months of training, sometimes in front of mirrors to gain additional feedback, all 8 finalists for the World Cup event—who had been complete paraplegics—became proficient at using a robotic exoskeleton to take steps, said Nicolelis.



Nicolelis is a 2010 NIH Pioneer Award winner.

PHOTOS: JEFF ELKINS



Nicolelis talks with attendees at a reception in the NIH Library following his NIH Director’s Lecture.

Pinto himself eventually regained feeling in his toes and became a partial paraplegic, following sufficient training.

Nicolelis has known patients to regain bladder and sphincter control, below the level of the lesion that caused paralysis, and one patient even conceived and bore a healthy baby.

“The return of autonomy—that is our goal,” he said.


Nicolelis is betting that BMI, paired with virtual reality, can rekindle the cortex, enabling patients to perform complex locomotion. “In stroke victims, we believe BMI can induce some level of recovery.”

He showed videos of Parkinson’s disease patients whose gait could be dramatically improved via electrical stimulation of the spinal cord. “We have 100 patients around the world in a trial, and it’s working in all of them,” he reported.

And therapy needn’t be continuous. One dose can last for days.

Nicolelis is now targeting epilepsy: “We hope to be able to modulate seizures, via the spinal cord, within the next 20 or 30 years—however much time I have left.”

During a brief post-lecture Q&A, a query by a man describing himself as a presidential candidate from the U.S. Transhumanist Party—who cited Elon Musk as an authority—gave Nicolelis an opportunity to state unequivocally that “human problems are going to be solved by humans, not by technology.”

The complete talk is available at <https://videocast.nih.gov/summary.asp?Live=35101&bhpc=1>. 



Tierra Robinson (l) and Dr. Symma Finn

## EDI Observes Native American History Month

In observance of Native American History Month in November, NIH's Office of Equity, Diversity, and Inclusion has recognized two NIH'ers—one as a “change agent” and the other as a “game changer.”

Tierra Robinson—the change agent—is a member of the Piscataway Conoy Native American tribe and is a physical scientist in the Waste and Recovery Branch, Division of Environmental Protection, ORS. She is also a former postbaccalaureate fellow at NINDS.

“I make a point in using social media to highlight the fun and amazing things I get to do during my career in hopes of capturing the attention of young people in my tribe,” she said. “I have been successful, and I'm often asked how they, too, can find opportunities to put them on the path to a STEM career.”

She continues, “Diversity is essential to science. New ideas are how sciences have evolved since time immemorial. The introduction of various thinking from varied backgrounds is how the field improves and changes the quality of life for entire populations.”

Dr. Symma Finn—the game changer—is program director for the NIH-EPA Centers of Excellence for Health Disparities Research and oversees outreach and dissemination activities for the Breast Cancer and the Environment Research Program. She is also the NIEHS point of contact for tribal research.

“Scientists have come to understand the importance of personalizing medical treatments based on the fact that people from different racial and ethnic backgrounds and socioeconomic status, among other attributes, react differently to biomedical and behavioral interventions,” she said. “It is, therefore, extremely important for both research participants and the scientists who conduct research to represent the diversity of the U.S. population. We will not understand the impact of disease risks or disease progression without taking into account the diversity of response. And, diversifying the scientific workforce allows for optimal engagement with research participants and ensures cultural appropriateness in research protocols.”

For more information about the observance, visit <https://www.edi.nih.gov/blog/communities>.

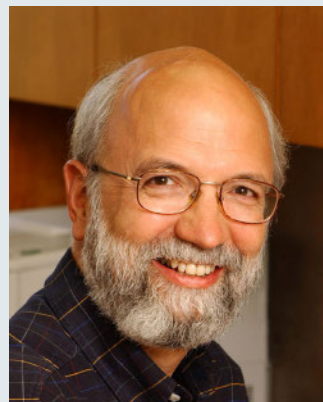
## Flu Vaccination During Pregnancy Saves Lives, Says Wilcox

Growing evidence shows that flu vaccination during pregnancy is safe for mothers and their children, according to a recent editorial in the journal *BMJ* by Dr. Allen Wilcox, NIEHS scientist emeritus, and Dr. Siri Haberg of the Norwegian Institute of Public Health.

Yet, in the 2017-2018 flu season, less than half of pregnant women in England were vaccinated. Comparable rates were found in the U.S. and Europe, the authors noted. Their editorial addressed a new study on the long-term safety of the flu vaccine for children exposed in the womb. The authors of that study analyzed Canadian health care data for more than 100,000 women pregnant during the 2009-2010 flu pandemic and records of their children's health up to 5 years of age.

The researchers reported no elevated risk for cancer, infections, neurodevelopmental problems or chronic diseases in the children of vaccinated mothers. These findings are consistent with results from other, similar studies, according to Wilcox and Haberg. “The net result is a resounding lack of evidence for harm from flu vaccination in pregnancy,” they wrote.

The coauthors emphasized that findings about the benefits of vaccination during pregnancy require a strong response from the medical community.

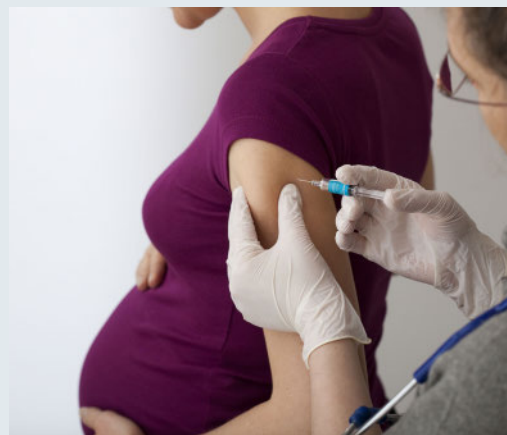


As a reproductive endocrinologist, Wilcox has authored more than 250 peer-reviewed journal articles and an influential book on fertility and pregnancy.

PHOTO: STEVE MCCAIV

“Vaccination of pregnant women averts a small but serious risk of dangerous complications and death for the mother and a chance of death for the child,” Wilcox and Haberg wrote. “A fear of harm to the child is ungrounded—children have no remotely comparable risk.”—**Marla Broadfoot**

NO ELEVATED RISK FOUND



An editorial by NIEHS's Dr. Allen Wilcox argued that the benefits of vaccinating pregnant women far outweigh the risks.

“In our role as researchers, we are obliged to question the strength of the evidence, probe its weaknesses, parse its conclusions and weigh its total contribution,” they wrote. “As physicians entrusted with the health of individuals and populations, we have a different role: When the facts allow, we are charged with speaking out loudly and clearly. Vaccination of pregnant women saves lives.”

Pregnant women who get the flu are at increased risk of complications such as difficulty breathing, pneumonia, sepsis and, in severe cases, multiorgan failure.

Global outbreaks can make problems worse. During the 2009 H1N1 pandemic, 5 percent of all flu-related deaths occurred in pregnant women even though they made up only 1 percent of the population.

Flu infections can also have serious consequences for the pregnancy itself, including miscarriage, stillbirth and preterm birth. For example, some research suggests that risk of preterm birth tripled among infected women who were hospitalized during the 2009 H1N1 pandemic.





**Takes one to know one.** Great Teacher lecturer Bolognia salutes more than a dozen of her own teachers, mentors and colleagues that she called “characters.” NIH’s own Dr. Stephen Katz (shown at center of slide above), the director of NIAMS who died last December, was one of her closest friends.

PHOTOS: CHIA-CHI CHARLIE CHANG

## Bolognia

CONTINUED FROM PAGE 1

That is, unless the lecturer happens to be esteemed Yale School of Medicine professor Dr. Jean Bolognia, editor of *Dermatology*—arguably the bible of textbooks on skin disorders. At an Oct. 23 Clinical Center Grand Rounds in Lipsett Amphitheater, Bolognia gave a clinic—both on diagnosing complex dermatological disorders and on simultaneously engaging and informing an audience.

Her lecture, “Stepping Back Is Sometimes Better Than a Closer Look,” was the latest session of the CC’s Contemporary Clinical Medicine: Great Teachers series. Her title served as an analogy involving pathology,



Medical Research Scholars Program student Christina Marcelus (l) joins NIAMS Dermatology Branch acting chief Dr. Edward Cowen in welcoming Bolognia.

histology and perspective—employing both a dermatologist’s tool-in-trade and a veteran physician’s experience and insights.

“This isn’t exactly an anti-dermatoscope talk,” Bolognia explained. “Rather it is a push for us to continue to think about the 4x clinical exam as well as the 100x clinical exam...When you look at 4x with a microscope you see an overview, then you go to 20x and sometimes to 100x. We can do that clinically as well. My push is for the 4x exam. What I’d like you to do in the future is to step back and drop the dermatoscope.”

Bolognia then presented several cases that, if viewed too closely and without the context distance provides, could confound novice as well as seasoned physicians. Consider, for example, the visual similarities between two conditions seen in hospital patients—a generalized bullous fixed drug eruption and toxic epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS).

“When I think about the difference between a morbilliform eruption due to a drug and SJS, I think of Kentucky Fried Chicken,” Bolognia said, to amused gasps from the audience. The former is KFC original recipe, she explained, whereas SJS presents additional characteristics, such as fragility and sloughing, and should therefore be categorized as “extra crispy.”

*Warning, non-dermatology folks: Under no circumstances should you Google these terms for images.*

“So, how would you treat a patient with TEN after you have established the diagnosis?” she said, showing a slide of lesions labeled with final diagnoses. “You have to decide on your favorite flavor. There’s only one randomized clinical trial. This is dermatology—we do a lot of cooking in the kitchen without a recipe. We’re chefs, not cooks.”

Bolognia also advised budding dermatologists to recognize that, in general, individuals often make their own unique types of moles (technically called nevi). If you can determine these “signature nevi” early in an initial examination, she counseled, then you can eliminate them as worrisome lesions (“unless there is a superimposed change”) and concentrate on “the outlier nevus—the ugly duckling. It will make your life a lot easier.”

Next, Bolognia addressed nevi that resemble fried eggs. Oftentimes, she noted, these moles draw a lot of attention from worried patients, parents and pediatricians.

• • •

*“..We don’t have people who stand up and passionately argue about the diagnosis anymore. We’re getting too homogenized in medicine.”*

-DR. JEAN BOLOGNIA

• • •

“For a good reason,” she pointed out. “They are large, they are noticeable. They are in a way sensational, but yet they have done nothing to have earned that reputation. So I nicknamed them the ‘Kardashian nevi,’ because I feel they’ve done nothing but be sensational because of their size and their look. These do not need to be removed unless there has been a superimposed change. Save the nevi! Save the biopsy for when you need it. Plus, when you remove these nevi, you often leave an unsightly scar because of their common location on the posterior trunk.”

Another common type of signature nevus looks like a solar eclipse, she pointed out. It’s generally “bland and innocent” and is often found on the scalp of children who

## Former IRTA Fearce Pursues Career Goals with Perseverance

ADVERSITY TO EXCELLENCE

BY SHANNON E. GARNETT

Chelesa Fearce's ultimate goal is to become an academic physician—practicing medicine and conducting research. That goal may not seem unique for someone who spent the past 2 years in the NIH postbaccalaureate Intramural Research Training Award (IRTA) program. However, Fearce—who recently started her first year at Yale University School of Medicine—is herself unique. And, it's not her career goals that make her so. Her sheer determination and perseverance in accomplishing those goals set her apart.

At age 24, Fearce has already had to overcome a lifetime of adversity. When she was 9 years old and in the fourth grade, her mom was diagnosed with cancer. With her mom unable to work and medical expenses accumulating, the family (which includes Fearce, her mom and three siblings) became homeless—often moving from shelter to shelter and even living in their car and sometimes in hotels. But Fearce never lost focus on her education.

"I used my little brother and sister as motivation," she said. "I wanted to be a good role model for them. I wanted them to know that despite what we were going through, they could accomplish whatever they set their minds to. I leaned on my religion a lot. I truly believe that there is a purpose for everything that we go through."

Fearce developed her love for science as a freshman in high school. She was heavily influenced by her African-American science teachers. "Seeing them really helped me see myself as someone who could do science in the future," she said.

Fearce excelled in high school, finished at the top of her class and was valedictorian at Charles Drew High School's graduation in Riverdale, Ga., in 2013.

She earned a full scholarship to Spelman College in Atlanta. While there, Fearce discovered an interest in research. She conducted computational and physical chemistry research, studying how molecules were formed using free radical mechanisms on the pre-biotic Earth. She also had an undergraduate summer research experience at the University of Cincinnati, where she helped identify compounds as tanning agents for the treatment of melanoma. She graduated from Spelman in May 2017 with a bachelor of science degree in biochemistry.

In June 2017, Fearce entered NIH's IRTA program, working in the laboratory of Dr. David Sibley in the molecular neuropharmacology section of NINDS's Division of Intramural Research. Her work involved studying the behavior of dopamine receptors and screening drugs for their ability to influence the receptors' activity. The goal was to discover compounds that could be used to treat schizophrenia. Fearce completed the program in May 2019.

"My lab was very supportive and really helped solidify my decision to pursue the dual degree," she said. "The other postbacs were most memorable; they made my time at NIH worthwhile. My mentors, Dr. Sibley and Dr. R. Benjamin Free, took a chance on me and I appreciate them giving me the opportunity to join their lab."

This fall, Fearce began the next leg of her career as an M.D./Ph.D. candidate at Yale University School of Medicine, where she intends to join the pharmacology or chemistry Ph.D. program.

"The future is brighter," said Fearce. "I know that it is easy to want to give up, but I encourage other individuals facing homelessness to realize that they too can be an inspiration to future individuals and that this experience will only make them stronger."



Bologna chats with attendees after her talk.

will develop an increased number of nevi over time.

Throughout her lecture, which was rich with humor and anecdote, her message was clear: Be careful, deliberative and open-minded in your observations, opinions and consultations. Both you and your patients will be better for it.

"I think in medicine we are starting to move too fast to treatment and not taking the time for differential diagnosis," she said.

Bologna closed her lecture with a nod to more than a dozen of her own teachers, mentors and colleagues she referred to as "characters."

"All the characters pictured here have passed away," she said, posting a slide filled with portraits. "Some I agreed with from the day I met them and some I never saw eye to eye with, and although we fought like cats and dogs, we remained friends...We're losing the characters in medicine. And I'm trying to bring them back. We don't have people who stand up and passionately argue about the diagnosis anymore. We're getting too homogenized in medicine. We're not arguing enough anymore."

During the Q&A period, Bologna was asked her view of contemporary medicine and medical training.

Recalling her own experiences as a med student, a resident and early days in her career, she reiterated the impact of having great teachers. Students in any field, she said, should never put themselves in a position where "all you know is what you've been taught by others...Take the best of several people as well as multiple books. Then combine those ingredients and be unique. I also don't believe everything should be taught in the classroom.

"Dermatology," she concluded, "still has a lot of apprenticeship learning—one on one, in the room with the patient. I still think that is a good way to learn—right at the bedside, not in the classroom." **R**



Chelesa Fearce recently began the next leg of her career as an M.D./Ph.D. candidate at Yale University School of Medicine.



## Feigenbaum

CONTINUED FROM PAGE 1

became deeply interested in the software that models human intelligence, perception and discovery, what is now called “AI,” or artificial intelligence.

That interest guided the career of Feigenbaum, a renowned AI scientist and computer science professor emeritus at Stanford University. He spoke to a packed Lister Hill Auditorium recently at the annual Donald A.B. Lindberg and Donald West King Lecture in Medical Informatics and/or Pathobiology, co-sponsored by NLM.

Feigenbaum and Dr. Joshua Lederberg led a research team that developed the first expert systems in artificial intelligence nearly 55 years ago. Considered the second



Feigenbaum defined the criteria for computer creativity in his talk.

began to emerge even in the earliest AI programs. In the second wave of AI, some “deep search” AI programs were written. They had weaker knowledge than expert



*“A creative act, for me, means these three things—It’s extremely surprising to those [who are] expert in the field; it’s novel, maybe even so novel that it’s new to mankind; and it evokes awe in the community of specialists in [that] area.”*

—DR. EDWARD FEIGENBAUM



wave of AI, these computer programs used encoded knowledge from human experts in specialized fields to help solve complex problems, including medical diagnosis and therapy. For example, an early expert system, done by a student in Feigenbaum’s lab, helped doctors diagnose blood and meningitis infections.

The famous codebreaker and “father of computer science” Alan Turing maintained that computers should be regarded as intelligent if their thinking behavior was indistinguishable from that of people, said Feigenbaum, a Turing Award laureate. But do computers simply churn out programmed information or do they have the capacity to be creative?

“A creative act, for me, means these three things,” said Feigenbaum. “It’s extremely surprising to those [who are] expert in the field; it’s novel, maybe even so novel that it’s new to mankind; and it evokes awe in the community of specialists in [that] area.”

By this definition, computer creativity

systems but could search far more deeply for novel solutions.

Take the game of chess, with  $10^{120}$  possible paths to win, lose or draw. For such astronomical computations, said Feigenbaum, we need heuristics. These knowledge-based methods help us prune searches to reasonable levels that can be accomplished in timeframes relevant to humans.

For a creative behavior, “You’re not looking just for a needle in a gigantic haystack,” he said. “You’re looking for a golden one in that gigantic search space.”

In 1997, the IBM Deep Blue computer and software found the golden needle to beat world champion chess grandmaster Garry Kasparov. A human champ might not have a computer’s vast search capacity, but does have superb expert pattern recognition and knowledge of chess that minimizes search. By contrast, Deep Blue searched deeply, though it didn’t search nearly the total number of possible paths. Deep Blue won what was a close match by making a brilliant move. The move inspired awe, astounding chess experts. Even Kasparov had noted creativity in the computer’s moves.

Deep search also proved victorious in a game with a much larger search space than chess. The ancient Chinese game of Go has an almost unfathomable  $10^{800}$  winning paths. Yet a program called AlphaGo, developed by AI scientists at the Google-owned DeepMind, eventually beat two human Go champs in 2015.

Again, the computer could not possibly search all potential winning paths, but it still won. One European champ exclaimed he’d never seen such play. It was creative, said Feigenbaum, in that it was a novel, awe-inspiring demonstration of skill.

It’s as if the computer says, “I don’t have to search to the bottom of the search space,” said Feigenbaum. “I just have to search deeper than you and I will find that golden needle in the haystack that you couldn’t find, because you’re human and can’t systematically enumerate and search all



Mary Lindberg, widow of Dr. Donald Lindberg, presents the lecture award.

PHOTOS: LISA HELFERT



those possibilities, even given the heuristic knowledge you have.”

AI may, in fact, be headed toward greater cooperative intelligence, said Feigenbaum, who envisions many creative acts in medicine and other areas stemming from human-computer teams, sometimes called “AI centaurs.”

“Working collaboratively, they’ll produce a result that’s better than either of them could do by themselves,” he said.

Feigenbaum recounted an early example of AI centaurs that took place 35 years ago. A Stanford computer science professor, Dr. Douglas Lenat, collaborated with EURISKO, an AI program he’d created, to find an unbeatable move in the war game Trillion Credit Squadron.

EURISKO would run all night, said Feigenbaum. Each morning, Lenat would pick a few “best” moves. EURISKO continued searching; Lenat continued evaluating and pruning the searches daily, for months. Together, Lenat and EURISKO found an unexpected winning move in the huge game search space that he took to the world championship, and won.

But most people don’t think of game-winning moves when they think of creativity. Often, creativity conjures up images of art or music. So Feigenbaum shared another early

example of an AI centaur in the art world.

British abstract artist Harold Cohen had aspired to capture his art in an expert system. Cohen, who spent 2 years at Stanford’s AI lab in the 1970s, wrote out rules based on the many artistic elements that went into his artwork and how each related to what came next to complete each image. From 1973 to 2016, Cohen wrote the computer program AARON, which generated new images based on Cohen’s thousands of rules that he believed captured his artistic skills.

“This is a human-computer interaction between Harold Cohen and what he knows about his art. AARON generates images in this enormous space,” said Feigenbaum, who considers this computer-generated art unequivocally creative. AARON’s images are still being shown at art galleries and museum exhibits internationally.

As computers become even more powerful, and as data grows more voluminous and complex, it will be fascinating to see what yet-unimagined capabilities future waves of artificial intelligence will bring.

Said Feigenbaum, “Using enormous combinatorial or textual searches...with an expert human partner, systems of collaborative intelligence will find superb creative acts that mankind unassisted did not, or could not, think of.” **R**

## Stone To Give NINR Director’s Lecture, Nov. 19

On Tuesday, Nov. 19, Dr. Patricia W. Stone will present “Informing Health Policy Through Science to Improve Healthcare for



Dr. Patricia W. Stone

Older Adults,” from 1 to 2 p.m. in Lipsett Amphitheater, Bldg. 10.

Stone is the Centennial professor in health policy at Columbia University School of Nursing.

She earned a Ph.D. from the University

of Rochester and completed post-doctoral training at Harvard University. Her research aims to enhance the quality of care for older adults including preventing health care-associated infection and improving infection management and end-of-life care.

Her program of research has contributed to policy changes, such as state and federal legislative mandates that hospitals report infections.

Stone’s passion is teaching the next generation of nurse scientists how to lead interdisciplinary research teams that generate knowledge, influence health policy and improve patient and population health.

The lecture will also be broadcast live and archived at <https://videocast.nih.gov>.

For more information and to register, visit <http://ow.ly/v0Ny50wWMff>.

## NIDA’s Gardner Wins Lifetime Achievement Award

NIDA’s Dr. Eliot Gardner recently received the Lifetime Achievement Award from the International Drug Abuse Research Society (IDARS). The award, which honors Gardner’s lifetime contributions to addiction medicine and addiction neurobiology, was presented at the IDARS meeting held Sept. 2-6 in Casablanca, Morocco.

Gardner counts his discovery that delta-9-THC activates the pleasure/reward circuitry in the brain, and that cannabis is therefore potentially addictive, among his greatest achievements. He has also worked on highly selective dopamine D3 receptor antagonists, cannabinoids, endocannabinoids and (most recently) tetrahydrocannabinol, as well as slow-onset, long-acting atypical dopamine transport blockers as potential anti-addiction, anti-craving and anti-relapse medications.

When asked about the importance of this award to him, Gardner replied, “It’s deeply important to me. The International Drug Abuse Research Society is comprised of some of the most creative and productive researchers in the field of addiction. The fact that George Koob is president of the society pretty much says it all. To be so honored by such an outstanding group of colleagues in addiction medicine and addiction biology is deeply moving and deeply appreciated.”



On hand as Dr. Eliot Gardner of NIDA’s neuropsychopharmacology section (third from l) accepts the Lifetime Achievement Award are (from l) Dr. George Koob, NIAAA director and president of IDARS; Dr. Sâadeddine El Othmani, head of government, Kingdom of Morocco; and Dr. Syed Ali, IDARS executive officer.



Exposure to acetaminophen in the womb may increase a child's risk for ADHD.

IMAGE: NATALIADERIABINA/GETTY

## Acetaminophen Exposure in Pregnancy May Be Linked to Higher Risk of ADHD, Autism

Exposure to acetaminophen in the womb may increase a child's risk for attention deficit/hyperactivity disorder and autism spectrum disorder, suggests a study funded by NIH and the Agency for Health Care Research and Quality. The study appears in *JAMA Psychiatry*.

Attention deficit/hyperactivity disorder (ADHD) is marked by a pattern of hyperactivity and impulsive behavior. Autism spectrum disorder (ASD) is a complex developmental disorder that affects how a person behaves, interacts with others and learns.

Researchers analyzed data from the Boston Birth Cohort, a long-term study of factors influencing pregnancy and child development. They collected umbilical cord blood from 996 births and measured the amount of acetaminophen and 2 of its byproducts in each sample. By the time the children were an average of 8.9 years, 25.8 percent had been diagnosed with ADHD only, 6.6 percent with ASD only and 4.2 percent with ADHD and ASD. The researchers classified the amount of acetaminophen and its byproducts in the samples into thirds, from lowest to highest. Compared to the lowest third, the middle third of exposure was associated with about 2.26 times the risk for ADHD. The highest third of exposure was associated with 2.86 times the risk. Similarly, ASD risk was higher for those in the middle third (2.14 times) and highest third (3.62 times).

The authors conclude that their results support earlier studies linking acetaminophen exposure in the womb with ADHD and ASD and underscore the need for additional research. The Food and Drug Administration urges careful consideration before using any pain-relieving medication during pregnancy.

## Pathogenic Tau and Cognitive Impairment Are Precipitated by a High-Salt Diet

High levels of dietary salt can activate a pathway in the brain to cause cognitive impairment,

according to a new study. The paper, which was published in *Nature*, shows that this effect is not due to a loss in blood flow to the brain as originally thought, but rather to clumps of a protein linked to several forms of dementia in humans. The research was funded by NINDS.

"This study continues the important story of the effects of a high-salt diet on the brain," said Dr. Jim Koenig, program director at NINDS. "This work in mice reveals a new target for therapies aimed at brain blood vessel dysfunction."

In a previous research study, scientists led by Dr. Costantino Iadecola, director and chair of the Feil Family Brain and Mind Research Institute at Weill Cornell Medicine in New York City, showed that mice that ate a diet high in sodium began to show symptoms of dementia due to changes that occurred in the gut. The diet also produced a drop in the flow of blood to the brain, which they thought would be the cause of the dementia symptoms. However, when they looked more closely, they found instead that a buildup of a protein called tau in the brain was the cause.

"This result was completely unexpected," said Iadecola. "We knew that a high-salt diet produced dementia-like symptoms in mice, and we went in thinking the culprit would be reduced blood flow to the brain. It turned out that wasn't the case at all."

Although Iadecola points out that the salt content consumed by the mice in this study is 8 to 16 times higher than normal and is likely to be more than a person would consume in a single day, their findings provide important links between diet, the blood vessels of the brain and cognition.

"Our results highlight the importance of thinking beyond blood flow when treating disorders affecting the brain's blood vessels," he said.

## Researchers Identify Genetic Variations Linked to Oxygen Drops During Sleep

Researchers have identified 57 genetic variations of a gene strongly associated with declines in blood oxygen levels during sleep. Low oxygen levels during sleep are a clinical indicator of the severity of sleep apnea, a disorder that increases the risk of heart disease,

dementia and death. The study, published Oct. 24 in the *American Journal of Human Genetics*, was funded by NHLBI.

"A person's average blood oxygen levels during sleep are hereditary, and relatively easy to measure," said study author Dr. Susan Redline of Brigham and Women's Hospital, a professor at Harvard Medical School. "Studying the genetic basis of this trait can help explain why some people are more susceptible to sleep-disordered breathing and its related morbidities."

When we sleep, the oxygen level in our blood drops, due to interruptions in breathing. Lung and sleep disorders tend to decrease those levels further, and dangerously so. But the range of those levels during sleep varies widely between individuals and, researchers suspect, is greatly influenced by genetics.

Despite the key role blood oxygen levels play in health outcomes, the influence of genetics on their variability remains understudied. The current findings contribute to a better understanding, particularly because researchers looked at overnight measurements of oxygen levels. Those provide more variability than daytime levels due to the stresses associated with disordered breathing occurring during sleep.

The researchers analyzed whole genome sequence data from NHLBI's Trans-Omics for Precision Medicine program. To strengthen the data, they incorporated results of family-based linkage analysis, a method for mapping genes that carry hereditary traits to their location in the genome. The method uses data from families with several members affected by a particular disorder.

"This study highlights the advantage of using family data in searching for rare variants, which is often missed in genome-wide association studies," said Dr. James Kiley, director of NHLBI's Division of Lung Diseases. "It showed that, when guided by family linkage data, whole genome sequence analysis can identify rare variants that signal disease risks, even with a small sample. In this case, the initial discovery was done with fewer than 500 samples."



Low oxygen levels during sleep are a clinical indicator of the severity of sleep apnea.

IMAGE: ISTOCK/GETTY



High levels of salt can activate a pathway in the brain to cause cognitive impairment.

IMAGE: PIXHOOK/ISTOCK



## NIA Mourns Morrison-Bogorad

Dr. Marcelle Morrison-Bogorad, who was director of NIA's Division of Neuroscience for 14 years, died in September in Costa Rica, where she retired from NIA in 2010 to enjoy "la pura vida."

During her 14-year tenure at NIA, Morrison-Bogorad was known best for her forward thinking and her ability to build programs by identifying priorities for scientific initiatives, recruiting the right talent and leveraging partnerships. As a leader, Morrison-Bogorad was credited with implementing an array of innovative initiatives in Alzheimer's research, such as critical expansions in genetic, epidemiological and translational research, and the groundbreaking Alzheimer's Disease Neuroimaging Initiative.



Dr. Marcelle Morrison-Bogorad

Morrison-Bogorad led the Division of Neuroscience when the field of aging was just beginning to make advances in the understanding of Alzheimer's initiation and progression. As a scientist committed to unraveling the underpinnings of age-related neurodegenerative diseases such as Alzheimer's, she was

passionate about developing drugs with the potential for halting its progression, knowing that postponing the diagnosis by several years could enable older adults to live longer with comfort and independence.

"Marcelle was insightful and creative in her focus on aging brain research, setting up programs and partnerships that evolved successfully over the years to accelerate progress in this field," said NIA director Dr. Richard Hodes. "She understood that advancing the science of aging and dementia required the collaboration and cooperation of researchers representing many disciplines. The breadth and depth of science in progress today for Alzheimer's disease and related dementias are a testament to the infrastructure she pioneered and established."

"She was an excellent scientist and a true leader, and we will miss her very much," said Dr. Nina Silverberg, who was recruited by Morrison-Bogorad in 2005 and now directs the Alzheimer's Disease Research Centers Program for NIA. "I have heard many wonderful stories over the years from grantees who appreciated her sage advice on a very wide range of topics."

Before her tenure at NIA, which began in 1997, Morrison-Bogorad was a researcher and professor in the department of neurology at the University of Texas Southwestern Medical Center in Dallas. Her research there focused on the molecular analysis of brain development, Alzheimer's disease and aging. In the 1970s, she was one of the first researchers to isolate and study the properties of eukaryotic messenger RNAs.

When Morrison-Bogorad joined NIA as a director, she continued to conduct research by setting up a small lab at NIA. In addition to neuroscience, her other passions included hiking, reading murder mystery books and her cherished dogs.

A native of Scotland, she received an honors degree in biochemistry from the University of Aberdeen and a Ph.D. in biochemistry from the University of Glasgow. She is survived by her sisters Isobel and Margaret, along with many friends and colleagues who remember her legacy. Her husband Alexander Bogorad died in 2017. **R**

### Patients with Fanconi Anemia Needed

NHLBI researchers need volunteers at least 4 years old with Fanconi anemia to participate in a study investigating a treatment to improve blood counts. Compensation for travel is provided. Study-related tests are provided at no cost and results are shared with you and your doctor. Call the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Read more at <https://go.usa.gov/xQyKp>. Refer to study 17-H-0121. Se habla Español.

### NIDDK Study for Healthy Male Volunteers

Researchers need healthy male volunteers, 18-35 years old with BMI 18.5-25, to help them learn how current FDA-approved anti-obesity/weight loss drugs affect metabolism. The findings may help treat obesity in the future. Compensation is provided. Become our partner in research: 1-800-411-1222, PRPL@cc.nih.gov. Refer to study 13-DK-0200, cohort 2. Read more at <https://go.usa.gov/xUmVp>.

### 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.

### Kidney Cancer Patients Needed

NHLBI researchers, in partnership with Loyola University Chicago, seek individuals with kidney cancer for a new treatment study using gene therapy. Gene therapy is a process of modifying patients' immune system to create tumor-fighting cells to recognize and kill their cancer. Study-related procedures, tests and medications are provided at no cost. For more information, call the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Self-referrals are welcome. Read more at <https://go.usa.gov/xVhXH>. Refer to study 18-H-0012.

### NIDDK Study for Healthy Men

Healthy Caucasian men, ages 55-75 with BMI 18.5-25, are needed for a metabolism research study at the Clinical Center. Participation requires an 11-day inpatient stay. Compensation is provided. Call the Office of Patient Recruitment at 1-800-411-1222. Refer to study 12-DK-0097, cohort 5. Read more at <https://go.usa.gov/xNdks>.

### NIAAA Needs Healthy Volunteers

NIAAA invites healthy volunteers, 21-60 years of age, to participate in a study researching if a gene and smoking affect drinking. Volunteers should be healthy, drug-free and not seeking treatment for alcohol-related problems. Research participation includes 3 outpatient visits that consist of alcohol consumption, brain scans (MRI), blood draws and filling out questionnaires. Compensation may be provided. For more information, call the Office of Patient Recruitment at 1-866-444-2214 (TTY users call via MD Relay 7-1-1) or visit <https://go.usa.gov/xp3zV>. Refer to study 17-AA-0171.

### Healthy Volunteers Needed

NIAID researchers seek healthy volunteers, 18-50 years old, for the study of an investigational product targeting malaria. Financial compensation is provided. To learn how to participate, call 1-866-833-5433 or email [vaccines@nih.gov](mailto:vaccines@nih.gov).





At the CFC kickoff event are (from l) NIH director Dr. Francis Collins; Diane Rehm, public radio talk show host; NEI acting director Dr. Santa Tumminia; and Brian Trent, NEI executive officer. At right, under the tent, CFC charities provide information on their services.

PHOTOS: CHIA-CHI CHARLIE CHANG

RAIN OR SHINE

**CFC Is Off to a Strong Start**

Public radio personality Diane Rehm helped launch the NIH 2019 Combined Federal Campaign on Oct. 16. “It may be raining outside, but there are no damp spirits under this tent,” said NIH director Dr. Francis Collins. More than 30 CFC-affiliated charities shared information about their work under a big tent that had been set up in front of Bldg. 1.

Rehm, who hosts the weekly podcast *On My Mind*, addressed end-of-life care, the subject of her forthcoming book *When My Time Comes*. “I believe that patients should be allowed to live with the same dignity and respect towards the end of their life and be able to legally choose end-of-life care options,” she said.

**2nd Annual NEI 5K Dedicated to CFC**

Sunshine prevailed at the second annual NEI 5K, held Oct. 24. NHLBI swept the event with Joe Chapman, Ryland Mortlock and Sarah Fritz placing first, second and third, respectively.

The Prevention of Blindness Society of Metropolitan Washington provided free eye health screenings. NEI showcased See What I See, a virtual reality experience that simulates vision with cataract and glaucoma.

**CFC Halloween Charity Fair**

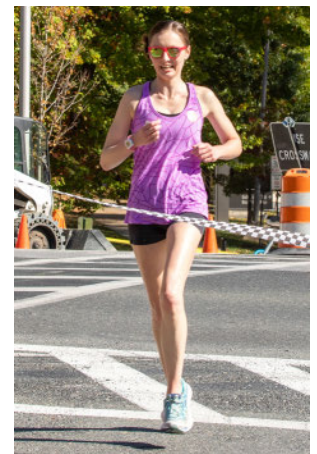
The CFC Halloween Charity Fair took place on Oct. 31. NIH staff put on their creative hats to enjoy this festive tradition. Some staff from NEI, who are the hosts for this year’s CFC, came dressed as characters from *The Wizard of Oz*, while other ICs came dressed as nature’s elements—earth, wind, water and fire. Beetle Juice and Avocado Toast were among the other costumed characters. A variety of CFC-affiliated charities provided information about their work.

To promote the CFC via social media, post a photo at #selfie4cfc.—Amishi Shah



At a CFC charity fair held on Halloween, NEI staffers—including Tumminia, a.k.a. Glinda the Good Witch—channel *The Wizard of Oz*.

PHOTO: DUSTIN HAYS



CFC enthusiasts are flanked by cutout co-chairs; at right, NHLBI’s Sarah Fritz came in third in the NEI 5K.

PHOTOS: DUSTIN HAYS