CRISPR Becoming Crisper, More Ubiquitous, Says Zhang
BY RICH MCMANUS

What plastics were to a young Dustin Hoffman in The Graduate and what computers were to a young Wozniak and Jobs in their garage-era tinkering is now occupied by CRISPR technology, suggested Dr. Feng Zhang of MIT in the final Wednesday Afternoon Lecture of 2017 on June 28.

Speaking in a packed Masur Auditorium, where he posed for selfies with audience members before taking the stage, Zhang traced CRISPR technology from its origins as a mechanism developed by bacteria to defend itself against pathogens to its current status as a sophisticated gene editor.

“It’s like a cursor in Microsoft Word,” said Zhang. “Wherever you can place it, you can make the edit.”

Only 35, Zhang has already revolutionized science in two ways, said NICHD microbiologist Dr. Gigi Storz, who introduced him.

He is an alumnus of optogenetics pioneer Dr. Karl Deisseroth’s laboratory at Stanford and, since early 2011, has been working to harness clustered regularly interspersed short palindromic repeats, or CRISPR, systems for genome editing.

“There is enormous biological diversity in nature,” Zhang said. “Even in bacteria, there is amazing and enormous diversity. We hope to understand and harness some of them for emerging biotechnologies.”

Even common detergents used in household kitchens include lipases, cellulases “and all sorts of enzymes harnessed from natural sources,” he explained.

Zhang’s interest is the more than 6,000 human genetic diseases, most of which cannot yet be treated. CRISPR technology may one day be able to reverse damaging mutations that cause illness, he predicted. Using homology-directed repair, scientists can already modify a single DNA base.

GOING VIRAL

Pediatrician Discusses Ethics Of Parents’ Online Posts
BY DANA TALESNIK

Many parents are quick to post photos of their kids on social media or blog about their child’s health. Parents have learned a thing or two from this practice—from foods to entice picky toddlers to favorite remedies for rashes and other common ailments—and often turn to online communities to share their experiences and network with other families.

Cancer-Causing Viruses Yield Clues to New Treatments
BY ERIC BOCK

There are at least 7 viruses that are known to cause cancer. Of those, Dr. Patrick Moore and his colleague and wife Dr. Yuan Chang discovered and characterized two. These insights are the first steps toward developing new cancer vaccines and treatments, Moore recounted at the George Khoury Lecture in Masur Auditorium recently.

“Viruses and other infectious agents are
Free Editing Help for NIH Fellows

The Fellows Editorial Board (FEB) was created in spring 2002 to meet the scientific editorial demands of postdoctoral and clinical fellows in the NCI Center for Cancer Research. Now, FEB provides free, fast and confidential scientific document editing services for the entire NIH and FDA fellow community.

At any given time, FEB has up to 40 members who edit submitted manuscripts, grant proposals, abstracts and other scientific documents for grammar, structure and clarity. However, FEB does not comment on scientific merit.

FEB is an all-volunteer organization composed of postdoctoral and clinical fellows. It accepts members from all NIH components; previous editing experience is not a requirement. However, due to the popularity of FEB, it is not uncommon for applicants to be on the wait list for 6 months.

The process is as follows: a senior editor assigns a manuscript to an associate editor. The associate then builds a team of three primary editors to thoroughly edit the submission. Although all board members review each submission for the weekly meeting, which is video-conferenced to NIH campuses in Baltimore, Frederick and North Carolina, the team leads the editing discussion for the manuscript. All editors’ comments are compiled and returned to the author, usually within 10 business days.

All NIH fellows (postbacs, graduate students, postdoctoral fellows and clinical fellows) can submit their scientific documents to FEB. The research does not have to have been completed at NIH or FDA, but the submitting author must currently be an NIH or FDA fellow.

FEB has edited more than 920 documents to date; FEB-edited manuscripts have been published in journals including Molecular and Cellular Biology, Cancer Research, Oncogene, the Journal of Biological Chemistry, Molecular Cell and Neuroscience Research.

For more information, visit https://ccr.cancer.gov/trainee-resources-editorial-board for submission instructions and membership applications or send an email to FEB editors at ncieditors@mail.nih.gov.

NCATS To Launch Toolkit for Patient-Focused Therapy Development

NCATS will launch its Toolkit for Patient-Focused Therapy Development online resource portal on Sept. 8 during a meeting at Natcher Conference Center. Patients, their caregivers and patient-support organizational representatives are invited to attend the full-day event to learn how the toolkit can help streamline the search for the right resources to help in their therapeutic development activities. Participants also will have the opportunity to provide input into how the toolkit can be expanded and made more useful.

Learn more at https://ncats.nih.gov/events#toolkit.

Improving Campus Pedestrian Safety Through Technology

Since 2014, 8 pedestrians and 1 bicyclist have been struck by vehicles on the Bethesda campus. It’s a sobering statistic. Even one accident is too many.

If you’ve walked on Center Dr. near Bldg. 3 or Lincoln Dr. between Multi-Level Parking Garage 6 and Bldg. 35, you’ve seen the latest measure installed on campus to address pedestrian safety. Using photo-electric sensors and directional infrared light, these pedestrian-activated, LED-lit crosswalks and flashing warning signs are typically in the middle of a block where there is no stop or yield sign. Once activated, the in-road lighting is directed at the eye level of motorists and cyclists, alerting them to pedestrians already in the crosswalk and increasing drivers’ warning times.

Many other places are also adopting this pedestrian safety technology, with Walter Reed, the City of Charlottesville, James Madison University, Norfolk Naval Base and Boiling Air Force Base as examples. More lighted crosswalks and warning signs are coming. This summer and fall, 12 additional crosswalks will be upgraded around campus with 8 more planned for the future. Locations were determined with NIH community input, selecting places with high-volume vehicle traffic, high-volume pedestrian traffic or both.

Even though additional lighted crosswalks will help NIH become a safer campus for all, they don’t replace the need for everyone to follow the rules of the road. NIH follows State of Maryland and Montgomery County laws as they pertain to pedestrian right-of-way. At a crosswalk, in most situations, the pedestrian has the right-of-way and a vehicle should come to a complete stop while a pedestrian is crossing or approaching the roadway. However, it’s not all on the driver. Maryland code also states “…a pedestrian may not suddenly leave a curb…and walk into the path of a vehicle which is so close that it is impossible for the driver to yield” safely. Also, no bike or other vehicle may pass another vehicle stopped to let a pedestrian cross the roadway.

Installation of these improvements has already begun. No road closures are expected. Lane closures are limited to nights and weekends and one lane of traffic will be open at all times. The Office of Research Facilities project officer overseeing installation is Michael Oppelt. He can be reached at michael.oppelt@nih.gov or (301) 435-7827.

Risk Management Reports Due by End of August

It is August—the end of the fiscal year approaches next month and the familiar hum of activity crescendos across NIH as budget offices work to meet close-out requirements and plan for next fiscal year. But there is another annual, mandatory, fiscal year requirement. This one is set forth by the NIH Risk Management Program and requires all institutes, centers and OD offices to submit an annual risk inventory report by the last Friday in August to the OD Office of Management Assessment. There is a management analyst within your IC/OD called the risk management champion. The champion plans, coordinates, manages and reports on your risk inventory.

Your champion is working to update your risk inventory. To create the inventory, your champion scheduled numerous interviews with leaders and managers across extramural and intramural programs to capture data. Champions brainstorm and collaborate with leaders and managers on initiatives to improve business processes. As this is an arduous undertaking, some champions start interviewing as early as March. After conducting interviews, your champion presents the risk inventory to your executive officer and your director.

For many, this may be your first realization that your organization has a risk inventory. As a leader and manager, you may recall participating in past interviews. If not, you may be interested in contributing to the identification of risks and finding out who your champion is. To find out, visit https://oma.nih.gov/RMAL/NIHRM/default/Pages/RMORMCh-Website.aspx.
Musician Milner Thanks NIH with Music

BY RICH MCMANUS

The tradition of grateful Clinical Center musician-patients who return to campus to give concerts was extended on July 26 when singer-songwriter Kevin Milner, 38, of Newport, Ky., played a noontime gig, mostly of his own compositions, in the atrium.

He was in town for a meeting with his medical team, including NICHD’s Dr. Karel Pacak, an authority on the rare tumor that inserted itself into Milner’s life utterly by surprise.

Milner was leading a musician’s life, touring the Midwest for much of the past 2 years and being a stay-at-home dad, when he learned that his little brother had a large tumor in his stomach. The cancer was successfully removed by physicians at the Mayo Clinic, but doctors there performed genetic tests showing that Kevin had a 50-50 chance of developing cancer himself.

“I had no symptoms at all,” said Milner, who credits geneticists at Dayton Children’s Hospital with finding the tumor that had developed, unbeknownst to him, in his chest and referring him to NIH. “They basically saved my life.”

Milner has a paraganglioma. It is scheduled to be removed in mid-August by NCI thoracic surgeon Dr. Chuang Hoang. Because of the tumor’s location in Milner’s chest, resecting it carries with it a 50 percent chance of depriving Milner of his voice. And perhaps his career.

Milner played guitar at age 18. He estimates he’s written more than 100 songs and is currently at work on his third album.

A native of Florence, Ky., he graduated from the University of Kentucky with a degree in political science.

“That explains why I’m a musician,” he observes.

He calls his music “death folk”; many of the lyrics deal with mortality.

“I perform mostly my own songs, but some of them are too dark for NIH, or have bad words,” he said. “My lyrics tend to have dark thoughts of impending doom, but that’s probably because of my disease.”

Milner first came to NIH last May; the July visit was his fourth.

The father of two daughters—ages 6 and 4 (the latter also carries a genetic mutation for cancer and “may be a patient here someday”)—Milner, like many musicians, has no health insurance.

“...I perform mostly my own songs, but some of them are too dark for NIH, or have bad words. My lyrics tend to have dark thoughts of impending doom, but that’s probably because of my disease.”

-KEVIN MILNER

“So I’m completely screwed,” he said. “That’s why I’m very appreciative to NIH. They saved my life. I’m really glad I got to play here.”

Milner planned to play one more gig in Indiana this summer before resting up for his surgery.

“I need to diet and exercise before the operation,” he said.

With his July performance, Milner joined a cadre that might be called the Grateful Living—musicians who came back to thank NIH with music. These include:

★ Famed classical pianist Leon Fleisher, who was successfully treated for dystonia at the Clinical Center. He filled Masur Auditorium in late 2004 in a concert given in gratitude for the care he received here.

★ Pianist and composer Clifford Smith, who said of the Clinical Center, “It is a holy place,” presented a concert of original music May 19, 2010, in the CRC atrium, in gratitude for successful treatment of prostate cancer.

★ Musician/dancer Ian Baptiste of Trinidad and Tobago brought his dance troupe to Masur on Sept. 2, 2004, to thank NIH for treating his aplastic anemia.

“I could play one last show here,” Milner said hopefully as he packed his guitar for the flight back to Kentucky. But just before he left town, his NIH medical team moved his procedure from mid-October to mid-August, effectively ending the summer tour.

Find out more about Milner’s music at kevinmilnermusic.com.
An enzyme produced by the CRISPR system known as Cas9 has been used to bind to a specific strand of DNA and cut it, eliminating the function of a targeted gene. But there has been concern about so-called “off-target” effects using Cas9—unwanted side effects that could be harmful to living organisms.

Zhang and his colleagues are improving Cas9 targeting specificity via engineering. Studies of its crystal structure and surface charge distribution have pushed the technology to the point that human studies are now foreseeable.

Zhang, whose talk can be seen in full at https://videocast.nih.gov/summary.asp?Live=23704&bhcp=1, said RNA guides for the CRISPR system can be easily synthesized and that loss-of-function and gain-of-function genetic screening are now possible. “We can now map noncoding elements of the genome,” he said.

Zhang and colleagues have modeled brain diseases in mice using CRISPR technology, especially in the context of autism, where they have found that the CHD8 gene is an important regulator of behavior.

“CRISPR diversity is also very exciting,” said Zhang, who is actively exploring the numerous distinct CRISPR systems with colleagues including Dr. Eugene Koonin, a senior investigator at the National Library of Medicine’s National Center for Biotechnology Information.

Cas9 is the best known editing system, but there are many others, he said, including Cas12, Cas13a and Cas13b.

NLM’s Koonin, whom Zhang described as “a genius,” is helping explore the diversity in two classes—single subunit and multi-subunit—in a systematic search for novel CRISPR effector proteins.

One targeting system, known as C2c2, can be used to detect biological pathogens and is the basis of the SHERLOCK detection assay, which can identify Zika virus via its RNA signature.

“Many more powerful tools and technologies await,” Zhang assured. “There are many additional tools to be discovered.”

Researchers Discuss Next Steps for Studying Hard-to-Treat Joint Tissue

Basic researchers, tissue engineers and orthopaedic surgeons recently met with NIAMS leadership and staff to discuss approaches for repairing injured or degenerated entheses.

An enthesis is a region where a tendon or ligament inserts into bone. Despite the many scientific discoveries that are illuminating the intracellular pathways and signaling molecules that contribute to tendon and ligament maintenance and healing, reattaching connective tissue to bone remains challenging. Preclinical advances in the field of regenerative medicine have enlisted scaffold technology, cell therapy and delivery of growth factors to re-establish the bone-tendon or bone-ligament interface, but few have been rigorously tested in patients.

Discussion focused on ways to address knowledge gaps that limit current treatment approaches to these injuries, to accelerate translation of basic findings to clinical interventions and to better understand and optimize therapies already in clinical use.
The congressional briefing, sponsored by the Alliance for Eye and Vision Research and the Tear Film and Ocular Surface Society, included (from l) Dr. Carolyn Begley, NEI-funded researcher and professor at Indiana University School of Optometry; Dr. Susan Vitale, research epidemiologist in NEI's Division of Epidemiology and Clinical Applications; and ORWH director Dr. Janine Austin Clayton.

PHOTO: DAVID EPSTEIN

New Dry Eye Therapies on Horizon, Report Highlighted on Capitol Hill

In recognition of Dry Eye Awareness month in July, the National Eye Institute shared news of how recent strides in understanding dry eye may lead to more effective and longer-lasting therapies for the condition, which affects millions of people in the United States.

One novel treatment undergoing testing in clinical trials is a synthetic form of lacritin, a protein that stimulates tear production. Another area of research is exploring factors that influence the ability of nerves in the eye to sense cooling from evaporation and trigger a tearing response.

Dry eye occurs when glands near the eye do not produce tears properly or when the tears evaporate too quickly. The result—which can feel like having sand in one's eye—is in some cases temporary. In others, it can be a chronic and progressive condition that leads to blurred vision or vision loss if left untreated. Currently available therapies for dry eye relieve symptoms, but do not address the underlying causes.

“Dry eye is a painful condition that more often affects women,” said Dr. Janine Austin Clayton, director of NIH's Office of Research on Women's Health. Health care providers need to be aware of this higher prevalence of dry eye among their female patients, she said at a July 12 Capitol Hill briefing.

The briefing also highlighted the newly released Tear Film and Ocular Surface Society Dry Eye Workshop II Report published in The Ocular Surface journal. The report updates the definition, classification and diagnosis of dry eye; critically evaluates the epidemiology, pathophysiology, mechanism and impact of the disease; addresses its management and therapy; and develops recommendations for the design of clinical trials to assess pharmaceutical interventions.

Pinn Symposium Celebrates Women’s Contributions to Health

BY MATTHEW E. ARNEGARD

Attendees at the 2nd annual NIH Vivian W. Pinn Symposium, held recently at Natcher Conference Center, engaged in an informative exchange on the important caregiving roles of women—as leaders and practitioners in health care and pivotal members of families and communities. Worsening health care trends for U.S. women were also discussed at the symposium, titled “Healthy Women Make Healthy Communities: Women as Makers.”

Prior to the main presentations, Dr. Janine Austin Clayton, director of the Office of Research on Women's Health, honored the accomplishments of Davene B. McCarthy White with the inaugural ORWH Director's Award for caregiving in the field of nursing and for dedication to the children and families of Washington, D.C. A neonatal nurse practitioner and Howard University clinical assistant professor of pediatrics and child health, McCarthy White founded the Boarder Babies Program in 1989 to help provide for the well-being of abandoned, abused and neglected babies. She also directs the HUH CARES (Howard University Hospital Comprehensive Area Resources Entitlements and Services) program, which offers medical and other support services for HIV-positive patients and their families.

Speakers at the symposium included: Jacquelyn Caglia, associate director of the women and health initiative at the Harvard T.H. Chan School of Public Health; Dr. Afaf Ibrahim Meleis, professor of nursing and sociology and dean emerita at the University of Pennsylvania School of Nursing and co-chair of the Commission on Women and Health; and Dr. Jennifer Karas Montez, assistant professor of sociology at Syracuse University.

Presentations featured the work of the Commission on Women and Health, a worldwide partnership led by The Lancet, Harvard’s women and health initiative and the University of Pennsylvania, as well as research on the impact of state-level policies on negative trends in U.S. women’s health.

Commission co-chairs Meleis and Caglia reported on the group’s 3-year effort to reframe women’s health to account for women’s contributions as caregivers—in their families, communities and health care institutions—as well as women's health care needs across the lifespan. The speakers recommended four ways to account more fully for women's roles, health and contributions: value women, count women, compensate women and be accountable to women.

In her presentation, Karas Montez painted a startling picture of declines in U.S. women’s health, zeroing in on county-level trends in mortality rates. She linked worsening trends in women's life expectancy to state policies. She said that 53 percent of the variation in women’s mortality rates from state to state can be attributed to state-level social, economic and policy factors, such as crime rate, unemployment rate and tobacco control measures. In contrast, state-level factors account for only 23 percent of the variation in mortality rates for men.

“What we’ve heard has the potential to deeply influence women’s health,” said Clayton in closing remarks. “Too often, women’s health is left out of the conversation, but it should be an integral part of every conversation related to health.” She encouraged attendees to count women, ask for the data associated with women, explicitly include women and do what they can to help improve the health of women in their individual spheres of influence.

The Pinn symposium was the pinnacle of ORWH’s celebrations of National Women’s Health Week. It honored ORWH's first full-time director, Dr. Vivian Pinn, who led the office for 20 years. Pinn, who attended the event, emphasized the importance of the information that was presented, saying she “couldn’t take notes fast enough.”

On one hand, blogging and posting on such sites as Facebook and Twitter raise questions of privacy and other concerns unique to the pediatric population. But posting such information often provides social and emotional support; this is particularly salient for parents of children with complex or critical illness.

“Since we know social support for parents with generally healthy children is important, it actually may be critical for parents of children with complex or life-limiting illness, particularly when a diagnosis requires daily care and monitoring,” said Dr. Silvana Barone, a pediatrician recently transplanted from Montreal who is currently a clinical fellow in pediatric hospice and palliative medicine at Johns Hopkins Hospital and a postdoctoral fellow at Johns Hopkins Berman Institute of Bioethics. She spoke at a recent NIH bioethics group discussion in Bldg. 50.

Barone specializes in caring for children with medical complexity. These chronically critically ill children face an uncertain prognosis and typically have prolonged, recurrent stays in intensive care.

During her residency, while caring for children in the neonatal and pediatric ICUs, Barone noticed parents documenting their children's health care journey online. That raised a multitude of questions including whether providers should engage online with families of patients.

“How can we, as providers, and should we, facilitate communication with these families for help with longitudinal decision-making, particularly for cases where outcomes are not so clear cut and there’s a lot of uncertainty?” Barone asked.

As technology evolves, so do guidelines for social media interactions in the medical community. “[The internet] changes the way we interact with our patients, for better or worse,” said Barone, and parents happen to be large consumers of social media.

But what happens when social media posts have the potential to compromise care?

Take the case of baby K, whose parents started blogging daily about her progress in the NICU. One of the nurses read the blog and was disheartened to see her competency questioned in such a public forum, especially since the parents never raised any concerns privately about her care. While the parents never named the nurse, the blog contained enough information to deduce her identity. The nurse, denied a transfer, nervously continued caring for the baby.

This is a clear case of a provider’s moral distress, said Barone, in which a professional

“...cannot perform optimally due to institutional or other constraints.

“There’s good data to suggest that moral distress among providers can lead to burnout, can impact quality of care and has been found to be a contributing factor to nurses and other providers leaving their profession.”

Should medical staff even read patient blogs? Some say they can learn about patients and provide better care, said Barone. Others suggest it’s wise to notify families before following them online. Some professional organizations encourage providers to use social media as an advocacy tool, but the Federation of State Medical Boards issued guidelines discouraging professionals from interacting with current or past patients on social media sites.

Baby K’s case also raises questions of privacy. “As providers, we have an obligation to maintain patient privacy and confidentiality,” said Barone. “But there’s no reciprocal obligation for members of the public.”

Parents who post about their kids on social media are free to praise or criticize medical staff and know they’re foregoing their privacy in the process.

“In pediatric cases, there’s an additional complexity to this issue of privacy,” said Barone. “because parents who choose to go public are no longer only foregoing their own privacy, but that of their child as well.”

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-DR. SILVANA BARONE

The ethical issues raised by social media aren’t new. “Professionals work to maintain patient privacy, to maintain appropriate therapeutic boundaries, to help patients and families make difficult decisions and to treat all patients fairly,” said Barone. “What’s changed is the speed with which complex issues can be publicized.”

The fact that social media posts can easily go viral means it’s just as easy for misinformation and hoaxes to spread quickly. Barone said physicians might have a responsibility to have a voice in this and set the record straight.

“I think there is a role for social media in modern health care delivery,” said Barone. “I think we need to remain relevant to those we seek to serve.”

**Ethics CONTINUED FROM PAGE 1**
Delaware Sen. Coons Visits, Gets Briefings on BRAIN, Parkinson’s, Ebola Vaccine

U.S. Sen. Chris Coons (D-DE), a member of the Senate appropriations committee, spent an afternoon at NIH on July 5. He met with NIH director Dr. Francis Collins before joining NINDS director Dr. Walter Koroshetz for an overview of the National Institute of Neurological Disorders and Stroke and the BRAIN Initiative.

Then, Dr. Daniel Reich, senior investigator in NINDS’s translational neuroradiology section, gave a presentation on multiple sclerosis research at NIH. Research in his lab focuses on the use of advanced MRI techniques to understand the sources of disability in multiple sclerosis and on ways of adapting those approaches for research trials and patient care.

Coons then visited the laboratory of Dr. Richard Youle, a senior investigator in the NINDS biochemistry section, who discussed his studies on the underlying causes of Parkinson’s disease and amyotrophic lateral sclerosis by deciphering the normal function of genes mutated in familial forms of neurodegenerative diseases. He has found interesting links between PD and the energy-producing mitochondria within the cell. His cell biology findings are followed up in animal models of PD and with drug-screening programs.

Dr. Jonathon Burman, an NINDS research fellow, demonstrated imaging technology of PD-linked proteins within cells and movies of PD mouse models showing that movement disorders are exacerbated by mitochondrial stress. Coons saw how drug-screening strategies are used to correct problems within the cell.

The senator later tweeted a photo of his chat with Burman, noting that “PD affects more than 2K Delawareans!”

Coons’s NIH tour concluded in the Vaccine Research Center, where he met with NIAID director Dr. Anthony Fauci (l) and visited Dr. Nancy Sullivan (r), VRC biodefense research section chief. After the briefings, Dr. Grace Chen, VRC Clinical Trials Program deputy chief, and Dr. Nancy Sullivan, VRC biodefense research section chief, joined the group for questions after the briefings.

Coons and company then visited Sullivan’s 2nd floor laboratory for her demo on VRC’s vaccine research activities and its efforts on an Ebola vaccine candidate that successfully progressed from basic research at NIH through human clinical trials domestically and internationally.

PHOTOS: CHIA-CHI CHARLIE CHANG
Moore
CONTINUED FROM PAGE 1

responsible for 1 out of 5 cancers worldwide,” said Moore, American Cancer Society professor at the University of Pittsburgh Cancer Institute. That number might be on the low side, he cautioned, since many developing countries are not likely to detect patients who have cancer caused by viruses.

In 1994, Moore and Chang discovered Kaposi’s sarcoma associated herpesvirus (KSHV), the viral cause of Kaposi’s sarcoma. Then, in 2008, they found Merkel cell polyomavirus (MCV), the viral cause of most Merkel cell carcinomas.

During the HIV/AIDS pandemic in the 1980s, the incidence of Kaposi’s sarcoma spiked. This is a cancer that can form in the skin, mucous membranes lining the mouth or nose, lymph nodes and other organs. At the time, “it was a remarkable incident in medicine,” said Moore, because cancers didn’t occur as epidemics. That school of thought changed when Moore and Chang discovered KSHV, the DNA virus responsible for Kaposi’s sarcoma. It became well-known that immunosuppressed patients developed sarcomas at higher rates.

“What’s different from other human tumor viruses is that KSHV in its evolution has stolen genes from the host genome,” Moore explained. “One thing that became quite clear is that many of these genes actually target the immune system.”

A healthy cell has a few options to ward off infection. It can, for example, stop dividing to prevent a virus from infecting other cells. The cell can also kill itself—a normal process called apoptosis. When KSHV infects a cell, he said, the virus disables the cell’s innate immune response and ability to kill itself.

Under certain circumstances, such as when a person’s immune system is weakened by HIV infection, KSHV can lead to the development of Kaposi’s sarcoma. Moore suspects the virus replicates only when certain functions in the immune system are weakened. When that happens, tumors can grow, as well. That suggests there’s an interplay between how the immune system controls infection and the prevention of tumor growth.

“If we have a tumor, which has a series of mutations and various tumor suppressor genes that happen to knock out innate immunity, then those tumor cells should

be more susceptible to viral infection,” he posited. This is the basis for viral oncolytic therapies that have been FDA-approved for treatment of melanoma, a serious form of skin cancer.

Moore then discussed MCV. A rare and aggressive form of skin cancer, Merkel cell carcinoma commonly occurs in patients with HIV and in elderly adults. Moore said identifying the virus was the result of a 7-year effort to develop a method that sequenced RNA found in tumors. The virus has two genes and it’s found in about 80 percent of all Merkel cell carcinomas.

MCV infections occur during childhood and are lifelong. The exact mechanism for how it persists is still not well characterized, but there are possible explanations. The virus integrates into human DNA. It cannot replicate on its own. Under most circumstances, Moore explained, MCV uses a mechanism called “protein-mediated viral latency.” This means the virus’s ability to replicate “has evolved to be constrained in expression.” In other words, the virus stays dormant until it becomes advantageous to replicate itself. That might be because cells mutate, for example.

“I don’t want to imply that this is the only mechanism that these small viruses use to maintain latency, but I think that it’s likely to be an important one,” he said.

There are many reasons why studying tumor virology is important, he noted. By learning, for instance, how viruses function, scientists can learn about interactions between the immune system and how tumors form.

These discoveries could be first steps toward developing vaccines for viruses responsible for causing 1 in 5 cases of cancer, which could “change the course of human cancer,” Moore concluded.
NINDS Welcomes New Class of Summer Students

BY SHANNON E. GARNETT

Each year, NINDS offers hands-on research training in brain and nervous system research to hundreds of students through its Summer Internship Program (SIP). This year, NINDS officially welcomed the 2017 class at an orientation on June 29.

“It’s really exciting to have all of the energy and enthusiasm we know you’re going to bring us this year,” said NINDS scientific director Dr. Alan Koretsky, who joined SIP coordinator Dr. Rita Devine, NINDS clinical director Dr. Avindra Nath and NINDS director Dr. Walter Koroshetz to give opening remarks.

The orientation featured presentations on NINDS’s Clinical Fellowship Program and Office of Technology Transfer, the NIH Blood Bank, as well as important IT security information and upcoming SIP event reminders.

SIP—founded more than 30 years ago by Levon Parker, former NINDS minority and special concerns program officer—provides a unique opportunity for academically trained high school, undergraduate, graduate and medical students to receive first-rate training in neurological research. Students get practical experience working with leading scientists in the institute’s Division of Intramural Research.

At the same time, students make a valuable contribution to the NINDS research mission.

“We really need people like you to think about neurological diseases and how you will contribute to therapies for them,” said Nath to the students.

This year’s class—consisting of 122 students from 20 different states and Guam—represent many of the country’s leading academic institutions, including NINDS grantee institutions. Over the past 10 years, the program has had a particular interest in attracting Native American students. This year, the class included more than 25 Native American students from more than 10 different tribes.

Throughout the summer, SIP students—94 first-timers and 28 returning to the program—are conducting research in 55 NINDS laboratories.

“As you are trying to decide your next steps in life,” said Koroshetz, “you want to shoot for something that will give you a fulfilling life. Science is one thing that can do that. For people who want freedom and power of thought, science offers that.”

As part of SIP, students engage in meetings and seminars within their labs and attend lectures and symposia. They also participate in other activities including NIH Summer Research Program Poster Day, which gives them an opportunity to present their work to the NIH scientific community, and NINDS’s Summer Program Awards ceremony, which recognizes exceptional students.

NHLBI Hosts Caribbean Capacity Building Workshop

While the burden of non-communicable diseases (NCDs) such as hypertension, heart disease, COPD and asthma has been pronounced in the U.S. for many years, rates of NCDs are now increasing in low- and middle-income countries (LMICs) at alarming rates. NCDs now constitute the primary causes of death throughout the world, with significant impact to the Caribbean region, where NCDs account for 2 out of 3 deaths overall and NCD management is overwhelming health care services.

Mitigating NCD burden in LMICs requires not only implementation of proven treatment strategies across the health care system, but also sufficient scientific and medical capacity to better understand effective intervention strategies and translate research into practice.

According to Dr. Glennis Andall-Breneron, senior technical officer for NCDs at the Caribbean Public Health Agency (CARPHA), “The NCD epidemic is having a negative impact on the populations and economies of our countries. There is an urgent need to identify what works and implement interventions which will be effective in reducing the burden of NCDs in the small island states of our region.”

In response, the Center for Translation Research and Implementation Science at the National Heart, Lung, and Blood Institute recently partnered with CARPHA to hold a 3-day capacity building technical assistance workshop in Georgetown, Guyana.

The workshop brought together more than 30 researchers and public health professionals from 5 Caribbean countries—along with representatives from the Global Alliance for Chronic Disease, CARPHA, Caribbean ministries of health, NHLBI, the National Cancer Institute, the Center for Scientific Review and Fogarty International Center—around a timely goal to better address the rise in NCD prevalence in the Caribbean region.

The workshop sought to provide early-stage research investigators and medical officers with the tools necessary to better utilize implementation science frameworks for driving improved health outcomes.

The workshop aimed to: expand knowledge of implementation science methodology and practice; introduce participants to both the NIH grant application and peer review processes; highlight key information about NIH funding mechanisms that best support participant research interests; and provide strategies for writing successful grant applications.

In response to the workshop, Dr. Kim Quimby, a participant from Barbados, remarked, “This workshop was a starting point for a new course in my career. It equipped me with the building blocks to study the implementation of proven interventions within my local health care setting. It has also made the process of applying to the NIH for funding feel much less daunting.”

Contact Dr. Brad Newsome (brad.newsome@nih.gov) for more information and conference resources.

PHOTO: SHANNON E. GARNETT

PHOTO: CARPHA

PHOTO: NIH
New Imaging Technique Overturns Longstanding Model Of DNA Folding

How can 6½ feet of DNA be folded into the tiny nucleus of a cell? Researchers funded by NIH have developed a new imaging method that visualizes a very different DNA structure, featuring small folds of DNA in close proximity. The study reveals that the DNA-protein structure, known as chromatin, is a much more diverse and flexible chain than previously thought. This provides exciting new insights into how chromatin directs a nimble interaction between different genes to regulate gene expression and provides a mechanism for chemical modifications of DNA to be maintained as cells divide. The results were featured in the July 28 issue of Science.

For decades, experiments suggested a hierarchical folding model in which DNA segments spooled around 11 nanometer-sized protein particles assembled into rigid fibers that folded into larger and larger loops to form chromosomes. However, that model was based on structures of chromatin in vitro after harsh chemical extraction of cellular components.

Now, researchers at the Salk Institute, La Jolla, Calif., funded by the NIH Common Fund, have developed an electron microscopy technique called ChromEMT that enables the 3-D structure and packing of DNA to be visualized inside the cell nucleus of intact cells.

Contrary to the longstanding textbook models, DNA forms flexible chromatin chains that have fluctuating diameters between 5 and 24 nanometers that collapse and pack together in a wide range of configurations and concentrations.

The newly observed and diverse array of structures provides for a more flexible human genome that can bend at varying lengths and rapidly collapse into chromosomes at cell division. It explains how variations in DNA sequences and interactions could result in different structures that exquisitely fine tune the activity and expression of genes.

“This is groundbreaking work that will change the genetics and biochemistry textbooks,” said Dr. Roderic Pettigrew, director of NIBIB, which administered the grant. “It’s an outstanding example of how constantly improving imaging techniques continue to show the true structure of everything from neuronal connections in the brain to the correct visualization of gene expression in the cell. It reveals how these complex biological structures are able to perform the myriad intricate and elaborate functions of the human body.”

Immune System May Wage an Attack in Parkinson’s Disease

A new study suggests that T cells, which help the body’s immune system recognize friend from foe, may play an important role in Parkinson’s disease (PD). The study, published in the journal Nature, was supported by NINDS.

PD is a neurodegenerative disorder in which dopamine-producing brain cells die off, resulting in tremors, muscle stiffness, loss of balance and slow movement. Additional symptoms may include emotional changes and disrupted sleep.

“This collaboration between neuroscientists and immunologists provides important new evidence for ways in which the immune system can play a role in PD, a link that can be used to further define this interaction,” said Dr. Beth-Anne Sieber, a program director at NINDS.

A research team examined the role of T cells in PD. Members collected blood samples from 67 individuals with Parkinson’s disease and 36 healthy controls. Immune cells were extracted from the samples and mixed with portions of the alpha-synuclein protein, which accumulates in the brains of people with PD and can result in cell death.

They found that T cells from people with PD responded to the presence of alpha-synuclein to a much greater degree than those gathered from the control group.

In particular, two regions of alpha-synuclein evoked reactions from T cells: a section that often contains mutations linked with PD and a portion undergoing a chemical change that can lead to accumulation of the protein in the brain.

The researchers identified four genetic variations that were associated with T cell reactivity to alpha-synuclein. More than half of people with PD carried at least one of those variants, compared to 20 percent of controls.

“These findings expose a potential biomarker for PD that may someday help in diagnosing the disease or be used to evaluate how well treatments are working,” said one of the researchers. According to the authors, the results suggest that PD may have characteristics of an autoimmune disease, in which the immune system incorrectly attacks the body’s own cells.

Researchers Unlock Regenerative Potential of Cells In Mouse Retina

Cells within an injured mouse eye can be coaxed into regenerating neurons and those new neurons appear to integrate themselves into the eye’s circuitry, new research shows. The findings potentially open the door to new treatments for eye trauma and retinal disease. The study appeared in the July 26 issue of Nature and was funded in part by NEI.

“The findings are significant because they suggest the feasibility of a novel approach for encouraging regeneration in the mammalian retina, the light sensitive tissue at the back of the eye that dies in many blinding diseases,” said Dr. Tom Greenwell, program director at NEI. “Importantly, the investigation also demonstrates that newly generated cells in the mouse retina not only look and behave like neurons, they also wire correctly to the existing neural circuitry at the back of the eye.”

The study looked to the zebrafish for clues about how to encourage regeneration in the mouse eye. When a zebrafish injures its eye, cells within the eye naturally regenerate, allowing the fish to maintain vision. Mammals lack this regenerative ability.

In studying zebrafish, the research team homed in on Müller glia, a type of retinal cell that supports the health and functioning of neighboring neurons and that also exhibits an innate regenerative ability. Sometimes referred to as the stem cells of the zebrafish eye, Müller glia are the cells from which all other types of retinal cells are regenerated in the fish.

“We’re showing for the first time that Müller glia in the adult mouse can give rise to new neurons after injury, and these neurons have the gene expression pattern, the morphology, the electrophysiology and the epigenetic program to look like interneurons instead of glia,” one of the researchers said.

The studied cells had formed functioning synapses—connections from one neuron to another—and responded to light in a way that’s typical of a type of interneuron. The cells had also integrated with retinal cells that convey signals to the brain.

The findings suggest that the regenerated cells were making synapses and integrating into both sides of the circuitry, presynaptically and postsynaptically. This approach could be useful for treatment of acute eye injuries and central retinal arterial occlusion—a stroke of the eye. The next step is to boost Müller glia numbers, researchers said.
Dr. Carol Pontzer, program director in the Division of Extramural Research at the National Center for Complementary and Integrative Health, died July 15 after a battle with brain cancer. As a program director, she oversaw a grants portfolio on complementary health approaches intended to modulate immunity. This included mitigation of symptoms, such as inflammation, and use of natural product interventions in diseases such as asthma/allergy and arthritis. She was a basic scientist with expertise in immunologic, genomic and proteomic methodologies.

Pontzer joined NCCIH in 2002. Prior to becoming a program director, she was a scientific review officer at NCCIH.

“NCCIH not only grieves the passing of a valued scientist colleague but also mourns the great loss to her family and the scientific community,” said Dr. Emmeline Edwards, division director. “Carol was a knowledgeable, devoted and effective colleague but also mourns the great loss to her family and the scientific community,” reported Dr. Emmeline Edwards, division director. “Carol was a knowledgeable, devoted and effective

Before joining NCCIH, Pontzer worked at the department of cell biology and molecular genetics at the University of Maryland. There she worked on the structure/function relationship of immune modifiers, creating a panel of type I interferons with mutations that altered receptor binding, JAK/STAT signaling and subsequent activity and toxicity.

Pontzer received her postdoctoral training at the University of Florida. It was there that she began working on structural studies of type I interferons and binding of staphylococcal enterotoxins to MHC using synthetic peptide mimetics and inhibitors. Together with Dr. Howard Johnson and Dr. Fuller Bazer, she identified and characterized the activity of a novel subtype of interferon, interferon tau.

Pontzer received a Ph.D. in biology from Marquette University. She taught immunology and microbiology for 11 years at UMD. She continued to teach immunology online until her passing. She had almost 70 peer-reviewed publications.

Memorial services were held at St. Leo Catholic Church in Ridgway, Pa. Pontzer’s family has established a memorial fund in her name at the Ridgway Public Library, 329 Center St., Ridgway, PA 15853.

Pontzer is survived by husband Norbert, children Nicholas Pontzer, Emily Nizialek and Peter Pontzer and several grandchildren.
The students who came to NIH on June 26 to narrow down their career choices were out of luck. They were introduced to more opportunities than they dreamed possible.

Through presentations, demonstrations, tours, NIH staffers wearing “Ask me about my awesome job” buttons and even a little wizardry, students from Johns Hopkins University’s Center for Talented Youth participated in a day of scientific inquiry designed especially for them.

Cosponsored by NLM and NHGRI, “Genetics, Bioinformatics and Biomedicine” attracted 75 middle and high school students, their parents and the occasional grandparent.

NLM director Dr. Patricia Flatley Brennan welcomed the students and immediately began busting myths. She listed three stereotypes about libraries: They’re all about books, being quiet and librarians as nice ladies who wear glasses.

While you can certainly find all of these at NLM—Brennan loves books, likes quiet and is a lady who wears glasses—this day for students wasn’t about any of them. Brennan encouraged the students to make some noise. This was to be a day to get excited about data as a platform for discoveries and pathways for engagement—and much more.

Dr. Terry Yoo from NLM’s Office of High Performance Computing and Communications could relate to the audience in a unique way: His profession has taken him from a kid who loved cartooning and animals to medical doctor to artist at NLM, where he combines many things he enjoys: writing, clinical medicine, public speaking, animation and cartooning.

Donald Bliss talked about his cutting-edge work—calling it “bleeding edge” work—and showed images, including a model of a dendritic cell that looks like it could be a rose.

“Most textbook models of dendritic cells show a cell body with finger-like appendages,” he explained.

Bliss made the case for doing what you love. He said, “Sometimes, I can’t believe I get paid to have this much fun.”

Elizabeth Tuck and the team leading the bioinformatics session from NHGRI set the students up with a simulation to experience how scientists investigate and narrow down a large data set.

She used the real-life example of Nic Volker, a child from Wisconsin who developed a mysterious, life-threatening disease that ravaged his intestines, making it impossible for him to eat normally and causing terrible pain. The students could see for themselves how gene sequencing helped researchers identify a mutation in Volker’s XIAP gene, which led to treatment that saved his life.

Tuck, a genomics education specialist, also had case studies on other illnesses, including cystic fibrosis and sickle cell disease. She said that students got the satisfaction of solving medical mysteries.

Throughout the day, parents—and students who were interested—took tours of the library, which included information about the architecture of the main library building and views of ancient medical texts.

During lunch, NHGRI and NLM staff mingled with the students so they could answer questions about anything from communicating about asthma to sequencing the genome for Zika.

Afternoon keynote speaker Dr. David Landsman of NLM shared information, fun facts and enthusiasm about his area of expertise and interest: merging results obtained in biology analyses with those derived from experiments in biochemistry, molecular biology, cell biology and genetics.

The senior investigator in the National Center on Biotechnology Information told the audience that there is a large amount of foreign DNA living on and in your body. He went on to explain how humans have bacteria and viruses on their bodies and that bacteria living in the crease of your elbow are different from the ones on your arms. He even rubbed his hands together and blew away some DNA.

In the Q&A session, he answered questions on everything from basic science to ethics.

In her remarks at the end of the program, Dr. Carla Easter, chief of NHGRI’s Education and Community Involvement Branch, wanted the students to realize that there is “an abundance of opportunities in every aspect of science. One day, maybe one of these students will become a colleague.”

Many students and parents stayed beyond the formal program to check out the NLM exhibition Harry Potter’s World: Renaissance Science, Magic, and Medicine, created in celebration of the 20th anniversary of the Harry Potter series.

Perhaps Prof. Albus Dumbledore’s words of wisdom to Harry Potter in The Chamber of Secrets summed up the day: “It is our choices, Harry, that show what we truly are, far more than our abilities.”