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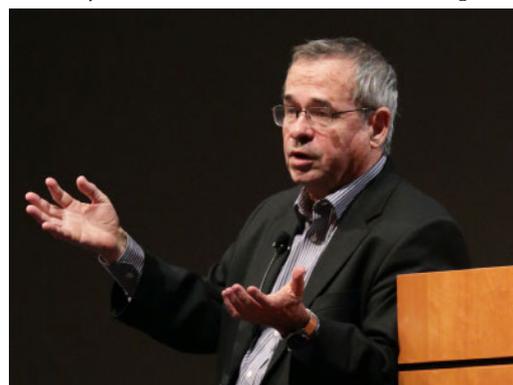
'Father of Computational Enzymology'

Nobel Laureate Warshel Visits NIH Ahead of Stockholm

By Carla Garnett

How do complex chemical systems in the body work? We can answer this question, see simulations of the answer and even possibly visualize what sometimes goes awry—largely because of work done by 2013 Nobel laureate Dr. Arieh Warshel, who spent the last 45+ years disproving an idea he had as an undergrad.

“So the overall issue is, how do you model biological functions?” he said, showing an unpublished scientific manuscript he wrote in 1965. “I have been interested in enzymes since my undergraduate work in the Technion [Israel], where I looked at the effect of ionic strengths on the speed of chymotrypsin and concluded that electrostatic [force] is not important, which of course is wrong.”



2013 Nobel laureate Dr. Arieh Warshel

SEE WARSHEL, PAGE 4

Can Chinese Herbs Treat Cancer Pain?

NCI Collaborates with Beijing Clinician-Scientist

By Belle Waring

When Dr. Zhizheng Zhao left Beijing to do research at NCI-Frederick, he brought 5 years of experience as a physician and scientist in the oncology department of Guang'anmen Hospital, one of the largest integrative medicine hospitals in China.

“I was quite interested in oncology,” he says, “because this will really benefit more patients.”

Zhao trained and practiced in Beijing, where air pollution is several times above WHO's recommended health threshold. More people die from lung cancer each year in China than from any other type of cancer.

“China has sacrificed the environment for economic growth,” Zhao says. “So we need a lot of methods to deal with diseases associated with environmental change.” These include chemotherapy, immunotherapy, surgery and TCM (traditional Chinese medicine). Successfully using TCM requires learning the theory behind it in order to correctly combine Western and

SEE ZHAO, PAGE 8

Geroscience Summit Examines Intersection of Aging, Chronic Disease

By Barbara Cire

Nearly 500 scientists, advocates and others interested in health and aging gathered in Natcher Conference Center recently for “Advances in Geroscience: Impact on Healthspan and Chronic Disease.”

The meeting's focus on “geroscience,” an integrated approach to the study of the diseases and disability associated with growing older, offered participants an opportunity to explore the interplay between chronic disease and its biggest risk factor—aging—in the hope of eventually opening new avenues for prevention and treatment.

NIH director Dr. Francis Collins welcomed participants, noting that geroscience represents the convergence of diverse areas of medical and scientific research on aging and disease. Increasingly, he said, a more careful study of the process of aging is allowing scientists to propose that risk factors for disease, including aging, need to be considered together rather than in isolation. This applies to most major chronic diseases including cardiovascular dis-

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NIH...Turning Discovery Into Health

briefs

STEP Forum on Health Equity, Feb. 13

The staff training in extramural programs (STEP) committee will present "Moving Towards Health Equity: What If We Were All Equal?" on Thursday, Feb. 13 from 9 a.m. to noon in Lister Hill Auditorium, Bldg. 38A.

We all want optimal health, but why is it elusive for some and not others? How do social determinants of health accelerate or impede individual and population-level strategies for achieving health equity? What makes health disparities so persistent and eliminating them so challenging? Join us to explore these questions and learn more about the science of health disparities, promising interventions and frameworks for achieving health equity for all.

Cell Day Set, Feb. 28

This year's Cell Day, an interactive web chat targeted to middle and high school students but open to all, is on Friday, Feb. 28 from 10 a.m. to 3 p.m. Scientists at NIGMS, which is sponsoring the event, will field questions about cells, careers in research and related topics. The activity is modeled on similar efforts by other NIH institutes and centers. See <http://publications.nigms.nih.gov/cellday2014/> to join the live event, read the transcript afterward and find out more.

Sailing Association Open House, Feb. 27

The NIH Sailing Association invites everyone to its open house on Thursday, Feb. 27 from 5 to 8 p.m. at the FAES House at the corner of Old Georgetown Rd. and Cedar Ln. Explore your interest in learning to sail and discover opportunities for sailing with the NIHSA. There will be information about 6-week basic training classes, the club's racing program and social activities offered by NIHSA. A fee of \$5 at the door includes pizza, drinks and snacks. Cash bar for beer and wine—\$2 each. Look for NIHSA posters and flyers around campus. For more information, visit www.nih sail.org.

NIH Management Intern Program Recruits

Unlock a new career path with the NIH Management Intern Program, which is recruiting Apr. 7-11. The MI Program is a highly competitive, 2-year career-development program for current NIH employees. MIs come from a variety of job backgrounds including both scientific and administrative fields. Upon completion of the program, MIs transition into an administrative-

management career in one of many areas throughout the NIH enterprise. Eligible employees are invited to apply. For program FAQs, upcoming information sessions and details about eligibility, visit <http://trainingcenter.nih.gov/intern/mi/>.

Author Vedantam To Present DDM Seminar

The Deputy Director for Management (DDM) announces the second seminar of the 2013-2014 series "Management and Science: Partnering for Excellence" on Thursday, Feb. 13 from 11 a.m. to 12:30 p.m. in Masur Auditorium, Bldg. 10. NPR science correspondent Shankar



Vedantam will discuss "The Hidden Brain." His talk will focus on judgment and decision-making in challenging times. Videocasting and sign language will be provided. Individuals who need reasonable accommodation to attend should call (301) 496-6211 or the Federal Relay Service at (800) 877-8339. For more information about the series, visit www.ddmseries.od.nih.gov or call (301) 496-3271.

Children's Inn Gets \$100K Gift

The Children's Inn at NIH recently received a donation of \$100,000 from Leidos, a company formerly known as SAIC, to support the inn's park and playground.

"We are tremendously grateful to Leidos for their continued commitment, both financially and through all the ways they make life easier for our families," said Kathy Russell, inn chief executive officer.

In addition to the recent donation, Leidos provided 25 gift cards to families staying at the inn during the holidays. "We understand the stress that the families endure while their children are getting treatment at the Clinical Center and it's especially difficult during the holidays," said Steve Comber, president of Leidos Health. "The gift cards were given to offset a small part of that stress."

The relationship between Leidos and the inn dates back to 2011. Leidos employees contribute to special projects such as construction of the inn's park and playground, which opened in 2013. The area offers children of all ages—and grown-ups, too—a place to relax and recharge after medical treatments. Some of the park's features were created after receiving design tips from children.

The donation marks a pledge of continued support from Leidos—nearly \$500,000 since 2011—coupled with ongoing volunteer support from Leidos employees.

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Shown above, gender summit participants included (from l): ORWH director Dr. Janine Clayton, Dr. Lynn Adams, Dr. Rosemarie Filart and Dr. Joan Nagel. At rear is Adams' poster, "NIH Supports the Advancement of Women in Biomedical Careers." In the photo at right, serving on a summit panel are (from l) Dr. Stephen Fiore, Dr. Susan Winter, Dr. Jeanne-Marie Guise, Dr. Judy Regensteiner and ORWH's Nagel. They participated in a discussion following the session "Fostering Interdisciplinary Careers."

PHOTOS: LYNN S. ADAMS

NIH Addresses Gender Issues in Research On International Stage

NIH's Office of Research on Women's Health recently convened the International Gender Summit 3-North America. More than 100 speakers from 20 countries participated. The summit engaged researchers, policy makers, science and innovation leaders and other stakeholders in science, technology, engineering and math to address gender issues in research and innovation with the goal of increasing the efficacy, quality and success of these sectors.

The GS3 also created an online community to facilitate sharing ideas and documents with other summit attendees. Discussions continued months after GS3 via the online community; given the level of enthusiasm, they may persist until GS4 in 2014.

ORWH participated in two workshops: "Integrating Gender Dimension into Medical Researcher Training," chaired by ORWH director Dr. Janine Clayton, and "Fostering Interdisciplinary Careers," chaired by Dr. Joan Nagel, ORWH medical officer. The sessions were designed to provide practical examples, approaches and methods that have been implemented within institutions for biomedical research and investigator training and that may be adopted more broadly across a range of areas where attention to gender issues is imperative.

"Sex and gender are fundamental variables that affect health and disease, in women and in men," said Clayton. "But they are different: Sex is defined by biology and gender is influenced by social, cultural and behavioral norms. This summit did a terrific job explaining why we need to incorporate sex and gender questions into research across the spectrum from cells to selves."

Panelists included experts from Germany, Canada, Mexico and the U.S. who identified challenges and offered practical solutions to issues such as measuring the health effects of gender, promoting more gender-aware diagnosing and treatment, sex effects in the susceptibility to cancer, how gendered innovations can be used for training and women's health curricula and inter-professional collaboration across health professions.

"Bringing women into the fold of biomedical research is one of the best ways to be sure we include diverse perspectives to solve problems that affect not only women, but also men," Clayton said. "But we need to do a better job developing women for leadership positions and an even better job at keeping them there."

During the poster session, Dr. Lynn Adams of ORWH presented, "NIH Supports the Advancement of Women in Biomedical Careers." It highlighted key accomplishments of the NIH working group on women in biomedical careers, including the Women of Color Research Network and the Leave Bank program, which was recently extended NIH-wide.

Overall, panelists made it clear that in order to make significant progress toward the goal of successfully integrating women into science and engineering as experimenters, research subjects and leaders, it is imperative to better integrate teams of scientists, physicians and patients as well as the policy community. 🗳

NIDDK's Tabor Reaches 70-Year Milestone

At the NIDDK Employee Appreciation Awards Ceremony on Jan. 6, NIDDK senior investigator Dr. Herbert Tabor (l) received a framed certificate commemorating his 70-year career at NIH from NIDDK director Dr. Griffin Rodgers. Tabor also received a congratulatory letter from President Barack Obama. Tabor and his colleagues were the first to discover the biosynthetic pathway of the polyamines spermidine and spermine and to study the function of the genes involved, as well as to develop sensitive assay procedures. This early research has spawned more than 13,000 papers involving the compounds spermidine or spermine. Tabor was named editor-in-chief of the *Journal of Biological Chemistry* in 1971 and is now editor-in-chief emeritus. In 1977, he was elected to the National Academy of Sciences.



PHOTO: BILL BRANSON

WARSHEL

CONTINUED FROM PAGE 1

Right:

Warshel (l), with NIH deputy director for intramural research Dr. Michael Gottesman, takes questions following the lecture.

Below:

The 2013 Nobel laureate pauses for a photo op with Dr. Dale Lewis of NCI.

PHOTOS: BILL BRANSON



Chymotrypsin, an enzyme active in the pancreas, breaks down proteins in the body's digestive system. Electrostatics describes the phenomena of electric charges that inhabit or are produced by just about everything. Warshel and colleagues have spent the last four decades uncovering the complicated functions of biological chemical systems at the molecular level and devising ways to make computers simulate those functions.

Offering a recent talk he described as “some part taken from the draft of the Nobel lecture, some part a little more hard-core,” Warshel was the final NIH-supported 2013 laureate scheduled to discuss his award-winning research here before accepting the prize in Stockholm in December.

A distinguished professor of chemistry at the University of Southern California, Warshel—along with Stanford's Dr. Michael Levitt and Harvard's Dr. Martin Karplus—won 2013's Nobel in chemistry for developing multiscale models of complex chemical systems.

In the month following announcement of the awards, NIH's lecture circuit was chock-full of grantee Nobelists: Dr. Randy Schekman, co-winner of the 2013 prize for medicine or physiology; Warshel's good friend and collaborator Levitt; and Warshel all spoke at NIH within 3 weeks of each other.

Introducing the guest speaker, NIH deputy director for intramural research Dr. Michael Gottesman said Warshel “combines classical mechanics with quantum mechanics to model large systems. This is a combination of two approaches to understand complicated molecules at multiple levels. For this reason, [he] is considered the father of computational enzymology...His calculations have made contributions to a wide range of biological problems, including understanding mechanisms in vision, photosynthesis, ion channels, protein transport and protein folding.”

An NIH grantee since 1976, with support from NEI, NIGMS and NCI, Warshel was born in a kibbutz in Israel and spent 3½ years in the Israeli army, reaching the rank of captain in the reserve. After military service, he resumed his interest in chemistry, eventually studying Cartesian force fields, molecular mechanics, protein folding and other enzymatic reactions.

Throughout his early research career, however, Warshel said he kept returning to his original problem: needing a model to truly understand how enzymes work.



“When you try to study the function of proteins, there are problems that it's very hard to understand—even when you have the biochemistry and the structure,” he explained. “You still don't really know how it works...In my view, you could do it only with a computer.”

He likened the pursuit to trying to see how a clock works, by simply viewing its inner cogs and wheels.

“I would say biochemistry is the discovery of the clock, crystallography shows us the parts, single molecules determine how fast the motion [of the wheels] is, but we still need a model,” he said.

Over the next several years, Warshel said he and colleagues “studied countless mutations and many different enzymatic reactions. We showed that we could reproduce the observed effect of mutations. More importantly, we showed that in any single case that we studied, at least 90 percent of the catalysis is due to electrostatic effect.”

Showing a self-deprecating sense of humor, Warshel liberally sprinkled his lecture—“Computer Simulations of Biological Functions”—with pop culture references. He used, for instance, an animation of the video game Pac-Man to illustrate chemical reactions versus regular reactions with and without enzymes. The soundtrack behind his animation of motor protein myosin's walking motion was *Gangnam Style*, the chart-topping recording by South Korean artist Psy.

“I gave the lecture in Korea, you see,” Warshel quipped in explanation.

The computer modeling system that he developed has just as broad appeal: It has implications for every biological function in health and disease, from perhaps predicting HIV's next move to calculating the path of drug resistance.

“There is nothing you cannot model relatively realistically, if you use a computer,” Warshel concluded.

The full lecture is archived online at <http://videocast.nih.gov/summary.asp?Live=13368>. ●

Kidney Cancer Genes Identified Through Trans-NIH Effort

By Eric Bock

When Dr. W. Marston Linehan came to NIH in 1982, kidney cancer was thought to be a single disease. Now, kidney cancer is known to be a number of different cancers that happen to occur in the kidney.

Linehan, chief of the Urologic Oncology Branch in NCI's Center for Cancer Research, reviewed progress made in understanding the genetic basis of kidney cancer when he gave the Astute Clinician Lecture in Masur Auditorium recently.

Linehan began his career at NIH as a senior investigator and urologist-in-charge at NCI. Early in his career, when he and his colleague Dr. Berton Zbar examined the tumors of patients with kidney cancer, they found the same chromosomal abnormality, a loss of a segment of chromosome 3. Their next step was to find the location of the chromosome 3 gene.

Linehan and his colleagues devoted a number of years to searching for the gene's location before they concluded that his strategy was too slow. At the rate they were going, it could've taken almost 55 years to pinpoint the gene and determine its sequence. A colleague advised him that if there were a hereditary version of kidney cancer, he might find the gene by studying kidney cancer families.

"We set up a hereditary cancer program here at NIH to bring in families and evaluate them and determine who is affected and who wasn't, so we could perform a genetic linkage analysis to identify the disease," Linehan said. "Over the years, we have had the unbelievable opportunity to evaluate nearly 1,000 families."

The program brings families to the Clinical Center, where NIH researchers can study them. Linehan assembled a team of urologic and general surgeons, geneticists, radiologists, nurses, data managers, urologic oncology fellows, neurosurgeons, ophthalmologists, basic scientists and statisticians to work together to find the genetic basis.

Since the program began, Linehan and his colleagues have discovered 5 different types of inherited kidney cancers and identified the genetic basis of 5 different types of kidney cancer. Each is caused by a different genetic mutation that interferes with cells' ability to recognize and react to abnormalities in oxygen, iron, nutrients or energy.

Linehan and his colleagues have used what they



NCI's Dr. Marston Linehan said of his branch's work, "We could not have done this anywhere other than here at the Clinical Center."

me the other day, "You work with 137 different people from 29 labs and branches, from 9 different institutes." ❶

learned to provide the foundation for the development of individual targeted therapeutic approaches for each type of kidney cancer. The FDA has since approved seven drugs for the treatment of advanced kidney cancer. "As thrilled as we are about this, we are not home yet," Linehan said. "We still have a ways to go before we will see the development of effective forms of therapy for every patient with this disease."

Linehan stressed that his research could not have taken place anywhere else. "We could not have done this anywhere other than here at the Clinical Center," he said. "It is truly an NIH project. My assistant told

NCI's Lewis Tops Photo Contest

Dr. Dale Lewis, a staff scientist at the National Cancer Institute, placed both first and second in the ORS Division of Occupational Health and Safety's third annual "In Focus! Safe Workplaces for All" photo contest. His first-place photo (top right) features a laboratory workplace and two employees wearing protective equipment, following safety procedures. His second-place photo (right) shows a crew of workers



washing windows at the new addition to the Porter Neuroscience Research Center. Third place was awarded to two other NCI employees, Diane Poole and Amanda Lyon, for their comic-strip style portrayal of "Safety Girl." At left, ORS director Dr. Alfred Johnson (l) presents Lewis his awards at a recent ceremony.

SUMMIT

CONTINUED FROM PAGE 1

Right:

NIA's Dr. Felipe Sierra, of the geroscience interest group, speaks at the recent summit.

Below:

NIH director Dr. Francis Collins discusses his research on progeria.

PHOTOS: BILL BRANSON



ease, cancer, Alzheimer's and many others.

As an example, Collins mentioned his own research interest in Hutchinson-Gilford progeria, a rare genetic disease that causes premature aging in young children. He pointed out that the immunosuppressant rapamycin, which has been found to minimize some of the effects of progeria, also has been shown in other aging-related research to extend the lifespan of mice by mimicking the effects of calorie restriction.

Geroscience, he said, is "a field in wonderful ferment...that has the potential of showing a path toward longevity."

The summit was developed by a relatively new organization—the trans-NIH geroscience interest group, or GSIG. With some 20 institutes and centers participating, the group was founded by program scientists from NIA and other institutes to find ways to collaborate and coordinate efforts.

The conference brought together 50 investigators from several disciplines to examine how the biology of aging drives chronic disease. Following Collins' remarks, Dr. Christopher Murray, professor of global health at the University of Washington; Dr. Brian Kennedy, president and CEO of the Buck Institute for Research on Aging; and Dr. Linda Fried, dean of the Mailman School of Public Health at Columbia University, presented talks.

Murray discussed the Global Burden of Disease, Injuries and Risk Factors Study, a systematic effort to assess and compare the magnitude of "health loss" worldwide. Health loss is a comparison of reported health and death rates in a population against some ideal, which in this case is full health with a life expectancy of 86 years. The study measures more than 1,000 clinical outcomes, including the prevalence of—and mortality due to—many chronic diseases, lifespan and years lived with disability.

Murray noted that the study, with its vast online database of results, helps identify patterns of disease and disability. It offers geroscientists a valuable source of data about changes in risk factors such as high blood pressure and obesity. Drilling down into these data could help scientists and others target interventions to improve health and guide public health policy and spending.

With the global population over age 65 projected to rise to 2 billion by 2050, Kennedy said, studying the molecular causes of aging could one day help humans live in better health. "The events that are driving aging are the events that are driv-



ing disease," he said, citing inflammation, stress and the adaptation to stress that occur during the aging process over time, changes in epigenetics, changes in metabolism and the onset of macromolecular damage with age. "It is my hope that thinking about aging processes and using this as an opportunity to look at diseases of aging from a new perspective may lead to new therapeutic approaches to treating them."

Fried, a clinician-researcher, addressed frailty and aging, asking about possible biological underpinnings. Frailty is a syndrome of shrinking, slowing and weakness with low activity and low energy that increases with age and predicts disability and mortality. It also is linked to a range of chronic diseases including cardiovascular disease, late-life depression and inflammatory diseases. "There is mounting evidence that the biological changes of aging are the drivers of frailty," Fried said, noting that changes at the molecular and genetic levels leading to frailty may also be involved in the development of disease.

Seven scientific sessions addressed topics in aging and chronic disease. At one panel, researchers discussed how low-grade, persistent inflammation associated with aging—a condition panel co-chair Dr. Claudio Franceschi of the Università di Bologna calls "inflammaging"—differs from the protective immune response and repair mechanism and contributes to risk for chronic disease. Another panel on epigenetics discussed several mechanisms by which it regulates genes at the chromatin level and how epigenetic changes contribute to aging and chronic disease. All the sessions explored such commonalities in aging and disease, looking at what is known and what would be beneficial to find out.

At the end of the conference, NIA director Dr. Richard Hodes said he hoped the meeting would encourage further conversations about commonalities of the mechanisms of aging and their impact on disease. NIH is committed to fostering this approach to research, he said, encouraging the audience "to maintain contact with those of us at NIA and all the institutes that have been collaborating here to make sure we make a go of this...we're certainly not going to be bashful about following scientific imperative." 🗣️

Obama Honors Outstanding Early Career NIH Scientists

In late December, President Obama chose three NIH intramural scientists and 17 grantees for the 2012 Presidential Early Career Award for Scientists and Engineers. PECASE is the highest honor bestowed by the government to outstanding scientists and engineers beginning their independent careers.

“This presidential award is extremely prestigious and recognizes the achievements of scientists early in their career,” said NIH director Dr. Francis Collins. “These scientists have demonstrated the value of their current work along with the promise of future discoveries to improve the health of our nation. We are very excited about the new PECASE recipients.”

The intramural awardees are:

Dr. Jessica Gill, Lasker clinical research scholar at NINR, “For an investigation of the predictors of neurological deficits and post-traumatic stress disorder onset following traumatic brain injury.”



Dr. Jessica Gill

Dr. Susan Harbison, Earl Stadtman investigator in NHLBI’s Laboratory of Systems Genetics, “For studies on the impact of drugs on genetic networks affecting sleep.”



Dr. Susan Harbison

Dr. Todd Macfarlan, head of the unit on mammalian epigenome reprogramming in NICHD’s Program in Genomics of Differentiation, “For research on mechanisms of mammalian epigenome reprogramming.”



Dr. Todd Macfarlan

Grantee winners include Dr. Debra Auguste, City College of New York; Dr. Jeremy Clark, University of Washington; Dr. Damien Fair, Oregon Health and Science University; Dr. Thomas

Fazio, University of Massachusetts Medical School; Dr. Andrew Goodman, Yale University School of Medicine; Dr. Xue Han, Boston University; Dr. Richard Ho, Vanderbilt University Medical Center; Dr. Shingo Kajimura, University of California at San Francisco; Dr. Young Kim, Yale University School of Medicine; Dr. Gaby Maimon, Rockefeller University; Dr. Sandra McAllister, Harvard Medical School; Dr. Quyen Nguyen, University of California at San Diego; Dr. Sallie Permar, Duke University School of Medicine; Dr. Katherine Radek, Loyola University Chicago; Dr. Katherine Rauen, University of California at San Francisco; Dr. Ida Spruill, Medical University of South Carolina; Dr. Andrew Yoo, Washington University School of Medicine.

Since the program began in 1996, NIH has funded 233 PECASE recipients. The NIH awardees will take their places along with 102 other highly accomplished scientists from a number of federal agencies. The young scientists will be honored by the President at a White House ceremony sometime in 2014. ●

NINR Launches Innovative Questions Initiative

The National Institute of Nursing Research recently kicked off its Innovative Questions (IQ) initiative with a workshop on symptom science. Leading scientists and interdisciplinary experts discussed research questions to guide the future of nursing science. The workshop set the tone for the broader IQ initiative, which features a series of workshops and a public web site designed for online engagement.

“The Innovative Questions initiative is designed to advance NINR’s research agenda by engaging with stakeholders within our community, providing you, your colleagues and the public opportunities to help shape the future of nursing science,” said NINR director Dr. Patricia Grady. “The IQ initiative will help us identify innovative research questions to guide our efforts.”

NINR supports clinical, biological and translational research in many areas, including symptom science, wellness, self-management and end-of-life and palliative care. Nursing science draws together experts from diverse disciplines and professions—from nursing and medicine to engineering and business management. “The interdisciplinary nature of nursing science is why continually engaging with a diverse group of stakeholders is important to its advancement,” explained Grady. “IQ is one strategy for facilitating this engagement here and across the country.”

Each IQ workshop will focus on major themes that flow from NINR’s strategic plan. The IQ web site, which launched in mid-November, solicits innovative research questions directly from the scientific community, professional organizations and the public. Visitors to the site have an opportunity to submit research questions and to review and comment on questions submitted by others.

“This initiative is an excellent opportunity for our community to play a role in guiding nursing science,” Grady said. “The questions identified through this initiative offer the promise of generating the novel research and interventions vital to the advancement of nursing science and health care now and in years to come.”

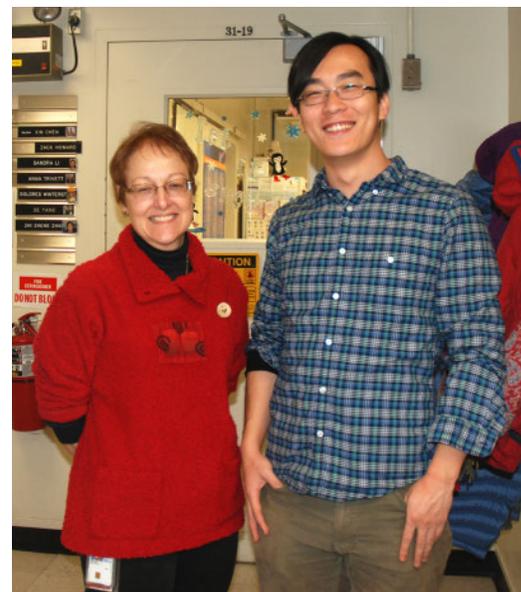
To learn more about the initiative or to submit innovative research questions, visit www.ninr.nih.gov/IQ.—Natalie Zeigler



NINR director Dr. Patricia Grady (c) addresses the “Symptom Science: Promoting Personalized Health Strategies” workshop participants.

ZHAO

CONTINUED FROM PAGE 1



Right:

Dr. Zhizheng Zhao (r) of China with his NCI mentor Dr. O.M. Zack Howard

PHOTO: BELLE WARING

Eastern therapies for optimum benefit to the cancer patient.

“Their version of integrative medicine means that you get what works,” says Dr. O.M. Zack Howard, Zhao’s lab supervisor and mentor. “They have clinics for acupuncture, cupping, moxibustion—you get TCM along with chemotherapy.”

Zhao’s goal: To improve the integration of traditional Chinese medicine with modern chemotherapy and immunotherapy.

Zhao has spent the past 2 years as an adjunct investigator in NCI’s Laboratory of Molecular Immunoregulation, part of the newly formed Cancer and Inflammation Program.

Howard met Zhao’s supervisor, Dr. Hongsheng Lin, at an international meeting hosted by NCI’s Office of Cancer Complementary and Alternative Medicine. Lin’s dedication to improving all patient outcomes by combining and standardizing Eastern and Western medicine led to their initial collaboration in 2007.

Zhao is the third scientist to visit the lab in the ongoing partnership between NCI and Guang’anmen Hospital, a clinical research center and part of the China Academy of Chinese Medical Sciences. He is the first to focus on cancer-induced hyperalgesia (increased sensitivity to pain).

His focus: Relief of cancer-induced hyperalgesia using FKI (Fufang Kushen injection), an extract of two herbal roots, *Sophora flavescens* and *Rhizoma smilacis glabrae*. FKI is widely used in Chinese hospitals to control cancer progression and cancer-related symptoms, especially pain.

His models: Both *in vitro* and *in vivo*, Zhao uses a mouse model of sarcoma, a type of cancer, injected near a major nerve.

The data has shown that FKI can both reduce pain and inhibit tumor growth in the mouse. So Zhao combined FKI with doxorubicin, the standard of care for sarcoma, to look for the best combination therapy. With Howard’s help, Zhao’s experiments showed that doxorubicin and FKI use signaling pathways that counteract, rather than support, each other. As a result, Zhao has not yet succeeded in finding the best drug combination therapy.

Still, Howard said, “He gave us an idea of how FKI works. And now that we know how it

works, we can identify tumors that would be likely to respond to it.”

Zhao’s model confirms existing mechanisms for cancer-associated pain. “He also showed us,” says Howard, “that this tumor itself, while it can destroy the region around the nerve, doesn’t actually invade the nerve until very late...This means that there are aspects of the inflammation that do destroy the nerves. And [since we are] a cancer and inflammation program, that’s important for us.”

As one of the body’s normal defenses against infection or injury, inflammation attracts immune cells. That’s acute inflammation—the helpful kind. But chronic inflammation is associated with tumor cell survival. Both types of inflammation contribute to pain.

“He came to us with a great understanding of systems analysis,” she continues. “He’s leaving us with some understanding of how systems and reduction of sciences can complement each other to come up with a better way to target cancer.”

A systems approach such as TCM looks at the whole. Western science, on the other hand, relies on reductionism, which dissects an area of study into its components and eliminates as many variables as possible.

“Here,” Zhao explains, “some of the labs are working on one molecule for a very long time, believing that there is one major signal pathway. But I think there are multiple things happening in those models.”

A signal pathway is a route for cells to perceive and communicate with each other using specialized signaling proteins.

These signaling proteins activate cascades, which act like exquisitely complex waterfalls to create still other proteins. Some, for example, carry messages vital to immune response.

This is important, because glitches in cell signaling are responsible for diseases such as cancer.

At Guang'anmen Hospital, Zhao says, "We were trying to use a [herbal] mixture, because we were not recognizing them as single components. We try to use TCM to treat patients and even in benchwork we were trying to find a couple of mechanisms."

Before his funding ends this month, Zhao will visit the University of Texas MD Anderson Cancer Center to see how its integrative medicine program works.

"We have to get his paper out before then," Howard says, "and we hope that when he gets back to China he has a job and funding to do his research."

The life of a young scientist is full of creative struggle, uncertainty and sacrifice: Zhao has not seen his family in China for 2 years. Yet even as he gives due respect to his former chief of oncology in Beijing, Dr. Hongsheng Lin, he has become part of NIH's extended family.

"My supervisors here, they were very caring," he says. "We get better training here, not only in scientific techniques, but [also] in your future plans. It's a good model for how we should do things in China to train our next generation, to make people think." 🗨️



Women's Health Studies Seek Healthy Volunteers

Healthy women ages 18-50 are invited to participate in outpatient research studies. Compensation is provided. Call (301) 496-9576. Refer to studies 81-M-0126, 88-M-0131 and 03-M-0138.

Premenstrual Syndrome Research Studies

Women ages 18-50 who struggle with irritability, anxiety or sadness prior to menstruation are invited to participate in outpatient research studies. There is no cost for participation. Compensation may be provided. Phone (301) 496-9576 (TTY 1-866-411-1010) and refer to study 81-M-0126.

Blood Test Identifies Early Pancreatic Cancer

By Jan Ehrman

In a finding that holds key clinical implications, National Cancer Institute-supported researchers in Baltimore have devised a simple blood test that rapidly and accurately detects the earliest stage of pancreatic cancer. If the results of the study hold up in additional trials, it could lead to earlier diagnosis and improved prognosis for those afflicted with the disease, which took the lives of more than 37,000 Americans in 2011.

Cancer of the pancreas (a 6-inch organ that lies between the stomach and the backbone) is a particularly aggressive carcinoma with a low rate of survival. It is the fourth leading cause of cancer-related death in the U.S.; only 5 percent of patients are alive 5 years after diagnosis. This is partly because early symptoms are usually vague or misinterpreted; diagnosis and treatment usually begin only after the tumor has already spread. Additionally, there has been no improvement in survival rates for the disease over the past three decades. At present, there are no detection methods or medical procedures that can reliably spot pancreatic cancer in its earliest form.

Reporting in the journal *Clinical Cancer Research*, Dr. Nita Ahuja, associate professor of surgery and oncology at Johns Hopkins University, led a team of investigators who analyzed the tissue samples of 201 patients—143 had pancreatic cancer and 30 patients had pancreatitis (a noncancerous inflammation of the pancreas). The remaining samples came from patients without cancer or with a pre-malignant form of the condition.



Dr. Nita Ahuja of Johns Hopkins University led the team of investigators.

"We were able to detect two genes in DNA that correlated significantly with the development of early pancreatic cancer. No one else has tried this—it's a first-of-its-kind study," noted Ahuja. Most prior tests have focused on later stages, when pancreatic cancer has already spread and is too advanced to treat effectively. However, the findings involving two blood biomarkers (BCN1 and ADAMST1) were particularly strong and occurred in the early stages of pancreatic cancer, she explained. Using the two markers combined, she added, the genetic alterations occurred in 97 percent of patients in stage 1 of the disorder.

Will this diagnostic test get from bench to bedside? "Yes, hopefully—my goal is to get it into the clinic," Ahuja said, adding that it first needs to be replicated in follow-up investigations. "We want to extend it to a larger set of patients both with cancer and with other noncancerous conditions."

If the findings hold up, she added, "We would only advocate patients get tested if they are at high risk for the disease, that is, if there is a history of extensive smoking, pancreatitis or a genetic inheritance (family history) of pancreatic cancer."

An additional piece of good news is that the procedure is cost-effective and therefore could be repeated as often as necessary for at-risk patients.

Ahuja and her team hope to make further progress against this deadliest of cancers.

Cognitive Training Shows Staying Power

Training to improve cognitive abilities in older people lasted to some degree 10 years after the training program was completed, according to results of a randomized clinical trial supported by NIH.

The findings showed training gains for aspects of cognition involved in the ability to think and learn, but researchers said memory training did not have an effect after 10 years.

The report, from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, appeared in the January 2014 issue of the *Journal of the*

American Geriatrics Society. The project was funded by the National Institute on Aging and the National Institute of Nursing Research.

“Previous data from this clinical trial demonstrated that the effects of the training lasted for 5 years,” said NIA director Dr. Richard Hodes. “Now, these longer term results indicate that particular types of cognitive training can provide a lasting benefit a decade later. They suggest that we should continue to pursue cognitive training as an intervention that might help maintain the mental abilities of older people so that they may remain independent and in the community.”

NIH-Created Toxin Can Kill HIV-Infected Cells That Persist Despite Treatment

A team including University of North Carolina and NIH scientists has demonstrated in a mouse model that an HIV-specific poison can kill cells in which the virus is actively reproducing despite antiretroviral therapy. According to the researchers, such a targeted poison could complement antiretroviral therapy, which dramatically reduces the replication of HIV in infected cells but does not eliminate them.

The 40 mice in the experiment were bioengineered to have a human immune system. They were infected with HIV for several months and then given a combination of antiretroviral drugs for 4 weeks. Half of the animals subsequently received a 2-week dose of a genetically

designed, HIV-specific poison, or immunotoxin, to complement the antiretrovirals, while the other half continued receiving antiretrovirals alone.

The scientists found that, compared to antiretrovirals alone, the addition of the immunotoxin significantly reduced both the number of HIV-infected cells producing the virus in multiple organs and the level of HIV in the blood. According to the researchers, these findings, coupled with results from previous studies, suggest that treating certain HIV-infected people with a combination of antiretrovirals and an immunotoxin might help achieve sustained disease remission, in which HIV can be controlled or eliminated without a lifetime of antiretroviral therapy. However, further study is required, the scientists said.

The immunotoxin was created in 1998 in the laboratories of NIAID’s Dr. Edward Berger and NCI’s Dr. Ira Pastan. The study appeared this month in *PLoS Pathogens*.

Research-Based Strategies Help Reduce Underage Drinking

Strategies recommended by the Surgeon General to reduce underage drinking have shown promise when put into practice, according to scientists at the National Institute on Alcohol Abuse and Alcoholism. These approaches include nighttime restrictions on young drivers and strict license suspension policies, interventions focused on partnerships between college campuses and the community and routine screening by physicians to identify and counsel underage drinkers.

NIAAA researchers Dr. Ralph Hingson and Dr. Aaron White evaluated studies conducted since the 2007 “Call to Action to Prevent and Reduce Underage Drinking.” A report of their findings appeared in the January issue of the *Journal of Studies on Alcohol and Drugs*.

“The downward trend in underage drinking and alcohol-related traffic deaths indicates that certain policies and programs put in place at the federal, state and local levels have had an impact,” said NIAAA acting director Dr. Kenneth Warren.

Since 2007, alcohol use and heavy drinking have shown appreciable declines in national surveys of middle and high school students. One study found that 12th-grade alcohol use declined from 66.4 percent to 62 percent in 2013, with a similar downward trend seen in 8th- and 10th-graders.



Training to improve cognitive abilities in older people lasted to some degree 10 years after the training program was completed, according to results of a trial supported by NIH.



milestones

Cashion Appointed NINR Scientific Director

Dr. Ann Cashion was recently appointed scientific director of NINR's Division of Intramural Research. For the past year, she has served as acting scientific director; before that, she was a senior advisor to the NINR Office of the Director.



PHOTO: CHIP ROSE

Cashion's research expertise focuses on genetic markers that predict clinical outcomes; her previously funded research and clinical interests target genetic/genomic and environmental components associated with outcomes of organ transplantation. Shortly after earning her Ph.D. from the University of Tennessee Health Science Center, Cashion graduated with the 2000 inaugural class of the NINR Summer Genetics Institute, an intensive research training program in molecular genetics.

Prior to her appointment at NINR, Cashion was a professor and chair of the department of acute and chronic care in the College of Nursing, University of Tennessee Health Science Center. During her tenure as professor, she shared her expertise, mentoring numerous doctoral students and enabling them to incorporate genomics into their programs of research. She also chaired an NIH integrated review group study section for training applications.

Cashion has numerous publications, serves as a scientific reviewer for multiple journals and professional organizations and is a well-known scientist and leader in the field with many awards and recognitions. Currently, she serves as a member of the Institute of Medicine's Translating Genomic-Based Research for Health Roundtable.

"Under Dr. Cashion's leadership, NINR's Division of Intramural Research will redouble its research efforts to better understand the underlying biological mechanisms of a range of symptoms, their effect on patients and how patients respond to interventions," said NINR director Dr. Patricia Grady. "She brings extensive expertise to the position and we are fortunate to have her leading our intramural program."

NINR Council Welcomes Five New Members

NINR director Dr. Patricia Grady recently welcomed five new members to the National Advisory Council for Nursing Research:

Dr. Cynthia Barnes-Boyd is a senior director for the office of the vice president for health affairs at the University of Illinois Health Sciences System, a clinical associate professor at the UI-Chicago School of Public Health and College of Nursing and director of UI-Health's Office of Community Engagement and Neighborhood Health Partnerships. She is experienced in guiding large-scale projects that include community partners and working to develop university/community partnerships to support collaborative research, educational and service initiatives to address health disparities.

Dr. Donna Hathaway is a university distinguished professor at the University of Tennessee Health Science Center College of Nursing. Her 20-year NINR-funded program of research investigates biobehavioral linkages to quality of life outcomes following organ transplantation.

Dr. Jillian Inouye is associate dean for research and the Tony and Renee Marlon Angel professor at the University of Nevada, Las Vegas School of Nursing and School of Allied Health. Her research program focuses on health disparities, chronic illness and cognitive behavioral interventions for lifestyle changes.

Dr. Bernadette Mazurek Melnyk is associate vice president for health promotion, university chief wellness officer and dean of the College of Nursing at Ohio State University. She is an internationally recognized expert in evidence-based practice, intervention research and child and adolescent mental health.

Dr. Marjana Tomic-Canic is a professor of dermatology and director of the Wound Healing and Regenerative Medicine Research Program at the University of Miami Miller School of Medicine. Her current research focus is the molecular and cellular mechanisms of wound healing, including human and diabetic models of wound healing, wound genomics analyses, generating primary cells from patients' wound biopsies, local sustained gene delivery, cellular assays of wound healing and the histology and immunohistochemistry of skin.



NINR director Dr. Patricia Grady (fourth from l) meets the newest members of the National Advisory Council for Nursing Research. They are (from l) Dr. Bernadette Mazurek Melnyk, Dr. Marjana Tomic-Canic, Dr. Cynthia Barnes-Boyd, Dr. Jillian Inouye and Dr. Donna Hathaway.

PHOTO: ERNIE BRANSON



NIAMS Launches ‘Year of Health’ with 2014 Multicultural Planners

For many years, planners have helped people organize their time and mark past, present and future events of significance. Building on the success of its inaugural 2013 health planners, NIAMS has created a new set for 2014, titled *A Year of Health*.

The planners are part of the institute’s National Multicultural Outreach Initiative (NMOI) to make health information about bones, joints, muscles and skin more accessible to people from underserved racial and ethnic communities. The health planners are tailored to four different audiences—African American, American Indian/Alaska Native/Native Hawaiian, Asian American/Pacific Islander and Hispanic/Latino—and include 12 months of disease management tips, recommended resources and reminder stickers for medical appointments, blood tests, prescription refills and other important self-care activities.

Even in this era of portable electronic planners, traditional hard-copy planners continue to be well received by specific audiences. “Our portfolio of diseases, which includes osteoporosis and osteoarthritis, skews toward an older population,” says Dr. Bob Carter, NIAMS deputy director and NMOI chair. “In our focus group research with multicultural communities, people indicated a strong preference for print over digital formats. A planner allows our health information to be visible over 12

months and the reminder stickers and large spaces for notes help people proactively manage their chronic conditions.”

In addition to their practicality, the health planners have been embraced for their cultural relevance. Striking images of people from different cultural backgrounds and the inclusion of cultural observances and values make the planners especially appealing. According to one community health worker, “We like the fact that [the planner] is culturally specific. We know that Native Americans are prone to diseases such as arthritis and it makes them feel more connected when they have that ethnically targeted [health] information.”

The health planners include resources from several NIH institutes and centers, as well as from other HHS agencies. As one community organizer said, “I especially like, in addition to the health information, the page with other federal resources. I think it communicates that our government cares about people and their health. Information like this is not readily available to most people, and especially the communities I work with.”

A Year of Health planners are available through the NIAMS Information Clearinghouse at 877-226-4267 (free call) (TTY 301-565-2966) or at www.niams.nih.gov/multicultural. After the printed copies have been distributed, a printable version will remain available on the web site.—Mimi Lising

Above: NIAMS has created a multicultural set of health planners for 2014, *A Year of Health*. The planners make information about bones, joints, muscles and skin more accessible to people from underserved racial and ethnic communities.