How the cheetah got stripes: A genetic tale

By Krista Conger

Feral cats in Northern California have enabled researchers to unlock the biological secret behind a rare, striped cheetah found only in sub-Saharan Africa, according to researchers at the School of Medicine, the National Cancer Institute and HudsonAlpha Institute for Biotechnology in Huntsville, Alabama. The study is the first to identify a molecular basis of coat patterning in mammals.

The scientists found that the two felines share a biological mechanism responsible for both the elegant stripes on the tabby cat and the cheetah’s normally dappled coat. Dramatic changes to the normal patterns occur when this pathway is disrupted: The resulting house cat has swirled patches of color rather than orderly stripes, and the normally spotted cheetah sports thick, dark lines down its back.

“Mutation of a single gene causes stripes to become blotches, and spots to become stripes,” said Greg Barsh, MD, PhD, emeritus professor of genetics and of pediatrics at Stanford and an investigator at the HudsonAlpha Institute.

The differences are so pronounced that biologists at first thought that cheetahs with the mutated gene belonged to an entirely different species. The rare animals became known as “king cheetahs,” while affected wild cats received the less-regal moniker of “blotched.” (The more familiar, striped cat is known as a mackerel tabby.)

The study was published Sept. 21 in Science. Christopher Kaelin, PhD, a senior scientist in the Barsh laboratory, is the co-first author; Xiao Xu, PhD, from the National Cancer Institute-Frederick National Laboratory for Cancer Research and the Sichuan Key Laboratory of Conservation Biology on Endangered Wildlife in Sichuan, China, is the other co-first author. Marilyn Menotti-Raymond, PhD, of NCI-Frederick is the senior author.

Barsh and his lab members have spent decades investigating how traditional laboratory animals such as mice develop specific coat colors. His previous work identified a variety of biologically important pathways that control more than just hair or skin color, and have been linked to brain degeneration, anemia and bone marrow failure. But laboratory mice don’t display the pattern variation seen in many mammals. “We were motivated by a basic question,” said Barsh of the turn to the study of big (and little) cats. “How do periodic patterns like stripes and spots in mammals arise? What generates them? How are they maintained? What is their biological and evolutionary significance? It’s kind of surprising how little is known. Until now, there’s been no obvious biological explanation for cheetah spots or the stripes on tigers, zebras or even the ordinary house cat.”

The research relied primarily on DNA samples from feral cats in Northern California captured for sterilization and release, on tissue samples provided by the City of Huntsville Animal Services and from endangered species in Saharan Africa, according to researchers at the School of Medicine, the National Cancer Institute and HudsonAlpha Institute for Biotechnology in Huntsville, Alabama. The study is the first to identify a molecular basis of coat patterning in mammals.

The nine Stanford researchers are among 81 recipients of the 2012 NIH Director’s Pioneer Awards, New Innovator Awards and Transformative Research Awards. This year’s total funding, from the NIH Common Fund and multiple NIH institutes and centers, is approximately $135 million.

NIH director Francis Collins, MD, PhD, noted that the funding provides opportunities for innovative investigators in any area of health research to take risks when the potential impact in biomedical and behavioral science is high.”

Pioneer Awards

Stanford has two of the 10 recipients of this year’s NIH Director’s Pioneer Awards. Each award carries a five-year, $2.5 million grant to be used in highly innovative approaches that have the potential to affect a broad area of biomedical or behavioral research.

Christina Smolke, PhD, associate professor of bioengineering, will use her Pioneer Award funding to explore the use of synthetic biology platforms and biosynthesis strategies — the use of microbes to produce complex chemicals — to dramatically advance natural—

Upper: Biologists had once thought that the rare striped king cheetah was a different species from the more common spotted variety. Lower: Analysis of a blood sample from a king cheetah named Kgosi, who lives in a wild animal park in Northern California, helped to explain why the cheetahs’ fur patterns may vary.

NIH selects 9 faculty members for grants to boost innovative research

By Erin Digitale

California’s pediatricians-in-training are not adequately educated about the methods to prevent recurrent sexually transmitted infections in teenagers. That’s the conclusion of a study from the School of Medicine and Lucile Packard Children’s Hospital examining pediatric residents’ knowledge of laws governing treatment of their patients’ sexual partners.

“We call this the ‘ping-pong effect.’” said Neville Golden, MD, an adolescent medicine specialist at Packard Children’s and professor of pediatrics at Stanford.

“We called this that the ‘ping-pong effect.’ Indeed, even after receiving antibiotics to clear their infections, 10 percent of teenage gonorrhea and chlamydia patients are diagnosed with a second bout of the same illness within a year. About half of all sexually transmitted infections in this country occur in teenagers.

Golden is the senior author of a study.
Making adolescence easier: Doctors have answers for acne

By Erin Digitale

For teenagers struggling with acne, Sophia Yen, MD, has a simple message: Your doctor can help.

“People don’t realize how easy it is to treat,” said Yen, an adolescent medicine specialist at Lucile Packard Children’s Hospital and clinical assistant professor of pediatrics. There are good reasons to visit a doctor for acne treatment, she added. Prescription acne medications work better than over-the-counter products; the treatment can be tailored to the severity of the acne; and for teens with insurance coverage, prescription treatments often cost less than those purchased over the counter.

Physicians can also help navigate the tricky terrain between parents and kids around seeking acne treatment. “It think it should totally be up to the teen to decide whether to treat her or his acne,” Yen said, adding that teens may feel self-conscious but not say so.

“Some patients, when I ask if they want to do something about their acne, say, ‘No, I’m fine,’” Yen said. “But after I tell them about the easy, effective and simple treatments we can offer, they say, ‘Uh, I think I do want that acne cream or pill you talked about.’”

Pediatricians, adolescent medicine specialists and dermatologists can all treat teen acne, and are excellent resources for hesitant teens or parents who don’t want to create a conflict about their child’s skin, she added.

Parents may be especially anxious if they struggle with acne themselves. “There is a genetic component to acne, Yen said, noting that genes influence the skin’s response to hormones and its propensity to scar. But acne medication can help prevent scarring, reduce inflammation, and build patients’ social confidence.

The first-line acne drug Yen recommends is topically-applied tretinoin, a vitamin A derivative that increases skin cell turnover, decreases the skin’s oil production and prevents pimples from forming. Because it can make the skin more sensitive, it takes six to eight weeks for patients’ skin to improve.

“I clear out all the zits that are on their way,” Yen said. “So I tell patients, ‘You gotta get through the ugly to get to the pretty.’” The drug also increases sun sensitivity, so patients must use a non-pore-clogging sunscreen, which is identified on some labels as “non-comedogenic.”

If tretinoin doesn’t help, doctors add oral antibiotics or benzoyl peroxide to kill acne-causing bacteria, or oral isotretinoin. Although very effective, isotretinoin is hard to treat topically. Young women who are perimenopausal or acne flares generally respond better to oral isotretinoin. “It’s important to talk to patients about their acne treatment options, including using both approaches, and what their different side effects are,” Yen said. “It’s helpful to have a shared decision-making approach.”

Treatments that work for teens can also help young adults. “If you like seeing how her patients’ self-confidence grows after she helps treat their acne. She recalls one patient who came to her office with a spiffy new hair style after her acne cleared. “I didn’t realize that had been an issue, that he was using his hair to hide acne on his forehead,” she said. “I want teens to know that if their acne bothered them, we can help.”

STD continued from page 1

published Sept. 17 in Pediatrics that examines whether California pediatric residents — new physicians receiving specialty training in pediatric medicine — know about expedited partner therapy, which helps doctors stop sexually transmitted diseases from bouncing back and forth within a couple. About half of pediatric residents had never used the practice, in spite of the fact that most had diagnosed STDs among their patients, the study found. Knowledge of expedited partner therapy was better in physicians enrolled in the state’s three residency programs that offer fellowships in adolescent medicine.

Expedited partner therapy laws, which were introduced in California in 2001 and have since been adopted in 30 other states, allow physicians to prescribe antibiotics to the sexual partners of gonorrhea or chlamydia patients without seeing the partner. Prior to 2001, laws authorized state health departments to contact sexual partners of people diagnosed with these infections and to test and treat the partners. However, most health departments lack the resources to offer this service widely. Expedited partner therapy has been shown to be an effective alternative, especially in cases where the patient says his or her partner is unlikely to visit a doctor.

The study focused on 289 pediatric resident physicians enrolled in 14 of California’s 17 pediatric residency programs. The pediatricians-in-training answered a questionnaire about their use of expedited partner therapy, their familiarity with EPT laws and their comfort with using the approach. Although 83 percent of those surveyed had diagnosed an STD, only 52 percent had used EPT. A large percentage of the physicians said they were not familiar with EPT laws. “It was clear that many of these residents did not know about these laws,” said Hsii. “This was an important lesson for our pediatric medicine residents.”

The study also found that only 46 percent of pediatric residents said they had ever been taught about EPT; and residents who were familiar with EPT laws and their comfort with using the approach. Among the common misconceptions are:

• **Myth:** People with acne should wash their face more often. **Fact:** Washing face frequently with face-washing strips can cause acne to worsen, as can squeezing, causing oil over-production that can worsen acne, Yen says. Two or three daily face-washes are plenty.

• **Myth:** Junk food causes acne. **Fact:** Food choices such as french fries and chocolate have never been scientifically linked to acne. However, working in a greasy environment (such as working at a fast food restaurant) can trigger acne outbreaks, as can stress, wearing a lot of pore-clogging makeup, or wearing a helmet. Regular exercise or sports equipment that puts pressure on the skin.

• **Myth:** You can get rid of pimples by squeezing them. **Fact:** Squeezing increases skin damage and makes pimples heal more slowly.

• **Myth:** Only teenage girls get acne. **Fact:** Although acne is common in high school, some people develop acne in their college years. “Whether the treatments that work for teens can also help adults,” Yen said, “I think people’s self-confidence grows after they help treat their acne. She recalls one patient who came to her office with a spiffy new hairstyle after her acne cleared. “I didn’t realize that had been an issue, that he was using his hair to hide acne on his forehead,” she said. “I want teens to know that if their acne bothered them, we can help.”

Child abuse, neglect to be subject of CME conference

On Oct. 12, the School of Medicine will host a one-day Continuing Medical Education conference, "Medical response to child abuse and neglect."

The symposium, intended for physicians, nurses, social workers, lawyers and law enforcement officers, will include work with children seeking to give practitioners state-of-the-art information on child abuse and neglect and acquaint them with the national guidelines for recognizing and treating child abuse according to evidence-based guidelines. Topics covered will include recognition and response, including understanding child abuse on the developing brain; current controversies in head trauma and “shaken baby” syndrome; and a guide for pediatricians and psychologists who work with families.

Online registration is available at the link http://cme.stanfordhospital.com/abuse. (more info)
The Flu Crew: Med students provide vaccinations to community

By Michelle L. Brandt

Medical student Rishi Mediratta vividly remembers the first time he gave someone a flu shot. “I was with a third-year medical student — and he was having to stick a needle in someone,” he said. The future physician was not so comfortable with the act involved. “I felt like I was liver health care to where people eat, pray, live and die,” she recalled. “I felt like I was so nervous in my first year, I had to have someone to do it with me.”

“Rishi and I were both on our teams,” said Rachel Rizal, of the Flu Crew, an educational intervention for medicine’s Pediatric Advocacy Program. But luckily, thanks to the training he received as a third-year medical student, Rizal was able to make the necessary move. “I’m sure this spares serious illness, possibly death,” said Rizal. “I’m proud to be in a profession that revolves around helping people.”

Both Rizal and Mediratta had done public-health projects before coming to Stanford. Rizal joined a World Health Organization project aimed at increasing hepatitis B vaccination among newborns in the Philippines, and Mediratta focused on preventive health services for Ethiopian children — and they consider the Flu Crew a “natural extension” of their previous work.

The programs all have a similar goal of protecting a population, explained Mediratta, noting that 42 percent of vaccines administered in 2011 were provided to low-income individuals in Santa Clara County.

Faculty advisor Pat Fast, MD, PhD, an adjunct associate professor, counts the group’s work with this population among its greatest achievements. “Last year, we vaccinated several hundred homeless individuals, a group that is at very high risk of complications from influenza — and a particular high point was immunizing women and their children at the battered women’s shelter in San Jose,” said Fast, who is also chief medical officer for the International AIDS Vaccine Initiative. “I’m sure this spares serious illness, possibly death, and also minimizes public expenditures for care.”

Aside from providing a service to the community, the program benefits participating medical students by giving them early clinical exposure. First-year students don’t always have the chance to work directly with patients, but here they are taught and able to practice how to greet, treat and even thank patients. “Even in a one-minute interaction, you’re learning to build rapport,” said Rizal. “It’s a good position to be in as a first-year.”

For some, the program also validates their decision to enter a profession that revolves around helping others. “Flu Crew is a weekly reminder of why I am in medical school,” one participant told Mediratta and Rizal last year.

As for the future, Flu Crew is thinking big, with a goal of providing 6,000 vaccinations in the community this fall. The program is now partnering with Khan Academy, a non-profit that offers free educational materials, in developing an online training module for the outside world, and its leaders recently shared their training documents and instructions with the University of California-San Francisco, which now has a similar program. Flu Crew also is now integrated into Stanford’s medical school curriculum, ensuring that all future students are trained in vaccination. For more information on Flu Crew and dates of upcoming vaccination events, please visit flu.stanford.edu.

Palliative care leader to give Oct. 2 King Lecture

Ira Byock, MD, chair of palliative medicine at the Audrey and Theodora Geisel School of Medicine at Dartmouth, will deliver Oct. 2 the annual Jonathan King Lecture, which is sponsored by the Stanford Center for Bio-medical Ethics. His talk is titled “The ethics and practice of loving care.”

A practicing physician and best-selling author, Byock serves as the director of palliative medicine at Dartmouth-Hitchcock Medical Center in Lebanon, N.H., and is a professor in the departments of Anesthesiology and Community and Family Medicine at Dartmouth. Byock’s books, including Dying Well (1997), The Four Things That Matter Most (2004) and The Best Care Possible: A Physician’s Quest to Transform Care, have sold more than 500,000 copies worldwide.

Six research teams that will work together with community agencies to conduct health research have received a total of $1.4 million in grants from Spectrum, which oversees Stanford’s Clinical and Translational Science Award from the NIH.

All of the projects aim to address health needs in San Mateo and Santa Clara counties. Two seek to improve child health in East Palo Alto and East Menlo Park through an effort to create more safe play areas in neighborhoods and a teacher-training program that fosters better mental health in the classroom. Two of the studies will test the use of mobile devices, including apps for diabetic teens to manage glucose levels, and for seniors to notify city officials about difficult mobility and unhealthful-food access in their neighborhoods. The other two studies will explore ways to strengthen bonds between academic medicine and the community, by teaching empathy skills to medical residents at safety net hospitals and by developing a mobile app to facilitate community research collaborations.

This year’s award recipients include:

• “Aiming to reach the next generation of community research advocates for safe physical activity in their community” — Lisa Chamberlain, MD, MPH, assistant professor of pediatrics, Elizabeth Baca, MD, clinical instructor of pediatrics, and Janine Bruce, MPH, program director for the School of Medicine’s Healthful Food Access Program.

• “An educational intervention for medical students at a safety net teaching hospital” — Lars Overtberg, MD, MPH, clinical associate professor and chief of emergency medicine at VA-Palo Alto, and Yeun Kim, MD, clinical assistant professor, with the Santa Clara Valley Medical Center.

• “Strengthening emerging community-based participatory research collaborations and practices” — Stafford and Lisa Goldman Rosas, PhD, MPH, instructor of medicine, both at the Stanford Prevention Research Center, partnering with the Indian Health Center of Santa Clara Valley.

These grants were awarded by Spectrum’s Office of Community Health, which aims to build community-representative programs at the School of Medicine and to meet the diverse health needs of surrounding communities. It does this by supporting leaders in community health who are committed to the development of sustained local partnerships and initiatives that address important public health challenges.
The Laboratory of Genomic Diversity at the National Cancer Institute has long championed the cat as an animal model of human disease," said Menotti-Raymond. "Studying color variation in cats provides the opportunity to uncover new principles of gene action and interaction that may have unexpected applications to understanding developmental and morphologic variation in natural populations, including humans." Comparing gene sequences of feral cats with different patterns allowed Kaelin and Xu to identify mutations in a gene they dubbed Taqpep associated with the blotched tabby markings: 58 of 58 blotched tabbies had a mutation in each of its two copies of Taqpep, while 51 of 53 mackerel tabbies had at least one unmutated version. Taqpep encodes a protease normally found in the cell membrane, but that can also be cleaved to allow it to diffuse outside the cell. This ability to float freely and interact with other molecules in the extracellular soup is a key component of a principle called reaction-diffusion proposed by the famous computer scientist Alan Turing, Ph.D., in 1952 as a way to explain how periodic patterns (like stripes and spots) can arise out of randomness.

"Turing realized that, under specific conditions, diffusible 'activator' and 'inhibitor' molecules can self-organize into a variety of periodic patterns," said Barsh. "We are excited about the idea that Taqpep might be an entry point to understand it, and how, reaction-diffusion mechanisms can explain 'how the leopard got its spots.'" After nailing down Taqpep’s role in tabby stripes (and analyzing its sequence in more than 350 other cats of 24 distinct breeds), Kaelin wondered if it might play a similar role in generating and maintaining the spots on wild and captive cheetahs. He obtained blood samples from a king cheetah named Kgosi, a resident of a wildlife education and conservation program in Northern California, and found that Kgosi also had a mutation in Taqpep. Kaelin next contacted Ann van Dyk, who maintains a cheetah conservation center in South Africa from which all captive king cheetahs, including Kgosi, originate. (Van Dyk was the first to learn, through meercat breeding records, that the king cheetah pattern is due to a recessive genetic mutation.) Van Dyk obtained DNA samples from all her cheetahs, allowing confirmation that a Taqpep mutation is responsible for the king cheetah pattern.

Mammals aren’t the only animals with patterned fur or skin, obviously. Fish, salamanders and some invertebrates also have stripes and spots. However, there is an essential difference. While the non-mammals simply add stripes or spots as they grow to adulthood, mammals keep the same number and pattern by increasing the surface area of the contrasting colors. Somehow, cells in the black stripes know they are in a black stripe and remember that fact throughout the organism’s life," said Barsh. "We were curious about what’s happening at the boundary between light and dark stripes and spots. How do these spots know to grow with an animal?"

When Kelly McGowan, M.D., Ph.D., a senior scientist in Barsh’s group, studied feral cat skin after seven weeks of gestation, she found that the tabby pattern begins to arise only when the hair begins to grow. In other words, there are no apparent differences between the cells themselves — only in the color of hair they produce. That suggested that the changes in color are due to differences in the levels of expression of certain genes within the cells.

Lewis Hong, a former graduate student in Barsh’s lab, used a technique he developed called EDGE to identify changes in gene expression levels between black and yellow areas of cheetah skin (obtained under anesthesia). He found several differences, many associated with a pathway influencing the expression of a gene called Edn3. McGowan found that Edn3 mRNA was produced at the base of the follicles making the black hairs. To test their theory, the researchers collaborated with a group at Florida International University to study a yellow-colored laboratory mouse that had been engineered to express Edn3. The coats of the resulting animals were much darker than their unmodified peers.

"This is very strong evidence that Edn3 is a critical regulator of black versus yellow hair in animals," said Barsh. The researchers hypothesize that expression of Taqpep is required to establish a pattern of stripes or spots in early fetal development that is then carried out by Edn3 as the hair grows. Clearly, not all cats are patterned. In particular, some big adult cats like African lions and mountain lions are distinctive for their lack of color variation even though their cubs are striped. Furthermore, Taqpep mutations are surprisingly common in some non-striped domestic cats like the Abyssinian and the Himalayan.

"We know there’s a mutation that suppresses pattern formation in some cats," said Barsh. "We’d like to investigate that mechanism as well." In addition to Kaelin, Barsh, McGowan and Hong, Stanford researcher and technician Hermogenes Manuel also participated in the study. The research was funded by the National Institutes of Health, the NCI and the HudsonAlpha Institute.

By comparing gene sequences of a variety of cats, scientists identified a gene, called Taqpep, that determines whether their fur is blotched (top cat) or striped. After figuring out the gene’s roles in tabbies, they studied cheetahs and discovered that it had a similar effect on the larger cats.

The Council for the Advancement and Support of Education, known as CASE, gave its top prize — a Gold Award — for Periodical Staff Writing for an External Audience to Stanford Medicine, the magazine published by the medical school’s Office of Communication and Public Affairs. "The judges were unanimously impressed by the writing submitted for this category, CASE reported. "It includes well-researched writing in a hallmark here, with qualities such as fresh description, tight transitions, compelling leads (especially in ‘Gender X’), authentic details and prose that take readers into the story." Along with the story ‘Gender X’ by former OCFA staff writer Dianne Klein, Stanford Medicine submitted in its entry four other stories: ‘Old brain, new technology’ by Nan Goldman; ‘The ‘other’ John Sanford’ by John Sanford, a writer in the communications office at Stanford Hospital & Clinics; and ‘Khmer Rouge on trial’ and ‘Drawn together,’ which are both by OCFA staff writer Tracie White. ‘The contents in these stories is full of concrete examples and well-structured narrative, which readily engage the reader and make complex content accessible,’ according to the statement from CASE. ‘Most impressive to the judges was the strength of all five entries across the board — not an easy feat.’

There were 44 entries in the category. Stanford Medicine was one of two Gold Award winners. The medical school communications office produces three issues annually of its magazine. Its editor is Rosanne Spector. OCFA organizes the annual Circle of Excellence Awards, which recognize outstanding work in these fields. CASE sponsors its annual Circle of Excellence Awards, which includes the periodical staff-writing category.
D. Barry Starr, PhD, is the director of the program, which is the culmination of the relationship between the Department of Genetics and the Tech Museum of Innovation in San Jose. The program teaches interested graduate students and postdoctoral scholars how to communicate science in an engaging, non-threatening way with museum visitors. Recently, the Stanford participants in the program contributed a chapter titled “Taste Like This,” which features their answers to some of the most interesting genetics questions that they have received. (The book was named for a question submitted to the group’s website.) Medical school science writer Krista Conger talked with Starr about the program and the book.

**9 QUESTIONS**

1. How did the idea of doing a book arise? Who wrote it?

**STARR:** The idea sprang from the “Understanding Genetics” website (http://genetics.thetech.org). I have been running in conjunction with Stanford’s Department of Genetics and the Tech Museum since 2004. The website has a section called “Ask a Geneticist” for which the public sends in genetics questions, and I or Stanford graduate students and postdoctoral fellows answer them. The website has become surprisingly popular with over 1.5 million unique visitor each year and we receive over 1,000 questions each month, most of which are answered by email, and a few of which are posted online.

2. Do you have a favorite section of the book?

**STARR:** One of my favorite sections in the book deals with a topic called chimerism. A chimera is really just a single person made up of two fraternal twins’ cells. Basically, fraternal twins fuse together at an early enough stage that the cells get along and there are none of the issues associated with conjoned twins. You end up with one person with half of his or her cells from one twin and half from his or her other twin.

Sometimes you can tell someone is a chimera because of stripes that appear under ultraviolet light called Blashko’s lines or because of something like having half of the hair on your head one color and the other half a different color. Usually though, you can’t tell someone is a chimera until you do a DNA test. Then all sorts of interesting things can happen.

It’s great for TV (a CSJ episode focused on chimeras), but it is also important in real life. For example, a woman who is denied welfare because her DNA did not match her children’s. Another woman who needed a kidney transplant found out her DNA didn’t match her sons. They were both chimeras. And another, a young man with a bone marrow transplant almost gets away with a crime because being a bone marrow recipient makes it impossible for the blood left behind at the crime scene — different from the rest of your DNA.

3. Who is the program’s target audience? 

**STARR:** A big target audience for the program is elementary and middle school kids. We want to get them excited about science and maybe even want to become scientists themselves. We accomplish this by having Stanford graduate students and postdoctoral fellows come down to the Tech Museum one morning each week to run hands-on genetics programs with the mostly elementary and middle school visitors.

The mostly elementary and middle school visitors get to see that scientists are people like them and not some weird, scary person like on TV; they get to see that science can be fun; and they see that science isn’t as hard as people make it out to be.

Another target audience is adults who are interested in genetics and they can reach that audience through our “Ask a Geneticist” website where, surprisingly, most of the questions come from adults. These questions most often focus on physical characteristics like hair and eye color and on genetic disease. We try to show them where to find good information on the Internet and that, despite the jargon, genetics isn’t as complicated as it looks. Hopefully they pick up enough skills to do a little exploring on their own after getting our answer.

The program started back in 2003 with a grant from the NIH through their Science Education Partnership Award Program. The grant funded the “Genetics: Technology with a Twist” museum exhibit, which is still going strong at the Tech and funded the Stanford at the Tech program, which is also ongoing. Since the grant ended in 2008, the program has been primarily funded through the Department of Genetics with help from the Howard Hughes Medical Institute.

4. It’s so important to make science fun. Can you remember a particular time or incident when you just really saw something click for a kid for the first time?

**STARR:** One of the great things about the programs we run is that we get to see this almost every day. We get to see kids’ eyes light up when suddenly natural selection makes sense or they begin to understand where they got their DNA.

One example I can think of happens with our PTC program. PTC is a bitter chemical that only some of us can taste. For the most part, it is controlled by two versions of a single gene. The “taste” version is dominant so usually people who can taste PTC have either two copies of the “taste” version or one of each while people who can’t taste have two “can’t-taste” versions.

It is surprising to me how few people (including adults) have really internalized the notion that we have two copies of each of our genes, one from mom and one from dad. But when we run this program with a family, you can see all the participants’ eyes light up with the realization that this is the case. And then they can predict which versions of the genes everyone in the group has, why we might not be able to know for sure which genes some tasters have and how and to figure it out. It’s incredibly satisfying.

5. How about a time when a kid asked you a question that either you didn’t know the answer to or that made you think about science in a totally new way?

**STARR:** Actually, this is one of the really fun parts about the “Ask a Geneticist” section of the website. I get to explore aspects of science that I never got to before. When I started, I knew very little about the genetics of physical characteristics like hair and eye color. I’ve also learned about all the rare and not-so-rare exceptions to the rules we all learned in high school and college. I can tell curious people that tongue rolling or ear lobe attachment are not simple traits so please don’t worry about your kids’ earlobes or tongue rolling ability. I can also now propose rare ways that a paretic with the blood type AB can have a type O child and lots of other real life rule breakers.

Answering people’s questions also makes me think more deeply about how some things happen. For example, there has been a lot of talk for the last few years focused on the fact that chimps have 48 chromosomes and humans have 46. Many intelligent design people use this fact as an example of why evolution isn’t real because they can’t imagine how something like that could happen. After all, extra or missing chromosomes leads to problems like Down syndrome, and besides, two species with different numbers of chromosomes couldn’t successfully breed (think donkeys, horses and their sterile offspring, mules).

This made me dig deeper into the science of chromosome fusion and to think about how something like that might spread. I found out that around 1 in 1,000 people have a balanced translocation where one chromosome is stuck to another. These folks are perfectly normal except they suffer from high rates of miscarriage. Now if two people with the same balanced translocation have kids together, one possibility is some one with the same chromosomes fused together. Now you have someone with the same amount of DNA just parsed out into a smaller number of chromosomes. Then you just need to propose a catastrophe where the survivors are mostly these new folks and voila, the species has a new number of chromosomes.

After we published this scenario on the website, a physician from China contacted us about a man in his practice who had 44 chromosomes because of something very similar to what I described. Basically his family had a certain balanced translocation, and after close relatives had children, this man with 44 chromosomes was born. He takes all of this beyond theory and shows that changes in chromosome number not only can but do happen.

6. How can people ask questions about genetics?

People can ask questions about genetics from students both in classroom settings and through the website, “Understanding Genetics.”

The Stanford Biology Center will sponsor a Café Scientifique program Sept. 27 on why there are so few new treatments for chronic and debilitating diseases and what can be done to change that. The talk takes off from the point that only 30 new drugs are approved by the FDA each year, even though billions of dollars is invested annually in medical research. The speaker, Scott Johnson, is president, CEO and founder of the Myelin Repair Foundation, a nonprofit organization focused on developing drug therapies for multiple sclerosis patients. Johnson knows firsthand the failure to produce new patient treatments, as he has suffered with MS for 36 years.

Johnson, a successful Silicon Valley entrepreneur, will begin speaking at 7 p.m. at the blood center’s Palo Alto site, 3373 Hillview Ave. Admission is free, and complimentary beverages and cookies will be served.

Café Scientifique is an international network of informal groups that brings scientific debate into local communities. For more information, visit http://bloodcenter.stanford.edu or contact Kevin O’Neill at 725-2540, konest@stanford.edu.
Online orientation preps grad students for first day of classes

By Tracie White

Gergana Vandova sometimes feels like she is an imposter.

“When my experiments don’t work, I think that it’s me — not my modeling or anything else — and that I’m an imposter,” she said, owning up to potential fears that she might not deserve to be a first-year graduate student in biochemistry at Stanford.

But through a new online orientation program that promotes dialogue among faculty and incoming students, Vandova learned she is not alone in her feelings. “The professors were talking about this ‘imposter syndrome,’” she said. “They explained that it exists, that it’s not only you that has it, and that you are not the most stupid person in your group.”

Vandova, 26, who has an undergraduate degree from Sofia University in her native Bulgaria and a master’s degree from University of Groningen in the Netherlands, is one of the 97 new biochemistry graduate students who start their first day of classes today and attend an orientation dinner, that will build on discussions that first started during summer online. The conversation will probe questions including, “How does being a graduate student differ from being an undergraduate?” and will provide tips and advice for success in graduate school and beyond.

“What we realized is that being a successful graduate student is almost the antithesis of being a successful undergraduate,” said Steve Fisch, PhD, senior associate dean of graduate education and professor of biochemistry. All of these students have excelled academically, and it sometimes requires a certain mind-bending psychological switch to enter the scientific world, he said. “Science most of your ideas will not pan out, and you have to get used to dealing with uncertainty, but that’s a necessary part of the process.”

Chosen from a pool of 1,820 applications, the new class will enter 13 different biosciences PhD programs, the majority of which will focus on the study of Medicine. The students come from 19 different countries, including Switzerland, South Africa, Iran and Ukraine. Fifteen have advanced degrees. The top two undergraduate alma maters for the new class are Massachusetts Institute of Technology and University of California-Berkeley.

The graduate students typically spend five years here before receiving their degrees. In their first year, they do lab rotations before settling into a research specialty of their own.

To help students get the most out of that time and “hit the ground running,” Harvard University’s Office of Career Services in collaboration with the office of graduate student affairs formed the online orientation program. He and colleagues chose to set up the program on the student side of the medical school’s Community Academic Profile Network, where professors could share orientation materials, post tips, give advice and ask questions in an informal atmosphere.

Students also could use the site to talk to each other and ask for tips about the more practical concerns of arriving at a new school — housing needs, transportation services, good places to eat.

“The interface is kind of cool because it mimics Facebook and other social networks,” said Krystal Renee St. Julien, a fifth-year biochemistry graduate student who works in a lab that studies cancer. “Some of the people are from my university, and it mimics Facebook and other social networks.”

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Even before arriving to start biochemistry graduate studies, Gergana Vandova was getting advice online.

Hannah Valentine and colleagues have put in place a major plan to promote work/life flexibility for medical school faculty careers.

The School of Medicine received today the Alfred P. Sloan Award for Excellence in Faculty Career Flexibility in recognition of its policies, commitment and plan to further enhance flexibility of faculty careers.

“Medical schools face unique challenges in not just finding, but keeping, highly specialized faculty,” said Claire Van Ummersen, PhD, American Council on Education senior advisor and project director. “The awardees have addressed this issue head-on. They should serve as examples not just for other medical schools, but for other institutions facing a crisis in retaining a highly trained workforce.”

Stanford will use the award to further its academic medicine mission, which is not only compatible with, but requires career flexibility that could become an integral part of the academic work-culture at the school by collaborating effectively with department chairs and division chiefs to help faculty members incorporate flexibility options into their career plans.

Christy Sandborg, MD, vice president of medical affairs at Lucile Packard Children’s Hospital and co-chair of the flexibility task force, summarized the plan: “ABCC involves the creation of individualized career plans over a faculty member’s entire career, with built-in options to flex up or down in research, patient care or education. The model is organized around teams of faculty members who will work in concert with their department chairs and professional career/life coaches, to create individual plans that will ensure faculty use existing and newly designed options to enhance work/work integration. The plan includes concrete benefits to support faculty at work and at home to make flexibility work.”

Jennifer Raymond, PhD, associate professor of neurobiology and associate dean for career flexibility who helped to create ABCC, explained: “Our initiative is unique because we are directly addressing the challenges of career integration without compromising the high standards of success for individuals and the institution. We are trying to create a flexibility culture that is truly sustainable and spans the American ethos of hard work and excellence. Achieving excellence in academic medicine is not only compatible with, but requires career flexibility that could become an integral part of the academic work-culture at the school. We envision an environment that encourages success, advancement and retention, in addition to faculty satisfaction.”

Dean Philip Pizzo, MD, thanked Valentine, Sandborg and their colleagues for what he called “transformational efforts,” and the Sloan Foundation and ACE for their support. “My personal observation of the challenges my own two daughters face in balancing life and professional careers — along with the challenges I have come to know in our faculty and trainees — is that many of our colleagues have covered effectively ways to support faculty who have the added struggle of the academic triple mission,” he said. “Without innovative, new work models, we risk losing generations of promising young physicians and scientists from academic medicine.”

Award honors medical school’s work/life flexibility plan, policies

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The Sanford Medicine X conference that will take place Sept. 28-30 will offer a high-quality streaming webcast for anyone who is unable to attend the event in person.


The campus event will cover such topics as patient-centered design, mobile apps for improving health, participatory medicine, the use of health information on the Internet and emerging technologies for health and biomedical research.

Speakers will include Michael Graves, an architect who was paralyzed from the waist down and went on to create functional and aesthetic change for hospitals; Susannah Fox, a statistician and director of digital strategy for the Pew Internet & American Life Project; Peter Binfield, PhD, publisher of the open-source scientific journal PLoS ONE; Dennis Boyle, a founding member of the Silicon Valley design firm IDEO; Anne Wojcicki, chief executive officer and co-founder of the personal genetics firm 23andMe; Aza Raskin, co-founder of the personal health information start-up Massive Health; and New York Times reporter John Markoff. Speakers will present 20-minute, narrative talks followed by moderated panel discussions.
New Innovators

Three Stanford faculty members will receive New Innovator Awards, designed to bridge the gap between basic research and development, for investigating the potential of their work to make possible the synthesis of an important class of molecules exhibiting diverse pharmacological properties and shed light on nature’s biosynthesis processes. Utilizing new capabilities for probing natural biosynthetic pathways will allow for the discovery and development of new and desperately-needed therapeutic agents. \textsuperscript{1} 

Anne Brunet, PhD, associate professor of genetics, will use her funding to study how longevity can be increased in both mammals and yeast. \textsuperscript{2}

"It is very clear that our life span is influenced by our genes and our environment; for example, our diet, or if we are exposed to toxins," said Brunet. "We are excited to understand whether longevity can also be influenced by a third component: the environment to which our parents or grandparents were exposed." 

Brunet will explore data from her lab suggesting that changes to chromatin — which helps package the DNA in the nucleus — could influence not only the life span of the organism, but also that of its descendants. These changes include the addition of chemical groups and other "tags" to DNA, in a process called epigenetic modifications. Brunet’s research suggests that, contrary to previous belief, some of these changes may not be removed when reproductive cells are formed. \textsuperscript{1, 3}

"We feel this research has potential to revolutionize our understanding of complex diseases, in particular age-dependent disorders such as cardiovascular diseases, type-2 diabetes, cancer and Alzheimer’s disease," said Brunet, who is also a member of the Stanford Cancer Institute.

Transformational Research Awards

These awards, open to both individuals and teams of investigators, are targeted to support particularly transformative projects that have the potential to create or overturn fundamental paradigms. The amount of these five-year awards will range from $4.3 million to $14 million over five years.

Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences, studies the brain as a complex biological system, exploring the extreme challenges of gathering high-resolution local information in specific parts of the brain, while maintaining a global perspective across the entire brain system. \textsuperscript{4}

The $22.48 million award that Deisseroth will receive will allow his interdisciplinary team to continue working on an approach, known as CLARITY, that may someday elucidate how the brain is organized, particularly in complex psychiatric diseases such as depression, PTSD, drug abuse, and schizophrenia. \textsuperscript{5}

"Specifically, we've united the tools of chemical engineering, molecular genetics and optics to gather detailed and specific information from within an intact brain," said Deisseroth, "However, these tools are not limited to the brain alone. They can be applied to study any intact biological system." 

Research on CLARITY was launched through Stanford's CNS Program, an interdisciplinary effort that includes key investigators Linquan Luo, Krishna Shenoy, Marc Levov and Philippe Mourenx. 

Helen Blau, PhD, the Donald E. and Delia B. Baxter Professor and a member of Stanford's Institute for Stem Cell Biology and Regenerative Medicine, will use her $4.3 million award to explore whether it is possible to transparently induce the lengthening of telomeres, which are thought to act as brakes that protect the ends of chromosomes. Abnormal telomere shortening has been implicated in many human diseases. \textsuperscript{6}

"We are really excited about this approach because it could aid in maintaining stem cells in a proliferative, non-senescent state for longer periods, enhancing their utility as disease models and for drug screening," said Blau. "In addition, the technology could prove useful in treating diseases characterized by prematurely shortened telomeres, like Duchenne muscular dystrophy. The most exciting aspect is that the potential applications are so broad; the impact on regenerative medicine could be immense." 

Ben Barres, MD, PhD, chair and professor of neurobiology, will use his $2 million New Innovator award to study how human’s superior cognitive ability arises because human astrocytes have evolved to have better synapse-controlling abilities than those of other animals. \textsuperscript{7}

Astrocytes outnumber neurons 5-to-1 in the human brain. Barres' lab has previously shown that chemical signals released by these cells are critical in the formation and function of synapses, the electrochemical contact junctions via which individual neurons communicate with one another. His lab will purify mouse and human astrocytes to a high degree and compare their ability to induce synapse formation and activity. If human astrocytes are more effective in forming synapses, they will then identify the relevant secreted chemical signal, bioengineer mice whose astrocytes can produce and test whether these mice have improved cognitive abilities. \textsuperscript{8}


Columbia University honors Shapiro with Horwitz Prize

Lucy Shapiro, PhD, is one of three recipients of the Horwitz Prize, an annual award given by the Center for Molecular and Genetic Medicine at Columbia University to Scientists who have made significant contributions to cell biology or medical research. Shapiro, who is the Virginia and D. Ludwig Chair in Cancer Research at the Department of Developmental Biology at Columbia University, has been recognized for her work on the regulation of cell cycle and DNA replication. Shapiro has made significant contributions to the understanding of the mechanisms that control cell division and the regulation of DNA replication. Her work has provided new insights into the processes that govern cell proliferation and have implications for the development of new therapies for cancer and other diseases.

Quake receives 2013 Nakasone Award

Stephen Quake, PhD, professor of bioengineering and applied physics at the Howard Hughes Medical Institute, has been selected to receive the 2013 Nakasone Award from the Human Frontier Science Program Organization for “proposals that have advanced biological measurement techniques.”

Quake is a pioneer in the discipline of bioengineering, which fuses engineering and life sciences to promote the development of new technologies and therapies in human health and environmental sustainability. Stanford’s Department of Bioengineering is a collaboration of the School of Engineering and the School of Medicine.

Quake’s research includes the development of new technologies for measuring the activity of biologic systems at the scale of individual cells and molecules. He has developed microfluidic devices that allow for the measurement of single cell responses to external stimuli, and has used these devices to study the behavior of stem cells in vitro. Quake has also developed new methods for analyzing single molecule DNA sequencing, which has revolutionized the field of genomics.

Quake’s work has been recognized with numerous awards and honors, including the National Academy of Sciences Award for Chemical Sciences, the MacArthur Foundation “genius” grant, and theirectioner Award in Medicine and Science.

OFS NOTE

required for significance scores and awards for faculty, staff and students

STEFAN HELLER, PhD, the Edward C. and Amy H. Sewall Professor in the School of Medicine, has been elected as a member of the American Phyto-Rhyn- Laryngologicum Amicicae Scurae. Established in 1926, CORLAS is an association of otolaryngologists with more than 400 members. Heller, a leader in stem-cell based research, has invented a technique for the inner ear, has recently focused on two pathways for potential treatment of deafness: drug therapy and stem cell transplantation into the inner ear. He delivered two presentations during the CORLAS annual meeting in Rome on Aug. 26-29.

SUN NIE CHAO, MD, has been named to the 2012 Association of Women Surgeons Hilary Sanfey Outstanding Resident Award for clinical excellence and accomplishments during professional development years. The award will be presented at the 2012 Annual Meeting of the American College of Surgeons from Sept. 30 to Oct. 4 in Chicago. Chao, who is now a chief resident in the Department of Surgery, will be joining the pediatric surgery division for a two-year fellowship at the completion of her residency. She is the third Columbia surgical resident to receive the award.

ANAND VERAVAGI, MD, a neurosur- gerist residing in the Washington, D.C., area, who has been named to the President Barack Obama to be one of the 15 members of the 2012-13 class of White House Fellows. This is the highest record of professional achievement, evidence of leadership potential and proven commitment to public service. Veravagi works on advancing minimally invasive diagnostic and surgical techniques for diseases of the central nervous system and has developed a novel radiothera-