INSIDE STANFORD MEDICINE

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Some chimps have a genetic variant that may help impede the progression of the primate equivalent of HIV.

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Residents set sail to keep life on an even keel

By Sara Wykes

"These are called the shrouds," explained sailing instructor Samuel Daly-Swenson, grasping a taut set of cables. "They hold up the mast of your new home for the next three hours."

His audience of passengers, waiting on a dock at the Berkeley Marina, listened attentively. "This is the boom," Daly-Swenson said, laying his hands on a thick pole, perpendicular to the mast and attached at one end to the bottom of it. "It's called that because of the sound it makes when it hits you in the head." From his audience came laughter of a somewhat nervous quality.

None of Daly-Swenson's passengers were where they often are — which is indoors, in hospital operating rooms — and that was the point. Instead, nearly all of these Stanford general surgery residents, plus a few of their supervisors, were preparing to set sail together as part of the Department of Surgery's Balance in Life Program, which aims to counteract the stress, both physical and mental, that accompanies the residents' typical 80-hour workweek.

"A lot of people would argue with the notion that such a program is necessary," said Ralph Greco, MD, the program's director. "I know our day of sailing may raise some eyebrows, but our faculty decided that we should do whatever we could to give these young people the tools they need to help them deal with the vicissitudes of life and medicine through the rest of their careers."

NORBERT VON DER GROEBEN

Surgery residents depart the Berkeley Marina to spend a few hours sailing around the San Francisco Bay during an outing organized by Balance in Life.

A little after noon, five sailboats full of surgeons hit the choppy, green waters of the bay. Some were content to sit and enjoy; others were eager to learn some sailing techniques.

In memorium

Balance in Life was founded four years ago and is dedicated to the memory of Greg Feldman, MD, a former chief surgical resident at Stanford who committed suicide in late 2010 while working as a surgical fellow at a hospital in the Midwest. Each year, the program has expanded the resources and activities it offers to general surgery residents. Now, they have a refrigerator stocked with healthy, fresh foods to sustain their physical well-being; attend group therapy sessions with a clinical psychologist for mental health; and, for social health, participate in mentoring partnerships and, if they want, social activities.

Resident Micaela Esquivel, MD, worked for a year to arrange the sailing activity. One of the biggest obstacles was figuring out a way to cover the absence of all 35 general surgery residents and several attending

See SAILING, page 6

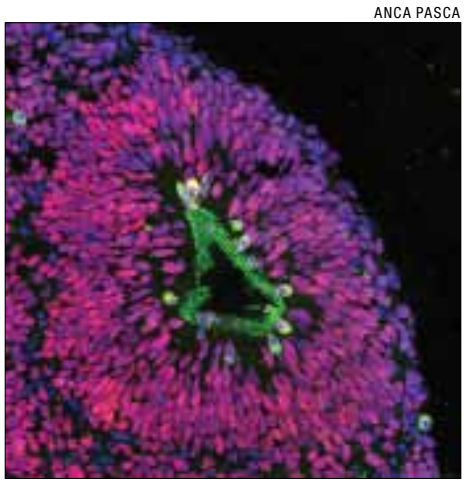
Spheres of human cells mimic the brain

By Krista Conger

The human brain is a highly organized, three-dimensional mass of cells responsible for our every move, thought and emotion. Snugly housed in the bony confines of the skull, it's also relatively inaccessible, making it difficult to study.

Now, researchers at the School of Medicine have devised a way to generate spherical, free-floating balls of human brain cells that mimic the architecture of the cerebral cortex, the outer layer of brain tissue responsible for how we experience and perceive the world around us and how we interact with others. The spheres contain functional neurons, working synapses and even critical support cells called astrocytes that maintain neural function. They also express genes in patterns similar to a human fetal brain midway through pregnancy.

ANCA PASCA



A cross-section of a human cortical spheroid shows organized neural progenitor cells (pink and purple) and cells undergoing division (green).

The researchers hope that tracking the development of the cortex-like spheroids over time and observing the interactions of their cells may shed light on human brain development and the molecular causes of neuropsychiatric disorders such as autism and schizophrenia.

"One of the major problems in understanding mental disorders is that we can't directly access the human brain," said Sergiu Pasca, MD, assistant professor of psychiatry and behavioral sciences. "These spheroids closely resemble the three-dimensional architecture of the cortex and have gene-expression patterns that mimic those in a developing fetal brain."

Previous attempts to create patient-specific neural tissue for study have either generated two-dimensional colonies of immature neurons that do not create functional synapses, or required an external matrix on which to grow the cells in a series of laborious and technically difficult steps.

In contrast, the researchers found they were able to easily make hundreds of what they've termed "human cortical spheroids" using a single human skin sample. These spheroids grow to be as large as 5 millimeters in diameter and can be maintained in the laboratory for nine months or more. They exhibit complex neural network activity and can be studied with techniques well-honed in animal models.

Pasca is the senior author of a study, published online May 25 in *Nature Methods*, that describes the work. Postdoctoral scholar and neonatology fellow Anca Pasca, MD, and graduate student Steven Sloan share lead authorship of the paper. (Sergiu Pasca and Anca Pasca are married.)

See BRAINS, page 7

Predicting and preventing disease, not just treating it, aim of precision health

By Ruthann Richter

Imagine a system where doctors can quickly comb through millions of anonymized patient records to find people with conditions and medical experiences just like yours. Through this massive, searchable database, doctors could determine how best to treat you, based on what has worked effectively for others with similar symptoms and characteristics.

Stanford Medicine is laying the groundwork for such a system, which will be able to quickly analyze information from large patient databases, medical literature, mobile monitoring and patients' real-life experiences with drugs, among other sources, to provide an evidence-based approach to medicine that's not been possible before.

See PRECISION, page 6

EVERYTHING POSSIBLE / SHUTTERSTOCK

Study: Adults harbor lots of risky autoreactive immune cells

By Bruce Goldman

Decades' worth of textbook precepts about how our immune systems manage to avoid attacking our own tissues may be wrong.

Contradicting a long-held belief that self-reactive immune cells are weeded out early in life in an organ called the thymus, a new study by School of Medicine scientists has revealed that vast numbers of these cells remain in circulation well into adulthood.

"This overturns 25 years of what we've been teaching," said Mark Davis, PhD, professor of microbiology and immunology and director of Stanford's Institute for Immunity, Transplantation and Infection. Davis, the senior author of the new study, is the Burt and Marion Avery Family Professor and a Howard Hughes Medical Institute investigator. The lead author of the study, published May 19 in *Immunity,* is Wong Yu, MD, PhD, a clinical instructor in hematology and a research associate in the Department of Microbiology and Immunology.

The vertebrate immune system is a complex of many specialized cell types working together to recognize and wipe out foreign invaders and developing tumors. T cells — so-named because they mature in the thymus — come in two major varieties. One particular class of these cells, called cytotoxic T cells or "killer T cells," is particularly adept at attacking cells harboring viruses or showing signs of being or becoming cancerous.

As T cells proliferate in early development, they undergo frequent DNA "scrambling" in a critical part of their genome. This DNA rearrangement results in an astounding diversity in which kinds of pathogens or unfamiliar tissues individual T cells can identify and distinguish from healthy, familiar tissues. Numerous rounds of cell replication bequeath the immune system a formidable repertoire of such cells, collectively capable of recognizing and distinguishing between a vast array of different antigens — the biochemical bits that mark pathogens or cancerous cells as well as healthy cells. For this reason, pathogenic invaders and cancerous cells seldom get away with their nefarious plans.

The current theory

But this same random-mutation process yields not only immune cells that can become appropriately aroused by any of the billions of different antigens characteristic of pathogens or tumors, but also immune cells whose activation could be triggered by myriad antigens in the body's healthy tissues. This does happen on occasion, giving rise to autoimmune disease. But it happens among few enough people and, mostly, late enough in life that it seems obvious that something is keeping it from happening to the rest of us from day one.

Much of the reasoning regarding why we aren't all under constant autoimmune attack derives from mouse studies, carried out with techniques that by today's standards are relatively primitive.

"A whole lot of that mouse work indicated that self-specific T cells are efficiently wiped out in the thymus — that as T cells mature in the thymus, some process within that organ singles out self-targeting T cells and marks them for destruction, and very few of them ever make it out of there alive," said Davis. "The problem with this, though, was that it would create 'holes' in our immune repertoire that pathogens could exploit by evolving ways to exploit these blind spots. But we've shown here that in both people and mice, self-specific T cells are not efficiently removed. While many are, lots of these cells get through, and so we don't believe there are any 'holes' to worry about."

For the study, Davis and his colleagues exposed T cells obtained from human blood donors to a number of "self" antigens, as well as several viral antigens. They were able to identify and count T cells targeting each of these antigens by using a sophisticated approach Davis pioneered in the 1990s. The approach allows researchers to distinguish small numbers of human T cells that recognize a particular antigen from the tens of millions of surrounding ones that don't.

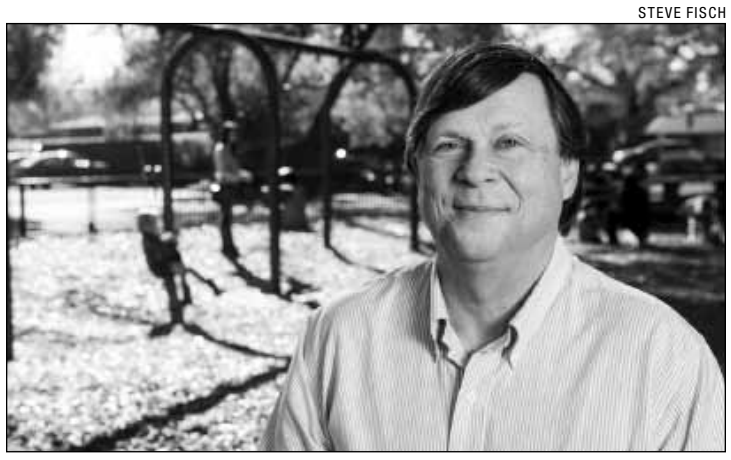
Looking at blood from dozens of human adult donors, the scientists found that the frequency of killer T cells recognizing self-antigens was almost equal to that of those recognizing foreign antigens. This in itself was a surprising result, challenging the assumption that wholesale destruction of self-reactive killer T cells had taken place in these donors before they'd reached adulthood. (The thymus begins to shrink in early adolescence, eventually withering and largely turning to useless fat.)

Why lots of killer T cells don't attack us

Davis and his associates then took an interesting tack. They compared men's and women's relative frequencies of T cells that recognized a protein that is encoded by the Y chromosome and that therefore only manifests in males. To women, this antigen is "foreign"; to men, it's "self." The researchers found that killer T cells targeting this antigen were only one-third as prevalent in men's blood as in women's. This implied, however, that only about two-thirds of killer T cells targeting this antigen in men had disappeared, leaving a substantial fraction of T cells that in principle should be able to attack any cell manifesting the target antigen — and there are all kinds of such cells in a man's body. Yet the male donors in the study showed no signs of autoimmunity.

In a further experiment, Davis' group tested the breadth of donors' immune repertoires against an antigen from a strain of the hepatitis C virus. This antigen is a small piece of one of the virus's proteins. Proteins are long strings of 20 different chemical building blocks called amino acids. The scientists created 20 versions of the antigen by substituting, at the same position along this snippet, one after another of the 20 amino acids. Doing this changed the antigen's shape and biochemical properties. No matter which amino acid the scientists inserted at this particular position on the snippet, there were always some T cells within the donor's repertoire that recognized it. Thus there were no "holes" that pathogens could have evolved to exploit.

STEVE FISCH



Mark Davis and his colleagues have found that vast numbers of certain immune cells remain in circulation well into adulthood, contradicting beliefs that the cells were weeded out in childhood.

But it's a Faustian bargain, Davis said. Or, put more benignly, a calculated risk. What keeps all those self-targeting killer T cells that aren't destroyed from running amok and attacking us?

An emergency brake

Another experiment conducted by Davis' team hints at a possible answer. Using single-cell microfluidics technology invented by Stephen Quake, PhD, a bioengineering professor and co-author of the study, they found that the activity levels of a small number of genes in self-targeting killer T cells differ from those of their foreign-targeting counterparts.

Davis said he thinks those genes may encode proteins that act as an internal emergency brake on self-reactive T cells, making it safe for the immune system to keep them around in case a nasty pathogen comes along against which these cells might put up a heroic defense. In a dish, the self-targeting killer T cells proved more resistant than foreign-targeting ones to immune-signaling substances known to initiate T cell replication and activation.

The downside of the Faustian bargain, Davis said, may occur when strong inflammation, induced by yet other receptors on immune cells that sense viral DNA or bacterial cell walls, becomes sufficiently intense to release a self-targeting T cell's emergency brake. While that might help to stave off a pathogen featuring an antigen that is very similar to the self-antigen this T-cell recognizes, it could also possibly trigger autoimmunity.

Other Stanford authors are postdoctoral scholars Niang Jiang, PhD, and Brian Kidd PhD (now both at Icahn School of Medicine at Mount Sinai, New York), Keishi Adachi, DVM, PhD (now at Nagasaki University, in Japan), Evan Newell, PhD (now at Singapore Immunology Network, in Singapore) and Michael Birnbaum, PhD; former graduate student Peter Ebert, PhD (now at Genentech); graduate student Peder Lund; former MSTP student Jeremy Juang, MD, PhD; research assistant Tiffany Tse (now at Fluidigm, Inc.); and Darrell Wilson, MD, professor and chief of pediatric endocrinology and diabetes at Lucile Packard Children's Hospital Stanford.

The study was funded by the National Institutes of Health, the Howard Hughes Medical Institute and the Damon Runyon Cancer Research Foundation.

Stanford's Department of Microbiology and Immunology also supported the work. **ISM**

Joanna Wysocka, Krishna Shenoy appointed HHMI investigators

By Krista Conger and Tom Abate

Two Stanford researchers were among 26 scientists from 19 institutions newly appointed Howard Hughes Medical Institute investigators, the institute announced May 19. They were chosen through a competitive selection process from a pool of nearly 900 candidates.

The two Stanford researchers are Joanna Wysocka, MD, PhD, an associate professor of chemical and systems biology and of developmental biology in the School of Medicine, and Krishna Shenoy, PhD, a professor of electrical engineering in the School of Engineering.

HHMI provides each investigator with a full salary, benefits and a research budget over their initial five-year appointment, which may be renewed for additional five-year terms. The institute will also cover other expenses, including research space and the purchase of critical equipment.

With today's appointments, Stanford now has 22 HHMI investigators, 18 of whom are faculty of the medical school.

Wysocka's research focuses on how gene-expression patterns enable cells in the developing embryo to migrate from a region known as the neural crest to form the skeletal and connective tissue of the head. In particular, she is interested in learning how genes may affect human facial structures and birth defects, such as cleft palate. Wysocka also recently published research showing that viral proteins may play a role in the earliest steps of human development.

"The flexibility of HHMI funding will allow us to further develop some high-risk projects that we have initiated in the lab," Wysocka said. "For example, we will use this funding to extend our work on genetic, regulatory and evolutionary principles that make our facial features uniquely human and uniquely individual. Given the faltering support for basic research in the United States, the HHMI appointment provides my team with the luxury to pursue fundamental questions and to think beyond the short-term outlook."

Lloyd Minor, MD, dean of the School of Medicine, said, "We congratulate Dr. Wysocka on her achievements that led to this great honor. The support of the Howard Hughes

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STANFORD MEDICINE

Researchers tie unexpected brain structures to creativity

By Bruce Goldman

Investigators at Stanford have found a surprising link between creative problem-solving and heightened activity in the cerebellum, a structure located in the back of the brain and more typically thought of as the body's movement-coordination center.

In designing the study, the researchers drew inspiration from the game Pictionary.

The cerebellum, traditionally viewed as the brain's practice-makes-perfect, movement-control center, hasn't been previously recognized as critical to creativity. The new study, a collaboration between the School of Medicine and Stanford's Hasso Plattner Institute of Design, commonly known as the d.school, is the first to find direct evidence that this brain region is involved in the creative process.

"Our findings represent an advance in our knowledge of the brain-based physiology of creativity," said the study's senior author, Allan Reiss, MD, professor of radiology and of psychiatry and behavioral sciences.

The study, published May 28 in *Scientific Reports*, also suggests that shifting the brain's higher-level, executive-control centers into higher gear impairs, rather than enhances, creativity.

"We found that activation of the brain's executive-control centers — the parts of the brain that enable you to plan, organize and manage your activities — is negatively associated with creative task performance," said Reiss, who holds the Howard C. Robbins Professorship in Psychiatry and the Behavioral Sciences.

"Creativity is an incredibly valued human attribute in every single human endeavor, be it work or play," he continued. "In art, science and business, creativity is the engine that drives progress. As a practicing psychiatrist, I even see its importance to interpersonal relationships. People who can think creatively and flexibly frequently have the best outcomes."

The collaboration began about 3½ years ago when Grace Hawthorne, MFA, MBA, a consulting associate professor at the d.school who teaches a design-thinking skills course called "Creative Gym," and one of her students approached Reiss, who has previously studied humor and other higher-level cognitive functions. They asked if he could objectively measure creativity, the better to confirm that Hawthorne's course can enhance it.

COURTESY OF THE REISS LAB

Participants in a study of creativity had their brain activity recorded while making drawings of words (above) and, as a control, of a zigzag line.

"We didn't know that much about how to do that," Reiss said. "So we decided to design a study that would give us baseline information on creativity's underlying neurophysiological processes."

How do you measure creativity?

As much as creativity may be in demand, it's not so easy to measure. At least 25 or 30 previous studies, mostly of professionally creative people such as jazz musicians and Emmy Award winners, have tried to look at neural correlates of creativity, said the study's lead author, Manish Saggar, PhD, an instructor in psychiatry and behavioral sciences and a member of the teaching team at the d.school.

"Everybody wants to think creatively," Saggar said. "But how do you get somebody to actually do that on command? Forcing people to think creatively may actually hamper creativity."

The problem is exacerbated by the fact that subjects' brain processes are monitored while they're confined inside a dark, cramped MRI chamber. This environment is not exactly the first place that comes to mind when you're thinking about places where creativity can flower, Saggar said.

"Creativity has to be measured in a fun environment," he said. "Otherwise, you're bound to have anxiety and performance issues."

Saggar came up with the idea of borrowing an approach from Pictionary, a game in which players try to convey a word through drawing to help their teammates guess what the word is. He selected action words like "vote," "exhaust" and "salute." Then he, Reiss and their colleagues serially tested 14 men and 16 women in an MRI chamber, recording activity throughout their brains via functional MRI scans while they drew either a word or, for comparison, a zigzag line, which required initiation and fine-motor control but not much creativity. Participants were given 30 seconds per word, long enough for a decent scan but short enough to elicit spontaneous improvisation and stave off boredom.

"We didn't tell anyone, 'Be creative!' We just told them, 'Draw the word,'" Reiss said.

The drawings were captured on a special MRI-safe electronic tablet designed by study co-author Robert Dougherty, PhD, research director at the Stanford Center for Cognitive and Neurobiological Imaging. The drawings were then sent to Hawthorne and Adam Royalty, a researcher at the d.school and co-author of the study. Hawthorne and Royalty separately rated the drawings on five-point scales of appropriateness — did it depict what it was supposed to? — and creativity — how many elements were in the drawing? How elaborate was it? How original?

When they emerged from the MRI chamber, subjects were asked to rate the words they'd been asked to draw for relative difficulty.

Increasing subjective difficulty of drawing a word correlated with increased activity in the left prefrontal cortex, an executive-function center involved in attention and evaluation. But high creativity scores later assigned by the raters were associated with low activity in the executive-function center. Higher creativity scores were associated with higher activation in the cerebellum.

On analysis, a number of brain areas were more active when subjects were engaged in drawing words than when they were drawing zigzag lines. Peak activation occurred in the cerebellum and regions of the cortex known to be involved in coordinating motor control or acting as a visual sketchpad. The latter regions' involvement in detailed drawing wasn't particularly surprising.

'The more you think about it, the more you mess it up'

But the heightened activity in the cerebellum was unexpected, as was its association with high creativity scores subsequently assigned by the raters. In monkeys, this brain region has been found to be especially active in learning and practicing new movements.

But those monkey findings may have thrown researchers off, Saggar said. Newer studies show that, unlike the monkey cerebellum, the human cerebellum has robust connections not only to the motor cortex, the brain's higher movement-control center, but to the other parts of the cortex as well.

"Anatomical and, now, functional evidence point to the cerebellum as doing much more than simply coordination of movement," Saggar said.

He and his colleagues speculate that the cerebellum may be able to model all new types of behavior as the more frontally located cortical regions make initial attempts to acquire those behaviors. The cerebellum then takes over and, in an iterative and subconscious manner, perfects the behavior, relieving the cortical areas of that burden and freeing them up for new challenges.

"It's likely that the cerebellum is an important coordination center for the rest of brain, allowing other regions to be more efficient," said Reiss.

"As our study also shows, sometimes a deliberate attempt to be creative may not be the best way to optimize your creativity," he said. "While greater effort to produce creative outcomes involves more activity of executive-control regions, you actually may have to reduce activity in those regions in order to achieve creative outcomes."

Saggar put it more bluntly. "The more you think about it, the more you mess it up," he said.

Other Stanford co-authors of the study are former postdoctoral scholar Eve-Marie Quintin, PhD; psychology graduate students Eliza Kienitz and Nicholas Bott; visiting researchers Zhaochun Sun, PhD, Yin-hsuan Chien, MD, and Daniel Wei-Chen Hong, MD; and research associate Ning Liu, PhD.

The study was funded by a grant from the Hasso Plattner Design Thinking Research Program, which is affiliated with Stanford's Center for Design Research.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

HHMI

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Medical Institute helps our researchers continue pushing the boundaries of bleeding-edge and paradigm-changing science."

Wysocka was named an Outstanding Young Investigator by the International Society for Stem Cell Research in 2010. She is member of the Stanford Cancer Institute and of Stanford Bio-X.

Brain-machine interfaces

Shenoy brings an engineer's perspective to understanding how the brain controls body movements. His lab has long been at the forefront of efforts to develop technologies to restore movement to people with paralysis.

Krishna Shenoy

Joanna Wysocka

By studying the brains of monkeys as they perform specific tasks, Shenoy and his colleagues have probed how groups of neurons coordinate and cooperate to generate arm movements. His lab has developed unique insights into the dynamic neural circuits that control motor activity. Through computational analyses of large-scale neural data, he has shown how the populations of neurons involved in motor activity evolve dynamically — an understanding that has prompted neuroscientists to reconsider how neural circuits function.

Shenoy is also considered a leader in the emerging field of brain-machine interfaces to control the movement of computer cursors and prosthetic limbs. He has developed computational methods to dramatically speed up the ability to decode messages from a person's brain. These algorithms have been incorporated into a system designed to allow people with paralysis to control a computer cursor with their thoughts. That system is now being evaluated in a clinical trial.

"Krishna's engineering approach to brain research is a source of inspiration to his colleagues and of hope for people with paralysis," said Persis Drell, PhD, dean of the School of Engineering.

Shenoy received a National Institutes of Health Director's Pioneer Award in 2009. He is a member of the Stanford Neurosciences Institute and of Stanford Bio-X. ISM

Sharing health data is key, experts at conference assert

By Bruce Goldman

Aggregating large quantities of health data could revolutionize physicians' ability to diagnose and treat diseases, but getting patients and organizations to share that data poses a challenge, according to speakers at Stanford's third annual Big Data in Biomedicine Conference.

The conference, held May 20-22 at the Li Ka Shing Center for Learning and Knowledge, drew some 500 attendees and more than 3,000 remote viewers.

The era of big data — the collection, storage and analysis of vast amounts of information gathered from disparate sources — is no longer in the future; it's happening today. The goal of tailoring all aspects of health care to specific individuals rather than adhering to a one-size-fits-all approach rests on the ability to pool and analyze data on large numbers of people.

But until efforts to share this information can overcome privacy concerns, lack of interoperability in the technical realm and disincentives within the research community, the promise of using big data to help patients and healthy people alike will go unrealized, many of the speakers said.

In his keynote address, Lloyd Minor, MD, dean of the School of Medicine, defined a term, "precision health," as "the next generation of precision medicine." Precision health, he said, is the application of precision medicine to prevent or forestall disease before it occurs. "Whereas precision medicine is inherently reactive, precision health is prospective," he said. "Precision medicine focuses on diagnosing and treating people who are sick, while precision health focuses on keeping people healthy."

The fuel that powers precision health, Minor said, is big data: the merging of genomics and other ways of measuring what's going on inside people at the molecular level, as well as the environmental, nutritional and lifestyle factors they're exposed to, as captured by both electronic medical records and mobile-health devices.

Monitoring behavior

Precision health requires looking beyond medical data to behavioral data, several speakers said. This is especially true in a modern society where it is behavior, not infectious disease, that's increasingly the cause of disability and mortality, noted Laura Carstensen, PhD, professor of psychology and founding director of the Stanford Center on Longevity.

In her talk, Carstensen showed a cartoon of one caveman musing to another: "Something's just not right. Our air is clean, our water is pure, we get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past 30." Along with predators, violent altercations and bouts of mass starvation, a huge factor in Og and his peers' truncated life expectancies was contagious disease. Periodic epidemics continued to wipe out large populations of entire continents throughout recorded human history until only a century or so ago.

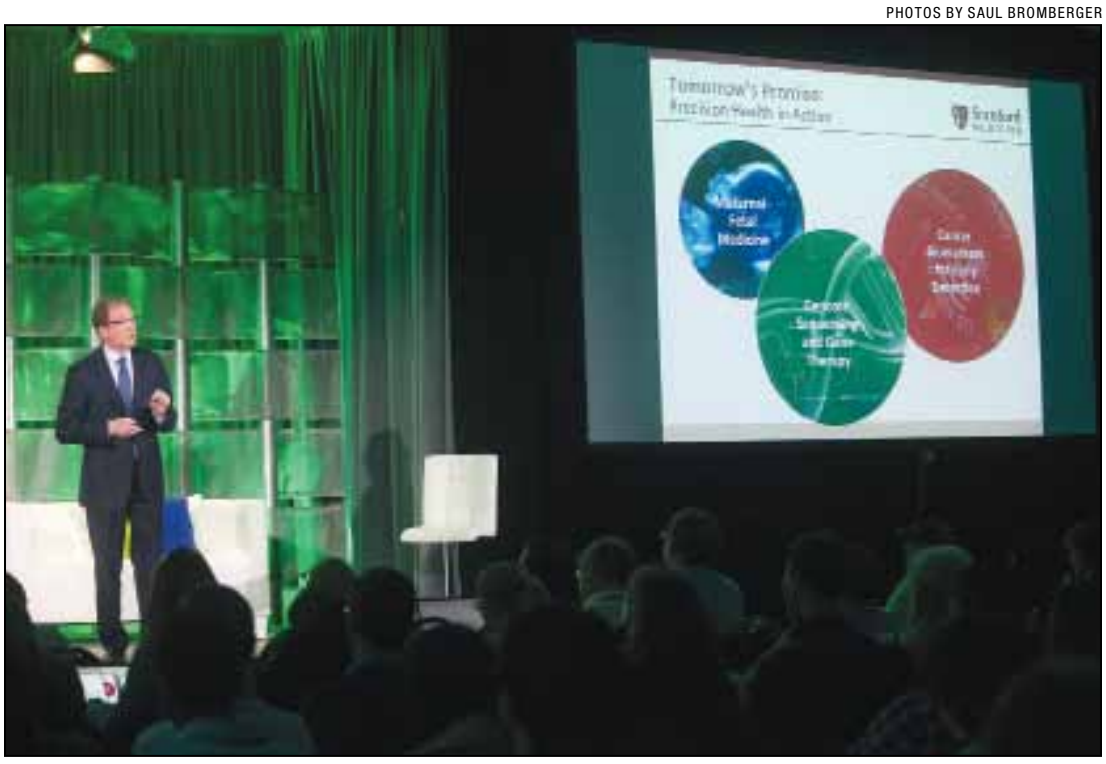
Now it's a different story, Carstensen said, because the scourge of contagious disease, which modern humans have largely defeated, has been replaced by an epidemic of chronic diseases of aging. For this reason, physical fitness is one of the greatest predictors of long-range health outcomes today, she said.

Ida Sim, MD, PhD, professor of medicine and co-director of biomedical informatics at the University of California-San Francisco, noted that one in four Americans has at least one chronic disease. "Chronic diseases account for 84 percent of health-care costs and 70 percent of deaths in the United States. And chronic disease is mostly caused by behavioral factors," she said.

That's where mobile devices for monitoring everyday behavior can be useful in ways electronic health records can't. Several speakers touched on the potential for using mobile-health devices to survey behavior and chronic disease and, perhaps, provide insights that could be used to support better behavior.

"There are 700 million people in the world with iPhones," said conference organizer Euan Ashley, MD, PhD, associate professor of cardiovascular medicine and of genetics. "That allows us to look at fitness in a very large population. Each of those iPhones is an accelerometer that can detect its owner's activity cheaply, without wearing down your battery too much."

PHOTOS BY SAUL BROMBERGER



Above: Lloyd Minor gives a keynote address at the Big Data in Biomedicine Conference, which ran May 20-22 at the Li Ka Shing Center. Top right: The event drew some 500 attendees, as well as more than 3,000 remote viewers. Bottom right: Stanford's Euan Ashley, far left, and Laura Carstensen, second from left, participate in a panel discussion with Ram Fish, vice president of digital health for Samsung, and Ida Sim, co-director of biomedical informatics at UCSF.

Scott Delp, PhD, professor of bioengineering and of mechanical engineering, is director of the new Stanford-based Mobilize Center, which is dedicated to understanding and increasing human movement. It is one of 12 Big Data to Knowledge Centers funded by the National Institutes of Health. "If you don't move, you're vulnerable to heart attacks, strokes and more," Delp said.

Phones and sensors are available to millions of people, he said. "They're low-resolution, but they're on all the time. We don't know how to use them effectively yet. We need to integrate video, cell phones and wrist accelerometers, and bring it all together to create an open-source motion-analysis software package that's free for all to use."

Intel fellow Eric Dishman, general manager of Intel Corp.'s health and life-sciences group, coined a word for the global study of behavior on a mass basis: behavioromics.

By monitoring 24/7 which room of one's home one is in at any given minute over a 100-day period, you can detect key changes in behavior — changes in sleep-wake rhythms, for instance — that can indicate or even predict the onset of a health problem.

An expert in analyzing conversations, Dishman recounted how he'd learned, for example, that "understanding the opening patterns of a phone conversation can tell you a lot," including giving clues that a person is entering the initial stages of Alzheimer's disease. Alternatively, "the structure of laughter in a couple's conversation can predict marital trouble months before it emerges."

Importance of shared data

"To understand the genes of the one, you need to study the genes of the many," said David Glazer, who founded and leads the genomics team at Google Inc. But that means sharing data, and there are some strong disincentives to doing that, said a number of speakers, including David Haussler, PhD, professor of biomedical engineering at UC-Santa Cruz.

"On June 1, 2000, the Human Genome Project announced the world's first human-genome sequence," said Haussler, who is scientific director of UCSC's Genomics Institute.

"In so doing, we became the first species to read our own recipe. What's emerged since then is a series of genome silos," he said. "Medical facilities won't share DNA information, because they feel compelled to protect patients' privacy. There are legitimate security and privacy issues. But sharing this information is vital. We'll never cure rare DNA diseases until we can compare data on large numbers of people. And at the level of DNA, every disease is a rare disease: Every disease from A to Z potentially has a genomic component that can be addressed if we share our genomes."

Disincentives for sharing are not just a problem for medical institutions. Several speakers noted the reticence of academics, who often withhold data until — and even beyond — journal publication in order to reap the rewards of being the first to publish a novel insight.

"It shouldn't just be that you just give up your career to do a good thing," said Brian Wandell, PhD, professor of psychology. "We need to find ways of giving credit to young researchers who've compiled huge data sets — for example, letting those researchers retain user rights for their primary data."

Sharon Terry, president and CEO of the Genetic Alliance, put it succinctly. "To herd cats," she said, "you need to move the food."

But it may be that ordinary people will step up to share personal data on a scale that enables the aggregation of huge piles of data, both behavioral and genomic.

A recently launched collaborative effort by Stanford and Apple called MyHeart Counts is doing just that, Ashley said. Almost 40,000 people have signed up for a research study that makes use of MyHeart Counts, a free app that collects data about physical activity as well as wearer-entered data related to cardiac risk factors. "Two months ago, it was zero," he said.

Jill Hagenford, chief medical officer of 23andMe, said the company was founded in 2007 with the goal of keeping people healthy by giving them access to their own genomic information, from which many useful things can be inferred: responses to specific medications, inherited health conditions and predispositions, ancestry, and "interesting traits" such as whether one finds broccoli bitter.

"23andMe holds the world's largest database of engaged, genotyped and phenotyped people," Hagenford said. The company has accumulated not only extensive genotypes on some 950,000 people, she added, but also a great deal of customer-supplied health and behavioral data that researchers can sift through. "About 80 percent of our customers have consented to their data being used for research," she said.

"People say, 'Why would you pay $99 to find out if you have wet or dry earwax? Just stick your finger in your ear.' But communicating the genetic basis of traits such as this one is a great way to introduce consumers to the power of the genome," Hagerford said. **ISM**

Wild chimps teach scientists about gene for HIV-fighting protein

By Bruce Goldman

A gene variant in chimpanzees in a Tanzanian wildlife preserve probably protects them from rapidly succumbing to the primate equivalent of HIV, School of Medicine scientists have discovered.

A gene variant is a naturally occurring difference in the DNA sequence of a gene. Part of the chimp variant strongly resembles that of an analogous human variant known to slow the human immunodeficiency virus' progression to AIDS.

The wild chimps inhabit Gombe Stream National Park, a 13.5-square-mile preserve where they have been continuously observed from afar since famed primatologist Jane Goodall, PhD, began monitoring them more than 50 years ago.

"The gene in question is subject to evolutionary pressures that normally cause it to change rapidly over evolutionary time."

The gene in question is subject to evolutionary pressures that normally cause it to change rapidly over evolutionary time, resulting in many variants with diverse sequences. So the striking similarity of a section of the chimp and a section of the human variant implies two things, said Peter Parham, PhD, professor of structural biology and of microbiology and immunology. First, hominids have been fighting off HIV-like viruses at least since the two related species diverged some 5 million years ago. Second, because that particular section of the gene variant hasn't changed much since then, it probably plays an important role in increased survival among those inheriting it.

"Only a part of the chimp gene variant's sequence looks a lot like the human one. That immediately tells us this is the important part of the gene," said Parham, the senior author of a study describing the findings, published online May 28 in *PLOS Biology*. Unlocking this sequence's significance could yield not only biological insights but also pharmaceutical or, someday, perhaps even gene-therapy applications that enhance HIV-infected people's ability to avoid disease progression to AIDS, he said.

The histocompatibility complex

One of Parham's research focuses is a set of three genes in the major histocompatibility complex. The MHC codes for proteins that help the immune system recognize foreign substances. These proteins sit on the surface of virtually every vertebrate cell, where they serve as display cases for peptides — small pieces of proteins, chopped out of proteins that once resided inside that cell. It's the fate of all of a cell's proteins to eventually be degraded into peptides, which get transported to the cell's surface and encased in MHC proteins. This enables roving immune cells called T cells to inspect tissues and detect any peptides carved from proteins that are of foreign origin, such as those of a virus that has infected a cell, or have been altered, as in a cancerous cell. T cells often quickly mount an attack on cells bearing foreign or altered proteins.

In humans, HLA-B, one of the three genes in the MHC complex, is the blueprint for a protein that is the appropriate display case for a peptide from Gag, an HIV protein that manifests early in the course of infection. Studies have shown that HIV-infected people who carry a particular variant of this gene, known as HLA-B*57:01, resist progression to AIDS. Scientists think this is because the cell-surface protein encoded by the B*57:01 variant, which is present in about one in 10 people, displays its captive Gag peptide in a way that especially catches T cells' attention. Although the virus can mutate so its Gag protein is invisible to T cells, it doesn't get much time to do that — and even then, success comes at a cost, Parham said. The resulting virus can't replicate as efficiently, so the disease can't progress as quickly to the full-blown, symptomatic stage.

The Gombe chimps belong to one of four subspecies. In genetic studies of the other chimp subspecies, the protective gene variant found in the new study hasn't previously been seen. But all those studies were done on captive chimps who weren't infected with simian immunodeficiency virus, a close relative of HIV.

In the Gombe chimps, SIV is endemic. "About one in four animals is infected," Parham said. But the likelihood of infection isn't distributed equally among them. The roughly 125 chimps occupying the Gombe's mountainous terrain during the study's course lived in three geographically distinct communities. While the northern and central groups had low SIV-infection rates, that virus has a strong grip on the southern community. In this community, the newly discovered gene variant became more frequent over the study period, suggesting it may have been naturally selected for its capacity to enhance chimps' survival to reproductive age and beyond. The Parham group's genetic analysis supports that suggestion.

The original thrust of the study, Parham said, was to compare the MHC diversity of wild versus captive chimp populations to see how real-world exposures to pathogens might affect relative frequencies of various versions of particular MHC genes.

DNA, RNA from chimp feces

Close human contact with the Gombe chimpanzees is prohibited, so obtaining genetic material from them wasn't easy. Lead author Emily Wroblewski, PhD, a postdoctoral scholar in Parham's lab, recruited her former PhD adviser from the University of Minnesota, behavioral ecologist Anne Pusey, PhD, who had done her graduate work in Gombe in the 1970s under the direction of Goodall. Wroblewski, who herself had spent 1½ years in the Gombe doing field work for her PhD thesis, also brought in prominent SIV virologist Beatrice Hahn, MD, now at the University of Pennsylvania. In 2000, Hahn developed methods for extracting DNA and RNA from chimp feces. Over the past 15 years, she has established a large collection of fecal samples, now housed in Philadelphia. Both Pusey, now at Duke University, and Hahn are co-authors of the study.

EMILY WROBLEWSKI

Some of the chimpanzees in the Gombe Stream National Park have a genetic variant that may help prevent them from rapidly succumbing to the primate equivalent of HIV.

Because the animals have been so carefully watched for so long, albeit always at a distance, each sample can be matched to a particular individual whose habits, maternal lineage and present social affiliations are known.

Wroblewski traveled to the Hahn lab, at the time in Birmingham, Alabama; coordinated the shipment of almost 300 fecal samples — at least two or three per chimp — from freezers in Hahn's laboratory to Stanford; and returned to Parham's lab, where she set up shop in one corner and began extracting DNA from the samples. Her DNA analysis permitted assessments of the chimps' MHC genes' status, and RNA analysis done by the Hahn lab enabled taking counts of SIV, which, like its cousin HIV, is an RNA virus.

Chimps have an MHC gene, PATR-B, that is functionally analogous to our HLA-B gene. The analysis found 11 different variants of PATR-B in the Gombe chimps, a surprisingly large number for such a tiny population. "Seven of these variants had never been seen in captive chimp populations," Wroblewski said.

After analyzing the first few dozen samples, Wroblewski noticed that the southern community showed an increase in frequency over time of one hitherto unseen variant of PATR-B called B*06:03. Further analysis showed that a stretch of B*06:03 was nearly identical to a stretch on B*57:01, the human gene variant associated with slower AIDS progression. Notably, fecal samples from SIV-infected chimps with the B*06:03 version of PATR-B had lower SIV tallies than those from similarly infected chimps without that variant.

"I found this to be quite exciting," said Wroblewski. "Fecal counts of SIV are a good proxy of viral load in the blood, which we have no easy way of measuring in Gombe chimps because we can't draw blood from them."

Parham said, "When a traditional field in biology starts to use new technology, it opens up enormous potential."

Other Stanford co-authors of the study are senior scientists Paul Norman, PhD, and Lisbeth Guethlein, PhD.

The study was funded by the National Institutes of Health. Stanford's Department of Structural Biology and Department of Microbiology and Immunology also supported the work. ISM

EMILY WROBLEWSKI

Fecal samples from wild chimps were shipped from a lab in Alabama to Stanford, and then genetic material was extracted from the samples for testing.

Sailing

continued from page 1

physicians from the hospital. Esquivel, who was a standout soccer player at Santa Clara University, said she understands the importance of teamwork. "The stronger your bond, the better," Esquivel said. "Critical things happen in the hospital, and the closer you are to your colleagues, the better chance you stand of surviving the intensity of that environment."

The numbers that motivate Esquivel, Greco and others involved with the program are distressing: One recent study compared residents to the general population and found them more likely to experience burnout and show symptoms of depression. A national study, published last year in *Academic Medicine*, found that 40 percent of surgeons said they were burnt out and 30 percent had symptoms of depression.

When Greco was a medical student, more than 40 years ago, a resident's workweek might last as long as 120 hours, he said. "But all we had to deal with were some blood tests and an X-ray," said Greco, who is the Johnson & Johnson Professor of Surgery. "There were no CTs, no MRI, no hundreds of blood tests, no genetic testing. And there weren't so many people watching what we did. It's a much more intense workload than we had."

Out of balance

The residents' evolution from first year to final year is being tracked. What some of that data shows so far, Greco said, is that only incoming residents feel they have a life that's well-balanced between work and play. "And by the time their training ends," he said, "they are out of balance. No shock there."

Residents think they can do it all, said Lisa Post, PhD, the clinical psychologist at Stanford who meets with the general surgery residents. "They are the most dedicated people and super responsible," Post said. "We try to help them slow down a bit, to manage their stress better — and when you are taking a break at home, you really take a break."

Greco believes Stanford's program is unique, but he hopes that will change as standard-setting medical associations pay more and more attention to the problem.

"The fact that we have this Balance in Life Program is great for recruitment of like-minded individuals," Esquivel said. "I can tell medical students considering us that they would be hard-pressed to find another program that cares enough about their well-being to offer what we do."

The residents said they did indeed appreciate their day on the bay. "Just being able to spend time together without the pressure of work is nice," said first-year resident Graeme Rosenberg, MD. "It gives you a better understanding and appreciation of the people you work with."

Added Elizabeth George, MD, another first-year resident, "Surgery is a team sport. You become more of a team and want to work harder for and support each other as a member of that team when you know a bit more about your colleagues."

Cara Liebert, MD, is a surgical education fellow and a general surgery resident who has been working with Greco to hone the program and monitor its effects. Liebert was as enthusiastic as everyone else, especially about being outside. Few of the residents see much daylight, she said. "You come in when it's dark and you leave when it's dark. This is the power of having a day outside, in the wind, in the fresh air." **ISM**

Sara Wykes is a writer for the Stanford Hospital & Clinics communications office.

NORBERT VON DER GROEBEN

NORBERT VON DER GROEBEN

Far left and left, surgery residents spend a few hours aboard sailboats on the bay last month as part of the Balance in Life Program. Each year, the program has expanded the resources and activities it offers to general surgery residents.

Precision

continued from page 1

The planned system is an example of how clinicians at Stanford Medicine are tapping health data to provide targeted, predictive and personalized care, an approach known as "precision health." What makes precision health unique is that it goes beyond treating existing diseases and conditions to predicting and preventing diseases before they manifest, said Lloyd Minor, MD, dean of the School of Medicine. It stands at the intersection of medicine, technology and big data, offering new ways to keep people healthy.

"Precision health is a way of translating data into information that can lead us to take care of our health in a way that we might not have done before," Minor said. "We are poised to have a whole new level of precision in maintaining health."

The dean led a discussion about precision health during a town hall meeting June 5 at the Li Ka Shing Center for Learning and Knowledge.

Moving beyond precision medicine

Precision health at Stanford Medicine has its roots in advances in both basic research and biomedical data science, which have given researchers the power to analyze vast quantities of information from a variety of sources: electronic medical records, genomic sequences, insurance and pharmaceutical records, wearable sensors and social and environmental data.

In sifting through this data, physicians and researchers can better predict individual risks for specific diseases, develop approaches to early detection and prevention, and arm clinicians with information to help them make real-time decisions about the best way to care for patients.

> "We are poised to have a whole new level of precision in maintaining health."

"Through our initiatives in precision health, we will be able to harness the availability of very large data sets and our ability to interpret and analyze that data to gain a more sophisticated understanding of the determinants of health and well-being, as well as specific risk factors and approaches for individual patients," Minor said.

Innovative environment

Stanford Medicine is well-positioned to advance what's possible through precision health because of its innovative and entrepreneurial culture, its ties to Silicon Valley, its multidisciplinary approach to problems and its leadership in biomedical data science and in multiple clinical disciplines, including stem cell biology, immunology, cancer biology, neuroscience, genomics, imaging and population health sciences.

Through collaborations that apply computation to clinical problems, scientists will be able to develop approaches that directly impact patients in the clinic. In cancer care, for instance, Stanford has a rare mix of expertise in both fundamental science and translational medicine, including cancer stem cells, genomic oncology, advanced diagnostics and clinical-trial infrastructure, all of which can be mined to develop targeted approaches to prevention and treatment.

"Our initiatives in precision health will influence how we care for patients in myriad ways," said Amir Dan Rubin, president and CEO of Stanford Health Care. "We have already seen the impact with Stanford Hospital's clinical genomics service, a collaboration that is enabling early and accurate diagnosis of disease and is a sterling example of personalized, patient-centered care."

"Precision health is a natural extension of the personalized, patient-centered approach we bring to every patient," said Christopher Dawes, president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health. Both Dawes and Rubin joined Minor at the June 5 town hall discussion.

The move to early diagnosis

Large-scale data analysis also is enabling researchers to develop more targeted and cost-effective methods for early diagnosis of disease before symptoms ever develop. Maximilian Diehn, MD, PhD, assistant professor of radiation oncology, and his colleagues did a study using a national library of DNA sequences of tumors to develop a technique sensitive enough to detect a single molecule of tumor DNA among thousands of healthy molecules. That means a blood sample could one day be enough to diagnose many types of solid cancers or to monitor the level of cancer in a patient's body.

In another recent study, School of Medicine researchers detected a pattern of gene activity that could lead to the development of a blood test to quickly and accurately detect sepsis, a deadly, whole-body inflammation syndrome. Sepsis is linked to 750,000 deaths each year in the United States and is the most common cause of hospital deaths. But it can be hard to pinpoint the condition, which can kill patients in a matter of hours. The researchers used publicly available patient data to identify specific immune-response genes associated with the condition, laying the groundwork for a simple diagnostic test for sepsis.

MARK TUSCHMAN

Christopher Dawes, Lloyd Minor and Amir Dan Rubin discussed the precision health initiative at a town hall meeting June 5.

Capitalizing on Silicon Valley connection

Other studies, which take advantage of Stanford's close ties to Silicon Valley, aim to use large collections of data to discern the factors that keep people healthy — or send them along a disease trajectory.

In collaboration with Google X and Duke University, Stanford researchers are conducting a pilot study, ultimately involving 10,000 healthy volunteers, to understand the biological markers of health, down to the molecular and cellular level.

In another study, researchers are collaborating with Apple Inc. on a first-of-its-kind iPhone app called MyHeart Counts, which will collect data about physical activity and cardiac risk factors in order to advance understanding of the human heart. Researchers will be able to gauge the "heart age" of participants and study what motivates people to improve their heart health.

"These partnerships with Silicon Valley innovators take advantage of new technologies, including mobile health devices, to do systematic studies of all the factors at play in maintaining a healthy state," Minor said. "That is the heart of precision health — using all the resources at our disposal to not only diagnose and treat the sick, but to broaden our understanding so that we can better advise patients on how sustain their health throughout their lives." **ISM**

Brains

continued from page 1

"The power and promise of this new method is extraordinary," said co-author Ben Barres, MD, PhD, professor of neurobiology, of developmental biology and of neurology and neurological sciences. "For instance, for developmental brain disorders, one could take skin cells from any patient and literally replay the development of their brain in a culture dish to figure out exactly what step of development went awry — and how it might be corrected. For Alzheimer's disease, one could do the same to determine if the neurons or glia are abnormal and, if so, what is malfunctioning. Now we can move away from mouse as a model and instead generate functional neurons and glia from humans with literally any disease."

Sergiu Pasca

Looking for a good model

The researchers embarked on the study after becoming frustrated with the lack of a good model system to study human brain development and function. Although techniques like functional magnetic resonance imaging allow scientists to broadly visualize brain activity, they don't give an up-close-and-personal look at the complex neural networks necessary for brain function. Post-mortem tissue can give a sense of brain structure, but not of function.

"I'm a neurobiologist," Sergiu Pasca said. "I need to study neurons that are firing."

The researchers first created seven batches of induced pluripotent stem cells, or iPS cells, from the skin of five people. IPS cells have the ability to become nearly any tissue in the body when grown under particular conditions. They grew the iPS cells into flat, multicellular colonies on the surface of a laboratory dish. The researchers then carefully detached the intact colonies and moved them to special laboratory dishes treated to make it difficult for cells to adhere to the dishes. Within a few hours, the colonies began to fold upon themselves to create spheres. They then treated the cells with a combination of growth factors and small molecules to promote their development into neural progenitor cells. After about seven weeks, nearly 80 percent of the cells in the spheres expressed a protein made by neural tissue. Furthermore, about 7 percent of the cells expressed another protein specifically made by astrocytes — star-shaped support cells that wrap around the synapses, the junctions between neurons.

"Astrocytes are really essential to neuronal signaling," Pasca said. "But it's been challenging to efficiently make both neurons and astrocytes at the same time. Until now, researchers have been relying on astrocytes from rodents or human fetal tissue, and trying to grow neurons on top of them. Our system generates astrocytes that develop in concert with and are genetically identical to the surrounding neurons."

When human cortical spheroids, or hCSs, were sliced, they exhibited architecture similar to the human cortex. "In contrast to monolayer cultures, we observed an orderly, three-dimensional arrangement of specific types of neuronal cells in the hCSs," Pasca said.

'Potential to bring novel insights'

That organization is primarily driven by the cells themselves, the researchers found.

"If anyone had asked me before we conducted this study what it would really take to recreate the human cortex, I would have said it would require all sorts of specific molecular cues and many other conditions of which we're not even aware," said Pasca. "But in reality, once the program starts, and a few conditions are met, the cells themselves are doing the rest of the job."

The final test of the human cortical spheroids was to slice them and perform functional tests. The researchers found that up to 80 percent of the neurons in the spheres were capable of firing when stimulated. Furthermore, 86 percent of the neurons exhibited spontaneous neural signaling and participated in neural network activity.

"We've been treating them just like we would slices of mouse brain," Pasca said, "and trying to answer functional questions. We've found that if we stimulate one side of the slice, we can record cortical activity on the other side."

The researchers hope their study will provide a launching point for many scientists to study human brain development and function. In the long run, they hope to help patients with a wide variety of neuropsychiatric disorders.

"I am a physician by training," Pasca said. "We are often very limited in the therapeutic options we can offer patients with mental disorders. The ability to investigate in a dish neuronal and glial function, as well as network activity, starting from patient's own cells, has the potential to bring novel insights into psychiatric disorders and their treatment."

Other Stanford co-authors are postdoctoral scholars Laura Clarke, PhD, Christopher Makinson, PhD, Nina Huber, PhD, and Khoa Nguyen, PhD; research assistant Jin-Young Park, PhD; senior research scientist Nancy O'Rourke, PhD; John Huguenard, PhD, professor of neurology and neurological sciences; and Stephen Smith, PhD, former professor of molecular and cellular physiology at Stanford.

The research was supported by a NARSAD Young Investigator Award, the National Institute of Mental Health, the National Institutes of Health, an MQ Fellow Award and the Korean Ministry of Science, ICT and Future Planning.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the work. ISM

Free skin cancer screenings scheduled for June 13

Free skin cancer screenings will be provided from 8 to 11:30 a.m. June 13 in the dermatology clinic at the Stanford Medicine Outpatient Center.

Skin cancer screening is especially recommended for people who get lots of sun exposure or have fair skin, many moles, atypical-looking moles or parents or siblings who have had skin cancer.

"It's a great opportunity for anyone in the community who has any concerns about their skin to come in and get checked out," said Carolyn Lee, MD, PhD, a clinical instructor of dermatology at the School of Medicine.

The clinic is on the fourth floor of Pavilion B of the Outpatient Center at 450 Broadway, Redwood City. For more information, call 723-6316. ISM

Software will help manage, track clinical research

By Kris Newby

Stanford is implementing a universitywide system for managing clinical research to make it easier for researchers to track studies, monitor participant recruitment and manage and share data.

The system is based on OnCore Enterprise Research software from Forte Research Systems, and its deployment is being overseen by Spectrum (the Stanford Center for Clinical and Translational Research and Education) and the Stanford Center for Clinical Research in the Department of Medicine. The Stanford Cancer Institute has used this system since 2005, and its technical team will be assisting Spectrum and SCCR in the launch.

"Our goal is to streamline Stanford's clinical trial processes so that our investigators can spend more time on research and less on paperwork," said Harry Greenberg, MD, the medical school's senior associate dean for research and the director of Spectrum.

"We are eager to provide the tools necessary to support and enhance the clinical research enterprise in the Department of Medicine and across the university, and we're delighted to be partnering with Spectrum on this important initiative," said Kenneth Mahaffey, MD, professor of cardiovascular medicine and vice chair of clinical research in the Department of Medicine.

The OnCore system's tracking capabilities will enable investigators across Stanford to more efficiently manage clinical research projects and programs. Over the years, the Stanford Cancer Institute has made great strides in adapting system modules to seamlessly work with enterprise software tools used at Stanford.

Also, by moving Stanford to an industry-standard management platform, it will be easier for investigators to participate in multicenter and industry-sponsored clinical trials.

Pilot testing of the system will begin this summer in select divisions within the Department of Medicine. Later in the year, the system will be rolled out to other divisions in that department and in the Department of Pediatrics, with universitywide availability beginning in 2016. Additional functions will be launched in future phases. For more information, contact Spectrum's process improvement manager, Yona Shulaker at shulaker@stanford.edu.

This project is currently supported by Spectrum, which is funded by the National Center for Advancing Translational Sciences at the NIH and SCCR. ISM

Kris Newby is the communications manager for Spectrum.

Fernando Mendoza receives medical school's diversity award

By Kim Smuga-Otto

Over his medical career, Fernando Mendoza, MD, a professor of pediatrics, has created programs that open doors for minorities to pursue careers in medicine and that train doctors to advocate for equal access to medical care.

For his efforts, he has been recognized with the 2015 Dr. Augustus A. White III and Family Faculty Professionalism Award.

Fernando Mendoza

The award, presented by the medical school's Office of Faculty Development and Diversity, recognizes individuals who help to reduce health disparities and empower underrepresented minorities to pursue careers in medicine. White, MD, the award's namesake, was the School of Medicine's first African-American graduate and served as its student body president. Throughout his career, he has been an advocate for equality in health care. White attended the award ceremony June 2 at Stanford Hospital.

Mendoza joined the faculty of the School of Medicine in 1981 as an assistant professor of pediatrics. In 1983, he was appointed associate dean for minority advising and programs. The following year he founded a summer program to encourage and guide minority medical students in pursuing careers in academia.

"At a time when summer programs for minority students really meant remedial programs, in 1984 Dr. Mendoza championed and established a summer program that promoted research, leadership and transition into medical school," Ronald Garcia, PhD, assistant dean for minority affairs at the medical school, wrote in his letter nominating Mendoza, who also is a pediatrician at Lucile Packard Children's Hospital Stanford. The program, now known as the Leadership in Health Disparities Program and open to any entering medical student, has evolved to focus on addressing health inequities in the United States.

Mendoza worked in the early 1990s to secure a federal Health Service and Administration grant to establish the medical school's Center of Excellence in Diversity in Medical Education, which trains doctors to be leaders in promoting health-care equality through service, advocacy and scholarship.

Mendoza has given presentations on immigrant-health issues before Congress and around the state and nation. He co-founded the medical school's Diversity Cabinet, an administrative group that in 2012 hosted a retreat that laid the groundwork for the school's diversity statement and its strategic plan for diversity. Throughout Mendoza's career, Garcia writes, "he has been a leader and voice for diversity at Stanford and the nation."

Also honored at the event were the 2015 Hispanic Center of Excellence/Office of Faculty Development and Diversity faculty fellows: Samuel Cheshier, MD; Nielsen Fernandez-Becker, MD, PhD; Tina Hernandez-Boussard, PhD; Julianne Mendoza, MD; Kim Rhoads, MD; and Reena Thomas, MD. ISM

Kim Smuga-Otto is a science-writing intern for the medical school's Office of Communication & Public Affairs.

Carla Shatz shares $500,000 Gruber Prize

By Amy Adams

Carla Shatz, PhD, a Stanford professor of biology and of neurobiology, has been awarded the 2015 Gruber Foundation Neuroscience Prize for her work in understanding how brain signaling controls wiring and plasticity in the brain.

Shatz will share the $500,000 prize with Michael Greenberg, PhD, a professor of neurobiology at Harvard.

In her research, Shatz, who holds the Sapp Family Provostial Professorship in Neurobiology and the David Starr Jordan Directorship of Stanford Bio-X, has uncovered mechanisms that the brain uses to select which connections to either strengthen or prune back as brain circuits form. She also discovered that well-known proteins, previously associated exclusively with the immune system, play a role in this pruning process.

NORBERT VON DER GROEBEN

Carla Shatz was awarded the 2015 Gruber Foundation Neuroscience Prize.

In a statement, the Gruber Foundation said that work by Shatz and Greenberg has "provided new insight into how neural circuit function regulates brain development and plasticity and how dysfunction can contribute to neuropsychiatric disorders such as autism and schizophrenia."

Shatz has studied how the brain merges visual signals from both eyes to form a single image. In early mammalian development, neurons that relay signals from the eyes make excess connections with the brain. The brain begins pruning back some of these connections in utero, before the animal has even opened its eyes, then refines the connections after birth when the eyes begin transmitting visual signals. As many as half of the initial connections are eventually clipped back.

The final connections allow the brain to detect a single, unified view of the world through two eyes.

A surprising finding from this work was that proteins responsible for regulating which connections to keep and which to eliminate turn out to be proteins originally considered the exclusive property of immune cells.

Shatz has said that she initially met some resistance when she proposed a role for those proteins in neurons. "At first, people thought we were wrong," she said. "Now we've shown that the nervous system has just as much right to these immune proteins as the immune system."

Shatz has also studied how brain connections are pruned away during Alzheimer's disease, work that she hopes could lead to better treatments.

Previous Stanford recipients of the Gruber Prize include Eric Knudsen, PhD, professor of neurobiology. **ISM**

Preview of *Searching for Home*, documentary on PTSD, set for June 20

A new feature-length documentary, *Searching for Home: Coming Back from War*, will be screened from 6-8 p.m. June 20 in Cubberley Auditorium at the Stanford Graduate School of Education.

The preview is free and open to the public.

Searching for Home explores veterans' struggles with post-traumatic stress disorder, from World War II, the Korean War and the Vietnam War to modern-day conflicts, chronicling the journey of men and women who face new and difficult challenges after returning home from combat zones.

After the screening, there will be a question-and-answer session with the director, Eric Christiansen; Amit Etkin, MD, PhD, Stanford assistant professor of psychiatry and behavioral sciences, who is featured in the film and was its scientific adviser; and veterans featured in the film, including Russ Toll, a graduate student in bioengineering at Stanford.

PTSD impacts as many as 20 percent of combat veterans, as well as an untold number of adults and children worldwide who experience traumatic events and environments. Etkin and his Stanford colleagues are working to develop new treatments for the condition.

The event is sponsored by Stanford Medicine Medical Center Development.

Seating is limited, so please register online by today at http://medicalgiving.stanford.edu/events/searching-for-home.html. **ISM**

OF NOTE

reports on significant honors and awards for faculty, staff and students

KARL DEISSEROTH, MD, PhD, the D.H. Chen Professor and professor of bioengineering and of psychiatry and behavioral sciences, has been awarded the Dickson Prize in Medicine from the University of Pittsburgh. Deisseroth was honored for pioneering optogenetics, a technology that uses light to control the behavior of neurons in living animals. He will receive $50,000 and deliver the Dickson Prize in Medicine Lecture on Oct. 8.

GARRY FATHMAN, MD, professor of medicine, delivered the keynote address for the Washington University School of Medicine's 2015 commencement ceremony. He received his medical degree from the university in 1969. His research interests include the role of T cells in immune response, gene therapy for autoimmune disease and rheumatoid arthritis.

WILLIAM FEARON, MD, was promoted to professor of medicine, effective April 1. His research focuses on the invasive assessment of coronary physiology using a wire-based technique. He has been instrumental in the development of a robust transcatheter aortic valve replacement program, which has treated more than 500 patients over the past seven years.

JASON HOM, MD, and **IAN NELLIGAN**, MD, MPH, have been selected as Rathmann Family Medical Education Fellows in Patient-Centered Care for 2015-16. The program provides part-time salary support to the fellows to help them pursue study and activities focused on the promotion of patient-centered care in medical education. Hom is a clinical instructor in medicine and hospitalist and is interested in patient-physician communication. Nelligan, a clinical instructor in medicine, is co-director of the Longitudinal Community Health Advocacy Medical Partnership, a new medical school course that provides community-based clinical experiences and mentorship.

Karl Deisseroth

Garry Fathman

William Fearon

Jason Hom

Ian Nelligan

Laurence Katznelson

Bingwei Lu

Ravindra Majeti

Daniel Rubin

Heather Wakelee

LAURENCE KATZNELSON, MD, professor of neurosurgery and of medicine, has received the H. Jack Baskin, MD, Endocrine Teaching Award from the American Association of Clinical Endocrinologists. The award recognizes a physician who has made a profound impact by teaching fellows. He previously directed the endocrinology fellowship program at Stanford, where he introduced many new techniques to teach endocrine specialties and pathology. He is also the associate dean of graduate medical education.

CARA LIEBERT, MD, a surgical education fellow, has received a 2015 Outstanding Resident Teaching Award from the Association for Surgical Education. She develops and teaches surgical curricula for medical students and residents and has worked with simulation-based training, flipped classroom curricula and medical student mistreatment. She is a degree candidate in the Master of Health Professions Education Program at the University of Illinois-Chicago. She will return to her clinical residency training at Stanford this summer.

BINGWEI LU, PhD, was promoted to professor of pathology, effective April 1. His research examines conserved mechanisms underlying the development, function and maintenance of the nervous system, focusing on the role of mitochondrial function and regulation. He hopes to develop new strategies to combat devastating brain disorders such as Alzheimer's disease, Parkinson's disease and brain cancer.

RAVINDRA MAJETI, MD, PhD, assistant professor of medicine, was awarded a Leukemia and Lymphoma Society Scholar Award. The award provides $110,000 a year over five years for salary and benefits. His research focuses on developing treatments for acute myeloid leukemia.

CAROLYN RODRIGUEZ, MD, PhD, was appointed assistant professor of psychiatry and behavioral sciences, effective July 1. She studies the molecular, physiological and neural mechanisms of rapid-acting treatments for mental illness. She is working to develop more effective treatments for obsessive-compulsive and hoarding disorders and related conditions.

DANIEL RUBIN, MD, MS, was promoted to associate professor of radiology and of medicine, effective May 1. He is principal investigator of two centers in the National Cancer Institute's Quantitative Imaging Network. His research focuses on quantitative imaging and integrating imaging data with clinical and molecular data to discover imaging phenotypes that can predict the underlying biology, define disease subtypes and personalize treatment.

HEATHER WAKELEE, MD, associate professor of medicine, has received the Young Investigator Award from the ECOG-ACRIN Cancer Research Group. The award recognizes extraordinary scientific achievements and leadership in research by young scientists. Wakelee leads Stanford's thoracic medical oncology program. Her research focuses on the use of adjuvant therapy for lung cancer.

JUERGEN WILLMANN, MD, was promoted to professor of radiology, effective April 1. He is clinical section chief of body imaging and director of the Translational Molecular Imaging Laboratory. His research focuses on the development, testing and clinical translation of acoustic-based molecular imaging technologies. He recently initiated the first human clinical trial in the United States on molecular imaging with ultrasound in cancer patients. **ISM**