INSIDE STANFORD MEDICINE

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Fifteen faculty members are among the cohort of 47 researchers appointed investigators at the Chan Zuckerberg Biohub.

Page 4

Researchers develop 1-cent 'lab on a chip'

By Devika G. Bansal

ZAHRA KOOCHAK

Rahim Esfandyarpour helped to develop a way to create a diagnostic "lab on a chip" for just a penny.

Researchers at the School of Medicine have developed a way to produce a cheap and reusable diagnostic "lab on a chip" with the help of an ordinary inkjet printer.

At a production cost of as little as 1 cent per device, the new technology could usher in a medical diagnostics revolution like the kind brought on by low-cost genome sequencing, said Ron Davis, PhD, professor of biochemistry and of genetics and director of the Stanford Genome Technology Center.

A study describing the technology was published online Feb. 6 in the *Proceedings of the National Academy of Sciences*. Davis is the senior author. The lead author is Rahim Esfandyarpour, PhD, an engineering research associate at the genome center.

The inexpensive lab-on-a-chip technology has the potential to enhance diagnostic capabilities around the world, especially in developing countries. Due to inferior access to early diagnostics, the survival rate of breast cancer patients is only 40 percent in low-income nations — half the rate of such patient in developed nations. Other lethal diseases, such as malaria, tuberculosis and HIV, also have high incidence and bad patient outcomes in developing countries. Better access to cheap diagnostics could help turn this around, especially as most such equipment costs thousands of dollars.

"Enabling early detection of diseases is one of the greatest opportunities we have for developing effective treatments," Esfandyarpour said. "Maybe $1 in the U.S. doesn't count that much, but somewhere in the developing world, it's a lot of money."

A two-part system

A combination of microfluidics, electronics and inkjet printing technology, the lab on a chip is a two-part system. The first is a clear silicone microfluidic chamber for housing cells and a reusable electronic strip. The second part is a regular inkjet printer that can be used to print the electronic strip onto a flexible sheet of polyester using commercially available conductive nanoparticle ink.

"We designed it to eliminate the need for clean-room facilities and trained personnel to fabricate such a device," said Esfandyarpour, an electrical engineer by training. One chip can be produced in about 20 minutes, he said.

Designed as a multifunctional platform, one of its applications is that it allows users to analyze different cell types without using fluorescent or magnetic labels that are typically required to track cells. Instead, the chip separates cells based on their intrinsic electrical properties: When an electric potential is applied across the inkjet-printed strip, cells loaded into the microfluidic chamber get pulled in different directions depending on their "polarizability" in a process called dielectrophoresis. This label-free method to analyze cells greatly improves precision and cuts lengthy labeling processes.

The tool is designed to handle small-volume samples for a variety of assays. The researchers showed the device can help capture single cells from a mix, isolate rare cells and count cells based on cell types. The cost of these multifunctional biochips is orders of magnitude lower than that of the individual technologies that perform each of those functions. A standalone flow cytometer machine, for example, which is used to sort and count cells, costs $100,000, without taking any operational costs into account.

Potential to democratize diagnostics

"The motivation was really how to export technology and how to decrease

See LAB, page 6

Physicians often fail to recommend genetic testing to high-risk breast cancer patients, researchers find

By Krista Conger

Physicians often fail to recommend genetic testing for breast cancer patients at high risk for mutations associated with ovarian and other cancers, according to a large study by researchers at the School of Medicine and five other U.S. medical centers.

Asian-Americans and older women were particularly likely to be "undertested." Not testing these women represents a critical missed health care opportunity, the researchers said.

Allison Kurian

"We found that genetic counseling and testing are not well-matched to medical need," said Allison Kurian, MD, associate professor of medicine and of health research and policy at Stanford. "Women are very interested in genetic testing but many fail to receive it. This is particularly worrisome because it means that doctors are missing the opportunity to prevent cancers in mutation carriers and their family members."

Kurian is the lead author of the study, which was published online Feb. 7 in *JAMA*. University of Michigan researchers Reshma Jagsi, MD, DPhil, and Steven Katz, MD, MPH, share senior authorship.

Surveying more than 2,500 women

Genetic testing can identify the presence of mutations in the BRCA1 and BRCA2 genes, which are strongly linked to the development of breast and ovarian cancers, as well as the presence of other cancer-related mutations.

Kurian and her colleagues surveyed 2,529 women with stage-0 to stage-2 breast cancer two months after surgery. The women were asked whether they wanted genetic testing and, if so, whether they had received it.

Although about two-thirds of the women said they wanted to be tested, only about one-third said they had been tested. About eight in 10 of those at highest risk for BRCA mutations wanted testing, but just over half of them were actually tested. About 56 percent of the women who were not tested attributed the lack of testing to the

See CANCER, page 7

Rat-grown mouse pancreases help reverse diabetes in mice, study says

By Krista Conger

Mouse pancreases grown in rats generate functional, insulin-producing cells that can reverse diabetes when transplanted into mice with the disease, according to researchers at the School of Medicine and the Institute of Medical Science at the University of Tokyo.

The recipient animals required only days of immunosuppressive therapy to prevent rejection of the genetically matched organ rather than lifelong treatment.

The success of the interspecies transplantation suggests that a similar technique could one day be used to generate matched, transplantable human organs in large animals like pigs and sheep.

To conduct the work, the researchers implanted mouse pluripotent stem cells, which can become any cell in the body, into early rat embryos. The rats had been genetically engineered to be unable to develop their own pancreas and were thus forced to rely on the mouse cells for the development of the organ.

Once the rats were born and grown, the researchers transplanted the insulin-producing cells, which cluster together in groups called islets, from the rat-grown pancreases into mice genetically matched to the stem cells that formed the pancreas. These mice had been given a drug to cause them to develop diabetes.

COURTESY OF THE NAKAUCHI LAB

A rat in which researchers were able to grow a mouse pancreas.

"We found that the diabetic mice were able to normalize their blood glucose levels for over a year after the transplantation of as few as 100 of these islets," said Hiromitsu Nakauchi, MD, PhD, a professor of genetics at Stanford. "Furthermore, the recipient animals only needed treatment with immunosuppressive drugs for five days after transplantation, rather than the ongoing immunosuppression that would be needed for unmatched organs."

Nakauchi, who is a member of Stanford's Institute for Stem Cell Biology and Regenerative

See PANCREAS, page 6

Algorithm matches dermatologists' ability to identify skin cancer

By Taylor Kubota

It's scary enough making a doctor's appointment to see if a strange mole could be cancerous. Imagine, then, that you were in that situation while also living far away from the nearest doctor, unable to take time off work and unsure you had the money to cover the cost of the visit. In a scenario like this, an option to receive a diagnosis through your smartphone could be lifesaving.

Universal access to health care was on the minds of computer scientists at Stanford when they set out to create an artificially intelligent diagnosis algorithm for skin cancer. They created a database of nearly 130,000 skin disease images and trained their algorithm to visually diagnose potential cancer. From the very first test, it performed with inspiring accuracy.

"We realized it was feasible, not just to do something well, but as well as a human dermatologist," said Sebastian Thrun, PhD, an adjunct professor of computer science at Stanford. "That's when our thinking changed. That's when we said, 'Look, this is not just a class project for students, this is an opportunity to do something great for humanity.'"

The final product, the subject of a paper in the Jan. 25 issue of *Nature*, was tested against 21 board-certified dermatologists. In its diagnoses of skin lesions, which represented the most common and deadliest skin cancers, the algorithm matched the performance of dermatologists.

Thrun is senior author of the paper.

Why skin cancer

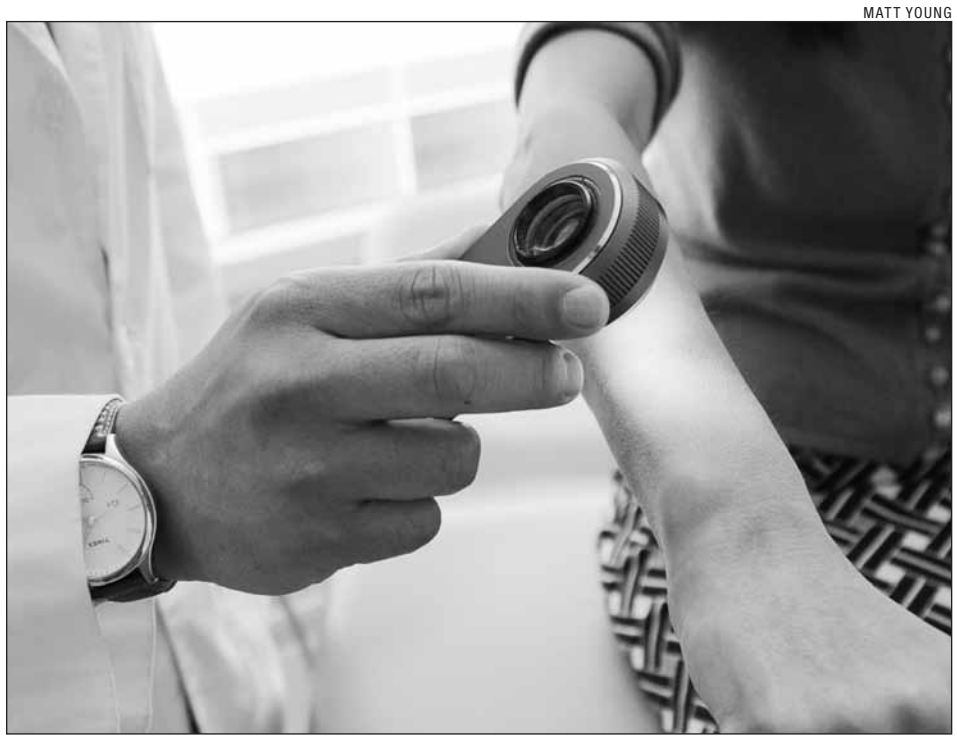
Every year there are about 5.4 million new cases of skin cancer in the United States, and while the five-year survival rate for melanoma detected in its earliest stages is around 97 percent, that drops to approximately 14 percent if it's detected in its latest stages. Early detection could likely have an enormous impact on skin cancer outcomes.

Diagnosing skin cancer begins with a visual examination. A dermatologist usually looks at the suspicious lesion with the naked eye and with the aid of a dermatoscope, which is a handheld microscope that provides low-level magnification of the skin. If these methods are inconclusive or lead the dermatologist to believe the lesion is cancerous, a biopsy is the next step.

Bringing this algorithm into the examination process follows a trend in computing that combines visual processing with deep learning, a type of artificial intelligence modeled after neural networks in the brain. Deep learning has a decades-long history in computer science, but it only recently has been applied to visual processing tasks, with great success. The essence of machine learning, including deep learning, is that a computer is trained to figure out a problem rather than having the answers programmed into it.

"We made a very powerful machine-learning algorithm that learns from data," said Andre Esteva, a lead author of the paper and graduate student in the Thrun lab. "Instead of writing into computer code exactly what to look for, you let the algorithm figure it out."

MATT YOUNG



A dermatologist uses a dermatoscope, a type of handheld microscope, to look at skin. Computer scientists at Stanford have created an artificially intelligent diagnosis algorithm for skin cancer that matched the performance of board-certified dermatologists.

The algorithm was fed each image as raw pixels with an associated disease label. Compared with other methods for training algorithms, this one requires very little processing or sorting of the images prior to classification, allowing the algorithm to work off a wider variety of data.

Training the algorithm

Rather than building an algorithm from scratch, the researchers began with an algorithm developed by Google that was already trained to identify 1.28 million images from 1,000 object categories. While it was primed to be able to differentiate cats from dogs, the researchers needed it to know a malignant carcinoma from a benign seborrheic keratosis.

> "My main eureka moment was when I realized just how ubiquitous smartphones will be."

"There's no huge data set of skin cancer that we can just train our algorithms on, so we had to make our own," said Brett Kuprel, the paper's other lead author and a graduate student in the Thrun lab. "We gathered images from the internet and worked with the medical school to create a nice taxonomy out of data that was very messy — the labels alone were in several languages, including German, Arabic and Latin."

After going through the necessary translations, the researchers collaborated with dermatologists at Stanford Medicine, as well as with Helen Blau, professor of microbiology and immunology at Stanford and co-author of the paper. Together, this interdisciplinary team worked to classify the hodgepodge of internet images. Many of these, unlike those taken by medical professionals, were varied in terms of angle, zoom and lighting. In the end, they amassed about 130,000 images of skin lesions, representing more than 2,000 different diseases.

During testing, the researchers used only high-quality, biopsy-confirmed images provided by the University of Edinburgh and the International Skin Imaging Collaboration Project that represented the most common and deadliest skin cancers — malignant carcinomas and malignant melanomas. The 21 dermatologists were asked whether, based on each image, they would proceed with a biopsy or treatment, or reassure the patient that the lesion was benign. The researchers evaluated success by how well the dermatologists were able to correctly diagnose both cancerous and noncancerous lesions in more than 370 images.

The algorithm's performance was measured through the creation of a sensitivity-specificity curve, where sensitivity represented the algorithm's ability to correctly identify malignant lesions and specificity represented its ability to correctly identify benign lesions. The algorithm was assessed through three key diagnostic tasks: keratinocyte carcinoma classification, melanoma classification, and melanoma classification when viewed using dermoscopy. In all three tasks, the algorithm matched the performance of the dermatologists with the area under the sensitivity-specificity curve amounting to at least 91 percent of the total area of the graph.

An added advantage of the algorithm is that, unlike a person, the algorithm can be made more or less sensitive, allowing the researchers to tune its response depending on what they want it to assess. This ability to alter the sensitivity hints at the depth and complexity of this algorithm. The underlying architecture of seemingly irrelevant photos — including those of cats and dogs — helps it better evaluate the skin lesion images.

Health care by smartphone

Although this algorithm currently exists on a computer, the team would like

See ALGORITHM, page 8

Five researchers elected to American Society for Clinical Investigation

Five faculty members at the School of Medicine have been elected members of the American Society for Clinical Investigation, an honor society for physician-scientists that recognizes their research accomplishments.

Following are the new Stanford members and a brief description of their work:

Ash Alizadeh

Maximilian Diehn

Brian Feldman

Aida Habtezion

Ravindra Majeti

• Ash Alizadeh, MD, PhD, is an assistant professor of oncology. His research uses genomics, molecular genetics and computational biology to understand the behavior of tumors with the goal of developing improved therapies.

• Maximilian Diehn, MD, PhD, is an assistant professor of radiation oncology. His research interests include lung cancer biology and the development of genomics-based, predictive and prognostic biomarkers, with a focus on circulating nucleic acids.

• Brian Feldman, MD, PhD, is an assistant professor of pediatrics. His research examines the relationship between hormones and stem cells with the goal of developing therapies for conditions such as diabetes, cancer and sarcopenia.

• Aida Habtezion, MD, is an assistant professor of medicine. Her research focuses on understanding the relationship between the immune system and conditions such as pancreatitis and inflammatory bowel disease, with the goal of developing new therapies.

• Ravindra Majeti, MD, PhD, is an associate professor of medicine. His research examines the role of stem cells in acute myeloid leukemia, with the goal of improving clinical outcomes. **ISM**

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STANFORD MEDICINE

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Taia Wang on why some develop severe dengue

Dengue is a mosquito-borne viral infection that can lead to severe disease and death. Endemic in at least 100 countries, it is carried by the same mosquitoes that transmit Zika, yellow fever and chikungunya infections. The incidence of dengue infection has risen sharply in recent years, with some 50 million to 100 million cases reported each year.

Some infected individuals become ill with flulike symptoms, such as high fever, headache, vomiting, muscle and joint pain and skin rash. But in a small number of cases, it leads to more serious symptoms, including severe abdominal pain, persistent vomiting and severe bleeding. As many as 20,000 people die every year of the disease, which has no specific treatment. A novel vaccine for dengue was introduced in late 2015 and is commercially available in some countries. But large-scale trials of the vaccine have shown it to be only about 60 percent effective in people older than 9, and less than 45 percent effective in children younger than that.

Stanford virologist Taia Wang, MD, PhD, an assistant professor of infectious diseases and geographic medicine, was the lead author of a study published Jan. 27 in Science *which found that some people may be more susceptible to severe dengue disease than others. Writer Ruthann Richter recently asked Wang about the disease and the study's findings.*

1 Why is dengue so difficult to prevent and treat?

WANG: Dengue viruses are an especially challenging target from a vaccine development perspective. Most effective vaccines work by producing antibodies, a subset of which can prevent the virus from entering a cell by "neutralizing" it. Unlike other viruses, antibodies that bind to dengue viruses but fail to neutralize it can actually enhance dengue disease. Making matters worse, there are also four major serotypes of dengue viruses, so an effective and safe vaccine would need to elicit neutralizing antibodies against all four types at once.

The treatment of patients who go on to develop dengue disease poses another set of challenges. Severe cases are most successfully managed when patients are caught early and treated in the hospital, yet we don't currently have a good way to predict who will develop severe disease. In addition, there are no specific medications that can be used to treat dengue disease; we rely on hydration and blood products for management of severe cases, which is very resource-intensive. This is a serious problem since most dengue infections occur in parts of the world where access to medical care is limited.

2 Who is at greatest risk for the disease and why?

WANG: The greatest risk factor for progression to severe dengue disease is virus infection in the presence of antibodies that bind to the virus, but do not neutralize it. We typically think of antibodies as protecting us from infection; dengue infections pose a rare example of a situation where some antibodies can enhance disease. This antibody-dependent enhancement most commonly occurs when someone is infected for the second time. When this happens, antibodies that were produced during the first exposure can enhance the severity of subsequent infection. Still, progression to severe disease during second infections is relatively rare, and the reason for progression has not been understood, which limits early clinical intervention. Our study was driven by a desire to understand why some people progress to severe disease during secondary dengue infection while others do not.

3 Can you tell us about the findings?

WANG: Our previous work showed tremendous variation in the type of antibodies produced by individuals. We were particularly interested in regions of antibodies called Fc domains and their receptors because they have been shown to be directly involved in enhancement of dengue disease. We hypothesized that the variability in Fc domains among people might determine progression to severe dengue. We discovered that people who develop the most severe forms of dengue disease do produce a different repertoire of antibodies — they make antibodies with Fc domains that work through a particular Fc receptor called Fc-gamma R3a. We went on to show that the antibodies with higher affinity for Fc-gamma R3a are involved in the development of severe dengue disease.

Taia Wang

4 What are the implications for vaccination programs?

WANG: Since people who develop severe dengue disease produce a distinct type of antibody, it may be possible to develop a screening test that identifies patients who are at highest risk for severe disease before they are ever infected. This would be useful for identifying patients who need a higher level of clinical care during dengue infection. Much more work will be required to determine whether such a test is possible.

In addition to the implications for clinical care, our findings may be used to guide vaccine development. Since we found that a specific phenotype of antibody contributes to severe disease, we would want to avoid stimulating production of those antibodies during vaccination. This could potentially be done by using specific vaccine antigens and/or vaccine adjuvants to guide the immune system to produce antibodies that are less likely to enhance disease.

5 Why not vaccinate everyone in disease-prone areas?

WANG: Vaccinating everyone in areas where dengue is prevalent with a safe, effective vaccine is the surest way to limit dengue disease. However, doing so would be expensive. In areas with limited resources, the next best thing is probably to target vaccination to people at highest risk for severe disease. For this reason, and because it could help guide clinical care of dengue patients, we are investigating inexpensive screening tests that could be used to identify people at highest risk for progression to severe dengue disease. **ISM**

Child Health Research Institute awards 26 grants for 2017

The Stanford Child Health Research Institute has awarded grants to support 26 research projects led by faculty members and postdoctoral scholars. The institute funds innovative clinical and translational research on maternal and child health.

The following individuals each received $35,000 to fund their pilot and early-career projects:

• Daniel Abrams, PhD, instructor of psychiatry and behavioral sciences, for "Longitudinal development of brain systems underlying voice processing in children with autism spectrum disorder."

• Tamar Green, MD, instructor of psychiatry and behavioral sciences, for "Brain and behavior in Noonan syndrome."

• Ngan Huang, PhD, assistant professor of cardiothoracic surgery, for "Bilayered nanofibrillar vascular graft for treatment of congenital heart defect."

• Prasanna Jagannathan, MD, assistant professor of medicine, for "Impact of DHA-PQ chemoprevention in pregnancy on transfer of antimalarial antibodies to newborns."

• Jiangbin Ye, PhD, assistant professor of radiation oncology, for "Targeting one-carbon unit metabolism for neuroblastoma differentiation."

Grants for new ideas

The following faculty members each received $35,000 to fund high-risk, high-impact projects outside their currently funded areas of research:

• Valerie Baker, MD, associate professor of obstetrics and gynecology, for "Vascular health of children conceived via in vitro fertilization."

• Anne Dubin, MD, professor of pediatrics, for "Stress inoculation through virtual reality in the pediatric electrophysiology laboratory."

• Sarah Heilshorn, PhD, associate professor of materials science and engineering, for "Development of a tissue-engineered small intestine."

• Desiree LaBeaud, MD, associate professor of pediatrics, for "The spectrum of Zika disease in Grenada."

• Olivia Martinez, PhD, professor of surgery, for "Evaluating for viral etiologies associated with liver failure of unknown etiology."

• Karen Parker, PhD, associate professor of psychiatry and behavioral sciences, for "Biomarker discovery in children with autism."

• Lee Sanders, MD, associate professor of pediatrics, for "School-system consequences of birth outcomes: A medical school-education school-school district collaborative."

• Dennis Wall, PhD, associate professor of pediatrics and of biomedical data science, for "The GapMap Project: A mobile surveillance system to map autism as well as gaps in autism services globally."

Grants for clinical research

The following clinician-educators each received $25,000 to fund their patient-oriented projects:

• Despina Contopoulos-Ioannidis, MD, clinical associate professor of pediatrics, for "Early life antibiotic exposure and childhood obesity."

• Victoria Cosgrove, PhD, clinical assistant professor of psychiatry and behavioral sciences, for "Who is bullied? An examination of biological and psychological correlates of adolescent peer victimization."

• Hayley Gans, MD, clinical associate professor of pediatric infectious diseases, for "Risk factors for cytomegalovirus and Epstein-Barr virus infections in pediatric solid organ transplant patients."

• Scott Sutherland, MD, clinical associate professor of pediatrics, for "Using kinetic GFR to identify AKI events and progression."

• Joyce Teng, MD, PhD, clinical professor of dermatology and of pediatrics, for "Investigating genetic mutations associated with lymphatic malformation."

Grants for postdoctoral scholars

The following individuals each received $55,000 to fund their postdoctoral fellowships:

• Barbara Baro, PhD, postdoctoral scholar in pediatric infectious diseases, for "Discovering essential host factors for Plasmodium falciparum malaria."

• Lang Chen, PhD, postdoctoral scholar in psychiatry and behavioral sciences, for "Representation and connectivity abnormality underlying face-processing deficit in children with ASD."

• Julia Co, PhD, postdoctoral scholar in pediatric infectious diseases, for "Elucidating Salmonella enterica Typhi infection using a novel human intestinal organoid model."

• Marianne Goodwin, PhD, postdoctoral scholar in pediatric stem cell transplantation and regenerative medicine, for "Gene editing of the FOXP3 gene for the cure of IPEX syndrome."

• Marko Jakovljevic, PhD, postdoctoral scholar in radiology, for "Functional ultrasound imaging in the neonate brain using coherent flow power doppler."

• Sooyeon Lee, PhD, postdoctoral scholar in endocrinology, gerontology and metabolism, for "The role of succinate dehydrogenase subunit B (SDHB) in beta-cell biology and diabetes."

• Jianfeng Li, PhD, postdoctoral scholar in orthopaedic surgery, for "Engineering 3-D in vitro co-culture models for deciphering pediatric brain tumor-vascular."

• Szu-Yuan Pu, PhD, postdoctoral scholar in infectious diseases, for "Roles of BMP2K in cell signaling and dengue viral infection." **ISM**

Brain-mapping technique reveals circuitry of Parkinson's tremors

By Tom Abate

If a piece of electronics isn't working, troubleshooting the problem often involves probing the flow of electricity through the various components of the circuit to locate any faulty parts.

Now, Stanford researchers have adapted that idea to studying diseases of the brain by turning on specific types of neurons and observing how the entire brain responds to their activation.

The goal is to give neuroscientists a way to probe brain ailments similar to how engineers troubleshoot faulty electronics. "Electrical engineers try to figure out how individual components affect the overall circuit to guide repairs," said Jin Hyung Lee, PhD, a professor of neurology and neurological sciences, of bioengineering and of neurosurgery.

Jin Hyung Lee

In the short term, the technique could help improve treatments for Parkinson's disease, which Lee studies. In the long run, it could help identify, map and guide the repair of neural circuits associated with other brain diseases.

The work is described in a paper published online Jan. 26 in *Neuron*. Lee is the senior author. The lead author is postdoctoral scholar David Bernal-Casas.

The circuit-mapping approach combines two experimental tools with a computational method. The first tool is optogenetics, which modifies specific types of neurons in the brain so they can be turned on in response to light. The second tool is called functional MRI, which detects areas of activity in the brain based on blood flow. The researchers used optogenetics to turn on a specific type of neuron and fMRI to observe how areas of the brain responded. Then, they used computational analysis to diagram the brain network that was activated, which allowed them to determine the function of the circuit specific to each neuronal type.

The technique could help improve treatments for Parkinson's disease.

Controlling Parkinson's tremors

One hallmark of Parkinson's disease is uncontrollable tremors. Neuroscientists believe these tremors are caused by malfunctions in the neural pathways that control motion. They know that different regions of the brain are constantly forming circuits to carry out tasks, whether motion or speech. However, prior to Lee's technique, researchers had no way to show how activating a specific type of neuron might cause a specific circuit to form in the whole brain.

Testing her approach on rats, Lee probed two different types of neurons known to be involved in Parkinson's disease. Her team found that one type of neuron activated a pathway signaling for greater motion, while the other activated a signal for less motion. Lee's team then designed a computational approach to draw circuit diagrams that underlie these neuron-specific brain-circuit functions.

"This is the first time anyone has shown how different neuron types form distinct, whole brain circuits with opposite outcomes," Lee said.

Lee said the findings in this paper should help to improve treatments for Parkinson's disease. Neurosurgeons are already using a technique called deep brain stimulation to calm Parkinson's tremors in their patients. DBS delivers tiny electric jolts to neurons thought to be responsible for the tremors. A more precise understanding of the how those neurons work to control motion could help guide more effective stimulation.

More broadly speaking, Lee thinks that her technique — optogenetic fMRI combined with computational modeling — gives researchers a new way to reverse-engineer the functions of the many different types of neurons in the brain and the bafflingly diverse array of neural circuits formed to carry out different commands.

Other co-authors are research scientist Hyun Joo Lee and graduate student Andrew Weitz.

Lee is a member of Stanford Bio-X and the Stanford Neurosciences Institute, and a faculty fellow at Stanford ChEM-H.

This work was supported by the National Institutes of Health, the National Science Foundation, an Alfred P. Sloan Research Fellowship and an Okawa Foundation Research Grant Award.

Stanford's departments of Neurology and Neurological Sciences, Bioengineering and Neurosurgery also supported the work. **ISM**

15 School of Medicine researchers named CZ Biohub investigators

Fifteen faculty members from the School of Medicine are among the cohort of 47 researchers appointed investigators at the Chan Zuckerberg Biohub.

The CZ Biohub is an independent nonprofit medical research organization that has the goal of harnessing the power of science, technology and human capacity to cure, prevent or manage all disease. It is funded through a $600 million commitment by the Chan Zuckerberg Initiative, which was created by Facebook founder Mark Zuckerberg and his wife Priscilla Chan, MD.

The investigators were selected from the three institutions participating in the CZ Biohub: Stanford, UC-San Francisco and UC-Berkeley. Each of the investigators will be given a five-year appointment and up to $1.5 million for research in their respective areas of expertise. More than 700 researchers applied for the funding; the selections were made by an international panel of 60 scientists and engineers.

The investigators include both senior researchers and up-and-coming researchers.

"The 47 CZ Biohub investigators we're introducing today are quite literally inventing the future of life science research," said Stephen Quake, PhD, co-president of CZ Biohub and professor of bioengineering and of applied physics at Stanford. "The CZ Biohub is distinguished by our emphasis on technology and engineering, and our researchers are inventing tools to accelerate science for the good of humanity."

"We are honored to have so many of our scientists selected to pursue their innovative and ambitious projects at the Chan Zuckerberg Biohub," said Lloyd Minor, MD, dean of the School of Medicine. "If past is prologue, giving such inventive thinkers the freedom to conduct fundamental research will result in truly outstanding discoveries, moving us toward a future where we can both cure and prevent what today seems incurable and unpredictable."

The 15 medical school faculty members are:

Senior investigators

• Carlos Bustamante, PhD, professor of biomedical data science and of genetics: He is focusing on the integration and analysis of massive data coming from consumer, health care and financial sources. He is especially interested in bringing together direct-to-consumer genetics and phenotype data in a secure space that can be explored by academic-, industry- and citizen-scientists.

• Brian Kobilka, MD, professor of molecular and cellular physiology: His pioneering X-ray crystallographic studies have revealed how the binding of a hormone to the extracellular pocket on a G-protein coupled receptor is transmitted across the cell membrane to trigger a signaling cascade. He is now carrying out structural studies of opioid receptors to identify more effective painkillers with fewer side effects.

• Matthew Porteus, MD, PhD, associate professor of pediatrics: He uses genome editing as curative therapy for genetic diseases, as exemplified by his correction of the mutation in sickle cell disease in hematopoietic stem and progenitor cells. He is now combining genome editing with synthetic biology to engineer cells having new phenotypic properties, such as resistance to HIV and enhanced wound healing.

• Lucy Shapiro, PhD, professor of developmental biology: She has established the bacterium *Caulobacter crescentus* as a powerful model organism for understanding self-organization and spatially controlled differentiation leading to daughter cells with different cell fates. She is developing a reaction-diffusion model that includes all essential cellular processes to gain a deeper understanding of asymmetric cell division and cell polarity.

• Christina Smolke, PhD, professor of bioengineering: She is engineering yeast to produce complex, plant-inspired medicinal compounds like those widely used as antihypertensives and anticancer agents. She interacts with experts in plant-specialized metabolism to identify gene clusters that can be inserted into her optimized yeast platform to accelerate the discovery of new therapeutic agents.

COURTESY OF THE CHAN ZUCKERBERG BIOHUB

The CZ Biohub is funded through a $600 million commitment by the Chan Zuckerberg Initiative, which was created by Facebook founder Mark Zuckerberg, above, and his wife Priscilla Chan.

• Tom Soh, PhD, professor of radiology and of electrical engineering: He has devised sensors capable of continuously monitoring specific biomolecules in vivo and a control system for achieving real-time, closed-loop controlled drug delivery in live animals. He plans to generate detection systems for hitherto untargetable biomolecules and to develop real-time sensors that can be implanted in vivo to detect multiple biomolecules that are medically important.

• Alice Ting, PhD, professor of genetics and of biology: She develops, scales up and broadly disseminates molecular technologies for mapping cells and functional circuits, as illustrated by her biotin-based method for protein mapping in living cells. She is devising methods for identifying the ensemble of neurons that encode or control a specific memory, behavior or emotional state by using a light- and calcium-gated transcription factor.

Junior investigators

• Catherine Blish, MD, PhD, assistant professor of infectious diseases: She aims to build an atlas of host-pathogen interactions to serve as a template to elicit immune responses that will promote pathogen eradication. She seeks to understand how to control the innate immune response mediated by natural-killer and other cells to eliminate infections and develop more potent methods of protection.

• Adam de la Zerda, PhD, assistant professor of structural biology: His goal is to image 100 million cells in living tissues at single-cell resolution by using optical coherence tomography. One of the potential uses of his technique will be to visualize cancer markers to delineate the margins of tumors.

• Polly Fordyce, PhD, assistant professor of genetics and of bioengineering: She is developing new biochip technologies for high-throughput functional characterization of proteins to enhance our ability to predict the function of a protein given its amino acid sequence. Her aim is to characterize the properties of more than 1,000 proteins, such as enzymes and transcription factors, in a single experiment.

• William Greenleaf, PhD, assistant professor of genetics: He studies the physical and spatial organization of the human genome at multiple scales and across different biological states. His aim is to unravel the quantitative relations between regulatory elements and gene expression in a massive, parallel way to generate a quantitative model of the regulatory wiring of cells.

See BIOHUB, page 7

$1.74 million in grants awarded to 43 health-related projects

By Kris Newby

This year, 43 projects at Stanford will receive a total of $1.74 million in research funding through the Spectrum pilot grant program.

Spectrum, the Stanford Center for Clinical and Translational Research and Education, focuses on accelerating the translation of medical research from bench to bedside. Its pilot grants are awarded to investigators with bold ideas that address health care problems through novel approaches and multidisciplinary teams.

Spectrum awarded grants in six areas: population health sciences; learning health care innovation; community engagement; medical technologies; predictive tools and diagnostics; and therapeutics. Awardees are mentored throughout the year by teams of experts in each of these areas.

The grant-receiving projects and their principal investigators are:

Population health sciences

• "The use of mobile phone technology to prevent and redress gender-based violence in Gujarat, India: Opportunities and barriers" — Jennifer Newberry, JD, MD, instructor of emergency medicine.

• "Cancer in the elderly: Establishing an infrastructure for research in the elderly at Stanford Medicine" — Ann Hsing, MD, professor of medicine.

• "Mining the EMR and extant population data sets to define normal human body temperature over time" — Julie Parsonnet, MD, professor of medicine and of health research and policy.

• "The effect of anti-immigrant policies on the health of immigrants and ethnic minorities: A quasi-experimental study" — Jens Hainmueller, PhD, professor of political science.

• "Desperation migration in the developing world: An empirical analysis" — Eran Bendavid, MD, assistant professor of medicine.

Learning health care innovation

• "Quality, cost and value: Studying the net value of diabetes management" — Karen Eggleston, PhD, senior fellow at the Freeman Spogli Institute for International Studies.

• "Toward personalizing and optimizing behavioral interventions in mobile health" — Jane Paik Kim, PhD, instructor of psychiatry and behavioral sciences.

• "Tracking ambulatory care-sensitive condition ER visits and hospitalizations in the context of a primary care redesign" — Marcelle Winget, PhD, clinical associate professor of medicine, and Megan Mahoney, MD, clinical associate professor of medicine.

• "The immune system and cancers using a gene-centric approach" — Ying Lu, PhD, professor of biomedical data science.

• "Patient-guided virtual hypertension management" — Lance Downing, MD, clinical assistant professor of medicine.

• "Population-based health information exchange for cancer prevention: Surveillance for cancer-related infections" — Summer Han, MD, assistant professor of neurosurgery and of medicine.

• "A population-based analytic resource for diabetes: Solano County health information exchange" — Jennifer Lee, PhD, associate professor of medicine.

• "Personalizing vital sign alarms" — Sarah Poole, graduate student, and Nigam Shah, MBBS, PhD, associate professor of medicine and of biomedical data science.

• "Machine-learning approaches to predicting medical readiness of new U.S. Army recruits" — Lianne Kurina, PhD, associate professor of medicine.

Community engagement

• "Pilot project to develop an initial infrastructure and data monitoring center for the study and prevention of local suicide clusters" — Rebecca Bernert, PhD, assistant professor of psychiatry and behavioral sciences.

• "Stress Experiences in Neighborhood and Social Environments, a pilot project in Santa Clara County" — Benjamin Chrisinger, PhD, postdoctoral scholar, and Abby King, PhD, professor of health research and policy and of medicine.

• "Implementing evidence-based mental health care in East Palo Alto school districts" — Flint Espil, PhD, social science research scholar.

Medical technologies

• "Management of hyperhidrosis using hydrogel-based iontophoresis" — Véronique Peiffer, PhD, postdoctoral scholar; Marlyanne Pol-Rodriguez, MD, clinical assistant professor of dermatology; and Justin Huelman, MS, biodesign fellow.

• "A novel device to decrease post-void residual urine in women with underactive bladder" — Ekene Enemchukwu, MPH, MD, assistant professor of urology, and Elise DeVries, biodesign fellow.

• "Passive home monitor for objective measures of asthma control in children" — David Cornfield, MD, professor in pediatric pulmonary medicine; Bronwyn Harris, MD, clinical instructor in pediatrics; and Michelle Huffaker, MD, postdoctoral scholar in allergy and immunology.

• "Development of a hybrid suture anchor-tendon graft for rotator cuff repair" — Dai-Fei Elmer-Ke, PhD, postdoctoral scholar, and Emilie Cheung, MD, associate professor of orthopaedic surgery.

• "Designing a wearable personal air pollution sensor and filter device for China and beyond" — Eric Sokol, MD, associate professor of obstetrics and gynecology; Jan Liphardt, PhD, associate professor of bioengineering; and Robert Chang, MD, assistant professor of ophthalmology.

• "Morphology-based high-throughput isolation of malignant cells in pleural effusions" — Mahdokht Masaeli, PhD, postdoctoral scholar, and Euan Ashley, MRCP, DPhil, associate professor of medicine, of genetics and of biomedical data science.

• "An automated oocyte/embryo orientation system for in vitro fertilization" — David Camarillo, PhD, assistant professor of bioengineering, and Barry Behr, PhD, professor of obstetrics and gynecology.

• "A novel method for personalized prediction of neurostimulation therapy efficacy" — Jin Hyung-Lee, MD, assistant professor of neurology, of neuruosurgery and of bioengineering, and Kevin Graber, MD, clinical associate professor of neurology and neurological sciences.

• "A low-cost, rapid, point-of-care nucleic-acid-based detection system" — Nate Cira, graduate student, and Stephen Quake, PhD, professor of bioengineering and of applied physics.

Predictive tools and diagnostics

• "Boronic acid-based fluorescent saccharide sensor for early detection of gastrointestinal cancer" — Sanjay Malhotra, PhD, associate professor of radiation oncology and of radiology, and Utkan Demirci, PhD, associate professor of radiology.

• "Engineering functionalized viruslike particles for circulating tumor cell detection and enumeration" — James Swartz, DSc, professor of engineering, of chemical engineering and of bioengineering, and Donna Peehl, PhD, professor emerita of urology.

• "Identification of diagnostic and prognostic biomarkers for RBM20-deficient dilated cardiomyopathy" — Lars Steinmetz, PhD, professor of genetics, and Ronald Davis, PhD, professor of biochemistry and of genetics.

• "A mobile autism initiative to detect autism spectrum disorder in Bangladeshi children under the age of 4" — Dennis Wall, PhD, associate professor of pediatrics, and Gary Darmstadt, MD professor of pediatrics.

• "Virtual agent-linked intelligent disease assessment tool engine" — Baldeep Singh, MD, clinical professor of medicine, and Nima Aghaeepour, PhD, postdoctoral scholar.

• "Gene signature to predict clinical outcome in hepatocellular carcinoma" — Meital Gabay-Ryan, PhD, postdoctoral scholar; Dean Felsher, MD, PhD, professor of medicine and of pathology; and Renu Dhanasekaran, MD, instructor of gastroenterology and hepatology.

• "Applications and validation assessments of consumer mobile and wearable devices and mobile applications for sleep monitoring" — Joseph Cheung, MD, clinical instructor of psychiatry and behavioral sciences; Emmanuel Mignot, MD, PhD, professor of sleep medicine; Jamie Zeitzer, PhD, assistant professor of psychiatry and behavioral sciences; and Katarzyna Wac, PhD, visiting professor.

• "VascTrac: A peripheral artery disease remote monitoring platform" — Oliver Aalami, MD, clinical associate professor of surgery.

• "Monitoring head impact exposure and predicting neurological deficit using an instrumented mouthguard" — David Camarillo, PhD, assistant professor of bioengineering, and Gerald Grant, MD, associate professor of neurosurgery.

Therapeutics

• "Therapeutic target for treating age-related neurodegenerative diseases by blocking leukocyte-endothelial crosstalk through very late antigen-4 and vascular cell adhesion molecule-1 interactions" — Hanadie Yousef, PhD, postdoctoral scholar, and Tony Wyss-Coray, PhD, professor of neurology.

• "Small molecules that restore a global immune response against cancer" — Stephanie Casey, PhD, postdoctoral scholar, and Dean Felsher, MD, PhD, professor of medicine and of pathology.

• "Visible light-based surface coupling of growth factors in situ to enhance ocular wound healing" — David Myung, MD, resident.

• "Targeting lipogenesis as a novel treatment for kidney cancer" — Arvin Gouw, PhD, postdoctoral scholar, and Dean Felsher, MD, PhD, professor of medicine and of pathology.

• "Development of small molecule activators of glucose-6-phosphate dehydrogenase deficiency for the treatment of hemolytic crisis and its sequalae" — Daria Mochly-Rosen, PhD, professor of chemical and systems biology.

• "Valine metabolism as a potential therapeutic target in leukemia" — Adam Wilkinson, PhD, postdoctoral scholar, and Hiromitsu Nakauchi, MD, PhD, professor of genetics.

• "Hypocretin receptor 2 small molecule agonists regulate ventricular function" — Marco Perez, MD, assistant professor of medicine, and Euan Ashley, MRCP, DPhil, associate professor of medicine, genetics and of biomedical data science.

• "Repurposing drugs for use against Entamoeba and other enteric protozoa" — Susmitha Suresh, PhD, postdoctoral scholar; Gretchen Ehrenkaufer, PhD, research associate; and Upinder Singh, MD, associate professor of medicine and of microbiology and immunology.

Spectrum pilot grants are administered by the Stanford Center for Population Health Sciences (population health, learning health care innovation and community engagement); Stanford Biodesign (medical technologies); the Stanford Predictives and Diagnostics Accelerator (predictive tools and diagnostics); and SPARK (therapeutics). Primary funding comes from Spectrum's $45.3 million Clinical and Translational Science Award from the National Institutes of Health. ISM

Pancreas

continued from page 1

Medicine, is the senior author of a paper describing the findings, which were published online Jan. 25 in Nature. Tomoyuki Yamaguchi, PhD, an associate professor of stem cell therapy, and researcher Hideyuki Sato, both from the University of Tokyo, share lead authorship of the paper.

Organs in short supply

About 76,000 people in the United States are currently waiting for an organ transplant, but organs are in short supply. Generating genetically matched human organs in large animals could relieve the shortage and release transplant recipients from the need for lifelong immunosuppression, the researchers say.

People suffering from diabetes could also benefit from this approach. Diabetes is a life-threating metabolic disease in which a person or animal is unable to either make or respond appropriately to insulin, which is a hormone that allows the body to regulate its blood sugar levels in response to meals or fasting. The disease affects hundreds of millions of people worldwide and is increasing in prevalence. The transplantation of functional islets from healthy pancreases has been shown to be a potentially viable option to treat diabetes in humans, as long as rejection can be avoided.

The researchers' current findings come on the heels of a previous study in which they grew rat pancreases in mice. Although the organs appeared functional, they were the size of a normal mouse pancreas rather than a larger rat pancreas. As a result, there were not enough functional islets in the smaller organs to successfully reverse diabetes in rats.

Mouse pancreases grown in rats

In the current study, the researchers swapped the animals' roles, growing mouse pancreases in rats engineered to lack the organ. The pancreases were able to successfully regulate the rats' blood sugar levels, indicating they were functioning normally. Rejection of the mouse pancreases by the rats' immune systems was uncommon because the mouse cells were injected into the rat embryo prior to the development of immune tolerance, which is a period during development when the immune system is trained to recognize its own tissues as "self." Most of these mouse-derived organs grew to the size expected for a rat pancreas, rendering enough individual islets for transplantation

Hiromitsu Nakauchi

> "This is very promising for our hope to transplant human organs grown in animals."

Next, the researchers transplanted 100 islets from the rat-grown pancreases back into mice with diabetes. Subsequently, these mice were able to successfully control their blood sugar levels for over 370 days, the researchers found.

Because the transplanted islets contained some contaminating rat cells, the researchers treated each recipient mouse with immunosuppressive drugs for five days after transplant. After this time, however, the immunosuppression was stopped.

After about 10 months, the researchers removed the islets from a subset of the mice for inspection.

"We examined them closely for the presence of any rat cells, but we found that the mouse's immune system had eliminated them," said Nakauchi. "This is very promising for our hope to transplant human organs grown in animals because it suggests that any contaminating animal cells could be eliminated by the patient's immune system after transplant."

Importantly, the researchers also did not see any signs of tumor formation or other abnormalities caused by the pluripotent mouse stem cells that formed the islets. Tumor formation is often a concern when pluripotent stem cells are used in an animal due to the cells' remarkable developmental plasticity. The researchers believe the lack of any signs of cancer is likely due to the fact that the mouse pluripotent stem cells were guided to generate a pancreas within the developing rat embryo, rather than coaxed to develop into islet cells in the laboratory. The researchers are working on similar animal-to-animal experiments to generate kidneys, livers and lungs.

Although the findings provide proof-of-principle for future work, much research remains to be done. Ethical considerations are also important when human stem cells are transplanted into animal embryos, the researchers acknowledge.

The research was funded by the Japan Science and Technology Agency, the Japan Agency for Medical Research and Development, the Japan Society for the Promotion of Science, a KAKENHI grant, the Japan Insulin Dependent Diabetes Mellitus Network and the California Institute for Regenerative Medicine.

Stanford's Department of Genetics also supported the work. ISM

$10.5 million awarded to researchers to work on DNA encyclopedia

By Jennie Dusheck

The National Human Genome Research Institute has awarded four grants, totaling $10.5 million, to five researchers at the School of Medicine to advance the work of the Encyclopedia of DNA Elements, or ENCODE.

The goal of ENCODE is to build a comprehensive parts list of the human genome, including both the parts that make up genes and the parts that influence gene activity. The grants are intended to fund four years of research in five labs and are part of a total of about $31.5 million that NHGRI plans to commit to ENCODE, pending the availability of funds.

The Stanford recipients and their grant amounts are:

- Will Greenleaf, PhD, assistant professor of genetics; Michael Bassik, PhD, assistant professor of genetics; and Anshul Kundaje, PhD, assistant professor genetics and of computer science: $1.18 million
- Mike Cherry, PhD, professor of genetics: $4.95 million
- Michael Snyder, PhD, professor of genetics; Howard Chang, MD, PhD, professor of dermatology; Greenleaf; Yiing Lin, MD, PhD, assistant professor of surgery at Washington University; and Kevin White, PhD, professor of human genetics and of ecology and evolution at the University of Chicago: $3.81 million
- Jonathan Pritchard, PhD, professor of genetics and of biology; Bassik; Kundaje; and Stephen Montgomery, PhD, assistant professor of genetics and of pathology: $558,000

Although scientists now know in detail the sequences of the genes that make up the genome, comparatively little is known about what the different genes do and how they work together. In particular, DNA sequences that code for polypeptides, which make up proteins, differ dramatically in function from so-called regulatory DNA sequences, which alter the activity of the coding genes.

The Pritchard lab will work on closing the gap between our understanding of coding DNA and the regulatory DNA. The team will, for example, develop a suite of tools, such as new machine-learning methods to identify genetic variants in the regulatory genes.

Greenleaf and Bassik will lead a "characterization center," one of five nationwide, to study how the regulatory DNA functions and how cells with altered gene activity grow under a variety of conditions. The goal is to better understand how regulatory genes influence the activity of coding genes.

Cherry's lab will continue to manage the ENCODE Data Coordinating Center at Stanford, which supports the ENCODE Consortium. The lab's work provides the greater biological research community with different ways of cooperatively accessing all the data. In addition, the center will provide multiple services, including written documentation, video tutorials, webinars and meeting presentations.

Snyder's grant will fund the Stanford ENCODE Production Center for Mapping of Regulatory Regions, where researchers will, among other things, map the binding sites for most of the gene activity that regulates molecules called transcription factors in five cell lines. The work will expand the catalog of known regulatory molecules in the human genome. ISM

Lab

continued from page 1

the cost of things," Davis said.

The low cost of the chips could democratize diagnostics similar to how low-cost sequencing created a revolution in health care and personalized medicine, Davis said. Inexpensive sequencing technology allows clinicians to sequence tumor DNA to identify specific mutations and recommend personalized treatment plans. In the same way, the lab on a chip has the potential to diagnose cancer early by detecting tumor cells that circulate in the bloodstream. "The genome project has changed the way an awful lot of medicine is done, and we want to continue that with all sorts of other technology that are just really inexpensive and accessible," Davis said.

Ron Davis

The technology has the potential to not only advance health care, but also to accelerate basic and applied research. It would allow scientists and clinicians to potentially analyze more cells in shorter time periods, manipulate stem cells to achieve efficient gene transfer and develop cost-effective ways to diagnose diseases, Esfandyarpour said. The team hopes the chip will create a transformation in how people use instruments in the lab. "I'm pretty sure it will open a window for researchers because it makes life much easier for them — just print it and use it," he said.

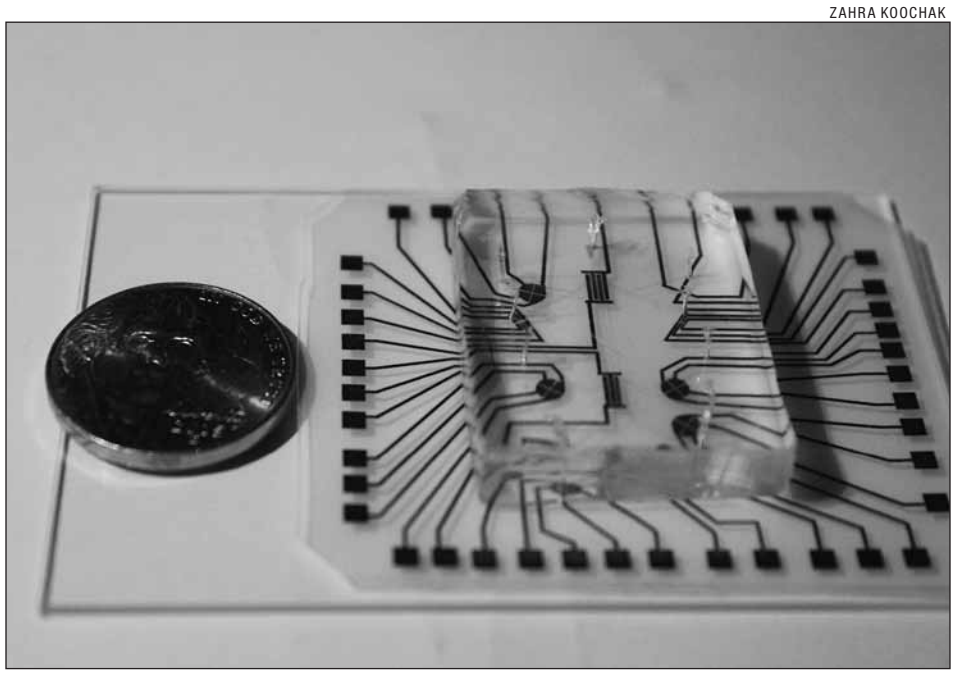
The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors of the study are graduate students Matthew DiDonato and Yuxin Yang; postdoctoral scholar Naside Gozde Durmus, PhD; and James Harris, PhD, professor of electrical engineering.

The research was supported by a grant from the National Institutes of Health.

The departments of Biochemistry and of Genetics also supported the work. ISM

ZAHRA KOOCHAK



The lab on a chip comprises a clear silicone microfluidic chamber for housing cells and a reusable electronic strip — a flexible sheet of polyester with commercially available conductive nanoparticle ink.

Center for Innovation in Global Health awards $300,000 in seed grants

By Rachel Leslie

The Stanford Center for Innovation in Global Health has awarded seed funding totaling $300,000 to six multidisciplinary teams of investigators that are evaluating technologies aimed at helping solve health care problems in resource-poor settings.

Michele Barry, MD, professor of medicine and senior associate dean for global health, said the grants were designed to jump-start projects with high-impact potential and foster new interdisciplinary collaborations among Stanford researchers and international partners.

"We firmly believe in the importance of seed funding and the transformative impact it can have," said Barry.

Following is a list of the principal investigators and a description of the projects they are leading:

Desiree LaBeaud, MD, associate professor of pediatrics, is leading a collaboration that combines complex data sets and deep learning to predict disease outbreaks. Using Rift Valley fever virus — a deadly vector-borne disease that infects livestock and humans — as a case study, the team will model the interplay between vectors, livestock, wildlife, climate and humans and apply machine learning to construct models for inference and prediction of future Rift Valley fever virus outbreaks. The team anticipates the approach will be transferrable to other outbreak scenarios and diseases because of advances in machine-learning technology.

Jennifer Newberry, MD, JD, an instructor of emergency medicine, is leading a collaboration among Stanford's departments of Emergency Medicine and of Pediatrics and partners in India to conduct a preliminary impact analysis of 181 Abhayam, a novel 24/7 helpline in Gujurat state providing phone counseling and assistance to women who are threatened with or have experienced violence. The researchers aim to fill a significant research gap in understanding the impact of the helpline model and to build the evidence base for women's crisis support and response in India.

Homero Rivas, MD, MBA, assistant professor of surgery, is initiating a pilot project that centers on the use of technology to enable access to medical care in marginalized communities in rural Mexico. Partnering with the local ministry of health, as well as robotics and technology experts, the study will evaluate the feasibility and scalability of using drone telemedicine units equipped with digital health systems as a way to bring prompt medical care to remote or isolated areas.

Robert Shafer, MD, professor of medicine, is working to increase testing capacity of HIV drug resistance in resource-poor settings. Collaborating with colleagues at Stanford, Silicon Valley-based InSilixa Inc. and the Biomedical Research Training Institute in Zimbabwe, the team aims to reduce mortality rates and costs attributable to HIV drug resistance in places where genotypic-resistant testing is unavailable. Project plans include developing point-of-care genotypic testing for drug-resistant HIV-1, as well as evaluating where the intervention is most needed in the HIV care continuum.

Shruti Sheth, MD, clinical assistant professor of oncology, is bringing together a multidisciplinary global cancer team to test a novel molecular technology to help improve breast cancer diagnosis in low-resource settings. She is partnering with the American Cancer Society, the Clinton Health Access Initiative and two comprehensive cancer centers in Nigeria.

Rebecca Walker, MD, MPH, assistant professor of emergency medicine, is leading an effort to create a mobile application designed to improve health care access and strengthen coordination of a first responder network in rural Nepal. More than 80 percent of the country's population lives in rural areas where health services are scarce and emergency care is unavailable. The application, available on smartphones and tablets, will give rural health care providers information about basic standards of care and better link first responders to create a more cohesive network.

All principal investigators are faculty fellows of the Center for Innovation in Global Health. The grants are funded by the Stanford Office of the President, the Office of the Dean of the School of Medicine, the Stanford Woods Institute for the Environment and the Bowman Family Foundation. **ISM**

Cancer

continued from page 1

fact that it was not recommended by their physicians.

Genetic counseling often unavailable

The survey also found that genetic counseling, either to help the patients decide whether to seek testing or to help them understand the results of their tests, did not occur. Only about 40 percent of all high-risk women, and 60 percent of those high-risk women who were tested, reported having a genetic counseling session.

"Genetic testing results can affect what sort of surgery a woman may choose to treat her existing breast cancer, as well as what treatments she should pursue to reduce the risk of forming new cancers in the future," said Jagsi, who is professor and deputy chair of radiation oncology at Michigan. "We don't have a crystal ball, but genetic testing can be a powerful tool for certain women. It is worrisome to see so many of those women at highest risk for mutations failing even to have a visit focused on genetic counseling."

Overall, the survey's results indicate that women are often not learning of genetic mutations that could lead to the development of additional cancers in them or in family members who may carry the same mutation. Women who know they carry a cancer-associated mutation may opt for more frequent or stringent screening, or sometimes even surgery to remove their breasts or ovaries before a cancer develops.

"The fact that many women are not offered genetic testing after a diagnosis of breast cancer is an important illustration of the challenges of driving advances in precision medicine into the exam room," said Katz, who is a professor of medicine and of health management and policy at Michigan.

"It is likely that some doctors don't realize the benefit that genetic testing provides," said Kurian. "They may also lack the ability to explain the testing process and results clearly with patients. Priorities for the future should include strategies to expand the genetic counselor workforce and interventions to improve physicians' skills in communication and cancer risk assessment."

Researchers from the University of Southern California, Emory University and the Memorial Sloan-Kettering Cancer Center also contributed to the study.

The study was supported by the National Institutes of Health.

Stanford's departments of Medicine and of Health Research and Policy also supported the work.

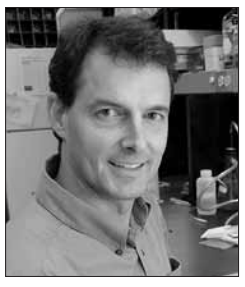
Kurian has received grant funding from Myriad Genetics, Invitae and Ambry Genetics. **ISM**

Three researchers receive grants from California Institute for Regenerative Medicine

By Krista Conger

Rosa Bacchetta

Roeland Nusse



Matthew Porteus

Three researchers from the School of Medicine have been awarded grants by the governing board of the California Institute for Regenerative Medicine to promote the discovery of potential stem cell-based therapies.

The awards, which were announced Jan. 19, were made as part of the state stem cell agency's Quest program, which funds the discovery phase of research expected to advance to the next stage of development within two years.

Rosa Bacchetta, MD, associate professor of pediatrics, was awarded $1.1 million to use a gene-editing technique to repair blood stem cells from patients with a rare but fatal genetic autoimmune disease called IPEX.

"Although it is a rare disease, IPEX is a prototype of a series of diseases with autoimmunity of genetic origin that overall severely affect children at a very early age," Bacchetta said in a statement from the agency about the awards, adding that she hopes the work will provide "a unique path forward in developing a definitive cure for this devastating genetic disease."

Roeland Nusse, PhD, professor of developmental biology and the Virginia and Daniel K. Ludwig Professor in Cancer Research, was awarded $1.7 million to investigate ways to grow liver stem cells in the laboratory while also maintaining their regenerative capacity. These cells could potentially be used to treat severe liver disease or to alleviate the shortage of donor organs.

Matthew Porteus, MD, associate professor of pediatrics, was awarded $2.2 million to investigate ways to use gene editing to correct cystic fibrosis mutations in airway stem cells.

"At CIRM we never underestimate the importance of early stage scientific research; it is the birth place of groundbreaking discoveries," said C. Randal Mills, PhD, president and CEO of CIRM, in a statement about the awards. "We hope these Quest awards will not only help these incredibly creative researchers deepen our understanding of several different diseases, but also lead to new approaches on how best to use stem cells to develop treatments."

In total, the agency awarded more than $20.5 million to 11 researchers during this round of funding. **ISM**

Biohub

continued from page 4

• Manu Prakash, PhD, assistant professor of bioengineering: He develops measurement tools, such as ultra-low cost microscopy platforms for field diagnostics of infectious diseases, for use in resource-poor areas of the world. His aim is to devise new, frugal platforms for the diagnosis and surveillance of schistosomiasis, leishmaniasis and malaria.

• Taia Wang, MD, PhD, assistant professor of infectious diseases: She studies human immunity and susceptibility to viral pathogens such as dengue virus. Her research is driven by the finding that humans have diverse immunoglobulin Fc domains that affect the severity of viral diseases and the effectiveness of vaccines.

• Ellen Yeh, MD, PhD, assistant professor of biochemistry, of pathology and of microbiology and immunology: She studies the apicoplast, a unique organelle in *Plasmodium falciparum* parasites, to identify new targets for the prevention and therapy of malaria. She aims to comprehensively identify the apicoplast proteome and to understand the novel secretory pathways of this unusual plastid in her search for novel therapeutic targets.

• James Zou, PhD, assistant professor of biomedical data science: He develops novel machine-learning tools that enable researchers to make complex predictions and quantify disease mechanisms using population genomics and epigenomics data. He is devising new deep-learning models to increase the accuracy of predicting genetic risk from genotypes and of identifying distinct cell populations based on single-cell transcriptional profiles.

Additionally, four Stanford faculty members from other schools were also named CZ Biohub investigators, along with 15 researchers from UCSF and 13 from UC-Berkeley. **ISM**

Deisseroth to receive Harvey Prize in Human Health

Karl Deisseroth, MD, PhD, the D.H. Chen Professor and a professor of bioengineering and of psychiatry and behavioral sciences, will be awarded the 2016 Harvey Prize in Human Health.

Deisseroth and Peter Hegemann, PhD, professor and chief of biophysics at the Humboldt University of Berlin, Germany, will share the $75,000 prize for their contributions to optogenetics.

Karl Deisseroth

"It is a great honor to receive the Harvey Prize in Human Health, which has a long and distinguished history in recognizing basic science discoveries, and I'm delighted to share the prize with my co-laureate and collaborator Peter Hegemann," Deisseroth said.

Optogenetics entails the installation of light-sensitive proteins, called opsins and derived from microbial organisms, into specific cells in a living, freely moving mammal. These cells can be either excited or inhibited by laser light, which is delivered via an implanted optical fiber.

The ability to turn on or turn off electrical activity in a set of cells in the brain allows researchers to gain insights into the causal mechanisms behind the organ's normal workings, as well as defects in function that accompany brain disorders such as Parkinson's disease, depression and schizophrenia. Optogenetics has also been used to turn on and off electrical activity in heart and kidney cells and in other tissues.

The Harvey prize, established with money from the estate of industrialist and inventor Leo Harvey, recognizes researchers who have made breakthroughs in science and technology of benefit to humanity. Optogenetics has "revolutionized neurobiology," the prize administrators wrote.

Deisseroth will accept the prize in June at the Technion-Israel Institute of Technology. In addition to the prize in human health, a Harvey Prize in Science and Technology will be awarded to three researchers for contributions to the understanding and observation of gravitational waves. **ISM**

Department of Ophthalmology secures $300,000 grant

The Department of Ophthalmology has been awarded a four-year, $300,000 grant from Research to Prevent Blindness to support research.

"I couldn't be more pleased to engage the support of RPB and their outstanding scientists and advisers," said Jeffrey Goldberg, MD, PhD, professor and chair of ophthalmology. "We are planning to support projects that leverage collaborations between scientists in the Department of Ophthalmology and across the breadth of Stanford's campus."

Potential projects include an investigation of brain stimulation to boost vision in patients with retinal or optic-nerve degeneration and work to identify molecular pathways to cue a retina to self-repair when damaged by disease, Goldberg said. **ISM**

OF NOTE

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

STEVEN FRICK, MD, was appointed professor of orthopaedic surgery, effective Dec. 1. He is the chief of pediatric orthopaedic surgery at Lucile Packard Children's Hospital Stanford and vice chair for education for the Department of Orthopaedic Surgery. His clinical interests include clubfoot and disorders of the foot and ankle, complex fracture care, hip dysplasia, osteogenesis imperfecta and neuromuscular disorders.

Steven Frick

Aaron Gitler

Susan Hiniker

Arden Morris

AARON GITLER, PhD, associate professor of genetics, was awarded one of 30 new R35 Research Program Awards from the National Institute of Neurological Disorders and Stroke. The grants, which are intended to promote creative research by providing stable funding, finance five years of research with a potential three-year extension. Gitler will use the funding to explore ways of innovating yeast and human genetic approaches to define mechanisms of neurodegenerative disease.

SUSAN HINIKER, MD, was appointed assistant professor of radiation oncology, effective Oct. 1. Her research interests include pediatric cancer, brain and central nervous system tumors, and Hodgkin's disease.

ARDEN MORRIS, MD, was appointed professor of surgery, effective Sept. 1. Her clinical work includes surgeries of the colon and rectum, and she uses mixed-methods research to focus on the quality of and disparities in surgical care. She directs the new Stanford-Surgery Policy, Improvement Research and Education Center. **ISM**

Algorithm

continued from page 2

to make it smartphone-compatible in the near future, bringing reliable skin cancer diagnoses to our fingertips.

"My main eureka moment was when I realized just how ubiquitous smartphones will be," said Esteva. "Everyone will have a supercomputer in their pockets with a number of sensors in it, including a camera. What if we could use it to visually screen for skin cancer? Or other ailments?"

The team believes it will be relatively easy to transition the algorithm to mobile devices, but there still needs to be further testing in a real-world clinical setting.

"Instead of writing into computer code exactly what to look for, you let the algorithm figure it out."

"Advances in computer-aided classification of benign versus malignant skin lesions could greatly assist dermatologists in improved diagnosis for challenging lesions and provide better management options for patients," said Susan Swetter, MD, a professor of dermatology and director of the Pigmented Lesion and Melanoma Program at the Stanford Cancer Institute, and a co-author of the paper. "However, rigorous prospective validation of the algorithm is necessary before it can be implemented in clinical practice, by practitioners and patients alike."

Even in light of the challenges ahead, the researchers are hopeful that deep learning could someday contribute to visual diagnosis in many medical fields.

Additional Stanford co-authors of this work are Roberto Novoa, MD, clinical assistant professor of dermatology and of pathology, and Justin Ko, MD, MBA, clinical associate professor of dermatology.

Thrun is founder and president of Udacity, a company that offers massive open online courses. Blau is the director of the Baxter Laboratory for Stem Cell Biology and a member of Stanford Bio-X, the Stanford Cardiovascular Institute, the Child Health Research Institute and the Stanford Cancer Institute.

This work was supported by the Baxter Foundation, the California Institute for Regenerative Medicine and the National Institutes of Health.

Stanford's departments of Computer Science, of Dermatology and of Microbiology and Immunology also supported the work. **ISM**

Photo ID Office moves to new location, establishes new hours

The Photo ID Office has moved to room HC021 on the ground floor of Stanford Hospital.

The office issues ID badges for Stanford Medicine faculty members, employees and students, among others.

Its new hours of operation are 9 a.m.-3 p.m. Monday through Friday. For more information, call (650) 498-6290 or send an email to photoid@stanfordhealthcare.org. **ISM**

Quinn McKenna named COO of Stanford Health Care

By Grace Hammerstrom

Quinn McKenna joined Stanford Health Care as chief operating officer on Jan. 3.

In this role, McKenna is responsible for overall operations, reporting directly to president and CEO David Entwistle. McKenna takes over from former COO James Hereford, who left Stanford Health Care after nearly four years to become president and CEO of Fairview Health Services in Minneapolis.

Quinn McKenna

McKenna previously served as COO of the University of Utah Hospitals and Clinics and as executive director of the University of Utah Hospital, with an annual budget of $1.7 billion and more than 10,000 employees. For nine years, he worked with Entwistle to lead the University of Utah system to national preeminence in quality, patient satisfaction and employee engagement, while simultaneously improving the efficiency of its staff and operations.

McKenna said his decision to join Stanford Health Care was motivated by the conversations he had with its staff and faculty. "They are extremely intelligent, with a high degree of curiosity," he said. "When you get buy-in and focus from that caliber of person, you can solve problems that other organizations can't even touch."

McKenna has also served in executive positions at the University of Washington in Seattle and at Providence Health System.

He earned a master's degree in health administration from the University of Washington and a bachelor's degree in business finance from Utah State University, with a minor in economics. He raised his four children in the Seattle area and is now a grandfather of three. An avid hiker, he said he is looking forward to the Bay Area's year-round outdoor opportunities.

McKenna joins Stanford at a time of increased competition in the health care marketplace. He said one of his first priorities will be to bring focus and prioritization to Stanford. That, he said, was the key to his success at University of Utah Hospitals. "My mantra has always been: We can solve any problem, but we cannot solve every problem at the same time," he said. **ISM**