INSIDE STANFORD MEDICINE

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Painter Ted Meyer makes art from scars and will be on campus this week to share his work with scientists and students.

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Biomarkers tied to chronic fatigue severity

By Bruce Goldman

STEVE FISCH

Jose Montoya and his colleagues have found evidence that inflammation may be the culprit behind chronic fatigue syndrome, a disease with no known cure. The researchers hope their findings will provide a basis for developing a blood test to diagnose the disease.

Researchers at the School of Medicine have linked chronic fatigue syndrome to variations in 17 immune-system signaling proteins, or cytokines, whose concentrations in the blood correlate with the disease's severity.

The findings provide evidence that inflammation is a powerful driver of this mysterious condition, whose underpinnings have eluded researchers for 35 years.

The findings, described in a study published online July 31 in the *Proceedings of the National Academy of Sciences*, could lead to further understanding of this condition and be used to improve the diagnosis and treatment of the disorder, which has been notably difficult.

More than 1 million people in the United States suffer from chronic fatigue syndrome, also known as myalgic encephomyelitis and designated by the acronym ME/CFS. It is a disease with no known cure or even reliably effective treatments. Three of every four ME/CFS patients are women, for reasons that are not understood. It characteristically arises in two major waves: among adolescents between the ages of 15 and 20, and in adults between 30 and 35. The condition typically persists for decades.

"Chronic fatigue syndrome can turn a life of productive activity into one of dependency and desolation," said Jose Montoya, MD, professor of infectious diseases, who is the study's lead author. Some spontaneous recoveries occur during the first year, he said, but rarely after the condition has persisted more than five years.

The study's senior author is Mark Davis, PhD, professor of immunology and microbiology and director of Stanford's Institute for Immunity, Transplantation and Infection.

'Solid basis for a diagnostic blood test'

"There's been a great deal of controversy and confusion surrounding ME/CFS — even whether it is an actual disease," said Davis. "Our findings show clearly that it's an inflammatory disease and provide a solid basis for a diagnostic blood test."

Many, but not all, ME/CFS patients experience flulike symptoms common in inflammation-driven diseases, Montoya said. But because its symptoms are so diffuse — sometimes manifesting as heart problems, sometimes as mental impairment nicknamed "brain fog," other times as indigestion, diarrhea, constipation, muscle pain, tender lymph nodes and so forth — it often goes undiagnosed, even among patients who've visited a half-dozen or more different specialists in an effort to determine what's wrong with them.

Montoya, who oversees the Stanford ME/CFS Initiative, came across his first ME/CFS patient in 2004, an experience he said he's never forgotten.

"I have seen the horrors of this disease, multiplied by See CFS, page 6

Is it nature or nurture? New study shows both affect behavior in mice

By Bruce Goldman

School of Medicine investigators have identified a cluster of nerve cells in the male mouse's brain that, when activated, triggers territorial rage in a variety of situations. Activating the same cluster has no such effect on female mice.

Moreover, whether a male mouse displays territorial aggression depends on whether it's recently been the sole occupant of a bachelor pad or living in the mouse equivalent of boarding school. The latter makes for good manners; the former, not so much.

In a study published online July 27 in *Neuron*, the researchers used sophisticated laboratory techniques to determine how much this aggressive behavior owed to environmental See SHAH, page 6

SHUTTERSTOCK

Imaging reveals how well patients with PTSD will respond to psychotherapy, study finds

By Emma Hiolski

A pair of studies led by researchers at the School of Medicine demonstrates that scientists can predict, with a high degree of accuracy, which patients with post-traumatic stress disorder will respond to a method of psychotherapy often used to treat the condition.

The researchers showed how the treatment, prolonged exposure therapy, works in the brains of PTSD patients and linked brain activity patterns to how well patients responded. The results could lead to personalized treatment for PTSD. The studies were published online July 18 in *The American Journal of Psychiatry*.

"We understand vanishingly little about how psychotherapy works and for whom it works well," said Amit Etkin, MD, PhD, the senior author of both studies and an associate professor of psychiatry and behavioral sciences at Stanford. "It's not even a knowledge gap — more like a knowledge ravine. This is especially an issue for PTSD because the only effective treatment is psychotherapy."

Lead authorship of the papers is shared by Stanford postdoctoral scholar Gregory Fonzo, PhD, and former Stanford postdoctoral scholar Madeleine Goodkind, PhD, now a psychologist at the New Mexico Veterans Affairs Health Care System and an adjunct assistant professor of psychiatry at the University of New Mexico School of Medicine.

LESLIE WILLIAMSON

Amit Etkin and his team found a way to predict which patients with PTSD will benefit from prolonged exposure therapy.

Revisiting traumatic experiences with psychotherapy

PTSD is a serious mental disorder that can develop after a dangerous or traumatic event. Patients experience recurring memories of the event; avoid situations, people or thoughts that remind See PTSD, page 7

Elective freezing of IVF embryos linked to higher pregnancy rates for some

By Erin Digitale

A delay in transferring embryos to the mother improves the success of in vitro fertilization in certain cases, according to a study by scientists at the School of Medicine, Celmatix Inc. and several other institutions.

Women undergoing IVF who have high levels of the hormone progesterone when their egg cells are retrieved benefit from having the resulting embryos frozen and transferred back to the uterus at a later date, the researchers found.

The study appears in the August issue of *Fertility and Sterility*. The lead author is Ange Wang, MD, a resident physician in obstetrics and gynecology at Stanford. Several other co-authors, including senior author Piraye Yurttas Beim, PhD, work for Celmatix, a company that makes software and a genetic test to help guide fertility treatments for women.

The IVF process starts with injections of reproductive hormones to stimulate the growth of multiple eggs. The eggs are retrieved and then fertilized in the laboratory. The resulting embryos can be transferred back to the woman's uterus a few days later (a "fresh" transfer) or frozen and then transferred in a subsequent hormonal cycle.

Ange Wang

The new study, which analyzed 2,910 attempts to establish pregnancy via IVF, is the largest ever to compare frozen with fresh embryo transfer. Given that the highest-quality embryos are typically transferred to a woman first and that the scientists wanted to diminish the possible influence of embryo quality on the results, IVF procedures in which a woman had "leftover" frozen embryos transferred following a failed fresh transfer were not included in the study.

The greatest difference between the frozen and fresh procedures was seen in women who had high progesterone levels and were older than 35. For these women, freezing the embryos before transfer was 73 percent more likely to produce an ongoing pregnancy than transferring the embryos immediately after IVF.

"This finding is important because it may suggest a group of women that benefits more from freeze-all IVF cycles," Wang said. In freeze-all cycles, all embryos are frozen for later transfer. "Higher progesterone levels may make it more difficult for embryos to implant — that is, adhere to the wall of the uterus to establish pregnancy — possibly due to premature maturation of the uterine lining."

The researchers speculated that freezing embryos and waiting to transfer them during a different cycle gives an opportunity for progesterone and other hormones to fall to levels more hospitable to implantation, although this idea was not directly tested.

The database the researchers used included information about implantation rates and also about which IVF cycles led to pregnancies lasting long enough for patients to be transferred from the care of fertility centers to regular obstetric practices, reported in the study as "ongoing pregnancy." Live birth data were not reported.

Common approach

Freezing embryos created during IVF before transferring them back to the patient has become increasingly common as freezing techniques have improved. Tests to examine embryos for chromosomal or genetic diseases are also becoming more widely used, and these often require freezing. But physicians have been unsure whether transferring frozen embryos changed pregnancy rates. Until now, only small studies have been done, and some have been inconclusive.

To compare success rates of transferring fresh versus frozen embryos, Wang and her colleagues used a large database maintained by Celmatix that contains records of hundreds of thousands of IVF treatments performed at 12 fertility treatment centers in the United States. From the database, two cohorts of 1,455 IVF transfers were selected to study: one group in which all the embryos were frozen before transfer, and another group in which fresh embryos were transferred. Patients in the two cohorts had similar ages, causes of infertility, reproductive histories, numbers of eggs retrieved, number of embryos created and levels of reproductive hormones.

A 73 percent higher pregnancy rate

Fifty-two percent of the embryo transfers performed after embryos were frozen led to ongoing pregnancies, whereas 45.3 percent of fresh transfers led to ongoing pregnancies. After analyzing all IVF transfers together, the researchers performed separate comparisons of women with lower and higher progesterone levels, as well as of women who were younger and older than 35. Women with lower progesterone levels who received previously frozen embryos did not experience better pregnancy outcomes, regardless of their age. However, among women with higher progesterone levels at the time of egg retrieval, transferring previously frozen embryos resulted in more pregnancies both in younger and older patients. The difference was greatest in patients with high progesterone levels who were older than 35. In this group, 48.4 percent of transfers using previously frozen embryos resulted in pregnancies, compared with 35.2 percent of fresh transfers. In other words, for older women with high progesterone levels, the odds of pregnancy were 73 percent greater following transfer of previously frozen embryos.

> "Higher progesterone levels may make it more difficult for embryos to implant."

The new findings may prompt physicians to suggest that patients with high progesterone levels at egg retrieval freeze their embryos and wait for a subsequent cycle to transfer them, said Wang. But other factors also influence the decision about which protocol to use, she said.

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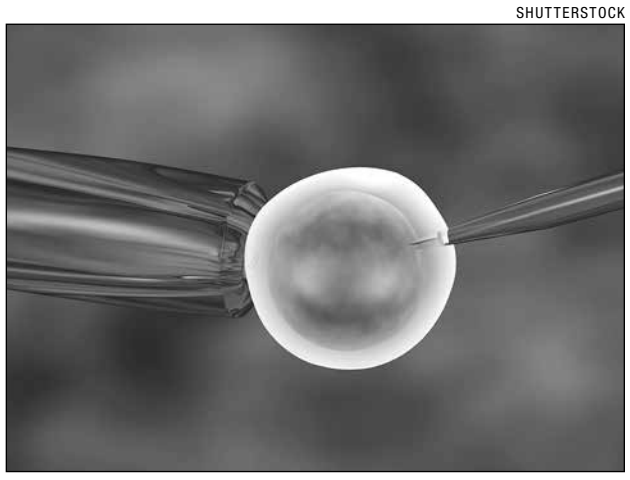

Some women who have high progesterone levels when their eggs are retrieved may have more success having their embryos frozen and then transfered at a later date, a new study shows.

"If I were counseling an IVF patient on whether to choose a freeze-all cycle, it would depend on the characteristics of her cycle, as well as her own desires," Wang said. "Though this data suggests promising effects of freeze-all transfers, it is still important to listen to patients' preferences. Some women do not want to wait to transfer embryos or have financial or other considerations that may impact their choice."

Lynn Westphal, MD, professor of obstetrics and gynecology, is another Stanford co-author of the study.

In addition, scientists from Reproductive Medical Associates of New York; the Mount Sinai Icahn School of Medicine; the University of Connecticut School of Medicine; the Center for Advanced Reproductive Sciences in Farmington, Connecticut; Reproductive Medical Associates of Michigan; and Shady Grove Fertility Center in Rockville, Maryland, co-authored the paper.

None of the authors disclosed financial conflicts of interest relevant to the study.

The study was funded by Celmatix. Stanford's Department of Obstetrics and Gynecology also supported the work. ISM

New center will work to find therapies for genetic diseases

At least 280 million people worldwide are living with a rare genetic disease. For many of these millions, the underlying cause of disease is known and well-defined, and yet eludes definitive treatment. At times, surgical interventions, public health measures, biological and small-molecule therapies can transform the health of these populations; often, however, the currently available treatment modalities result in mere palliative, rather than curative, medicine.

Stem cell and gene therapy hold enormous promise to cure conditions with well-defined genetic causes by engineering cells to treat disease or alter a patient's personal DNA to "fix" an abnormality. To bring these new stem cell and gene therapies to their patients, Stanford Medicine has announced the opening of the Stanford Center for Definitive and Curative Medicine, a joint initiative of the School of Medicine, Stanford Health Care and Stanford Children's Health.

The center provides the organizational and physical infrastructure to support investigator-initiated clinical translational studies on stem cell and gene therapy from initial discovery through completion of clinical proof-of-concept studies. Stanford Medicine is in a unique position to develop the CDCM because of its outstanding expertise in disease pathophysiology, cell and stem cell biology, and an optimal and collaborative environment between the medical school and the hospitals.

"The Center for Definitive and Curative Medicine is going to be a major force in the precision health revolution," said Lloyd Minor, MD, dean of the School of Medicine. "Our hope is that stem cell and gene-based therapeutics will enable Stanford Medicine to not just manage illness but cure it decisively and keep people healthy over a lifetime."

Stanford Medicine's clinical enterprise provides an exemplary clinical environment in which to deploy cures. The center will support the development of life-changing and curative treatments for patients who come to Stanford to receive the highest level of care.

"We are entering a new era in medicine, one in which we will put healthy genes into stem cells and transplant them into patients. And with the Stanford Center for Definitive and Curative Medicine, we will be able to bring these therapies to patients more quickly than ever before," said Christopher Dawes, president and CEO of Stanford Children's Health.

"The work of the center is not being done anywhere else in the country — only at Stanford," added David Entwistle, president and CEO of Stanford Health Care. "We have a pipeline of clinical translational therapies that the center is now driving forward, enabling us to translate basic science discoveries into state-of-the-art therapies for diseases which up until now have been considered incurable."

Strong leadership

Housed within the Department of Pediatrics, the new center will be directed by renowned clinician and scientist Maria Grazia Roncarolo, MD, the George D. Smith Professor in Stem Cell and Regenerative Medicine, and professor of pediatrics and of medicine.

"It is a privilege to lead the center and to leverage my previous experience to build Stanford's preeminence in stem cell and gene therapies," said Roncarolo, who is also chief of pediatric stem cell transplantation and regenerative medicine, co-director of the Bass Center for Childhood Cancer and Blood Diseases and co-director of the Stanford Institute for Stem Cell **See CDCM, page 3**

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STANFORD MEDICINE

5 QUESTIONS

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

Kelly Ormond on setting rules for germline editing

A team of genetics experts has issued a policy statement recommending that research on editing human genes in eggs, sperm and early embryos continue, provided the work does not result in a human pregnancy.

Kelly Ormond, MS, professor of genetics at the Stanford School of Medicine, is one of three lead authors of the statement, which provides a framework for regulating the editing of human germ cells. Germ cells, a tiny subset of all the cells in the body, give rise to eggs and sperm. Edits to the genes of germ cells are passed on to offspring.

The statement, published Aug. 3 in the American Journal of Human Genetics *was jointly prepared by the American Society for Human Genetics and four other human genetics organizations, including the National Society of Genetic Counselors, and endorsed by another six, including societies in the United Kingdom, Canada, Australia, Africa and Asia.*

Germline gene editing raises a host of technical and ethical questions that, for now, remain largely unanswered. The ASHG policy statement proposes that federal funding for germline genome editing research not be prohibited; that germline editing not be done in any human embryo that would develop inside a woman; and that future clinical germline genome editing in humans not proceed without a compelling medical rationale, evidence supporting clinical use, ethical justification, and a process incorporating input from the public, patients and their families, and other stakeholders.

Ormond recently discussed the issues that prompted the statement's creation with writer Jennie Dusheck.

1 Why did you think it was important to issue a statement now?

ORMOND: Much of the interest arose a couple of years ago when a group of researchers in China did a proof-of-principle study demonstrating that they could edit the genes of human embryos.

The embryos weren't viable [meaning they could not lead to a baby], but I think that paper worried people. Gene editing in human germ cells is not technically easy, and it's not likely to be a top choice for correcting genetic mutations. Still, it worried us that somebody was starting to do it.

Kelly Ormond

We've been able to alter genes for many years now, but the new techniques, such as CRISPR/Cas9, that have come out in the past five years have made it a lot easier, and things are moving fast. It's now quite realistic to do human germline gene editing, and some people have been calling for a moratorium on such work.

Our organization, the American Society of Human Genetics, decided that it would be important to investigate the ethical issues and put out a statement regarding germline genome editing, and what we thought should happen in the near term moving forward.

As we got into the process, we realized that this had global impact because much of the work was happening outside of the United States. And we realized that if someone, anywhere in the world, were moving forward on germline genome editing, that it was going to influence things more broadly. So we reached out to many other countries and organizations to see if we could get global buy-in to the ideas we were thinking about.

2 Are there regulations now in place that prevent researchers from editing human embryos that could result in a pregnancy and birth?

ORMOND: Regulations vary from country to country, so research that is illegal in one country could be legal in another. That's part of the challenge and why we thought it was so important to have multiple countries involved in this statement.

Also, since 1995 the United States has had regulations against federal funding for research that creates or destroys human embryos. We worry that restricting federal funding on things like germline editing will drive the research underground so there's less regulation and less transparency. We felt it was really important to say that we support federal funding for this kind of research.

3 Is germline editing in humans useful and valuable?

ORMOND: Germline editing doesn't have many immediate uses. A lot of people argue that if you're trying to prevent genetic disease (as opposed to treating it), there are many other ways to do that. We have options like prenatal testing or IVF and pre-implantation genetic testing and then selecting only those embryos that aren't affected. For the vast majority of situations, those are feasible options for parents concerned about a genetic disease.

The number of situations where you couldn't use pre-implantation genetic diagnosis to avoid having an affected child are so few and far between. For example, if a parent was what we call a homozygote for a dominant condition such as BRCA1 or Huntington's disease, or if both members of the couple were affected with the same recessive condition, like cystic fibrosis or sickle cell anemia, it wouldn't be possible to have a biologically related child that didn't carry that gene, not unless germline editing were used.

4 What makes germline editing controversial?

ORMOND: There are families out there who see germline editing as a solution to some genetic conditions. For example, during a National Academy of Sciences meeting in December of 2015, a parent stood up and said, "I have a child who has a genetic condition. Please let this move forward; this is something that could help."

But I also work in disability studies, as it relates to genetic testing, and there are many individuals who feel strongly that genetic testing or changing genes in any way makes a negative statement about them and their worth. So this topic really edges into concerns about eugenics and about what can happen once we have the ability to change our genes.

Germline gene editing impacts not just the individual whose genes are edited, but their future offspring and future generations. We need to listen to all of those voices and try to set a path that takes all of them into account.

That's a huge debate right now. A lot of people say, "Let's not mess around with the germline. Let's only edit genes after a person is born with a medical condition." Treating an existing medical condition is different from changing someone's genes from the start, in the germline, when you don't know what else you're going to influence.

5 There was a paper recently about gene editing that caused mutations in excessive numbers of nontargeted genes, so called "off-target effects." Did that result surprise you or change anything about what you were thinking?

ORMOND: No. And, again, I think part of the problem is that this research is moving very fast. One of our biggest challenges was that you can't do a good ethical assessment of the risks and benefits of a treatment or technology if you don't know what the risks are.

We keep learning about potential risks, including off-target mutations and other unintended consequences. Before anyone ever tries to do germline gene editing in humans, it is very important that we do animal studies where the animals are followed through multiple generations, so that we can see what happens in the long term. There's just a lot that we don't know.

There are so many unknowns that we don't even know what guidelines to set. For example, what's an appropriate new mutation level in some of these technologies? What is the risk we're willing to take as we move forward into human studies? And I think those guidelines need to be set as we move forward into clinical trials, both in somatic cells [cells of the body, such as skin cells, neurons, blood cells] and in germline cells.

It's really hard because, of course, we're talking about, for the most part, bad diseases that significantly impact quality of life. So if you're talking about a really serious disease, maybe you're willing to take more risk there, and these new mutations aren't likely to be as bad as the genetic condition you already have. But we don't know, right?

We haven't had any public dialogue about any of this, and that's what we need to have. We need to find a way to educate the public and scientists about all of these issues so people can have informed discussions and really come together as this moves forward, so that were not in that reactive place when it potentially becomes a real choice.

And that goes back to your first question, which is why did we feel like we needed to have a statement now? We wanted to get those conversations going. **ISM**

CDCM

continued from page 2

Biology and Regenerative Medicine. "Stanford Medicine's unique environment brings together scientific discovery, translational medicine and clinical treatment. We will accelerate Stanford's fundamental discoveries toward novel stem cell and gene therapies to transform the field and to bring cures to hundreds of diseases affecting millions of children worldwide."

The center consists of several innovative pieces designed to allow the rapid development of early scientific discoveries into the clinic that in the past have languished. This includes an interdisciplinary team of basic and clinical scientists to shepherd nascent therapies developed at Stanford. The team will be headed by associate directors Matthew Porteus, PhD, associate professor of pediatrics, and Anthony Oro, MD, the Eugene and Gloria Bauer Professor and professor of dermatology.

To help with clinical development, the center boasts a dedicated stem cell clinical trial office with Sandeep Soni, MD, clinical associate professor of pediatrics, as medical director. In addition, the center has dedicated clinical trial hospital beds in the Bass Center for Childhood Cancer and Blood Diseases located on the top floor of the soon-to-open Lucile Packard Children's Hospital. From work performed by scientists over the past decade, the center already has a backlog of nearly two dozen early stage therapies whose development the center will accelerate.

"The center will provide novel therapies that can prevent irreversible damage in children, and allow them to live normal, healthy lives," said Mary Leonard, MD, professor and chair of pediatrics and physician-in-chief at Stanford Children's Health. "The stem cell and gene therapy efforts within the center are aligned with the strategic vision of the Department of Pediatrics and Stanford's precision health vision, where we go beyond simply providing treatment for children to instead cure them definitively for their entire lives."

Laboratory for Cell and Gene Medicine

One of the unique features of the center is its close association with the recently opened $35 million Stanford Laboratory for Cell and Gene Medicine, a 23,000-square-foot manufacturing facility located on California Avenue in Palo Alto. One of the first of its kind in the world, the laboratory has the ability to produce newly developed cell and gene therapy therapies according to the Good Manufacturing Practice standards as required for patient treatment.

Headed by executive director David DiGiusto, PhD, the lab can produce diverse cellular products for patient use, such as genetically corrected bone marrow cells for sickle cell anemia, genetically-engineered skin grafts for children with the genetic disease epidermolysis bullosa or genetically-engineered lymphocytes to fight rejection and leukemia.

NORBERT VON DER GROEBEN

Maria Grazia Roncarolo will direct the Stanford Center for Definitive and Curative Medicine.

"We are fortunate that Stanford researchers have created such a strong portfolio of innovative candidate therapeutics to develop," said DiGusto. "The capabilities of the laboratory will bridge the gap between research and clinical investigation so that the curative potential of these exciting cell and gene therapies can be realized."

For more information about the center, or for information about trials associated with the center, contact Jennifer Howard at jmhoward@stanford.edu. **ISM**

Rothschild gift creates Stanford Center for Cancer Cell Therapy

By Ruthann Richter

The Stanford Cancer Institute has received a $10 million gift from Silicon Valley entrepreneur Jeffrey Rothschild and his wife, Marieke, to advance research in cancer cell therapy, which is considered the vanguard of cancer treatment today.

The gift launches the Stanford Center for Cancer Cell Therapy, which will support research and clinical trials of treatments that use the power of the patients' own immune system to attack and kill tumor cells.

"This gift to establish the center will enable us to test new, targeted cell therapies, which have the potential to transform our fight against cancer," said Lloyd Minor, MD, dean of the School of Medicine. "We are immensely grateful to Jeff and Marieke Rothschild for their commitment to our precision health vision and their foresight in supporting this exciting venture."

"We were interested in supporting promising research, and this is an area that I had been paying attention to," Jeffrey Rothschild said. "There's not been as much progress in cancer therapy as people had thought there might be 20 years ago. Here's something which looks like a path that holds real promise, harnessing the immune system. That just seems very exciting."

A computer scientist by training, Rothschild was the vice president of infrastructure engineering at Facebook and has co-founded several technology companies, including Veritas Software and Mpath Interactive.

'Appetite for risk'

Marieke Rothschild said she and her husband are attracted to projects that may be high-risk but have the potential for meaningful and enduring social impact. Their philanthropic investments have been focused on health care and education, including scholarships for students who might not otherwise attend school. Five years ago, they established an eye hospital in western Kenya, where clinicians now provide care at little or no cost to 3,500 patients a year with cataracts and glaucoma.

"We have an appetite for risk," Marieke Rothschild said. "We ask the question, 'What can really yield results? What are the projects that are not being funded? Where, with a relatively small amount of funding, can you have impact?'"

The Center for Cancer Cell Therapy was established to directly benefit patients and spur innovation in a field that is considered one of the frontiers in cancer care.

The center will be led by Crystal Mackall, MD, professor of pediatrics and of medicine and one of the pioneers in the field of cancer cell therapy. Mackall's work has focused on CAR T cells, immune cells engineered to express receptors that lock onto and destroy malignant cells.

While at the National Cancer Institute, she led several clinical trials using these modified T cells to treat children with leukemia whose condition hadn't improved with other therapies. The response rates were remarkable, with 70 to 90 percent of children improving with a single treatment.

"Here's something which looks like a path that holds real promise."

A variation on this treatment, now being tested in young patients at Lucile Packard Children's Hospital Stanford, was recommended for approval by a Food and Drug Administration panel July 12 and could be the first CAR T cell therapy to reach the market.

'Potentially transformational'

"I think it has the potential to be highly impactful. That's why I'm committing myself to it," Mackall said. "If we can optimize the functioning of these

ROD SEARCEY

(From left) Beverly Mitchell, Marieke Rothschild, Jeffrey Rothschild and Crystal Mackall hope the new center will advance treatments that use a cancer patient's immune system to kill tumor cells.

cells, they have the potential to effectively kill an established cancer and to remain functional for years after one infusion. That's the goal — to have a product that will work on behalf of the patient. When optimized, they could remain active for months or years, preventing a recurrence of cancer. So for me, it's potentially transformational."

Among the challenges of these therapies is that they work for some patients but not others, and aren't effective in treating all types of cancers. Scientists at Stanford Medicine and elsewhere are looking at ways to apply the therapies more broadly and to minimize potential side effects of the treatment.

"This is an incredibly promising approach to immunotherapy," said Beverly Mitchell, MD, professor of medicine and director of the Stanford Cancer Institute. "I think it has to overcome some problems, one of which is that there is occasional toxicity. And many solid tumors have yet to respond, so there is a lot of research that needs to be done to bring it to the broadest spectrum of patients. I have great confidence that it will become the mainstay of treatment for leukemias and lymphomas and will then extend into solid tumors, including brain cancers and sarcoma. I think it's the next frontier."

She said the Rothschild gift will enable Stanford Medicine researchers to move forward with a series of clinical trials using variations of CAR T cells in different types of cancers.

Until this point, these trials at Stanford have been industry-sponsored; the new gift will support the first investigator-initiated trial using a therapy that Mackall developed in her lab. Expected to begin in August, this trial may enroll up to 50 children and adults with B-cell leukemias and lymphomas, using a CAR T cell that involves a "double-punch," simultaneously targeting the CD22 and CD19 antigens on cancer cells, Mackall said. Previous therapies have been directed at the CD19 antigen alone and the CD22 antigen alone, but over time, some patients lose these targets and no longer respond to the treatment, she said.

In 2018, trials will expand to children and adults with brain tumors and children with solid tumors, such as neuroblastoma and osteosarcoma, she said.

David Miklos, MD, associate professor of medicine and specialist in bone marrow transplantation, will co-direct the new center, which includes many other Stanford Medicine physician-scientists who care for both adults and children with cancer. With the Rothschilds' support, Stanford also will recruit new faculty in cancer immunotherapy to join the effort.

The new center is expected to complement the work of the Parker Institute for Cancer Immunotherapy at Stanford, which Mackall directs. The institute brings together six academic medical centers nationwide working collaboratively to advance the field.

As for the Rothschilds, they say their goal is to contribute to knowledge in the field.

"We just hope to be able to affect things in a positive way — have some impact," Jeffrey Rothschild said. "That's all you ever can hope for." ISM

Reversing signaling imbalance in brains of mice eases symptoms of autism

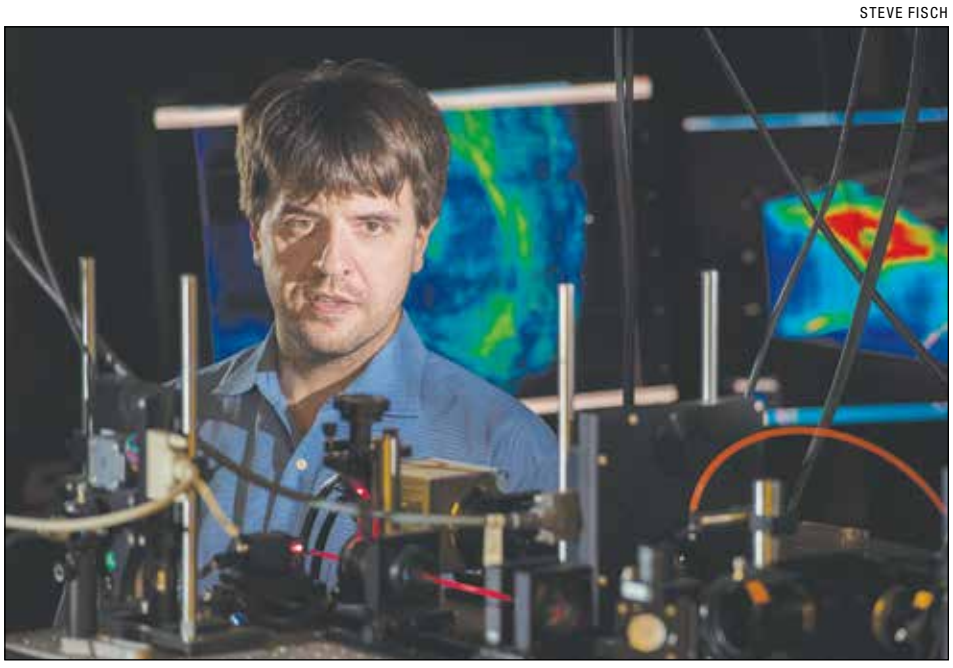
By Bruce Goldman

A study by Stanford investigators suggests that key features of autism reflect an imbalance in signaling from excitatory and inhibitory neurons in a portion of the forebrain, and that reversing the imbalance could alleviate some of its hallmark symptoms.

In a series of experiments conducted on a mouse model of the disorder, the scientists showed that reducing the ratio of excitatory to inhibitory signaling countered hyperactivity and deficits in social ability, two classic symptoms of autism in humans.

The study was published Aug. 2 in *Science Translational Medicine*. Karl Deisseroth, professor of bioengineering and of psychiatry and behavioral sciences, is the study's senior author. The lead author is former graduate student Aslihan Selimbeyoglu, PhD.

STEVE FISCH



Karl Deisseroth and his colleagues discovered that reducing the ratio of excitatory to inhibatory signaling in a portion of the brains of mice could alleviate two classic symptoms of autism.

In 2011, Deisseroth's group published a study in *Nature* showing that autismlike behavioral deficits could be induced in ordinary mice by elevating the ratio of excitatory to inhibitory neuronal firing patterns in the mice's medial prefrontal cortex.

The new study shows that decreasing that ratio restores normal behavior patterns in a strain of lab mice bioengineered to mimic human autism. These mice carry a mutation equivalent to a corresponding mutation in humans that is associated with autism spectrum disorder.

Autism incidence increasing

For reasons that are not understood, the incidence of autism spectrum disorder has increased steadily in recent years, said Deisseroth, a practicing psychiatrist. Around 1 in 80 American children may be diagnosed with the disorder, which is characterized by repetitive behaviors and difficulty with social interaction. To date, there are no medications that treat the fundamental underpinnings of the disorder.

"In all of psychiatry, there's no lab test that can diagnose this condition," said Deisseroth. "It's been associated with numerous genetic variants, many of which appear to exert only small individual influences."

Deisseroth, who holds the D.H. Chen Professorship, notes that UCSF psychiatrist John Rubenstein and his colleagues, among others, have theorized that an excitation-inhibition imbalance might account for these phenomena.

While myriad genetic variations contribute to autism, many of them may do so by impairing, in diverse ways, a single process or a small number of processes necessary for overall healthy brain function, such as a balance between excitatory and inhibitory signaling in key brain regions.

One of those regions is the medial prefrontal cortex, which plays a major role in executive functions, such as planning, prediction, attention and integrating information from other individuals' behaviors and speech for clues as to what they might be thinking.

Testing the hypothesis

"Social interaction may be the hardest thing a mammal can do," Deisseroth said. "It's an immensely complex phenomenon that requires rapid, highly integrated communication among disparate, distant parts of the brain. Specific brain states well-suited for rich information handling

See DEISSEROTH, page 5

Scar painter Ted Meyer to lecture and lead workshops at Stanford

By Rosanne Spector

Ted Meyer's career as an artist was succeeding beyond his dreams. Though he was often in great physical pain — a result of Gaucher disease he had faced since childhood — his paintings were critically acclaimed, shown in galleries around the world.

Then, in his mid-30s, he lost his muse: He had begun a newly available treatment for Gaucher disease, and his symptoms vanished.

"All of a sudden, everything that had been the motivation for my artwork disappeared. I wasn't in pain or fatigued. I wasn't worried about dying young," said Meyer, whose paintings had been expressions of his anguish.

He felt great, he said, but as an artist he was lost — until a conversation at an art opening with a woman in a wheelchair wearing a backless dress that showed a long scar running down her spine. Though partly paralyzed, she was nonetheless an actress and dancer. Their meeting set him on a new course: creating art that tells the stories of survivors of health crises.

TED MEYER

After meeting this woman who was partly paralyzed from a zip line accident, Meyer was inspired to print the former dancer's scar, adding paint and other effects. He paired it with a photo of the dancer with the scar on her back covered in paint.

TED MEYER

Artist Ted Meyer creates paintings that tell the stories of survivors of health crises. He will discuss his work at Stanford Aug. 14-17.

'Scarred for Life'

Meyer, this year's Sterling Visiting Professor in the Department of Chemical & Systems Biology, will be at Stanford Aug. 14-17 to speak and lead workshops that continue telling those stories. His aim, he said, is to round out the medical profession's view of patients' lives.

Attendees will learn about his project "Scarred for Life: Mono-prints of Human Scars." The project began when Meyer printed the dancer's scar — a result of surgeries to repair damage from the zip line accident that had paralyzed her. He added details to the print with paint and color pencil and paired the result with a photograph of the dancer showing the scar slathered with paint on her back.

Now 59, Meyer still paints. He also teaches medical students. As the artist in residence at the Keck School of Medicine of USC, he brings artists with chronic illnesses to the medical school to exhibit their work and meet with students.

"My hope is that over the month each show is up, it is not only beautiful or compelling but it tells the story of what the life is like for an artist," said Meyer.

"You can see a lot of things besides, 'I was in pain for five years.' If the med students see it over and over, I hope it will remind them that they're really dealing with patients and not a pile of symptoms."

The talks and workshops at Stanford, listed below, are open to the public:

- Talk — A Patient Life, 4-6 p.m. Aug. 14 in Munzer Auditorium at the Beckman Center.
- Workshop — Scarred for Life, 10 a.m. Aug. 15 in rooms 4105-4107 of the Center for Clinical Sciences Research. The event will feature a round-table discussion on the representation of scars and the meaning and stories behind them, as well as the creation of prints of workshop participants' scars.
- Workshop — The Collective Experience: Charting Illnesses that have Touched You, Your Family and Friends, 10 a.m. Aug. 16 rooms 4105-4107 of the Center for Clinical Sciences Research.
- Talk and presentation — Art and Med, 4-6 p.m. Aug. 17 in Munzer Auditorium. ISM

Among Meyer's works are (from left) Leg/Pelvis Amputation, Double Mastectomy and Damaged Leg from Suicide Bomber.

Deisseroth

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may be needed for effective social communication and behavior."

To test the excitation-inhibition balance hypothesis, the Stanford scientists launched a set of experiments employing the mutant mice, which display hyperactive behavior and impaired social interaction. Interestingly, these mice also share a less visible characteristic with humans carrying the equivalent mutation: a shortage, compared with normal mice and humans, of parvalbumin neurons, a particular category of inhibitory nerve cell found throughout the brain. In a 2009 *Nature* paper, Deisseroth and his team reported that parvalbumin neuron activity can improve the information-handling capacity of forebrain neurons.

The researchers used optogenetics, an advanced laboratory technology that Deisseroth pioneered, to insert genes for two types of light-sensitive proteins, or opsins, into two distinct sets of neurons in the medial prefrontal cortex of the mice.

The researchers inserted one type of opsin into parvalbumin inhibitory neurons in that region of the mice's brains. It made the neuron more excitable if it received a pulse of blue light, delivered via an implanted optical fiber.

The other opsin, also activated with a pulse of blue light, had the opposite effect: When activated, it rendered the neuron on which it sat more resistant to firing. The scientists put this inhibitory opsin in a set of excitatory medial prefrontal cortex neurons called pyramidal neurons.

Reducing the excitation-inhibition ratio by either diminishing the excitability of the pyramidal neurons or by increasing the excitability of the parvalbumin neurons led to the same result in the mice: more time spent engaging in social encounters with other mice and less hyperactivity during those encounters or when the mice were by themselves.

"In all of psychiatry, there's no lab test that can diagnose this condition."

"Excitation-inhibition balance can take many forms and may be important at different stages of life," Deisseroth said. "Together, these findings suggest that this form of regulating the ratio of excitatory- to inhibitory-cell firing in the medial prefrontal cortex may be significant in normal social behavior and in autism."

Deisseroth is a member of the Stanford Neuroscience Institute and of Stanford Bio-X, an interdisciplinary consortium of physical and medical scientists and engineers.

Other Stanford study co-authors are postdoctoral scholars Christina Kim, PhD, and Masatoshi Inoue, PhD; former postdoctoral scholars Soo Yeun Lee, PhD, and Thomas Davidson, PhD; laboratory technician Alice Hong; graduate student Isaac Kauvar; laboratory manager Charu Ramakrishnan; former graduate student Lief Fenno, PhD; and psychiatry instructor Matthew Wright, MD, PhD.

The study was funded by the National Institute of Mental Health, the National Institute on Drug Abuse, the U.S. Defense Advanced Research Projects Agency, the Simons Foundation, the Wiegers Foundation, the Gatsby Foundation and the National Science Foundation.

Stanford's departments of Bioengineering and of Psychiatry and Behavioral Sciences also supported the work.

The Department of Bioengineering is jointly operated by the School of Medicine and the School of Engineering. ISM

CFS

continued from page 1

hundreds of patients," he said. "It's been observed and talked about for 35 years now, sometimes with the onus of being described as a psychological condition. But chronic fatigue syndrome is by no means a figment of the imagination. This is real."

STEVE FISCH

Mark Davis, senior author of the new study about chronic fatigue syndrome, says the findings "show clearly that it's an inflammatory disease and provide a solid basis for a diagnostic blood test."

Antivirals, anti-inflammatories and immune-modulating drugs have led to symptomatic improvement in some cases, Montoya said. But no single pathogenic agent that can be fingered as the ultimate ME/CFS trigger has yet been isolated, while previous efforts to identify immunological abnormalities behind the disease have met with conflicting and confusing results.

Still, the sporadic effectiveness of antiviral and anti-inflammatory drugs spurred Montoya to undertake a systematic study to see if the inflammation that's been a will-o'-the-wisp in those previous searches could be definitively pinned down.

To attack this problem, he called on Davis, who helped create the Human Immune Monitoring Center. Since its inception a decade ago, the center has served as an engine for large-scale, data-intensive immunological analysis of human blood and tissue samples. Directed by study co-author Holden Maecker, PhD, a professor of microbiology and immunology, the center is equipped to rapidly assess gene variations and activity levels, frequencies of numerous immune cell types, blood concentrations of scores of immune proteins, activation states of intercellular signaling models and more, on a massive scale.

Finding patterns

This approach is akin to being able to look for and find larger patterns — analogous to whole words or sentences — in order to locate a desired paragraph in a lengthy manuscript, rather than just try to locate it by counting the number of times in which the letter A appears in every paragraph.

The scientists analyzed blood samples from 192 of Montoya's patients, as well as from 392 healthy control subjects. The average age of patients and controls was about 50. Patients' average duration of symptoms was somewhat more than 10 years.

Importantly, the study design took into account patients' disease severity and duration. The scientists found that some cytokine levels were lower in patients with mild forms of ME/CFS than in the control subjects, but elevated in ME/CFS patients with relatively severe manifestations. Averaging the results for patients versus controls with respect to these measures would have obscured this phenomenon, which Montoya said he thinks may reflect different genetic predispositions, among patients, to progress to mild versus severe disease.

When comparing patients versus control subjects, the researchers found that only two of the 51 cytokines they measured were different. Tumor growth factor beta was higher and resistin was lower in ME/CFS patients. However, the investigators found that the concentrations of 17 of the cytokines tracked disease severity. Thirteen of those 17 cytokines are pro-inflammatory.

TGF-beta is often thought of as an anti-inflammatory rather than a pro-inflammatory cytokine. But it's known to take on a pro-inflammatory character in some cases, including certain cancers. ME/CFS patients have a higher than normal incidence of lymphoma, and Montoya speculated that TGF-beta's elevation in ME/CFS patients could turn out to be a link.

One of the cytokines whose levels corresponded to disease severity, leptin, is secreted by fat tissue. Best known as a satiety reporter that tells the brain when somebody's stomach is full, leptin is also an active pro-inflammatory substance. Generally, leptin is more abundant in women's blood than in men's, which could throw light on why more women than men have ME/CFS.

More generally speaking, the study's results hold implications for the design of future studies of disease, including clinical trials testing immunomodulatory drugs' potential as ME/CFS therapies.

"For decades, the 'case vs. healthy controls' study design has served well to advance our understanding of many diseases," Montoya said. "However, it's possible that for certain pathologies in humans, analysis by disease severity or duration would be likely to provide further insights."

Other Stanford co-authors of the study are clinical research coordinator Jill Anderson; Tyson Holmes, PhD, senior research engineer at the Institute for Immunity, Transplantation and Infection; Yael Rosenberg-Hasson, PhD, immunoassay and technical director at the institute; Cristina Tato, PhD, MPH, research and science analyst at the institute; former study coordinator Ian Valencia; and Lily Chu, MSHS, a board member of the Stanford University ME/CFS Initiative.

The study was funded by the National Institutes of Health, the Stanford ME/CFS Initiative Fund and an anonymous donor.

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

Shah

continued from page 1

factors and how much was genetically hard-wired. Their findings suggest that social forces can override genetically programmed behavior. The findings also could potentially help explain the ill effects of solitary confinement on prisoners, as well as what underlies psychiatric disorders characterized by bursts of violent anger.

Male mice are naturally territorial. In the wild or in the lab, they attack other male mice even if plenty of room, food and females are available.

A typical male mouse who's been dug in for a while as the sole occupant of a chunk of turf will normally attack any other male placed into that territory, said Nirao Shah, MD, PhD, professor of psychiatry and behavioral sciences and of neurobiology.

"But selectively activating just this tiny cluster — about 5,000 nerve cells in a brain with 80 million nerve cells — escalates the level and extent of male mice's aggressiveness dramatically," said Shah, the study's senior author. The lead author is postdoctoral scholar Taehong Yang, PhD.

The cells, designated as PR+ VMHvl nerve cells, are found in a part of a brain structure called the ventromedial hypothalamus and are distinguished by the fact that they contain receptors for sex hormones.

Turning mouse Jekyll into mouse Hyde

Stimulating PR+ VMHvl cells in a male lab mouse who's spent a week to 10 days in a cage of its own triggers fierce displays of territorial aggression even when such behavior would rarely occur, the scientists found. This mouse not only will attack a female, which male mice normally never do, or a member of another species, which mice also rarely do, but will threaten a mirror placed in its cage or even an inflated surgical glove. Even if neutered, the resident male will launch an attack on another mouse introduced to its cage. (Circulating testosterone is normally indispensable for displays of male territorial aggression.) In effect, stimulating these cells makes the solitary male lash out violently and indiscriminately.

In an earlier study, Shah and his colleagues showed that selectively killing PR+ VMHvl nerve cells radically reduces territorial aggression in male mice. This cluster therefore appears to be essential to a male mouse's display of territorial aggressiveness. The new study indicates that the circuitry's activation is also sufficient to trigger territorial aggression in a broad range of circumstances.

Nevertheless, this genetically hard-wired behavior seems to be subject to complex social etiquette. For one thing, the study showed, a solitary-resident male mouse wouldn't start exhibiting displays of aggression if it was all alone, regardless of how amped up its PR+ VMHvl circuitry was. But the sighting of an unfamiliar object — even the nonreflective side of a mirror — in its cage was enough to trigger tail-rattling threats. Such a mouse would also attack when inserted into the turf of another aggressive, solitary male. On the other hand, a male mouse that had been housed with other males would not attack the aggressive solitary male on the latter's home turf, even when the researchers revved up PR+ VMHvl activity in the socially housed male. Something about social housing, Shah said, seems to powerfully temper male mice's aggressiveness — so much so that even directly activating the intruders' "rage center" wasn't enough to coax it into attacking.

That something, said Shah, is likely to be related to mice's acute ability to sense pheromones, which are chemical compounds released by members of a species to signal their social and reproductive status to other members of the species.

"You can tell male and female mice apart by the way they smell," said Shah, an experienced rodent researcher. Unlike female mice, males smell "pretty offensive." Ponder the scent of moldy socks and dirty T-shirts in a teenage boy's gym locker.

Previous work showed that a solitary male hanging out on his home turf attacks a male intruder because of the intruder's pheromones. The new study showed that pheromones exuding from such a solitary male on his home turf deter aggression from a socially housed male intruder. Strikingly, if the socially housed male could no longer sense the solitary male resident's pheromones, he would attack the resident once his PR+ VMHvl cells were revved up.

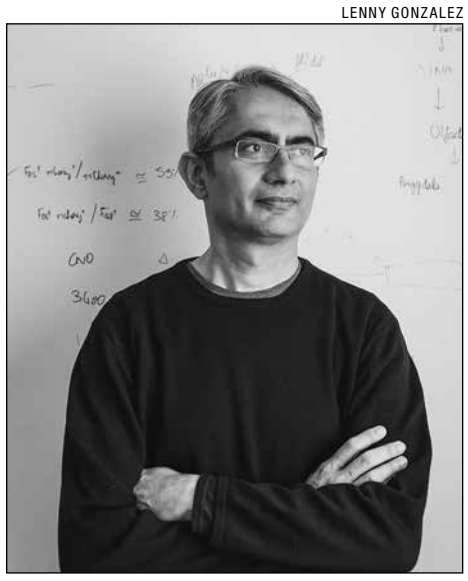
'Nature versus nurture is a false dichotomy'

"Nature versus nurture is a false dichotomy," said Shah. "We've showed, on the one hand, that genetically programmed circuitry massively influences mammalian behavior. And we've seen that, under certain circumstances, nurture wins: Your social conditions can override your natural impulse to fight."

The human brain, like that of the mouse, also features a ventromedial hypothalamus. While this brain region's functions haven't been fully elucidated in humans, Shah said, case studies suggest at least a degree of similarity to those of a mouse.

The study's findings, therefore, may bear on the question of whether solitary confinement of aggressive male criminals is counterproductive. In addition, some 5 percent of adults are estimated to experience, at some time in their lives, episodes of a psychiatric condition called intermittent explosive disorder — impromptu outbursts of ferocity in the face of what would usually be considered inadequate triggers for that ferocity. It could be, Shah speculated, that the human equivalent of PR+ VMHvl nerve cells are involved, and that learning how to modulate their activity in mice could lead to treatments for this disorder in people.

LENNY GONZALEZ



Nirao Shah says the new findings show that both genetics and environment can affect behavior in mice. "Nature versus nurture is a false dichotomy," he adds.

Other Stanford co-authors are graduate student Niru Maheswaranathan; postdoctoral scholar Sayaka Inoue, PhD; and assistant professor of applied physics Surya Ganguli, PhD.

Researchers from the University of California-San Francisco also contributed to the study.

The study was funded by the National Institutes of Health, the Ellison Medical Foundation, and the Brain & Behavior Research Foundation.

Stanford's departments of Psychiatry and Behavioral Sciences and of Neurobiology also supported the work. **ISM**

Small drop in measles vaccinations would have outsized effect, study shows

By Erin Digitale

Small reductions in childhood measles vaccinations in the United States would produce disproportionately large increases in the number of measles cases and in related public health costs, according to a new study by researchers at the School of Medicine and at Baylor College of Medicine.

A 5 percent drop in the number of children ages 2 to 11 inoculated against the measles, mumps and rubella would triple the number of annual measles cases in this age group, the study found. The MMR vaccine is an inoculation against the three diseases.

The additional measles cases would increase annual public health expenditures by at least $2.1 million, or $20,000 per case of measles.

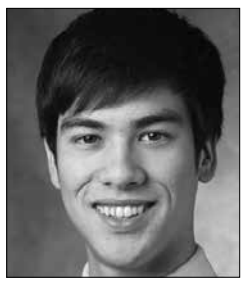
The study was published July 24 in *JAMA Pediatrics.*

"We focused on measles as an example of the effects of declining vaccine coverage because it is highly infectious," said Nathan Lo, the study's lead author and a Stanford MD-PhD student. "It's likely to be the first infectious disease causing outbreaks if vaccination declines."

Lo said he hopes the findings will be considered by state legislators making decisions about vaccination policy.

"I think our study is a wake-up call for what we can expect in the coming months and years as vaccine coverage rates continue to decline in the 18 states that now allow non-medical or philosophical belief exemptions," said senior author Peter Hotez, MD, PhD, dean of the National School of Tropical Medicine at Baylor.

Across the country, several regions are near the threshold of 90 to 95 percent vaccine coverage needed to prevent measles outbreaks. The new study predicts a sharp rise in measles cases if vaccination further declines.



Nathan Lo

Highly infectious

Although vaccination has been successful at controlling measles in the United States, a few dozen to a few hundred cases occur here every year, usually when U.S. citizens travel abroad and unknowingly bring the virus home. Infected people can spread the virus by sneezing and coughing for four days before they show symptoms. Measles lingers in the air and remains infectious for up to two hours, an unusually long time for an airborne virus, and a high percentage of unvaccinated people exposed to the infected air become sick themselves.

All 50 states require the MMR vaccine and other childhood vaccinations prior to enrollment in elementary school or day care. In all states, children can be exempted from vaccination for medical reasons.

All but three states also allow parents to decline vaccination for religious reasons, and 18 states have exemptions for personal beliefs. (California eliminated its religious and personal-belief exemptions in 2015 following a large measles outbreak that originated at Disneyland.)

Lo analyzed MMR vaccination data from the U.S. Centers for Disease Control and Prevention. He constructed a mathematical model from the data to predict the effects of declining vaccination rates in children ages 2 to 11, simulating about 10,000 scenarios that could occur as measles is introduced by returning travelers into different locations around the country at a rate similar to that of recent years.

The researchers also estimated the cost of declining vaccination rates if children younger than 2 were included in the models — a scenario that increased the predicted public health costs by another $400,000 per year beyond the $2.1 million cost for older children. (Infants are not eligible for their first dose of the MMR vaccine until they're 1, making them especially vulnerable to measles.)

The public-health costs estimated in the new paper from declining vaccination rates are conservative, Lo said. The costs are for measles alone, and do not include other infectious diseases that may rise with lower vaccination coverage. The costs include some health care expenditures and outbreak-containment tasks, but not the costs of hospitalization or days of work missed by parents of ill children.

Geographic hotspots

Children ages 2 to 11 now account for about 30 percent of U.S. measles cases, meaning that the impact of declining vaccination rates would be significantly larger than the figures predicted in this study if all age groups were considered.

Unvaccinated people tend to cluster in certain geographic areas, and introducing measles in these areas would cause significant outbreaks, the researchers noted. One such outbreak took place in 2014, when 383 measles cases occurred in unvaccinated Amish communities in Ohio.

"Even in states with a high level of vaccine coverage, there can be very large differences within the state, including poorly vaccinated pockets of communities that may be masked," Lo said.

If travelers bring home measles to well-vaccinated communities, the number of cases is much lower than if they come home to a poorly vaccinated region. The study capped the outbreak size in the researchers' calculations at 100 cases, although individual outbreaks can become larger, especially with declining vaccine coverage.

The study was also conservative in the level of infectiousness it built into its calculations, said Yvonne Maldonado, MD, professor of pediatric infectious diseases at Stanford. Maldonado, an expert on vaccination, was not involved in the study.

Lo hopes state lawmakers will consider the study's findings as they contemplate vaccination policies, especially non-medical personal belief exemptions to childhood vaccination requirements.

"This study quantifies the consequences of a rise in measles cases and state dollars that will be spent if personal belief exemptions that can reduce vaccine coverage are in place," he said.

Lo is supported by the Medical Scientist Training Program at the Stanford School of Medicine. Stanford's Department of Health Research and Policy also supported the work. ISM

PTSD

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them of the event; and experience altered mood and thinking patterns. Nearly 7 percent of people in the United States will suffer from PTSD at some point in their lifetime, according to the National Institute of Mental Health, which funded the work.

Prolonged exposure therapy for PTSD consists of a series of sessions and homework assignments that lead patients to gradually approach trauma-related memories and situations. Patients begin by imagining scenarios that trigger their PTSD symptoms — such as a crowded park. Then, they work up to deliberately putting themselves in those scenarios. Revisiting traumatic experiences in this manner can, over time, allow the brain to slowly reduce its response to emotional triggers. However, not all PTSD patients derive benefit from the treatment, and about a third drop out of the arduous process, said Etkin. About two-thirds of patients receiving prolonged exposure therapy see a 50 percent reduction in symptoms, and 40 percent of them achieve remission, he said.

To learn how exposure therapy works in the brain, the studies used functional magnetic resonance imaging to measure the brain activity of 66 patients diagnosed with PTSD as they completed five tasks tapping a variety of emotional and cognitive functions.

After the initial brain imaging, about half the participants underwent nine to 12 sessions of prolonged exposure therapy; the remainder did not. At the end of the trial, all participants went through the same emotional response and regulation tests while researchers measured brain activity.

A step closer to personalized treatment

One of the studies focused on whether brain activity levels before treatment could help scientists predict which participants would respond well to prolonged exposure therapy. The researchers measured how active certain brain regions were during the five tasks and looked for associations with reduced symptoms post-treatment.

Prior to receiving prolonged exposure therapy, patients with both lower activity in the amygdala and higher activity in various regions of the frontal lobe during certain tasks showed a larger reduction in PTSD symptoms following therapy. Fonzo refers to the amygdala, seated deep within a primitive region of the brain, as the brain's alarm system, as it plays an important role in fear and other emotional responses. The frontal lobe is the outer layer of the human brain in the area behind the forehead; it plays a role in complex functions such as behavior, personality and decision-making.

The researchers also found that patients with greater activation in a deep region of the frontal lobe when ignoring the distracting effects of conflicting emotional information — such as viewing a picture of a scared face with the word "happy" written across it — responded better to exposure therapy.

"The better able the brain is at deploying attention- and emotion-controlling processes, the better you respond to treatment," said Fonzo.

Using this information about how the brain responds in emotional regulation and processing tasks, the team was able to predict how effective prolonged exposure therapy treatment would be for patients with up to 95.5 percent accuracy. This kind of screening approach, perhaps using the less expensive and more widely available electroencephalogram rather than fMRI, could help doctors determine the best course of PTSD therapy in the future, the researchers said.

"Not only could it provide a ray of hope for patients who would benefit from prolonged exposure to make it through the tough course," said Goodkind, "it means patients who wouldn't derive a benefit wouldn't have to start the treatment."

Therapy changes the brain

In the second study, the researchers found that prolonged exposure therapy led to lasting changes in participants' brains that were associated with improvement in PTSD symptoms. About four weeks after therapy ended, fMRI showed elevated activity in the front-most region of the frontal lobe, an area called the frontopolar cortex. This region is the most recently evolved part of the human brain. It balances internal and external attention and helps coordinate multiple processes in the brain simultaneously, said Fonzo, as would occur when multitasking and remembering future to-do list items.

The role the frontopolar cortex plays in prolonged exposure therapy was surprising, Fonzo said, because much of the scientific attention on emotional processes in PTSD has centered on the amygdala.

Specifically, the changes the researchers observed in frontopolar cortex activity occurred when participants were instructed to regulate their emotional response to an image of a negative or stressful scenario, such as one depicting an argument. The researchers also noted changes in frontopolar cortex activity in these participants during a resting, nonfocused state.

The post-therapy brain changes also included increased connectivity between the frontopolar cortex and deeper brain regions closer to emotional processing areas. The authors wrote that psychotherapy may train the frontopolar cortex "to better evoke or amplify attention toward an internal regulatory process that mediates successful emotion regulation."

The degree to which activity in the frontopolar cortex increased following therapy was associated with the degree of improvement in PTSD symptoms and emotional well-being.

Exploring transcranial magnetic stimulation

To confirm whether the frontopolar cortex controls important brain regions for emotional processing, the team used a noninvasive method of stimulating brain activity called transcranial magnetic stimulation, or TMS, to activate the frontopolar cortex in healthy people. They simultaneously recorded brain activity with fMRI and confirmed that the frontopolar cortex modulated downstream activity in lower cortical regions closer to emotion-processing parts of the brain.

They also explored whether TMS might help PTSD patients respond to prolonged exposure treatment. Building off their findings that greater frontal lobe and less amygdala activation predicts better treatment outcome, the researchers activated a region of the frontal cortex with TMS probes while imaging the brain. They found that doing so inhibited activity in the amygdala, and the degree to which that happened also predicted the degree to which a patient's symptoms improved. In the future, stimulating this region may help increase patients' responsiveness to psychotherapy, they said. Indeed, some small-scale studies in which therapeutic TMS was used daily on the same region of the frontal cortex, without the addition of psychotherapy, have already shown promising results.

"These findings put a place marker in our understanding of psychotherapy writ large. We can really put psychiatric disorders on the map in terms of hard science and help fight the stigma that surrounds these illnesses and their treatment," said Etkin. "Within the field of PTSD, it gives a concrete sense of hope for people undergoing treatment and starts laying the groundwork for new treatments based on understanding brain circuitry." ISM

Jennifer Cochran will become chair of bioengineering Sept. 1

By Bruce Goldman

Jennifer Cochran, PhD, has been appointed chair of Stanford's Department of Bioengineering, which is jointly operated by the School of Medicine and School of Engineering. Her five-year term begins Sept. 1.

"This department has an amazing energy due in no small part to its faculty, students and staff," said Cochran, associate professor of bioengineering. "These individuals — nearly 500 of them, in all — have an unwavering commitment to research, learning and service, and they exude a spirit of collegiality and collaboration that permeates our department and the broader Stanford community."

Cochran's research is interdisciplinary, integrating chemistry, engineering and biophysics. Her laboratory focuses on protein-based drug discovery for applications including oncology and regenerative medicine, and the development of new technology for high-throughput protein analysis and engineering.

'A superb scholar and educator'

"In addition to being a superb scholar and educator and a proponent of deeper connections with Silicon Valley's burgeoning biotechnology activities, Jennifer is an enthusiastic, dynamic individual who will bring exciting leadership to the department and be a key contributor to the schools of Engineering and Medicine," Lloyd Minor, MD, dean of the School of Medicine, and Jennifer Widom, PhD, dean of the School of Engineering, said in a joint statement.

Jennifer Cochran

Cochran will succeed Norbert Pelc, ScD, professor of bioengineering, who has chaired the department since 2012. "Norbert's vision and leadership has brought the department to new heights," Minor and Widom said. "The remarkable strength of our still relatively new Bioengineering Department reflects Norbert's tireless work and deep dedication."

Cochran earned a PhD in biological chemistry from the Massachusetts Institute of Technology in 2001. After a postdoctoral fellowship at MIT in biological engineering, she arrived at Stanford in 2005 as an assistant professor of bioengineering. In 2012, she was promoted to associate professor. She also advises cancer biology and biophysics graduate students and serves as director of the Stanford National Institutes of Health Biotechnology Predoctoral Training Program and as co-director of the Stanford National Institute of Standards and Technology Predoctoral Training Program.

Interdisciplinary training

The Department of Bioengineering includes more than 30 tenure-track faculty, 70 postdoctoral scholars and 200 graduate students with a variety of backgrounds and interests.

"Now, more than ever, interdisciplinary training and awareness is critically needed for bioengineering to be broadly productive and impactful. Stanford excels in this arena," Cochran said.

"One of my goals is to work with students, staff and faculty to build stronger connections with Silicon Valley and the world at large," she added. "I'd also like to help enable the department to tackle new technology developments and innovations in biotechnology, medical devices, mobile health and data and measurement science, and forge new connections in areas such as agriculture, environment, humanities, policy and the arts." **ISM**

OF NOTE

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

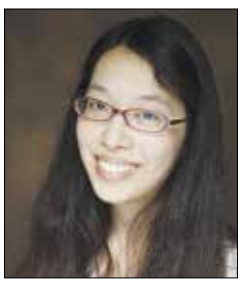
Valerie Baker

Ben Barres

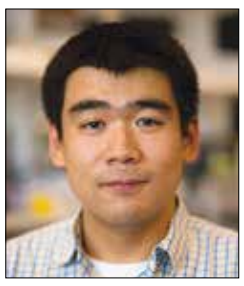
Jennifer Caswell-Jin

Heike Daldrup-Link

Aaron Gitler



Victoria Hung



Shaogeng (Steven) Tang

Jin Hyung Lee

Amy Krystosik

Winnie Kwofie

VALERIE BAKER, MD, was promoted to professor of obstetrics and gynecology, effective June 1. She has served as medical director of the Stanford Fertility and Reproductive Health Center and chief of reproductive endocrinology and infertility. Her research interests include pregnancy outcomes following infertility, assisted reproductive technology and primary ovarian insufficiency.

BEN BARRES, MD, PhD, professor of neurobiology, of developmental biology and of neurology and neurological sciences, has received the Inge Grundke-Iqbal Award for Alzheimer's Research from the Alzheimer's Association. The honor recognizes the senior author of the most impactful study published about Alzheimer's research in the past two years. His work advanced the understanding of the role played by the apolipoprotein E gene in controlling the rate of synapse pruning by astrocytes in the brain.

JENNIFER CASWELL-JIN, MD, postdoctoral scholar in medical oncology, was awarded a 2017 Damon Runyon Physician-Scientist Training Award from the Damon Runyon Cancer Research Foundation. The grant provides more than $100,000 a year for four years. She also received a three-year Susan G. Komen Postdoctoral Fellowship and a one-year American Society for Clinical Oncology Young Investigator Award. Caswell-Jin plans to develop a model of HER2-positive breast cancer evolution that will help her examine how the cancer changes when treated with HER2-targeted therapy.

HEIKE DALDRUP-LINK, MD, PhD, was promoted to professor of radiology, effective June 1. She is the associate chair for diversity and director of the pediatric molecular imaging program in the Department of Radiology. She co-directs the cancer imaging and early detection program at the Stanford Cancer Institute.

AARON GITLER, PhD, was promoted to professor of genetics, effective June 1. His research examines the mechanisms of human neurodegenerative diseases including Parkinson's disease and amyotrophic lateral sclerosis.

VICTORIA HUNG, PhD, postdoctoral scholar in developmental biology and in genetics, and **SHAOGENG (STEVEN) TANG**, PhD, postdoctoral scholar in biochemistry, have been named Damon Runyon Fellows by the Damon Runyon Cancer Research Foundation. The fellowship provides $231,000 over four years to support basic and translational cancer research. Hung is examining how phosphorylation of ribosomal components leads to the specialization of ribosomes. Tang is developing small-molecule inhibitor drugs that target human immune checkpoint proteins. Tang was also selected as a Merck Fellow by the foundation.

JIN HYUNG LEE, PhD, was promoted to associate professor of neurology and neurological sciences, of bioengineering and of neurosurgery, effective May 1. Her research focus is on analyzing and manipulating brain circuits to develop new therapies for neurological diseases.

AMY KRYSTOSIK, PhD, postdoctoral scholar in infectious diseases, was awarded the Robert E. Shope International Fellowship from the American Society of Tropical Medicine and Hygiene. The fellowship provides $25,000 for a short-term arbovirology or infectious disease research experience in the tropics. Krystosik plans to conduct field tests of a miniaturized, automated, whole-blood cellular analysis system to test immunity to arboviruses in Kenya.

WINNIE KWOFIE, assistant director of facilities operations for the Office of Facilities Planning & Management, has received the 2017 Pacesetter Award from APPA, an educational facilities professional organization. The honor recognizes individuals who have made significant contributions to the educational facilities management profession and industry.

DAVID MYUNG, MD, PhD, was appointed assistant professor of ophthalmology, effective June 1. He is the co-director of the Stanford Ophthalmic Innovation Program, a one-year, project-based fellowship. His research interests include regenerative medicine and drug delivery, as well as global health through telemedicine and emerging smartphone-based diagnostic platforms.

KATHLEEN SAKAMOTO, MD, PhD, professor of pediatrics, has been awarded a $100,000 grant from the Bear Necessities Pediatric Cancer Foundation to develop new small-molecule compounds to target CREB-dependent pathways for the treatment of relapsed acute leukemia. She holds the Shelagh Galligan Professorship in the School of Medicine.

PETER SANTA MARIA, MBBS, PhD, was appointed assistant professor of otolaryngology-head and neck surgery, effective June 1. His clinical focus is on adult and pediatric surgery for hearing, balance and facial nerve disorders. His research interests include tympanic membrane regeneration, biofilm treatment, oral wound healing and medical device development.

DEBANTI SENGUPTA, PhD, postdoctoral scholar in radiation oncology, was given the Alavi-Mandell Award from the Society of Nuclear Medicine and Molecular Imaging for being the lead author of "Single-cell characterization of 18F-FLT uptake with radioluminescence microscopy," a paper published in the *Journal of Nuclear Medicine* in July 2016. The award recognizes a trainee who is the lead author of an outstanding paper published in the journal.

GEOFFREY TABIN, MD, was appointed professor of ophthalmology, effective June 1. He is a cornea and cataract specialist whose work focuses on reducing global blindness and developing systems of eye care in Asia and Africa. He is the co-founder of the Himalayan Cataract Project.

KATHRYN TAYLOR, PhD, postdoctoral scholar in neurology and neurological sciences, was awarded a Damon Runyon-Sohn Pediatric Cancer Fellowship Award. The award provides $231,000 over four years to support research with the potential to significantly impact the prevention, diagnosis or treatment of pediatric cancer. Taylor is investigating the effect of neural activity on pediatric high-grade glioma invasion. **ISM**

David Myung

Kathleen Sakamoto

Peter Santa Maria

Debanti Sengupta

Geoffrey Tabin

Kathryn Taylor